# MASARYKOVA UNIVERZITA

## LÉKAŘSKÁ FAKULTA

**Moderní přístupy v chirurgické léčbě Crohnovy choroby**

## HABILITAČNÍ PRÁCE

komentovaný soubor prací

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**Komentář**

**Úvod:** Crohnova choroba (CD - Crohn's disease) patří mezi chronická zánětlivá onemocnění střev. V současnosti je problémem narůstající incidence CD převážně ve vyspělých zemích světa. Proto je nutné hledat nové a moderní léčebné metody (jak stran konzervativní léčby, tak chirurgické).

**Metody:** Tato habilitační práce je souborem komentovaných prací (celkem 23 vědeckých článků a 3 abstraktů z mezinárodních kongresů). Články byly publikovány mezi lety 2016 – 2020 a jsou doplněny a vzájemně propojeny doprovodným textem s odkazem na nejnovější literaturu.

**Výsledky:** V IBD chirurgii je preferován miniinvazivní přístup. Chirurgicky navozená remise u pacientů s CD zvyšuje kvalitu života. Kombinace perorální ATB profylaxe s předoperační ortográdní přípravou střeva se zdá být vhodná předoperační příprava před střevní resekcí u pacientů s CD k dosažení minimální pooperační morbidity. Dvě a více mutací v genu NOD2 jsou spojeny s agresivnějším typem CD a tito pacienti vyžadují také častěji resekci ilea oproti jiným CD pacientům. Časná laparoskopická ileocekální resekce u zánětlivého postižení je v současnosti brána jako alternativa léčbou Infliximabem. Pozitivní mikroskopická zánětlivá aktivita CD v resekční linii u ileocekální resekce má vliv na časnou rekurenci onemocnění v anastomóze. Peroperační využití konfokální laserové mikroskopie (confocal laser endomicroscopy - CLE) by mohlo být nápomocné při určování resekční linie a snížit tak časnou rekurenci CD v anastomóze. Další studie s CLE na větších souborech pacientů jsou ale nutné.

**Závěr:** Pozitivní mikroskopický resekční okraj u ileocekální resekce je rizikový faktor časné endoskopické rekurence a CLE by v budoucnu mohla být užitečná k peroperačnímu určování resekční linie a snížení rekurence CD.

**Klíčová slova:**
Crohnova choroba – idiopatické střevní záněty rekurence – anastomóza – konfokální laserová endomikroskopie – minimálně invazivní chirurgie – gen NOD2 – kvalita života

**Commentary**

**Background:** Crohn's disease (CD) is a chronic inflammatory bowel disease. Currently, we face a growing incidence of CD, mainly in developed countries. It is necessary, then, to find new and modern treatments (both conservative and surgical).

**Methods:** This habilitation thesis is a set of annotated works (a total of 23 scientific articles and 3 abstracts from international congresses). The articles were published between 2016 and 2020 and are supplemented and interconnected by an accompanying text with links to the latest literature.

**Results:** In IBD surgery, a mini-invasive approach is preferred. Surgically induced remission in patients with CD increases quality of life. The combination of oral ATB prophylaxis with preoperative orthograde bowel preparation appears to be an appropriate preoperative preparation before intestinal resection in patients with CD, to achieve minimal postoperative morbidity. Two or more mutations in the NOD2 gene are associated with a more aggressive type of CD, and these patients also require more frequent resection of the ileum than other CD patients. Early laparoscopic ileocecal resection in inflammatory disease behaviour is currently considered an alternative to Infliximab treatment. Positive microscopic inflammatory activity of CD in the resection margins in cases of ileocecal resection affects the early recurrence of the disease in the anastomosis. Perioperative use of confocal laser endomicroscopy (CLE) could be helpful in determining the resection line and reduce early recurrence of CD in the anastomosis. However, further studies with CLE in larger patient populations are needed.

**Conclusion:** A positive microscopic resection margin in ileocecal resection is a risk factor for early endoscopic recurrence, and CLE could be useful in the future to perioperatively determine the resection line and reduce CD recurrence.

**Keywords:**
Crohn's disease – inflammatory bowel disease – recurrence – anastomosis – confocal laser endomicroscopy – minimally invasive surgery – gene NOD2 – quality of life

Konflikt zájmů

Prohlašuji, že jsem práci vypracoval samostatně s využitím citovaných zdrojů a nejsem v souvislosti se vznikem této práce ve střetu zájmů.

Datum: …….

14.12.2020 podpis autora

## Předmluva

Tato habilitační práce plynule navazuje na již získané poznatky během mého doktorandského studia a rovněž se zabývá chirurgickou léčbou Crohnovy choroby. Dochází tak k rozšíření a ucelení vědomostí daného tématu. V současné době je v léčbě IBD vyžadován multioborový přístup ve spolupráci chirurga, gastroenterologa, radiologa a na vědecké úrovni se neobejdeme i bez pomoci statistika či patologa. Předkládaná habilitační práce se snaží tento trend a přístup respektovat.

Habilitační práce je koncipována jako soubor jednotlivých komentovaných vědeckých článků, které jsou vzájemně a tematicky propojené.

Práce je rozdělena do 3 tematických celků:

1. Obecná část
2. Klinická část
3. Experimentální část


## Poděkování

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**Věnováno památce mého otce MUDr. Lumíra Kunovského (1951 - 2002).**

Obsah

# 1. Obecná část

## 1.1 Úvod

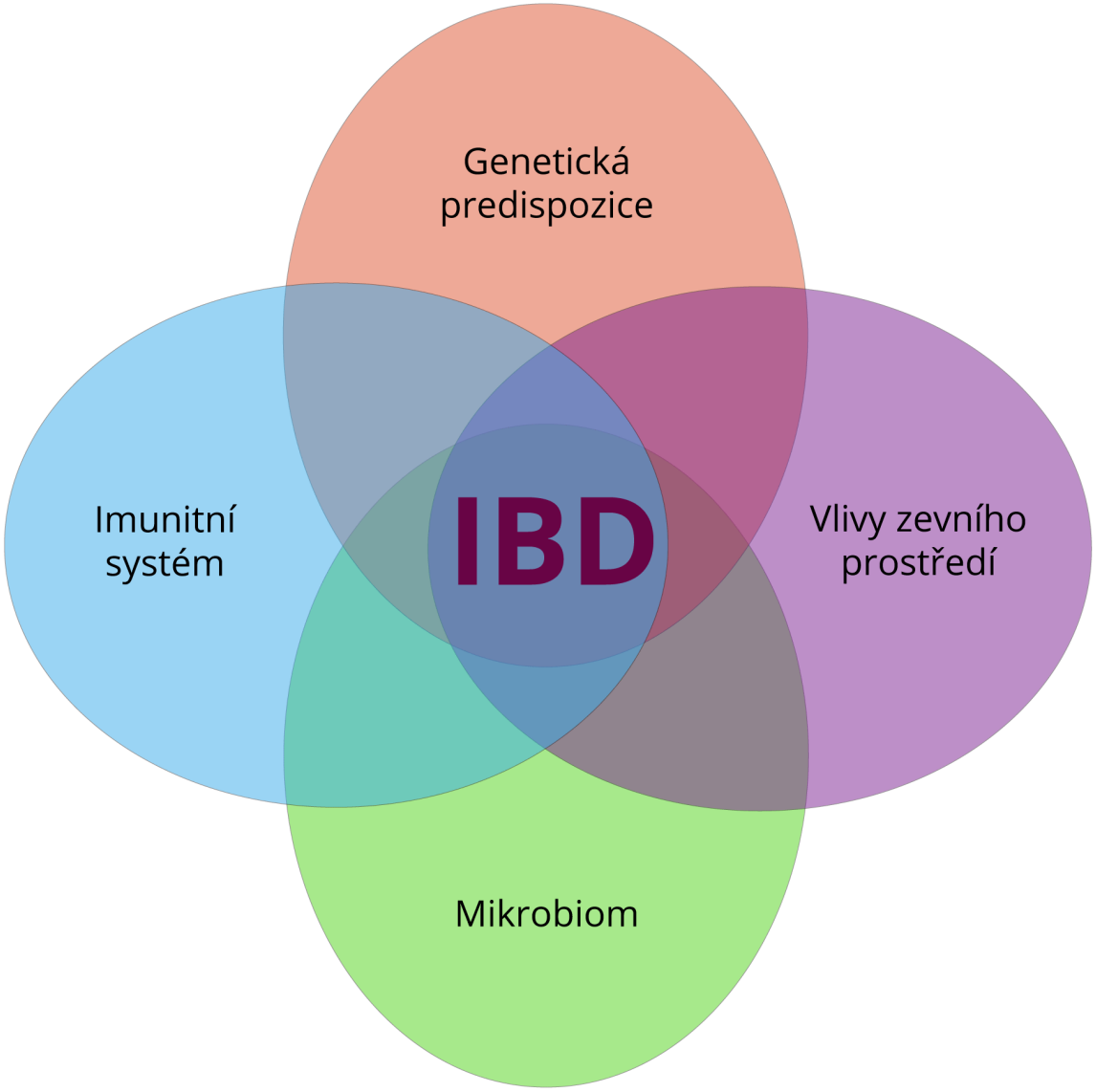
Crohnova choroba (CD - Crohn's disease) společně s ulcerózní kolitidou (UC - ulcerative colitis) patří mezi chronická zánětlivá onemocnění střev, které souhrnně označujeme jako tzv. idiopatické střevní záněty (IBD - inflammatory bowel disease). Pro obě onemocnění je charakteristické střídaní klidového stádia tzv. remise a aktivního zánětu neboli relapsu.

CD se od UC odlišuje v několika směrech. CD může postihovat jakýkoliv úsek trávící trubice a postihuje celou stěnu střeva s až možnou penetrací a tvorbou fistulací. Zánětlivé změny při UC jsou ohraničeny na sliznici a šíří se od rekta kontinuálně směrem proximálně [1,2].

V roce 1932 byla publikována významná práce od autorů Burrilla Crohna, Leona Ginzburga a Gordona Oppenheimera. Jednalo se o soubor 14 pacientů s regionální ileitidou [3]. Vzhledem k tomu, že v té době časopis Journal of the American Medical Association (JAMA) řadil autory dle abecedního pořadí, byl tak Crohn uveden mezi autory jako první. V následujících letech se jeho jméno začalo používat pro pojmenování této nemoci. Nutno říci, že B. Crohn dodal do celého souboru pouze 2 pacienty a existují určité kontroverze na jednotlivé přispění autorů ke článku a tedy i k samotnému lékaři, po kterém je choroba pojmenována (leč k tomu částečně přispělo abecední pořadí) [4].

## 1.2 Etiopatogeneze a incidence

Etiopatogeneze IBD je stále neobjasněna. V současnosti je přijímán model kombinace a vzájemného ovlivňování několika faktorů: genetická predispozice (první z identifikovaných genů ve vztahu k CD byl NOD2 - Nucleotide-binding oligomerization domain 2 v roce 2001 [5,6], později bylo až do dnešní doby identifikováno dalších zhruba 240 rizikových genetických mutací), zevní faktory (strava, kouření, hygiena, okolní prostředí), střevní mikrobiom a reakce imunitního systému (viz obr. 1 upraveno dle Sartor et al. [7]).

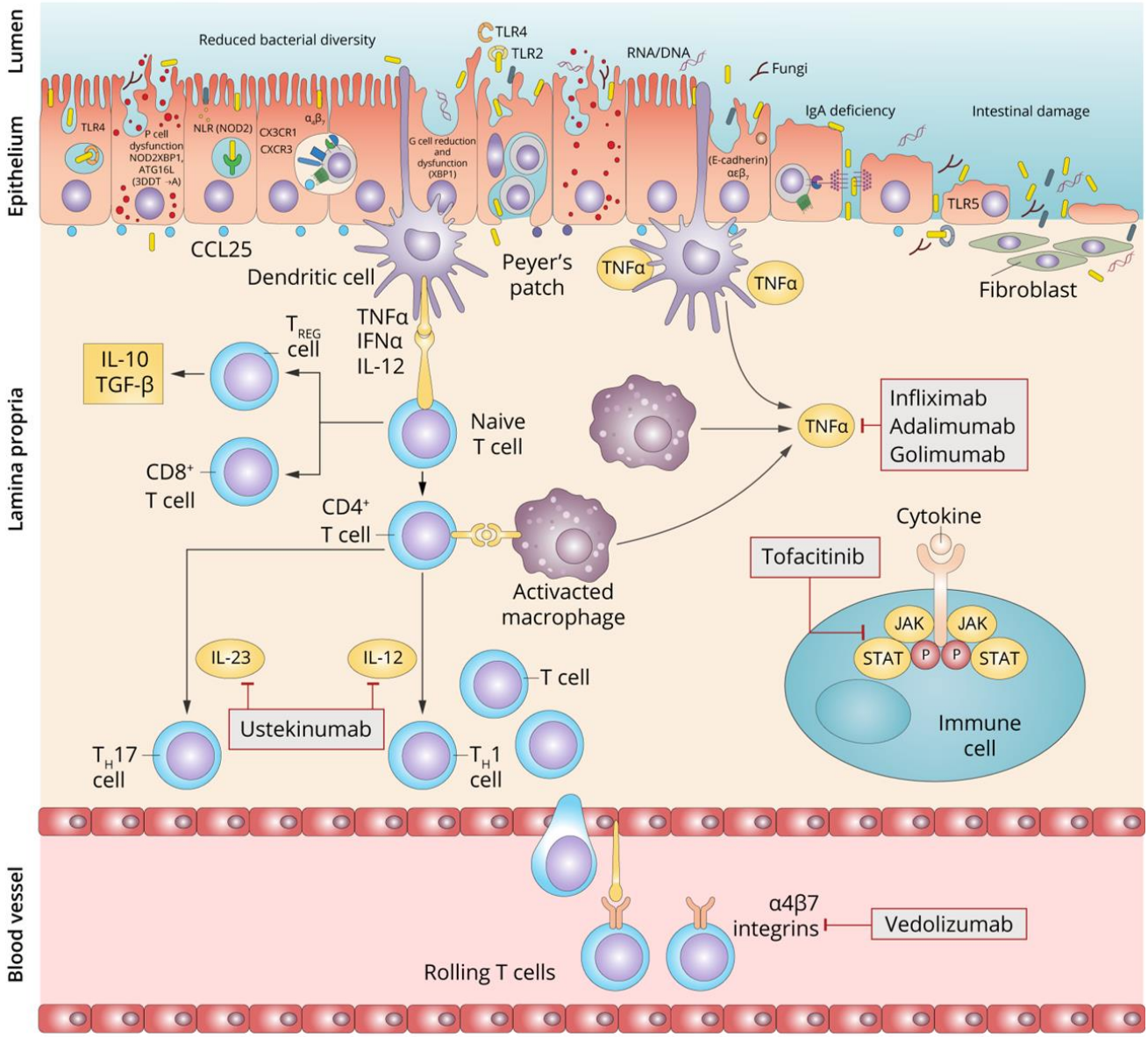



**Obr. 1.** Model znázorňující vzájemně se ovlivňující 4 faktory na vzniku IBD. Upraveno dle Sartor et al. [7], vytvořeno ve spolupráci se Servisním střediskem pro e-learning, Fakulta informatiky Masarykovy univerzity.

Velmi zajímavá práce zabývající se vztahem zevního prostředí na dánské imigranty a vznik IBD byla publikována Agrawalem et al. [8]. V této populační studii, kdy byla získávána data od dánských občanů a imigrantů do Dánska mezi lety 1977 – 2018, prokázali vyšší vznik rizika IBD u přistěhovalců až po 20 letech pobytu v Dánsku u první generace, zatímco druhá generace dánských imigrantů již měla stejně vysoké riziko vzniku IBD jako dánská populace. Zevní prostředí se zde tedy ukázalo jako jasný rizikový faktor pro IBD.

Samotný mechanizmus zánětlivé odpovědi na molekulární úrovni je velmi složitý a není ještě zcela jednoznačně objasněn. Přehledně je celý mechanismus znázorněn na obr. 2 (upraveno dle

Baumgart et al. [1] a Danese et al. [9]). Nejnovější medikamentózní léčba IBD, tedy biologická léčba (anti-TNF a non-anti-TNF) a tzv. malé molekuly (JAK2 inhibitory) [10] jsou přesně cíleně zamířeny na blokování jedné z cest v imunitní zánětlivé odpovědi (viz. obr. 2).



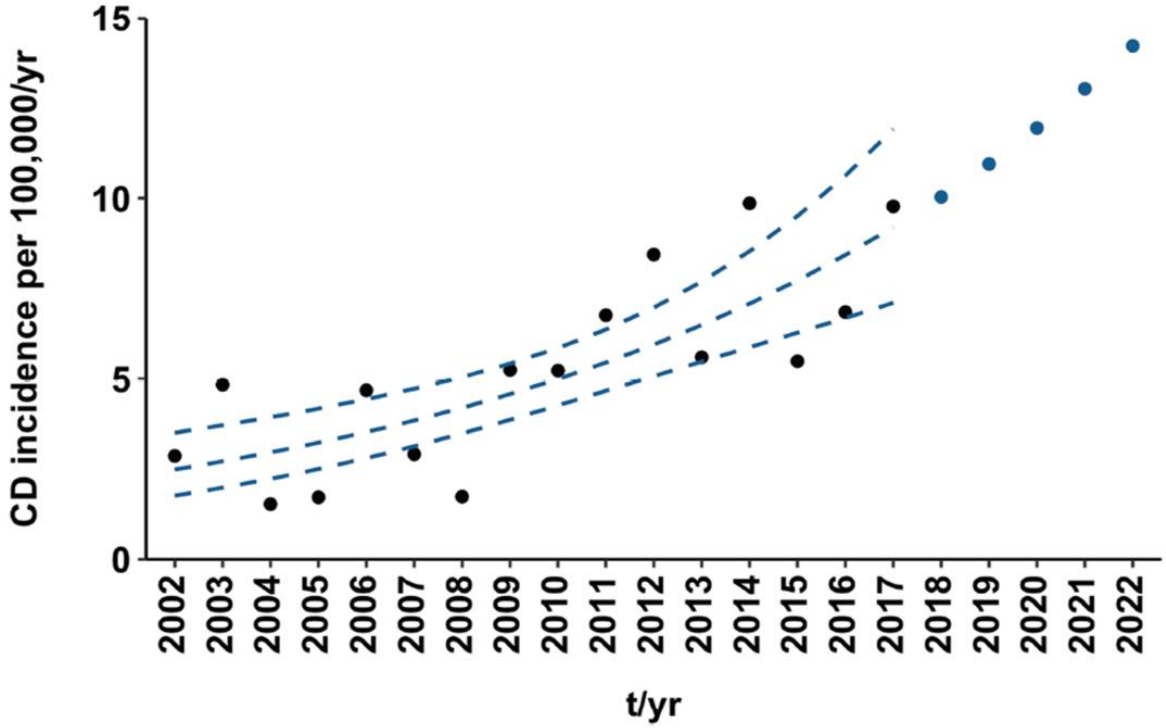

**Obr. 2.** Schéma zobrazující jednotlivé dráhy zánětlivé odpovědi při vzniku IBD a současné možnosti jejího blokování v rámci konzervativní léčby. Upraveno dle Baumgart et al. [1] a Danese et al. [9], vytvořeno ve spolupráci se Servisním střediskem pro e-learning, Fakulta informatiky Masarykovy univerzity.

V posledních desetiletích je zaznamenán vzestup incidence IBD především ve vyspělých státech (Severní Amerika, Austrálie a západní Evropa). Tyto země si udržují dlouhodobě nejvyšší incidenci (10 až 20/100 000) a stejně tak prevalenci v celosvětovém měřítku [11–13].

Dle některých nejnovějších meta-analýz se však ukazuje, že incidence IBD ve vyspělých západních zemích světa začíná být stacionární či dokonce s mírným poklesem. Na druhou stranu se však ale potvrzuje nárůst incidence v rychle se rozvíjejících státech světa (Asie, Jižní Amerika) a znepokojivá je i stále velmi vysoká a rostoucí prevalence onemocnění celosvětově [14–16]. Tato skutečnost vede samozřejmě k usilovnému výzkumu a vývoji stále nové efektivnější léčby v oblasti IBD.

### 1.2.1 Vlastní příspěvek k problematice

V naší práci s názvem „Regional Incidence of Inflammatory Bowel Disease in a Czech Pediatric Population: 16 Years of Experience (2002-2017)“ (příloha 1) [17] jsme prokázali statisticky signifikantní nárůst incidence CD v pediatrické populaci v letech mezi 2002 až 2017 v Jihomoravském kraji. Stoupající trend byl zaznamenán i u pacientů s UC a indeterminovanou kolitidou, ale neprokázala se statistická významnost jako u CD. Incidence CD v roce 2017 byla 9,8/100 000 a byl potvrzen fakt, že se tak řadíme k zemím s největším výskytem choroby na světě. Navíc je patrný trend neustále narůstající incidence v dalších letech i podle prognostického modelu (obr. 3, použito z publikace [17]). Můžeme předpokládat, že důvodem tohoto nárůstu v posledních letech je fakt, že v České republice došlo k řadě socioekonomických změn s vlivem na okolní životní prostředí a také styl západního stravování.

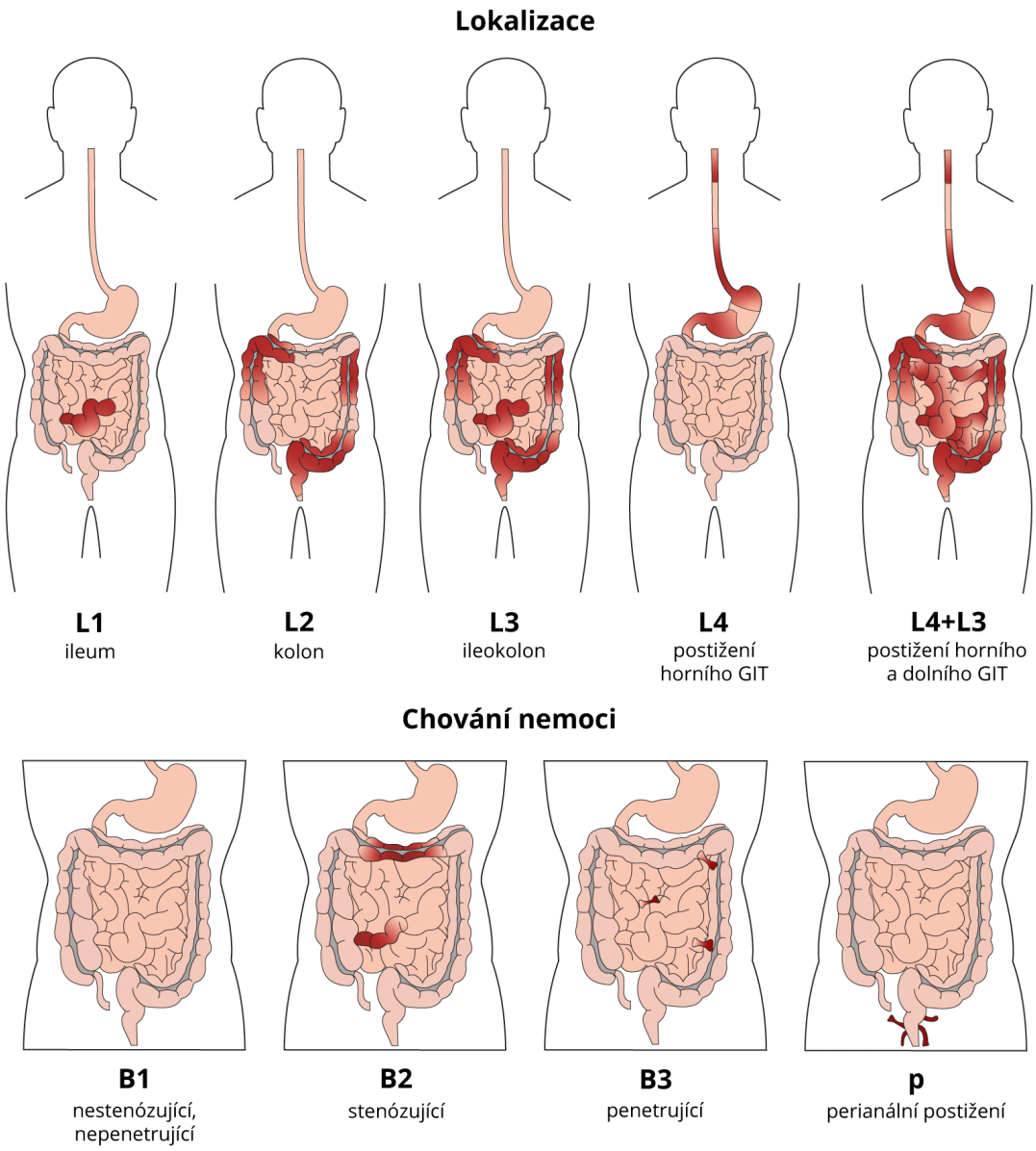



**Obr. 3.** Graf narůstající incidence v dětské populaci mezi lety 2002-2017 v Jihomoravském kraji a model narůstající incidence v dalších letech. Použito z publikace Jabandžiev et al. [17].

### 1.3 Diagnostika a klasifikace nemoci

Diagnostika je založena na anamnéze, klinickém vyšetření, laboratorních testech, endoskopickém, radiologickém a histologickém nálezu [18].

CD se klasifikuje podle Montrealské klasifikace [19]. Dle lokalizace (Location – L) může být postižení jen tenkého střeva (L1), postižení jen tlustého střeva (L2), postižení tenkého tlustého střeva (L3) a postižení horního trávicího traktu (L4). Chování nemoci (Behaviour – B) může být buď nestenózující-nepenetrující (B1), stenózující (B2), penetrující (B3) a modifikátor perianálního postižení. Lokalizace a chování nemoci přehledně zobrazeno na obrázku 4 (upraveno dle Baumgart et al. [1]).




**Obr. 4.** Lokalizace a chování nemoci dle Montrealské klasifikace (upraveno dle Baumgart et al. [1], vytvořeno ve spolupráci se Servisním střediskem pro e-learning, Fakulta informatiky Masarykovy univerzity).

### 1.3.1 Vlastní příspěvek k problematice

V současnosti probíhá řada studií na nové diagnostické a prediktivní markery zjistitelné z krevního séra či tkání pacienta. V naší přehledové práci „The Emerging Role of Noncoding RNAs in Pediatric Inflammatory Bowel Disease“ (příloha 2) [20] jsme shrnuli dostupné znalosti v tomto nově se rozvíjejícím odvětví a to konkrétně využití nekódující RNA v diagnostice a predikci průběhu IBD v dětské populaci. V naší přehledové práce jsme zpracovali veškeré dostupné studie s touto problematikou se zaměřením na microRNA (miRNA). miRNA je malá nekódující RNA, která hraje roli v posttranskripční regulaci genové exprese [21]. První studie se objevují v roce 2013, kdy byla publikována práce od Koukose et al. [22]. Poukazuje na signifikantní odlišnost exprese miRNA-101 a miRNA-26 mezi IBD a non-IBD populací. Následovaly další práce, kdy miRNA byla získávaná jak z krevního séra, tak zároveň ze tkání. miRNA byly studovány nejen využitelnosti stran diagnostiky, diferenciální diagnostiky IBD [23–25], ale také např. rozlišení aktivního zánětu u CD a pacientů s CD v remisi (byl zaznamenán signifikantní rozdíl v downregulaci u miRNA-15a [26]). V neposlední řadě následovaly práce studující vliv exprese miRNA jako odpověď na léčbu prednisonem či infliximabem [27–29].

Využití miRNA jako biomarkeru u IBD se zdá jako velmi potenciální a slibná metoda do budoucna. Nutné je ale zapotřebí provedení dalších studií na větším souboru pacientů, přesné ozřejmení funkce a specifikace konkrétní miRNA a jejich validizace v rámci diagnostiky i terapie.

## 1.4 Diferenciální diagnostika

Jak zmíněno výše diagnostika IBD je založena na klinickém vyšetření, laboratorních výsledcích, nálezech na endoskopii, zobrazovacích metodách a histologickém vyšetření. Ani tak nemusí být diagnóza IBD vždy jednoznačná.

Anemie může být jeden ze symptomů u IBD, ale rovněž se také vyskytuje u řady jiných onemocnění. Při došetřování anémie tedy musíme v rámci diferenciální diagnostiky myslet na široké spektrum chorob.

V níže uvedeném „vlastním příspěvku k problematice“ je zdůrazněna diferenciální diagnostika u ileocekální formy CD a náhlou příhodou břišní, a také fakt, že sami pacienti s CD mohou mít náhlou příhodu břišní (a to jednak v rámci komplikace CD nebo i nezávisle při postižení jiného orgánu).

Dále rovněž pojednáváme o možnosti koiincidence IBD s jinými autoimunitními chorobami a dalšími vzácnějšími diagnózami.

### 1.4.1 Vlastní příspěvek k problematice

Anemie může být také projevem dekompenzované celiakie (která rovněž často bývá brána v úvahu při diferenciální diagnostice CD). V článku „Small bowel adenocarcinoma diagnosed by capsule endoscopy in a patient with celiac disease: a case report and review of literature“ (příloha 3) [30] byla anémie prvním symptomem komplikace celiakie, kdy následně pomocí kapslové enteroskopie byl diagnostikován adenokarcinom tenkého střeva. Kapsle u pacientky retinovala před tumorózní stenózou a v subakutním režimu byla provedena resekce tenkého střeva s dostatečnou lymfadenektomií. V dalším publikovaném případu „Multiple neuroendocrine tumor of the small bowel: a case report and a review of literature“ (příloha 4) [31] jsme pomocí kapslové enteroskopie diagnostikovali mnohočetný neuroendokrinní nádor tenkého střeva. Následovala opět resekce tenkého střeva s lymfadenektomií.
V kazuistice „Gastric antral vascular ectasia and solitary rectal ulcer syndrome - two rare diagnoses as the cause of anemia in a single patient: case report“ (příloha 5) [32] poukazujeme na diferenciální diagnostiku benigního solitárního rektálního vředu, IBD a neoplázie pro jejich někdy nesnadně endoskopicky odlišitelný nález. Stěžejní roli zde hraje biopsie [33–35].

CD může být někdy pacientovi chybně diagnostikována a časem se ukáže, že pacient trpěl jinou chorobou. Vzácné autosomálně recesivně přenášené genetické onemocnění mitochondriální neurogastrointestinální encefalomyopatie (MNGIE - mitochondrial neurogastrointestinal encephalomyopathy) může zpočátku právě CD velmi dobře imitovat. Klinická manifestace onemocnění zahrnuje neurologické a gastrointestinální symptomy (bolesti břicha, gastrointestinální dysmotilita, malnutrice) a často bývá MNGIE chybně diagnosticky zaměněno za celiakii, mentální anorexie nebo právě IBD [36–38]. V článku „Mitochondrial Neurogastrointestinal Encephalomyopathy Imitating Crohn’s Disease: A Rare Cause of Malnutrition“ (příloha 6) [39] popisujeme svízelnou diagnostiku této choroby.

Ileocekální CD se často manifestuje bolestí v pravém podbřišku. Bolesti v pravém hypogastriu v diferenciální diagnostice ale zahrnují velké množství diagnóz. Musíme myslet nejen na ileocekální postižení CD, ale při náhlém vzniku potíží také na náhlou příhodu břišní. Stěžejní roli zde hraje klinické vyšetření, ale také především zobrazovací metody. V přehledovém článku „Zobrazovací metody u neúrazových náhlých příhod břišních“ (příloha 7) [40] pojednáváme o využití klasického rentgenového snímku, abdominálního ultrazvuku (UZ) a CT vyšetření v diagnostice náhlých příhod břišních. V článku je rovněž poukázáno na důležitou roli UZ a CT v diferenciální diagnostice akutní apendicitidy a ileocekální CD.

V Rozhledech v chirurgii jsme v článku „Rare cases imitating acute appendicitis: Three case reports and a review of literature“ (příloha 8) [41] publikovali 3 diagnózy imitující akutní apendicitidu. V prvním případě jsme popsali akutní pravostrannou divertikulitidu, která může být častá v asijských zemích, ale v západních zemích se incidence pohybuje kolem 1-2 % [42–45]. Předoperační správná diagnóza pravostranné divertikulitidy je náročná, vzhledem k podobným klinickým projevům. Většina pravostranných divertikulitid je tak zjištěna až během diagnostické laparoskopie [46,47]. U druhé pacientky popisujeme torzi pravých adnex pro objemnou dermoidní cystu v pokročilém měsíci gravidity. Torza adnex v graviditě bývají relativně časté v prvním a druhém trimestru, ale ne ve třetím trimestru jak u naší pacientky [48–50]. V posledním třetím případě demonstrujeme spontánní perforaci apendikální mucinózní neoplázie. Nádory apendixu nejsou moc časté a vyskytují se méně než u 1 % provedených apendektomií, z toho apendikální mucinózní neoplazie tvoří ještě nižší počet případů [51,52].

Nesmíme však zapomínat, že i u pacientů s CD se může vyskytnout jak „klasická“ náhlá příhoda břišní, tak i náhlá příhoda břišní v rámci komplikace CD.
V International Journal of Colorectal Diseases jsme v roce 2016 publikovali článek „Crohn disease and pregnancy: a case report of an acute abdomen“ (příloha 9) [53] popisující volnou perforaci do dutiny břišní jako komplikaci CD u gravidní pacientky. Případ je zajímavý tím, že zhoršení průběhu CD v době gravidity nebývá častý [54,55]. Stěžejní u těchto pacientek s CD je graviditu plánovat a otěhotnět v období remise. V tomto případě většinou těhotenství probíhá nekomplikovaně a novorozenci mají stejné porodní vlastnosti jako novorozenci u zdravých matek [56–58].
Naopak mnohdy se setkáváme u pacientů s CD s ileózním stavem vzniklého na podkladě zánětlivého postižení (ať už dekompenzované chronické stenózy či akutní exacerbací CD) jak popisujeme v článku „Náhlé příhody břišní u pacientů s Crohnovou chorobou – kazuistiky“ (příloha 10) [59]. U těchto pacientů je dle European Crohn’s and Colitis Organisation (ECCO) guidelines doporučeno postupovat konzervativně a operační výkon odložit s provedením limitované resekce [60]. Indikací pro akutní operaci v tomto případě je buď úplná obstrukce nereagující na konzervativní terapii nebo podezření na střevní ischemii.

U pacientů s IBD můžeme také pozorovat koincidenci jiných autoimunitních chorob. Autoimunitní pankreatitida (AIP) je dělena na 2 typy. AIP typ 1 je častější, bývá spojován s vyšší hladinou IgG4 protilátek a současný výskyt IBD je vzácný. U pacientů s AIP typu 2 je výskyt IBD častý [61].

V našem přehledovém článku „Autoimmune pancreatitis – An ongoing challenge“ (příloha 11) [62] jsme popsali současné znalosti o AIP od její patogeneze, diagnostiku až po její léčbu. V tomto článku v tabulce 1 je patrný vztah a výskyt IBD u pacientů s AIP typu 1 a typu 2 (u AIP typu 1 se IBD vyskytuje u méně než 10 % pacientů, naopak u AIP typu 2 nalezneme IBD u více než 40 % pacientů).
V kazuistickém sdělení „Idiopatický střevní zánět a 1. typ autoimunitní formy pankreatitidy: kazuistika“ (příloha 12) [63] se nám ale podařilo publikovat raritní výskyt AIP typu 1 a současné koincidence IBD jako prvního pacienta v České republice. Pacient podstoupil ileocekální resekci pro CD v roce 2012 a v roce 2016 mu byla diagnostikována AIP typ 1 s elevací IgG4. Pacient velmi dobře zareagoval na léčbu kortikoidy, která probíhala po dobu 3 měsíců. Na kontrolních zobrazovacích metodách po léčbě byla slinivka normalizována.

Dále jsme také publikovali velmi zajímavé sdělení 24leté pacienty, která byla sledována pro familiární adenomatózní polypózu a zároveň ji byla diagnostikována CD. Pacientka byla z důvodu mnohočetných velkých polypů a známek aktivity CD na terminálním ileu indikována ke kolektomii s terminální ileostomií se zachováním rekta a resekcí terminálního ilea. V článku „Ileocaecal Crohn’s disease and familial adenomatous polyposis in one patient - a case report“ (příloha 13) [64] rozebíráme možnosti obnovení kontinuity trávicího traktu. Výhody a nevýhody jednotlivých výkonů (dokončení proktektomie a našití ileopouch-anální anastomózy, našití ileo-rekto anastomózy nebo abdominoperineální resekce rekta s trvalou terminální ileostomií).

Naše další kazuistika s názvem „Spinal epidural abscess – a rare complication of Crohn´s disease: case report“ (příloha 14) [65] dokazuje, že u pacientů s IBD se mohou vyskytnout i takto raritní komplikace jako spinální epidurální absces.

## 1.5 Miniinvazivní přístup u IBD pacientů

Výhody laparoskopie oproti otevřené chirurgii v oblasti kolorektální chirurgie jsou všeobecně přijímány a prokázány řadou studií [66–68]. V oblasti IBD chirurgie je laparoskopický miniinvazivní přístup rovněž preferován (kratší doba hospitalizace, dřívější obnova peristaltiky, časnější rekonvalescence, nižší pooperační morbidita, nižší výskyt incizionálních hernií a lepší kosmetický efekt). Na druhou stranu ale díky specifickým vlastnostem CD (penetrující formě s tvorbou fistulací a intraabdominálních abscesů, malnutrice, imunosuprese, atd) musí být zvláště u těchto pacientů indikace miniinvazivního přístupu pečlivě zvažována (event. další možností je kombinace laparoskopického výkonu s otevřenou chirurgií z minilaparotomie) [69–71].

### 1.5.1 Vlastní příspěvek k problematice

V přehledovém článku „Možnosti miniinvazivní chirurgie u pacientů s Crohnovou chorobou a ulcerózní kolitidou“ (příloha 15) [72] jsou jednak rozebrány samotné indikace akutních a elektivních výkonů u CD i UC, tak zároveň jsou i diskutovány právě výhody miniinvazivního přístupu.

Dle doporučení ECCO je preferován laparoskopický přístupu IBD pacientů. Jednoznačně je doporučován u nekomplikovaných ileocekálních resekcí a primárních tenkostřevních resekcí [73,74].

Obezřetní ale musíme být u komplikované CD, a to hlavně u penetrující formy nebo již po proběhlé střevní resekci v minulosti (rekurentní CD). Nedávno publikovaná meta-analýza u rekurentní CD s nutností opakované střevní resekce však prokázala bezpečnost při užití laparoskopického přístupu, bez signifikantního nárůstu pooperačních komplikací [75]. Dle doporučení ECCO z roku 2020 je tak laparoskopický přístup doporučován i v případě již proběhlé střevní resekce v minulosti [74].

Optimistické a bezpečné se zdají být i výsledky u pacientů s penetrující formou CD s benefitem laparoskopického přístupu pro pacienta v porovnání s otevřenou chirurgií, zvláště ale pokud je pacient operován v centrech specializujících se na IBD chirurgii [69,76]. U těchto pacientů je sice vyšší riziko konverze v otevřený výkon, delší operační čas, ale nebyl popsán vyšší výskyt pooperačních komplikací [77,78].

Na základě nejnovějších doporučení ECCO z roku 2020 může být laparoskopická resekce ileocekální oblasti nabídnuta jako alternativa Infliximabu a to i pouze u zánětlivé formy (nestenózující, nepenetrující) CD [74] (bude blíže pojednáno v další kapitole této práce).

Žádoucí je miniinvazivní přístup u IBD pacientů i z toho důvodu, že toto onemocnění je diagnostikováno většinou již v mladém věku pacienta. Diagnóza IBD je nejčastěji stanovena

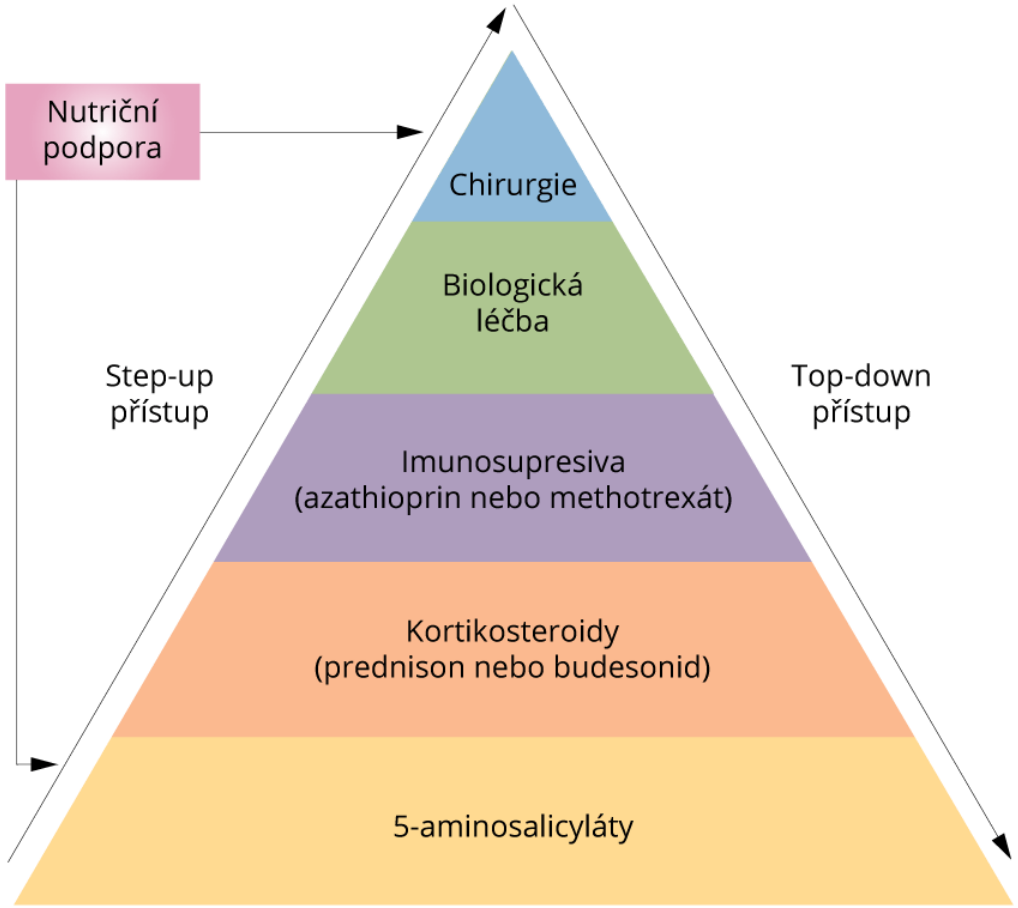
v období druhé a třetí dekády života (více než polovina pacientů má diagnostikovanou chorobu do 30 roku života) [54,79,80] a kosmetický efekt pro tyto pacienty je tak důležitý.
U pacientů s CD existuje zhruba 70-80% šance, že pacient bude pro tuto chorobu během svého života operován [81–83]. Pacient navíc může mít i další reoperace v budoucnosti, a tak tedy i z hlediska nižší tvorby pooperačních srůstů v dutině břišní je vhodný laparoskopický přístup [84].

O tom, že laparoskopická technika v chirurgii se rozšiřuje i mimo kolorektální chirurgii a IBD problematiku svědčí i námi publikované dvě kazuistiky. První práce s názvem „Laparoscopic pancreaticoduodenectomy for ampullary adenocarcinoma: a case report and review of literature“ (příloha 16) [85] pojednává o možnosti provedení laparoskopické hemipankreatoduodenektomie u pacientů s karcinomem Vaterské papily. V článku pojednáváme zároveň o laparoskopické resekci pro jiné periampulární nádory (tumor hlavy slinivky břišní nebo distálního choledochu) a výhodách a nevýhodách laparoskopické techniky v pankreatobiliární chirurgii.
Laparoskopická hemipankreatoduodenektomie je v současné době považována za jeden z nejnáročnějších laparoskopických výkonů. Pooperační morbidita i mortalita zůstává stále vysoká i po otevřené hemipankreatoduodenektomii [86]. Srovnávací studie laparoskopické a otevřené hemipankreatoduodenektomie stran pooperačních komplikací ukazují obě metody jako srovnatelné [87–90]. Dokonce některé systematické meta-analýzy ukázaly nižší pooperační komplikace u laparoskopie [91–93]. Porovnání výsledků stran onkologické radikality a dlouhodobého přežívání pacientů se ukázaly rovněž jako srovnatelné [87,88,91]. U laparoskopického výkonu se potvrdily výhody, a to v menší pooperační bolesti břicha, kratší době hospitalizace, rychlejšího zotavení po operaci a lepšího dosaženého kosmetického efektu [87,89,92,93]. Délka výkonu se naopak ukázala kratší u otevřeného výkonu v některých studiích. S rostoucími zkušenostmi operatéra se ale tento rozdíl snižoval [94].
Dále v druhém kazuistickém sdělení jsme publikovali možnost laparoskopické resekce jater v článku „Laparoscopic liver resection for alveolar echinococcosis“ (příloha 17) [95]. Popsána je možnost jaterní laparoskopické resekce u infekčního onemocnění, konkrétně alveolární formy jaterní echinokokózy.
Poslední meta-analýzy jasně ukazují výhody u jaterní resekce při porovnání otevřeného a laparoskopického přístupu, a to jak u benigních, tak i maligních diagnóz. Výhody jsou prokázány signifikantně a to v kratší době hospitalizace, dřívější obnovení peristaltiky a nižší pooperační spotřebě analgetik [96,97].

## 2. Klinická část

### 2.1 Step-up nebo top-down přístup?

Klasické pyramidové schéma v léčbě IBD je zobrazeno na obr. 5 (upraveno dle Aloi et al. [98]). Na spodině pomyslné pyramidy se nachází léky s nejslabším protizánětlivým účinkem 5-ASA (5-aminosalicyláty). Zároveň jsou to ale léky nejbezpečnější stran nežádoucích účinků. Nad nimi stojí kortikosteroidy s naopak mohutným protizánětlivým efektem, ale zvláště jejich dlouhodobé užívání je spojeno s řadou nežádoucích účinků. K udržení remise se proto často užívá imunosupresiv. Na samotném vrcholu pyramidy stojí pak léčba biologická a chirurgická. Správné zajištění nutričního stavu pacienta je důležité v každém stupni pyramidy. Léčba může být započata léky s nejnižšími nežádoucími účinky, ale zároveň s také nejnižší efektivitou léčby. Pokud dochází k selhávání léčby je volen lék s vyšší účinností (tzv. step-up přístup). V indikovaných případech můžeme podat biologickou či přímo zvolit chirurgickou léčbu (top-down přístup).




**Obr. 5.** Pyramida zobrazující léčebné možnosti u IBD (step-up a top-down přístup). Upraveno dle Aloi et al. [98], vytvořeno ve spolupráci se Servisním střediskem pro e-learning, Fakulta informatiky Masarykovy univerzity.

5-ASA jsou stále užívány v léčbě u UC, jak k navození remise u lehké a středně těžké zánětlivé aktivity, tak k udržení remise onemocnění. Postavení 5-ASA v léčbě CD se naopak změnilo. Dle současných doporučení ECCO má 5-ASA v léčbě pacientů s CD shodnou efektivitu léčby jako placebo a není tedy v léčbě CD doporučováno [99]. V léčbě CD bývají při akutním relapsu nejčastěji využívány buď topické nebo systémové kortikoidy a k následné udržení remise je užito imunosupresiv či biologické léčby. U prognosticky nepříznivého průběhu nemoci (rizikové faktory jako perianální postižení, extenzivní postižení tenkého střeva, rychle progredující penetrující forma do stádia intraabdominálních abscesů a píštělí, a také primodiagnóza v mladém věku) může být biologická léčba nasazena v krátkém odstupu od stanovení diagnózy (top-down přístup) [100]. Indikace chirurgické léčby pro CD můžeme zjednodušeně rozdělit na akutní a elektivní výkony [60,73,74,101,102]. Mezi akutní výkony patří perforace do volné dutiny břišní, masivní krvácení, akutní těžká kolitida, toxické megakolon nebo akutní porucha pasáže. K elektivním výkonům řadíme selhání či intoleranci medikamentózní terapie, symptomatickou chronickou stenózu, fistulující či abscedující formu CD a malignitu v terénu CD.

Jak bylo zmíněno v úvodu práce je u ileocekální resekce pro stenózující a nyní také i penetrující formu doporučován laparoskopický přístup [60,73,74]. U čistě zánětlivého postižení (nestenózující, nepenetrující forma) ileocekální oblasti se v současnosti standardně v léčbě používá medikamentózní terapie (kortikoidy, imunosupresiva a biologická léčba) [18,99].

Původní velké naděje a očekávání vkládané do biologické léčby po jejich zavedení do praxe na významné snížení chirurgických střevních resekcí se zcela nenaplnily [103–105].

Navíc byly publikovány výsledky dlouho očekávané holandské studie srovnávající časný chirurgický přístup s podáním biologické léčby u zánětlivé (nestenózující, nepenetrující) ileocekální CD. V roce 2017 byly nejdříve publikovány první výsledky studie LIR!C [106] a nedávno byly publikovány i její dlouhodobé výsledky v roce 2020 [107]. Kvalita života ve srovnání chirurgické léčby a biologické vyšla srovnatelná (v některých parametrech a dle některých dotazníků kvality života, však pacienti dosahovali lepší kvalitu života po časné ileocekální resekci) a také ve skupině léčených časnou chirurgickou resekcí byla prokázána nižší ekonomická zátěž.

Další zajímavé zjištění bylo, že během 5letého folow-upu 48 % pacientů z ramene léčeného Imfiximabem nakonec stejně dospělo k ileocekální resekci (oproti pouze 26 % pacientů z ramene léčeného primárně resekci vyžadovalo nasazení Infliximabu). Navíc 22 % pacientů z ramene léčeného primárně chirurgicky během 5letého sledování nevyžadovalo žádnou medikamentózní léčbu stran CD.

Obě studie LIR!C shrnují své výsledky, že u pacientů se zánětlivou ileocekální formou CD ( s postižením kratším než 40 cm ilea), po selhání konvenční léčby se časná laparoskopická ileocekální resekce jeví jako vhodná alternativa léčbě Infilximabem (dokonce se tedy ukazuje, že časná chirurgická léčba přináší určité benefity oproti biologické léčbě). Doporučení se již objevilo v posledních ECCO guidelines z roku 2020 [74].

## 2.2 Riziko pooperační rekurence

Znepokojivé je vysoké procento pooperační rekurence po střevních resekcích u CD. Endoskopická rekurence vznikne zhruba u 70 % pacientů do 1 roku od operace a klinickou rekurenci má kolem 55-60 % pacientů za 5 let od operace [81,82,108–110]. Zajímavé je, že ani díky novým medikamentózním možnostem se příliš pravděpodobnost klinické rekurence nezměnila a to konkrétně od roku 1990, kdy data publikoval Paul Rutgeerts [108] a téměř po více než 30 letech, kdy velmi podobná data publikoval v roce 2020 Hammoudi et al. [110] (poznámka autora: prof. Paul Rutgeerts zemřel letos 12. září 2020 ve věku 72 let. Díky jeho studiím s významným dopadem do klinické praxe a jeho „nadčasovosti“ se stal jedním z nejvýznamnějších gastroenterologů a endoskopistů na poli IBD).

Neméně je také znepokojující fakt, že 30-50% pacientů vyžaduje další resekci během následujících 5-10 let od primární operace [111–113].

Na rekurenci CD mají vliv 3 možné sféry oblastí a to konkrétně faktory týkající se samotného pacienta (kouření, mužské pohlaví), samotné choroby (penetrující forma, perianální postižení) a operační technika (typ anastomózy, resekční okraje).

Dle současných dostupných dat a meta-analýz byly určeny rizikové faktory pro pooperační rekurenci CD. Mezi tyto rizikové faktory patří především kouření, předchozí střevní resekce pro CD, penetrující forma, perianální postižení, absence profylaktické pooperační léčby a z histologických znaků zastižení granulomů v resekátu a myenterická plexitida [73,114–116].

### 2.2.1 Typ anastomózy a vliv mesenteria na pooperační rekurenci

Dle doporučení ECCO je v současnosti doporučována široká side-to-side anastomóza [73,74]. V porovnání s end-to-end anastomózou bylo zaznamenáno nižší procento pooperačních komplikací u side-to-side anastomózy, rozdíl v pooperační rekurenci v anastomóze ale zaznamenán nebyl [117,118]. Zdůrazňovaná je však role širokého našití lumen anastomózy jako faktoru prevence rekurence. [119].

V roce 2011 byla poprvé představená tzv. Kono anastomóza z japonského pracoviště v Asahikawě (název podle japonského chirurga Toru Kona) [120]. Snahou bylo vymyslet takový typ anastomózy, u kterého by docházelo k minimální rekurenci CD a zároveň, aby byla zatížena minimem pooperačních komplikací [121].
Možné lepší výsledky této anastomózy jsou založeny na předpokladu, že rekurence CD v anastomóze vzniká na mezenterické straně střeva. Další potenciální výhoda Kono anastomózy je udávána její konstrukce s dostatečně širokým lumen (oproti klasické end-to-end anastomóze).
Velmi příznivé výsledky publikoval Shimada et al. [122] v roce 2018. Po provedené resekci s rekonstrukcí pomocí Kono anastomózy u pacientů s CD dospělo během follow-upu (medián 54 měsíců) k následné chirurgické rekurenci pouze 3,4 % pacientů oproti 24,4 % u kterých byla našita end-to-end anastomóza.
Recentně publikovaná randomizovaná kontrolovaná studie v tomto roce autory Luglio et al. [123] z italské Neapole potvrdila nižší pooperační rekurenci při užití techniky Kono anastomózy a zároveň Kono anastomóza nebyla zatížena vyšším rizikem pooperačních komplikací v porovnání s konvenční side-to-side anastomózou.

Mesenterium obsahující tukové buňky, nervy, cévy, včetně lymfatického systému jsou zdrojem četných imunitních reakcí a mesenterium tak hraje roli v patogenezi a progresi CD. Je tak předpoklad , že mezokolická excize u ileocekální resekce by mohla snížit imunitní odpověď a migraci fibroblastů do stěny střeva a následně tak vést ke snížení pooperační rekurence [113].
Coffey et al. [124] publikoval v roce 2018 optimistická data, kdy provedení mezokolické excize snížilo významně nutnost reoperace pro pooperační rekurenci CD oproti skupině pacientů, kde byla provedena standardní ileocekální resekce bez lymfadenektomie (konkrétně bylo kumulativní riziko reoperace 2,9 % oproti 40 % ve skupině bez lymfadenektomie, $p = 0,003$). Nutno ale podotknout, že studie byla provedena na relativně malém souboru pacientů.
V současnosti probíhají další randomizované kontrolované studie, zda provedení mezokolické excize u ileocekální resekce u CD bude mít za následek snížení pooperační rekurence a zda naopak nebude souviset s nárůstem pooperační morbidity [125].

### 2.2.2 Mikroskopické známky Crohnovy choroby v resekční linii

Dřívější proběhlé práce z 80. a 90. let minulého století neprokázaly, že by pozitivní resekční linie u CD, neměla vliv na zvýšené riziko rekurence nemoci při provedené resekci střeva [126–128]. Snaha je tedy o střevo šetřící operační techniku a hranice resekce tenkého střeva by neměla přesahovat hranici makroskopického postižení [101].

Později se objevily práce, kde se ukázala souvislost mezi pozitivním aktivním resekční okrajem při chirurgické střevní resekci pro CD a zvýšeným výskytem pooperačních komplikací (konkrétně s vyšším počtem septických intraabdominálních pooperačních komplikací) [129]. Následovaly práce poukazující, že mikroskopická aktivita v resekční linii po střevní resekci by nakonec mohla mít vliv na časnou rekurenci v anastomóze [130–132].

### 2.2.3 Vlastní příspěvek k problematice

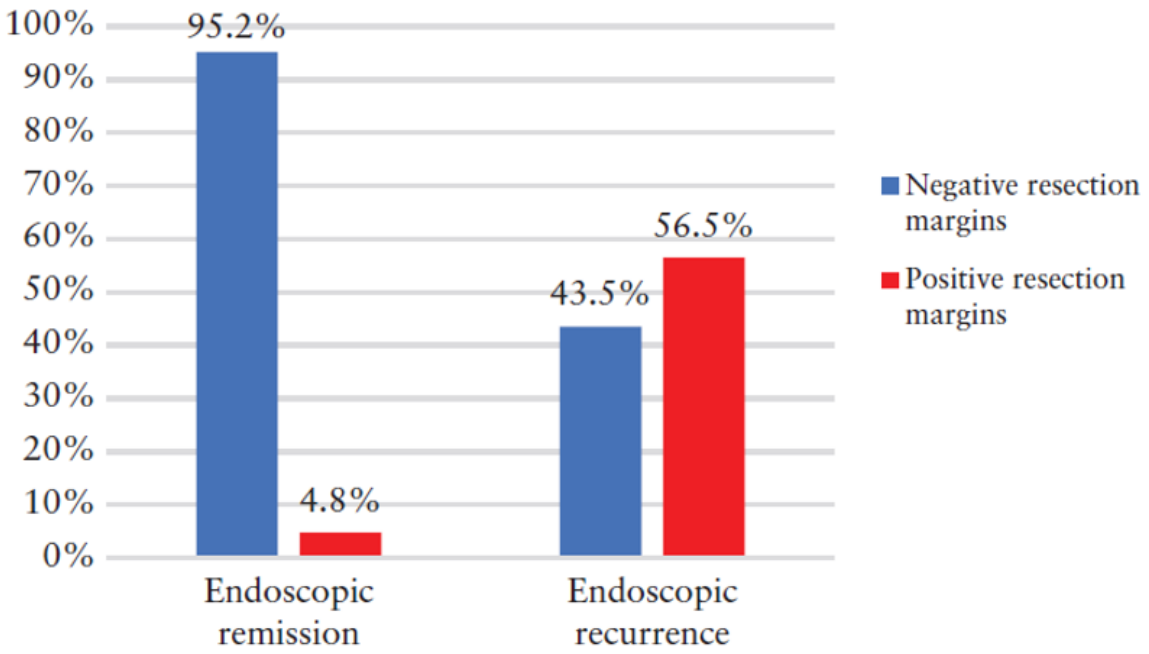
V naší studii jsme se snažili zjistit, zda histologická aktivita CD v resekčních okrajích po ileocekální resekci ovlivňuje časnou endoskopickou recidivu.

Prospektivně jsme sledovali pacienty s CD, kteří podstoupili ileocekální resekci na Chirurgické klinice FN Brno v letech 2012 až 2018. Během operace byla resekční linie zvolena vždy v makroskopické zdravé tkáni. Resekáty střeva byly po operaci standardně histologicky vyšetřeny, včetně obou resekčních okrajů (resekční okraji tenkého i tlustého střeva) na přítomnost mikroskopických známek CD. Endoskopická recidiva byla stanovena dle Rutgeerts score během koloskopie 6 měsíců po ileocekální resekci. Na základě těchto dat jsme hodnotili, zda histologické výsledky resekčních okrajů korelují s endoskopickou recidivou CD. Jako sekundární výstupy práce jsme hodnotili vliv známých rizikových faktorů a předoperační terapie na endoskopickou recidivu CD.

Celkem jsme do studie zařadili 107 pacientů. Endoskopickou recidivu CD jsme zaznamenali celkem u 23 pacientů (21,5 %) s šesti měsíčním odstupem po ileocekální resekci. Mikroskopické známky CD v resekčních okrajích byly spojeny se signifikantně vyšší endoskopickou recidivou v anastomóze (56,5 % oproti 4,8 %, $p < 0,001$). Znázorněno na obr. 6. Trvání nemoci od stanovení diagnózy po operaci ($p = 0,006$) a délka resekovaného střeva ($p = 0,019$) byly signifikantně delší u pacientů s prokázanou endoskopickou recidivou. Kouření bylo rovněž rizikovým faktorem pro endoskopickou recidivu CD ($p = 0,028$).

Prokázali jsme tak, že mikroskopické známky CD v resekční linii u ileocekální resekce byly významně spojeny s vyšším rizikem časné pooperační endoskopické recidivy.

Konečné výsledky naší práce se podařilo publikovat jako original article v prestižním časopise Journal of Crohn's and Colitis s názvem „The influence of microscopic inflammation at resection margins on early postoperative endoscopic recurrence after ileocaecal resection for Crohn's disease“ (příloha 18) [133].




**Obr. 6.** Vliv histologického/mikroskopického zánětu CD v resekční linie na endoskopickou rekurenci. Použito z publikace Poredská et al. [133].

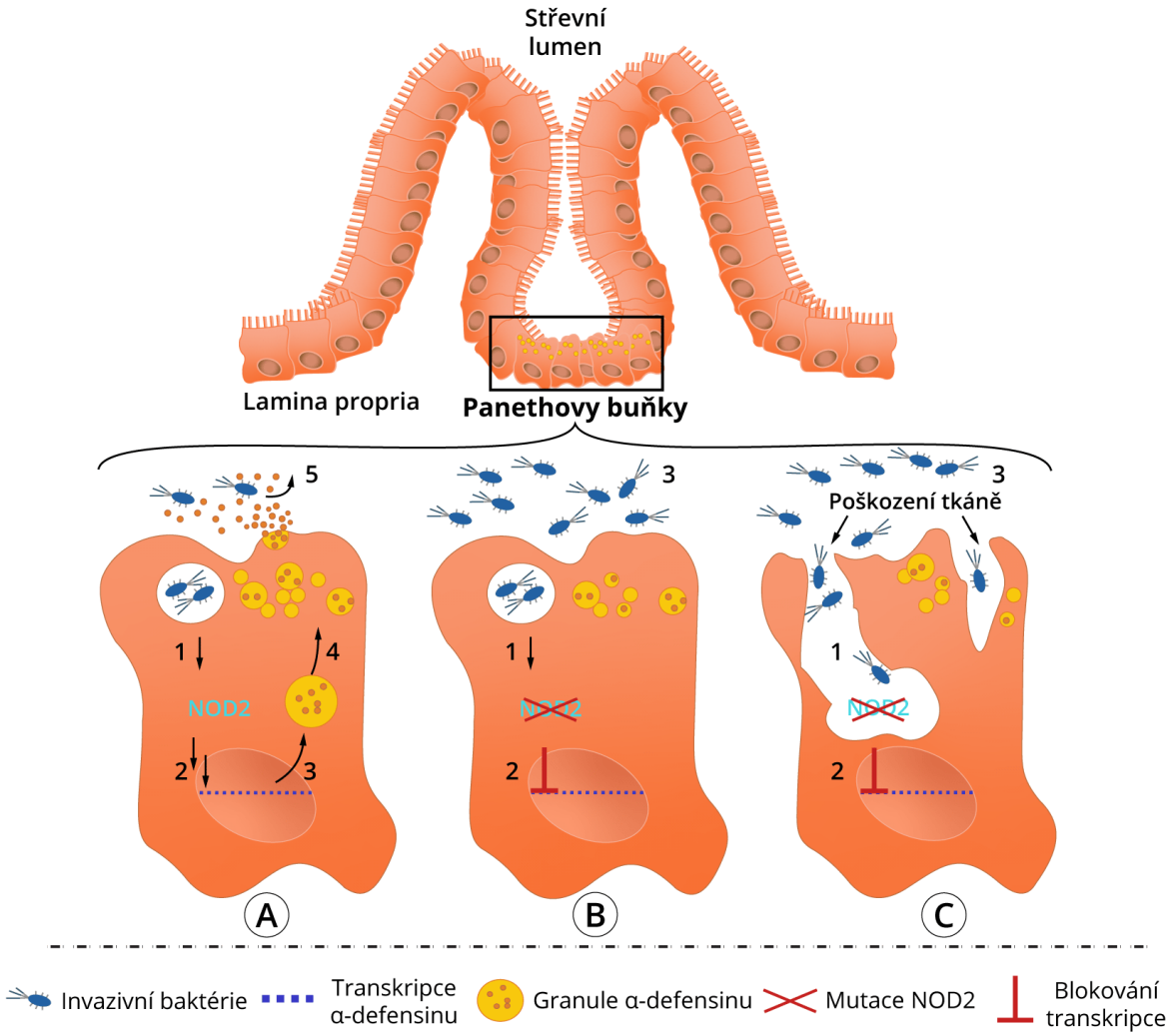
K podobným výsledkům došli i kolegové z jiných významných evropských pracovišť. Wasmann et al. [134] z amsterdamské univerzity prokázali, že aktivní resekční okraj na tlustém střevě souvisí s endoskopickou rekurencí CD. Riault et al. [135] z francouzského pracoviště potvrdili, že pozitivní resekční linie zvyšuje také riziko klinické i chirurgické rekurence CD. Práce Hammoudiho et al. [136] z pařížského pracoviště prokázala, že transmurální zánět v resekční linii tenkého střeva zvyšuje signifikantně jak endoskopickou, tak klinickou rekurenci CD.

Naše studie byla rovněž zahrnuta a citována v nedávno publikované meta-analýze v prestižním časopise Clinical Gastroenterology and Hepatology. Tandon et al. [137] se ve své meta-analýze zabývá histopatologickými znaky zjistitelnými z pooperačního resekátu, které by měly vliv na rekurenci CD. Tato meta-analýza ukázala, že pozitivní resekční okraje, myenterická plexitida a granulomy v resekátu signifikantně zvyšují riziko pooperační rekurence CD a potvrdila tak výsledky naší práce.

Výsledky naší práce byly také prezentovány na mezinárodním kongrese (ESGE - European society of gastrointestinal endoscopy) pod názvem abstraktu „Endoscopic recurrence after ileocaecal resection for Crohn´s disease relating to microscopic inflammation at resection margins“ (příloha 19) [138].

### 2.3 Genetika a Crohnova choroba

Jak již bylo nastíněno v úvodu samotné práce prvním z identifikovaných genů mající roli v patogenezi CD byl v roce 2001 gen NOD2/CARD15 (Nucleotide-binding oligomerization domain 2/ Caspase recruitment domain 15) [5,6]. Jedná se mutaci způsobující zamezení transkripce alfa granulí, hrající stěžejní roli ve slizničních obranných mechanismech a imunitě střeva [139,140]. Celý mechanismus je podrobně znázorněn na obrázku 7 (upraveno dle Jensen et al. [140]).




**Obr. 7.** Role genu NOD2 na slizniční imunitu střeva. Upraveno dle Jensen et al. [140], vytvořeno ve spolupráci se Servisním střediskem pro e-learning, Fakulta informatiky Masarykovy univerzity.

V současnosti již ale bylo identifikováno více než 240 genetických mutací, které mají souvislost se vznikem a vývojem IBD [141–143]. CD tedy můžeme zařadit do skupiny komplexních onemocnění s polygenní dědičností. Na druhou stranu, však řada studií prokázala souvislost mezi mutací v genu NOD2 a ileálním postižením u CD.

Některé dřívější studie poukázaly na vztah mezi mutací genu NOD2 a komplikovaným průběhem CD [144,145]. Souvislost mezi agresivním průběhem CD a genem NOD2 se ukázala především u pacientů s CD diagnostikovaných v mladém věku, stenózující či penetrující formou a zvláště dominantním postiženým ilea [146–148].

Výsledky dat z těchto zmíněných studií jsme využili při koncipování naší studie s genem NOD2.

### 2.3.1 Vlastní příspěvek k problematice

Cílem studie bylo zjistit, zda u pacientů s CD lze využít genetické vyšetření NOD2 k možné predikci chirurgické léčby (k definování agresivního typu onemocnění, při kterém by pacient mohl profitovat z časné operace).

Do studie byli zařazeni pacienti, kteří byli vyšetřeni na gen NOD2 a podstoupili v letech 2010 až 2016 střevní resekci pro CD na Chirurgické klinice Fakultní nemocnice Brno. Kontrolní skupinu tvořili pacienti s CD, kterým byla diagnostikována CD nejméně 5 let před genetickým vyšetřením a nevyžadovali během tohoto období žádný chirurgický zákrok. Druhou kontrolní skupinou byli zdraví jedinci.

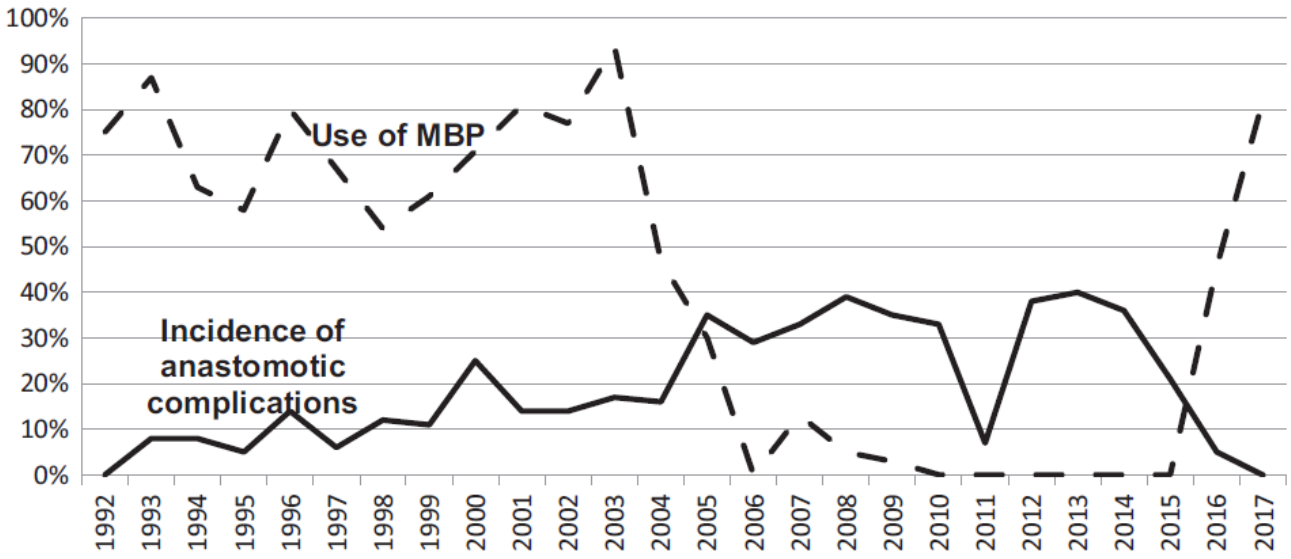
Celkem bylo do studie zařazeno 117 operovaných pacientů s CD, dále 77 pacientů s CD, kteří nebyli operováni a 30 zdravých subjektů. Skupina operovaných pacientů s CD měla významně vyšší distribuci alespoň jedné genetické mutace na rozdíl od neoperované skupiny. U pacientů s alespoň jednou genetickou mutací bylo zjištěno riziko nutnosti chirurgické léčby CD 1,96krát vyšší než u pacientů bez mutace ($p = 0024$). Pacienti se dvěma nebo více mutacemi byli obvykle operováni v mladším věku (věk 24 let; $p = 0.005$), v kratší době od stanovení diagnózy (1 rok od diagnózy; $p = 0.024$) a každý pacient měl provedenou částečnou resekci ilea ($p = 0.016$).

U pacientů se dvěma nebo více mutacemi byl pozorován agresivnější průběh onemocnění, jak bylo zmíněno výše (operace v mladším věku a v krátkém čase od stanovení diagnózy, resekce ilea u každého pacienta). Právě tato skupina pacientů by mohla mít benefit z konzervativní akcelerované step-up léčby nebo časné chirurgické léčby (např. u ileocekální resekce). Tato práce byla publikována v časopise International Journal of Colorectal Diseases pod názvem „The role of the NOD2/CARD15 gene in surgical treatment prediction in patients with Crohn's disease" (příloha 20) [149].

## 2.4 Mechanical bowel preparation

Ortográdní příprava střeva (MBP - mechanical bowel preparation) před chirurgickou střevní resekcí je v chirurgii dlouhodobě řešené a diskutované téma. Publikovaná rozsáhlá meta-analýza z roku 2019 v Annals of surgery od Rollinse et al. [150] poukazuje na výhody při užití peroralní ATB profylaxe v prevenci pooperačních komplikací v kolorektální chirurgii. Signifikantně nižší % pooperačních komplikací bylo dosaženo při užití MBP v kombinaci s perorální ATB profylaxí oproti pacientům s podanou pouze MBP. Nebyly nalezeny signifikantní rozdíly ve srovnání MBP s perorálními ATB a samotné perorální ATB profylaxe. Ukázal se ale trend, kdy nejnižší procento pooperačních komplikací bylo dosaženo při užití MPB a současně podané perorální ATB profylaxe.

V roce 2018 publikoval Iesalniks et al. [151] své výsledky u pacientů s CD po střevní resekci. Na obr. 8 je patrný vztah klesající morbidity při častějším užití MBP u pacientů před střevní resekcí. Ve skupině pacientů, kteří podstoupili MPB před operací bylo zaznamenáno signifikantně nižší výskyt anastomotických komplikací v porovnání s pacienty, kteří MPB neužili (12 % vs. 29,5 %; $p < 0,001$). Při srovnání čistě ileocekálních resekcí s penetrující formou byly výsledky s MBP ještě lepší (11 % vs. 36 %; $p < 0,001$).




**Obr. 8.** Výskyt anastomotických komplikací u pacientů s CD v závislosti na podané ortográdní přípravě. Použito z publikace Iesalniks et al. [151].

### 2.4.1 Vlastní příspěvek k problematice

Na základě výše popsaných prací a výsledků jsme s Dr. Iesalniksem (chirurgická klinika, Mnichov) začali spolupracovat na navazující prospektivní studii v rámci mezinárodní spolupráce s Mnichovskou nemocnicí a univerzitou.

V roce 2020 na mezinárodním kongrese ECCO ve Vídni jsme již prezentovali naše první výsledky této prospektivní bicentrické studie (Mnichov, Brno). V abstraktu s názvem „Increased risk of anastomotic leak in Crohn's disease patients unable to complete preoperative mechanical bowel preparation" (příloha 21) [152] jsme prezentovali pilotní výsledky studie, zabývající se zda nekompletní MBP (pacient nevypije před operací kompletně 2 litry vyprazdňovacího roztoku - polyethylenglykol) má vliv na vyšší incidenci anastomotických leaků po ileocekální resekci, ve srovnání s pacienty, kteří předoperačně vypijí kompletně 2 litry roztoku. 28 % pacientů MBP nedokončilo, a to z důvodu nauzei, zvracení nebo bolestí břicha. Současně byla všem pacientům podána předoperačně perorální ATB profylaxe. Nekompletní předoperační užití 2 litrů vyprazdňovacího roztoku před ileocekální resekcí se zdá být jako faktor zvyšující riziko anastomotického leaku. Konkrétně riziko anastomotického leaku bylo signifikantně vyšší u pacientů, co nedokončili MBP (9 %), oproti pacientům, kteří kompletně MPB dokončili (0 %), p = 0,004. Definitivní výsledky studie plánujeme publikovat v roce 2021-2022.

## 2.5 Kvalita života u pacientů s Crohnovou chorobou

CD jako chronické zánětlivé onemocnění významně ovlivňuje kvalitu života (QoL – quality of life) u těchto pacientů.

Mezi klasické symptomy zhoršující QoL u pacientů s CD patří bolesti břicha, časté stolice s krví či hlenem, ztráta hmotnosti, extraintestinální manifestace nebo nutnost dlouhodobého užívání farmakoterapie [153].

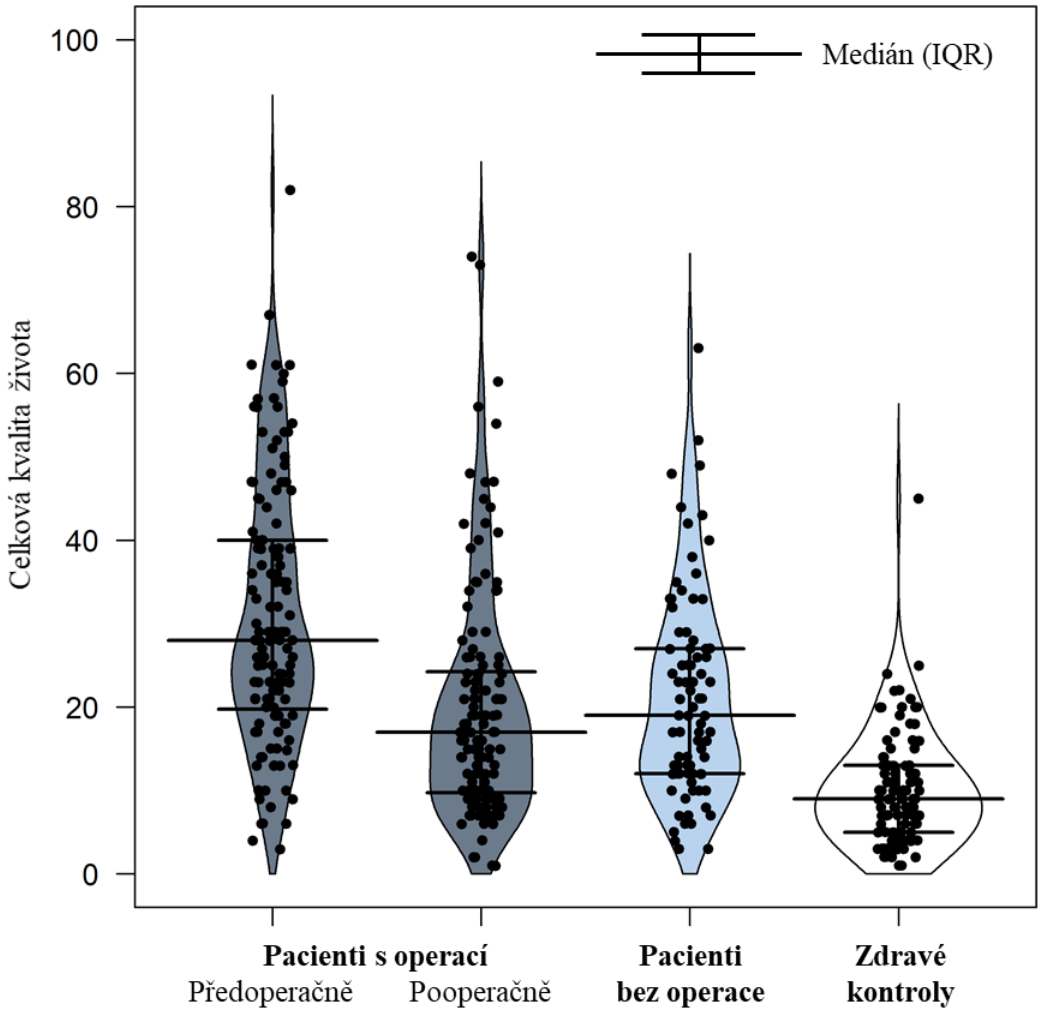
Populační studie ukázaly zhoršenou QoL ve srovnání se zdravou populací, zvláště pro chronickou povahu onemocnění, nepředvídatelnost akutního relapsu onemocnění, primodiagnózy onemocnění v mladém věku, atd [153–155]. Ukázalo se, že nejvýznamnějším faktorem ovlivňujícím QoL u pacientů s IBD je aktivita onemocnění [156–160]. U pacientů s navozenou dlouhodobou remisí, se ukázal trend ke srovnatelné QoL se zdravou kohortou.

### 2.5.1 Vlastní příspěvek k problematice

Cílem naší studie bylo stanovit, jaký vliv má chirurgická léčba na QoL u pacientů s CD a zároveň se pokusit určit faktory, které ovlivňují pooperační QoL. V období mezi lety 2010 až 2016 byla porovnávána QoL před operací a v pooperačním období u pacientů, kteří podstoupili na Chirurgické klinice FN Brno střevní resekci z indikace CD. Pacienti vyplňovali standardizovaný dotazník k měření QoL QLQ-CR29 v předoperačním období a znovu po operaci s odstupem 2 měsíců. Kontrolní skupinu představovali pacienti s CD, kteří byli v remisi onemocnění a nepodstoupili chirurgickou léčbu (resekci střeva). Druhou kontrolní skupinou byla zcela zdravá kohorta osob. Do studie bylo celkem zahrnuto 132 operovaných pacientů pro CD (resekce střeva), 83 pacientů s CD bez nutnosti operace (remise) a 104 zdravých jedinců. Pooperační zlepšení QoL bylo zjištěno celkem u 104 operovaných pacientů (78,8 %), u 2 pacientů nebyla zaznamenána žádná změna v QoL (1,5 %) a u 26 pacientů (19,7 %) bylo zjištěno zhoršení pooperační QoL. Výsledky byly statisticky signifikantně významné ($p < 0,001$). Grafická distribuce celkové QoL u všech pozorovaných skupin je zobrazena na obr. 9. Prokázali jsme signifikantní zlepšení celkové QoL po střevní resekci u pacientů s CD v měřeném intervalu 2 měsíců od operace a mužské pohlaví bylo vyhodnoceno jako jediný statisticky významný faktor zlepšující pooperační QoL.

První předběžné výsledky jsme publikovali v roce 2016 pod názvem „Quality of life after bowel resection for Crohn's disease - first results“ (příloha 22) [161] a finální výsledky nakonec v roce 2018 s názvem „Impact of surgery on quality of life in Crohn´s disease patients: final results of Czech cohort“ (příloha 23) [162].

Naše výsledky se tak shodovaly s ostatními zahraničními publikacemi [157,163–166], kdy stěžejní pro QoL je u pacientů s CD navození remise (ať konzervativní či chirurgickou léčbou).



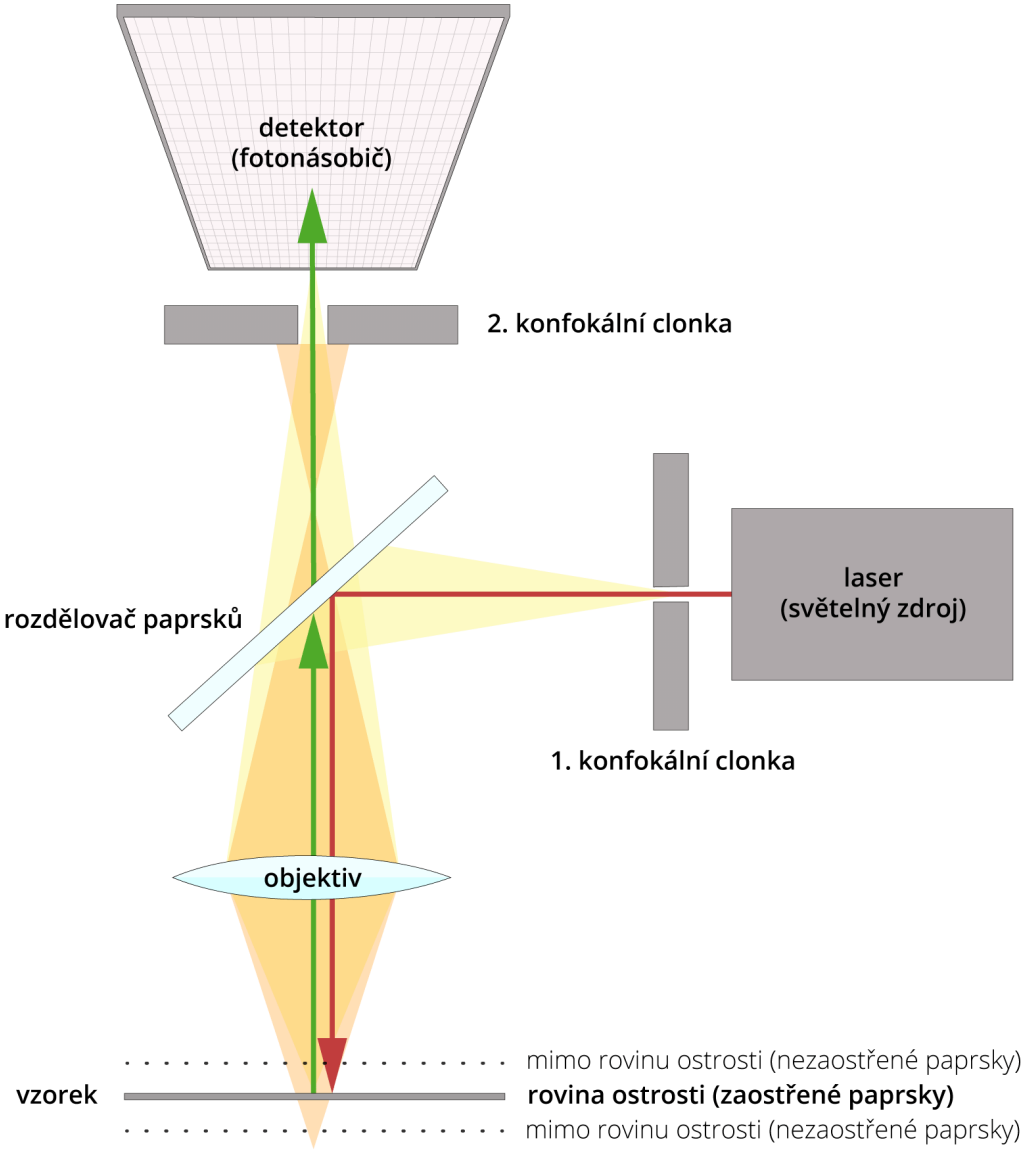

**Obr. 9.** Grafická distribuce celkové QoL u všech pozorovaných skupin (operovaní pacienti pro CD, neoperovaní pacienti s CD a zdravá kohorta). Použito z publikace Kunovský et al. [162].

## 3. Experimentální část

### 3.1 Konfokální laserová mikroskopie

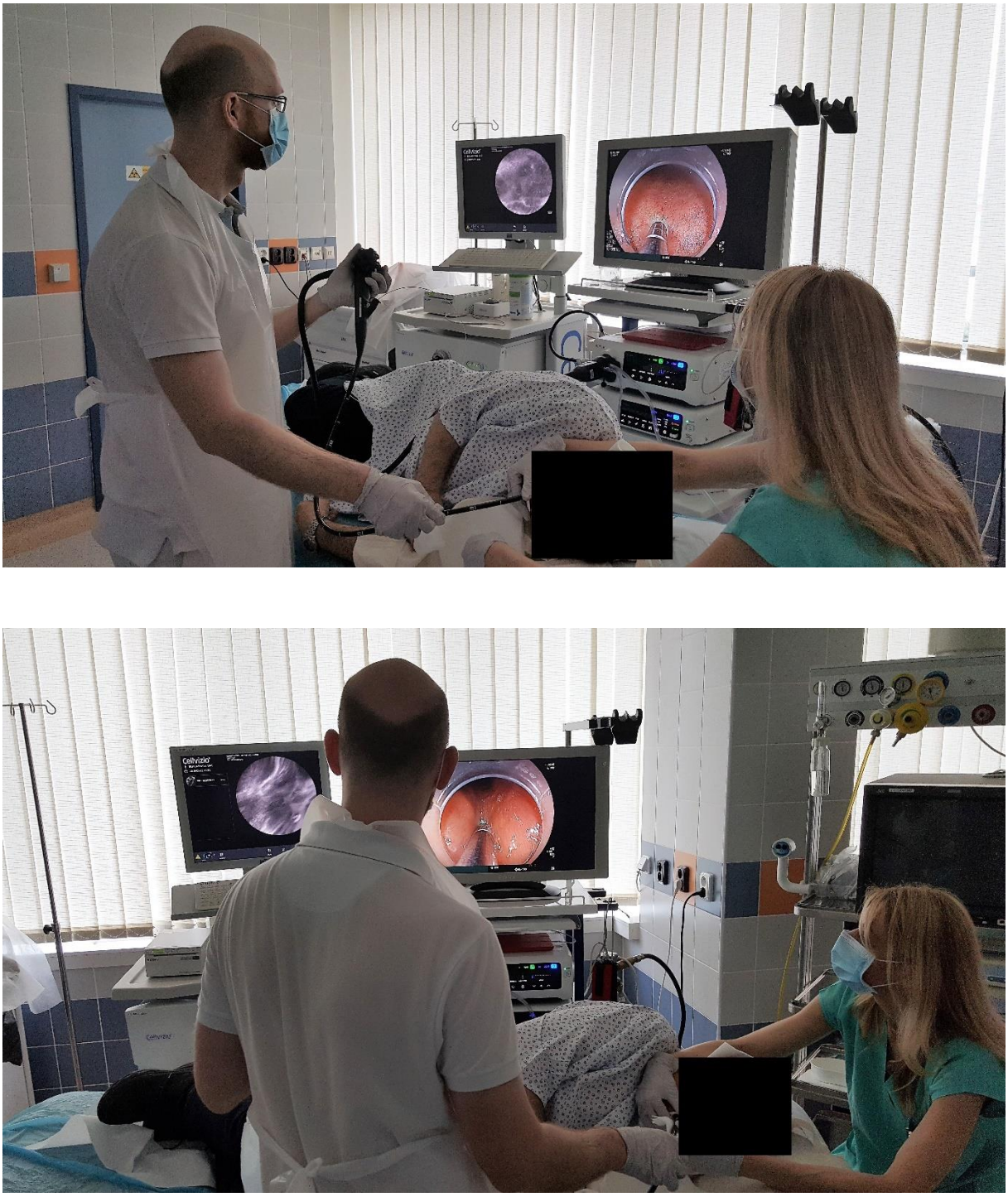
Konfokální laserová mikroskopie (confocal laser endomicroscopy - CLE) je na Chirurgické klinice FN Brno využívána již od roku 2015. V této experimentální části bude pojednáno o získaných zkušenostech s CLE a jejího možného využití v klinické praxi.

Samotný princip CLE byl poprvé popsán americkým matematikem a vědcem Marvinem L. Minskym v roce 1957. Princip fungování CLE je znázorněn na obrázku 10 (upraveno dle Pláška [167], Kubínové [168], Rouse [169] a webových stránek www.laser2000.co.uk [170]).



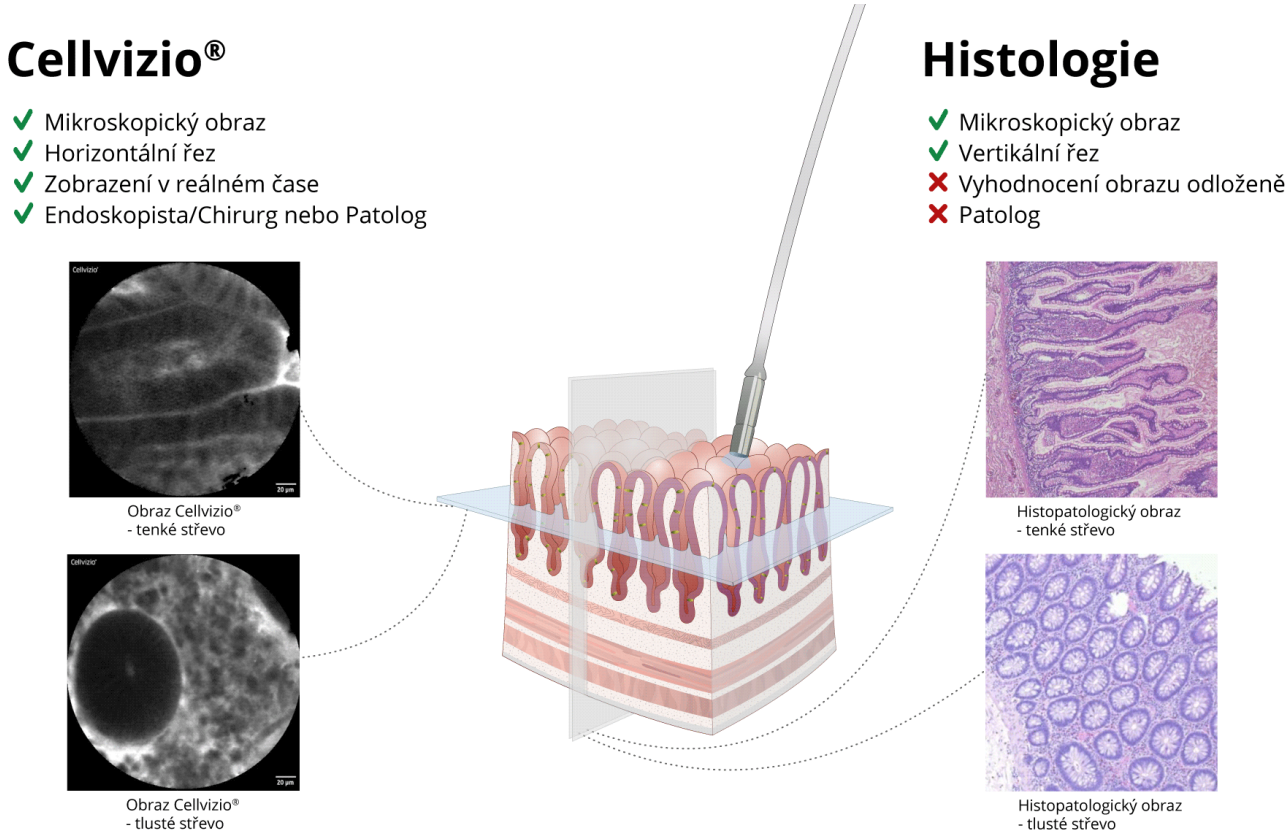

**obr 10.** Schéma fungování konfokálního laserového mikroskopu. Upraveno dle Pláška [167], Kubínové [168], Rouse [169] a webových stránek www.laser2000.co.uk [170], vytvořeno ve spolupráci se Servisním střediskem pro e-learning, Fakulta informatiky Masarykovy univerzity).

V roce 2006 firma Manua Kea Technologies uvedla na trh systém Cellvizio®, který se skládá z pracovní věže s monitorem a speciálně upravené sondy, jejíž využití bylo primárně zaměřeno na endoskopické vyšetření, ale uplatnění našlo i v chirurgii. Obr. 11a a 11b znázorňuje použití CLE během gastroskopie a pozici endoskopické věže Fujifilm® a pracovní věže Cellvizio® (použito z publikace Kunovský et al. [175]).



**Obr. 11a a 11b.** CLE (systém Cellvizio®) při gastroskopickém vyšetření. (použito z publikace Kunovský et al. [175]).

Na obr. 12 jsou schematicky zachyceny hlavní rozdíly klasického histologického vyšetření oproti CLE (Cellvizio®) (upraveno dle www.cellvizio. net [171]).




**Obr. 12.** Hlavní rozdíly klasického histologického vyšetření oproti CLE (Cellvizio®). Upraveno dle www.cellvizio. net [171], vytvořeno ve spolupráci se Servisním střediskem pro e-learning, Fakulta informatiky Masarykovy univerzity).

### 3.1.1 Vlastní příspěvek k problematice

Jak zmíněno výše, je CLE na Chirurgické klinice FN Brno používána již od roku 2015. První naše výsledky jsme prezentovali na mezinárodním kongrese v Berlíně (EPC - European pancreatic club) v oblasti chirurgie pankreatu v roce 2017. V abstraktu „Intraoperative use of confocal laser microscope (CLM) in pancreas surgery“ (příloha 24) [172] jsme prezentovali naše první zkušenosti a využití CLE při resekci pankreatu pro karcinom, kdy jsme CLE využívali k peroperačnímu určování pozitivní/negativní resekční linie na pankreatu a žlučových cestách.

V roce 2017 jsme publikovali přehledový článek v klinické onkologii s názvem „Konfokální laserová mikroskopie v diagnostice onkologických onemocnění gastrointestinálního traktu“ (příloha 25) [173]. V této práci systematicky rozebíráme možnosti jak endoskopického využití CLE, tak využití CLE peroperačního. V endoskopii je CLE využívána jako experimentální

metoda při diagnostice a dispenzarizaci Barrettova jícnu, cystických lézí pankreatu, diferenciální diagnostice indeterminovaných žlučových stenóz a lézí tlustého střeva. Právě velmi slibné se CLE jeví v diferenciální diagnostice cystických lézí pankreatu. V této problematice se hojně zasloužil francouzský gastroenterolog a endoskopista Bertrand Napoleon z Lyonu, jehož pracoviště jsem měl možnost navštívit formou krátkodobé stáže v roce 2018. Napoleon et al. [174] ve svých posledních výsledcích publikovali velmi povzbudivá data, kdy CLE dosahovala v diferenciální diagnostice cystických pankreatických lézí srovnatelných výsledků s klasickou endoskopickou ultrasonografií s biopsií.

Nedávno jsme publikovali pilotní výsledky využití CLE u onemocnění jícnu. Jedná se o původní práci s názvem „Confocal laser endomicroscopy in the diagnostics of esophageal diseases: a pilot study“ (příloha 26) [175]. V článku pojednáváme o našich prvních zkušenostech a možném využití CLE u diagnóz adenokarcinomu jícnu, Barrettova jícnu, refluxní ezofagitidy a zdravé kohorty pacientů. Cílem studie bylo získat základní obrazy CLE k těmto jednotlivým diagnózám. Obrazy z CLE byly poté porovnávány s klasickým histopatologickým obrazem a vyhodnoceny ve spolupráci s patologem. Správná diagnóza byla endoskopistou stanovena pomocí CLE (real-time) celkem u 11 ze 14 vyšetřených pacientů (78,6 %). CLE se tak zdá být novou slibnou metodou, a to především k surveillance Barrettova jícnu a detekci časných neoplastických lézí jícnu. Nutné jsou ale další studie na větších souborech pacientů.

### 3.2 Konfokální laserová mikroskopie u pacientů s IBD

CLE se také snaží najít uplatnění u pacientů s IBD. Jsou publikované studie zabývající se diferenciální diagnostikou CD a UC pomocí CLE [176,177], dále jsou práce věnující se CLE a jejího možného využití v predikci vývoje IBD (udržení remise či časný relaps) [178–181] nebo predikci odpovědi na biologickou terapii [182,183]. Potenciál má CLE rovněž ve screeningu kolorektální neoplázie u pacientů s IBD [184–186].

#### 3.2.1 Vlastní příspěvek k problematice

Na základě našich publikovaných dat o zvýšené časné rekurenci CD při mikroskopickém zánětu v resekční linii u ileocekální resekce (pojednáno výše) [133], jsme se v naší zatím nepublikované studii snažili určit, zda je možné peroperativně pomocí CLE určit mikroskopicky aktivní zánět přímo v resekční linii a odhalit tak potenciálně časnou rekurenci nemoci.

**Metodika:**

Mezi lety 2016 až 2020 byla peroperační CLE provedena u 36 pacientů. Do studie byli zařazeni pouze pacienti podstupující ileocekální resekci u CD. Jiné operační výkony pro CD nebyly do studie zařazeny.

K hodnocení konvenčních střevních resekátů v barvení pomocí hematoxylin-eosinu našimi histopatology zabývajícími se IBD bylo využito standardních hodnotících schémat dle Magro et al. [187] a Feakins et al. [188]. Při klasickém histopatologickém vyhodnocení resekátů tak byly stěžejní tyto mikroskopické známky a parametry znázorněné v tabulce 1.

**Tabulka 1.** Mikroskopické (histologické) známky CD (upraveno dle Magro et al. [187] a Feakins et al. [188]).

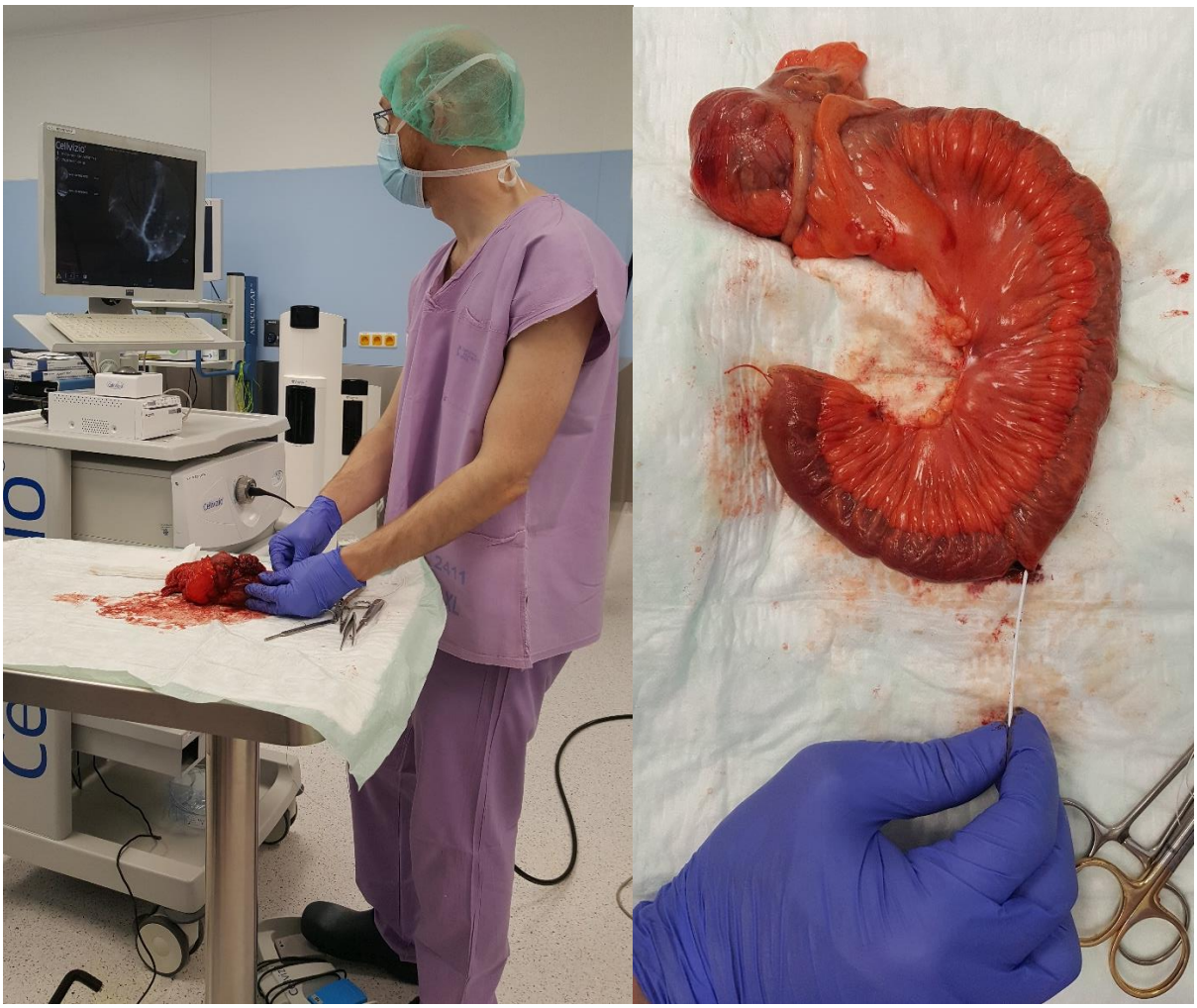
| |
|---|
| Distorze architektoniky krypt |
| Transmurální zánět s lymfoidními agregáty a bazální plazmocytózou |
| Zánětlivá aktivita (přítomnost neutrofilů) |
| Epiteloidní granulomy |
| Ulcerace, eroze |
| Fibróza |

K hodnocení vyšetření CLE byly nastudovány doposud publikované studie zabývající se CLE a IBD. Následně s našimi patology věnujícími se IBD byly vytvořeny parametry k hodnocení peroperačního vyšetření CLE. Vycházeli jsme především z prací Kiesslicha et al. [189] (Watson grade) a práce Neumanna et al. [190]. Tyto parametry byly dále ještě rozšířeny o nové studie věnující se CLE a CD [177–179,191,192]. Hodnocené parametry jsou uvedeny v tabulce 2.

**Tabulka 2.** Hodnocené parametry u CLE (upraveno dle Kiesslicha et al. [189] a Neumanna et al. [190]).

| |
|---|
| 1. Funkční defekty – ztráta bariérové funkce (únik fluoresceinu) |
| 2. Strukturální defekty – ztráta bariérové funkce (přítomnost mikroerozí) |
| 3. Charakter cév (zvýšený počet cév nebo zvětšené lumen cévy, nepravidelný průběh cév) |
| 4. Krypty tlustého střeva (tvar a pravidelnost krypt, tvar lumen v kryptách, vzdálenost mezi jednotlivými kryptami) |
| 5. Pravidelnost klků tenkého střeva (tvar, mikroeroze, únik fluoresceinu) |
| 6. Lamina propria – infiltrace zánětlivými buňkami (bez přítomnosti zánětlivé celulizace, lehce zvýšená či výrazná zánětlivá celulizace) |

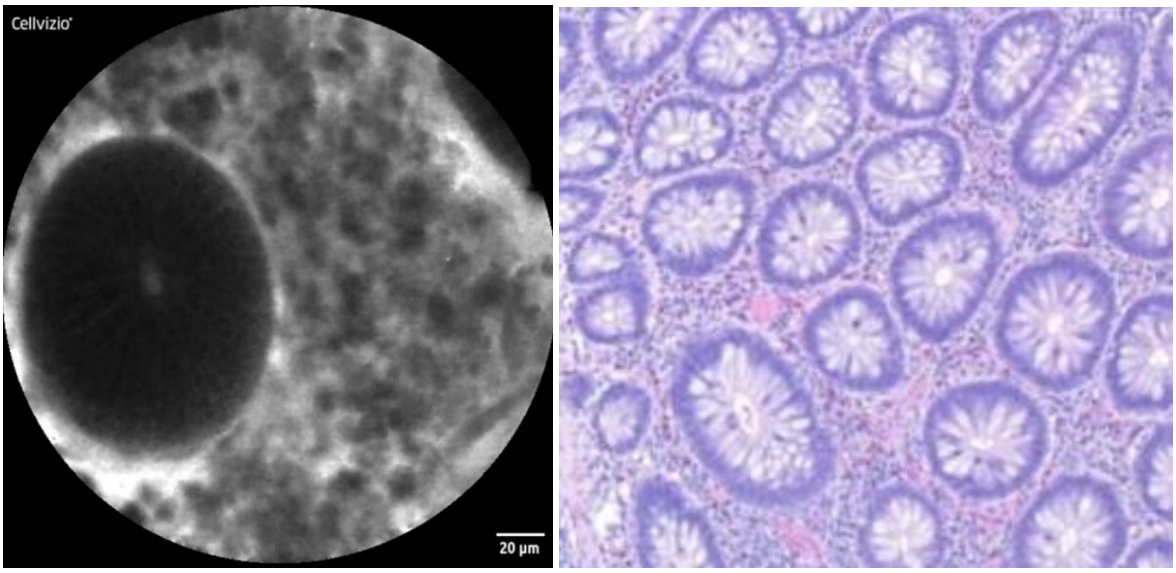
Během ileocekální resekce byly standardně vytyčeny resekční linie v makroskopicky zdravé tkáni. Před přerušením arteria ileocolica a střeva, bylo podáno barvivo fluorescein. Následně samotné CLE bylo provedeno na resekátu střeva. Znázorněno na obr. 13a a 13b. Záznamy vyšetření CLE byly pořízeny ze serózy střeva i ze strany mukózy, a to v místě centrálního zánětlivého postižení infiltrátu CD, resekční linii na tlustém střevě a resekční linii na tenkém střevě. Místa vyšetření CLE byla pro histopatology zaznačena stehem.



**Obr. 13a.** Provedení CLE (systém Cellvizio®) na resekátu terminálního ilea u CD.
**Obr. 13b.** Detail na zavedení sondy CLE do lumen střeva k vyšetření mukózy.

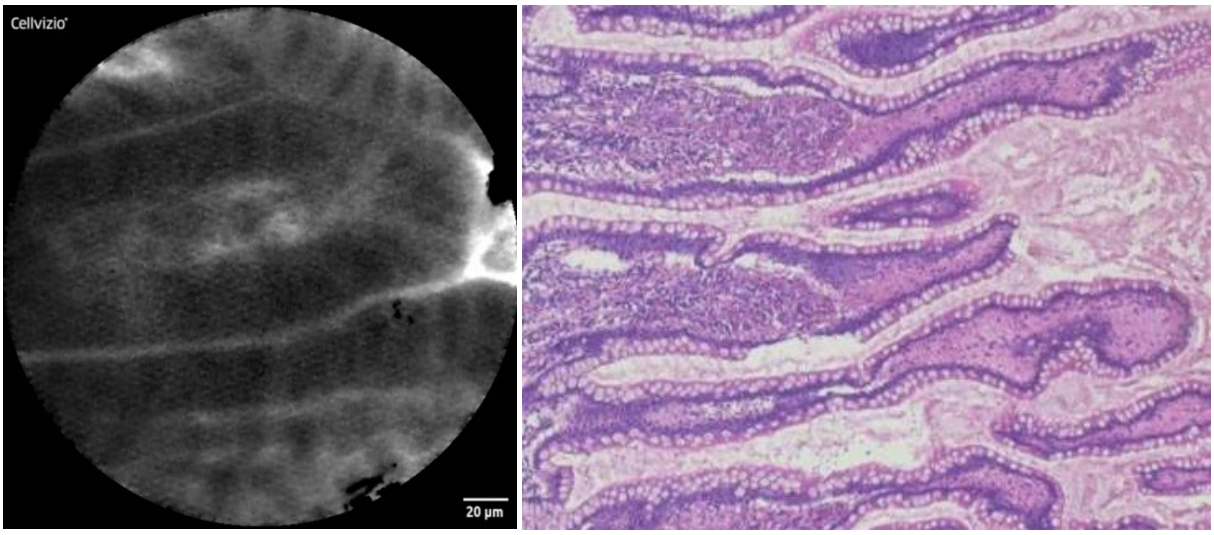
Finálně byly poté srovnávány záznamy z CLE a mikroskopické snímky z konvenční histopatologie v barvení hematoxylin-eosinem a byla provedena statistická analýza. Přehledné srovnání obrazů klasické histologie a CLE je zobrazeno na následujících snímcích.

Na obr. 14a zobrazení z CLE u negativní resekční linie tlustého střeva. Na obr. 14b poté korelát v klasickém histologickém obraze barvení hematoxilyn-eozin.



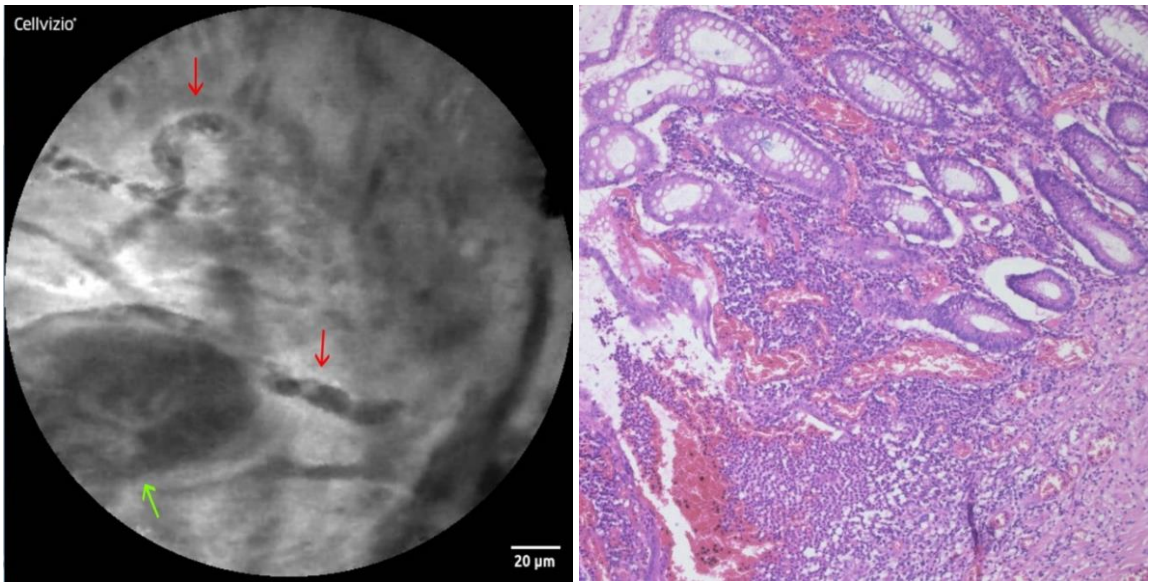

**Obr. 14a** (CLE). Zcela pravidelná krypta sliznice tlustého střeva, bez vaskularizace okolí či zánětlivé celulizace. **14b** (histologie). Pravidelné krypty tlustého střeva, bez známek distorze architektoniky, lamina propria přiměřeně zánětlivě celulizovaná.

Na obr. 15a zobrazení z CLE u negativní resekční linie tenkého střeva. Na obr. 15b korelát v klasickém histologickém obraze barvení hematoxylin-eosin.



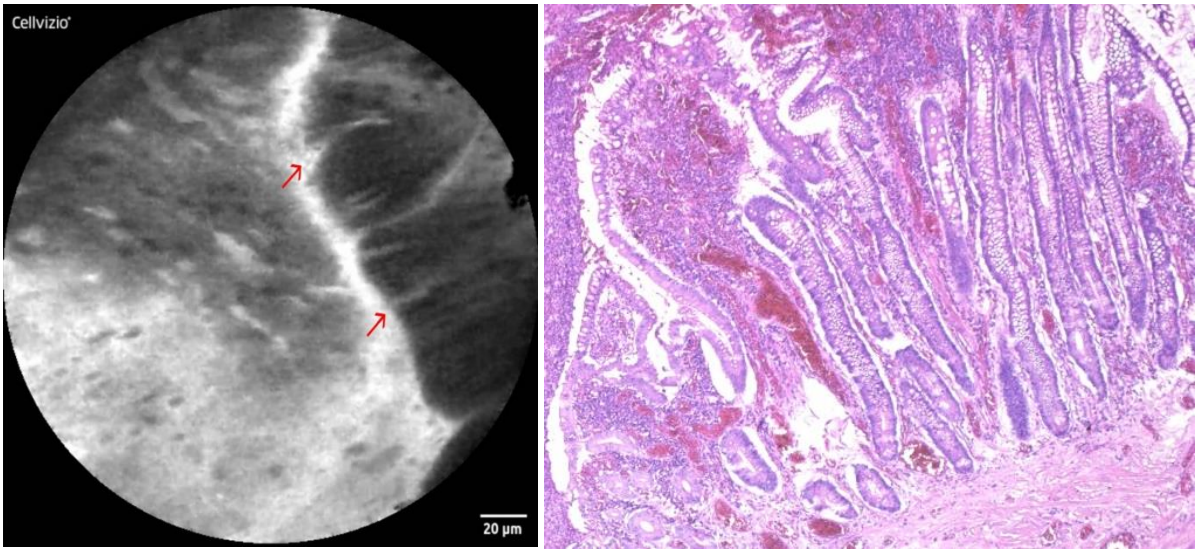

**Obr. 15a** (CLE). Pravidelné a zachovalé klky tenkého střeva s dobře patrnými enterocyty. **15b** (histologie). Pravidelné klky tenkého střeva, lamina propria přiměřeně celulizovaná.

Na obr. 16a CLE u pozitivní resekční linie tlustého střeva. Na obr. 16b korelát v klasickém histologickém obraze barvení hematoxylin-eosin.



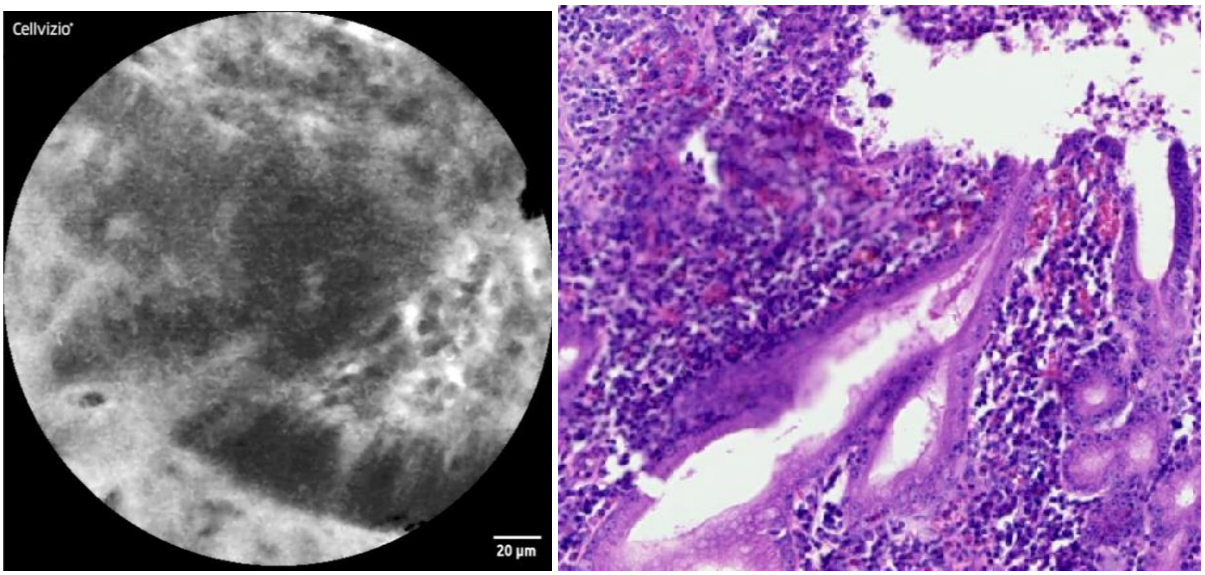

**Obr. 16a** (CLE). Výrazná asymetrie krypty tlustého střeva (zelená šipka), četné a chaoticky probíhající cévy (červené šipky). **16b** (histologie). Sliznice tlustého střeva fokálně erodovaná, krypty jsou s naznačenou poruchou architektoniky, lamina propria je překrvená a obsahuje zvýšenou lymfoplazmocytární celulizaci.

Na obr. 17a CLE u pozitivní resekční linie tenkého střeva. Na obr. 17b korelát v klasickém histologickém obraze barvení hematoxylin-eosin.



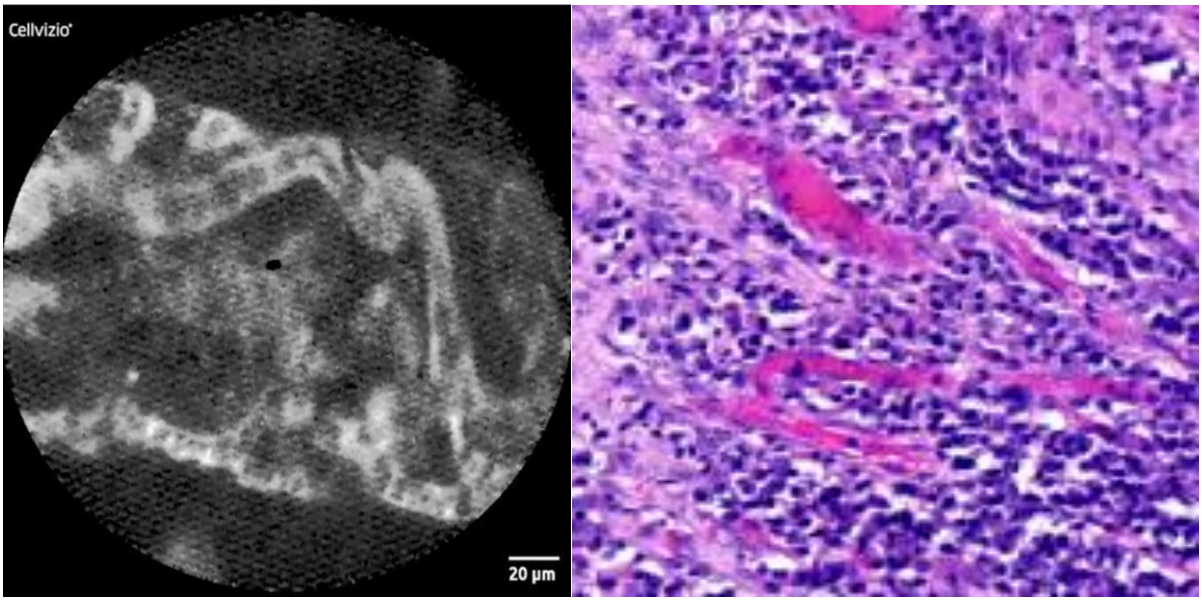

**Obr. 17a** (CLE). Nepravidelné uspořádání střevních klků s širšími rozestupy mezi enterocyty (epithelial gaps) a únik fluoresceinu (červené šipky). **17b** (histologie). Klky tenkého střeva nepravidelné stavby, přítomny jsou vícečetné mikroeroze, lamina propria je překrvená, obsahuje zvýšenou lymfoplazmocytázní celulizaci.

Na obr. 18a zobrazení z CLE u pozitivní resekční linie tenkého střeva. Na obr. 18b poté korelát v klasickém histologickém obraze barvení hematoxylin-eosin.




**Obr. 18a** (CLE). Masivní zánětlivá celulizace, přerušený průběh enterocytů, únik fluoresceinu. **18b** (histologie). Sliznice tenkého střeva s poruchou architektoniky klků, přítomna je eroze, lamina propria obsahuje zvýšené množství lymfoplazmocytární celulizace s příměsí neutrofilů.

Na obr. 19a zobrazení CLE se známkami zánětlivého postižení CD terminálního ilea. Na obr. 19b korelát v klasickém histologickém obraze barvení hematoxylin-eosin.




**Obr. 19a** (CLE). Patrná zánětlivá celulizace, četné chaoticky probíhající cévy.
**19b** (histologie). Spodina ulcerace s patrnou intenzivní lymfoplazmocytární celulizací a tvorbou granulační tkáně.

**Metodika statistického hodnocení:**

Pro sumarizaci sledovaných spojitých (kvantitativních) parametrů u pacientů CD po ileocekální resekci byla použita základní popisná statistika, tedy průměr, směrodatná odchylka (standard deviation - SD), medián, minimum a maximum. Kategoriální (kvalitativní) parametry byly sumarizovány pomocí absolutních a relativních četností.

Pro zhodnocení vztahu mezi určením pozitivity resekčních linií tlustého a tenkého střeva pomocí klasického histologického vyšetření (standardní metoda) a pomocí CLE Cellvizio® (experimentální metoda) byly použity základní ukazatele správnosti diagnostických testů – senzitivita (schopnost experimentální metody určit pozitivitu resekční linie), specificita (schopnost experimentální metody určit negativitu resekční linie) a celková správnost (celková schopnost rozpoznání pozitivity a negativity resekční linie pomocí experimentální metody) včetně 95% intervalu spolehlivosti (IS). Pro srovnání pravděpodobnosti výskytu pozitivity a negativity resekčních linií mezi jednotlivými vyšetřovacími metodami byl použit McNemarův test (test hypotézy o symetrii). Vyznačeny jsou *p*-hodnoty statisticky významné na hladině významnosti 5 %.

**Předběžné zatím nepublikované výsledky:**

Celkem bylo vyšetření pomocí CLE provedeno u 36 pacientů po ileocekální resekci pro CD. Z celkových 36 pacientů bylo 20 (55,6 %) mužů, průměrný věk pacientů při stanovení diagnózy byl 32 let (medián 27 let), průměrná doba trvání od stanovení diagnózy do operace byla 4,6 let (medián 2 roky). Většina pacientů měla lokalizované onemocnění pouze v ileu (63,9 %), a třetina měla lokalizaci v ileu i kolon. Chování (behaviour) CD bylo nejčastěji penetrující (44,4 %) nebo stenózující (41,7 %), u 8 pacientů (22,2 %) se vyskytovalo perianální postižení. Všichni pacienti byli před operací léčení, nejčastěji 5-ASA (47,2 %) a/nebo antibiotiky (41,7 %). Více pacientů podstoupilo laparoskopickou než otevřenou operaci (61,1 % vs. 38,9 %), u všech pacientů byla provedena anastomóza S-t-S. Základní charakteristika pacientů je uvedena v tabulce 3.

**Tabulka 3.** Základní popisná statistika pacientů s CD (n = 36).

| **Charakteristika** | **Kategorie** | n | % |
|---|---|---|---|
| **Pohlaví** | Muži | 20 | 55,6 % |
| | Ženy | 16 | 44,4 % |
| **Věková kategorie při stanovení diagnózy** | Do 17 let (A1) | 2 | 5,6 % |
| | 17-40 let (A2) | 24 | 66,7 % |
| | Nad 40 let (A3) | 10 | 27,8 % |
| **Lokalizace** | Ileum (L1) | 23 | 63,9 % |
| | Ileum + kolon (L3) | 13 | 36,1 % |
| **Chování choroby (behaviour)** | Zánětlivý (B1) | 5 | 13,9 % |
| | Stenózující (B2) | 15 | 41,7 % |
| | Penetrující (B3) | 16 | 44,4 % |
| **Perianální postižení** | Ne | 28 | 77,8 % |
| | Ano | 8 | 22,2 % |
| **Kouření cigaret** | Nekuřák | 19 | 52,8 % |
| | Bývalý kuřák | 8 | 22,2 % |
| | Kuřák | 9 | 25,0 % |
| **Rodinný výskyt CD** | Ne | 32 | 88,9 % |
| | Ano | 4 | 11,1 % |
| **Terapie ≤ 12 týdnů před operací** | Žádná | 0 | 0,0 % |
| | 5-ASA | 17 | 47,2 % |
| | Lokální GCS | 9 | 25,0 % |
| | Systémové GCS | 4 | 11,1 % |
| | AZA | 11 | 30,6 % |
| | MTX | 0 | 0,0 % |
| | Anti-TNF | 4 | 11,1 % |
| | Antibiotika | 15 | 41,7 % |
| **Operační přístup** | Otevřeně | 14 | 38,9 % |
| | Laparoskopický | 22 | 61,1 % |
| **Anastomóza** | E-t-E | 0 | 0,0 % |
| | S-t-S | 36 | 100,0 % |
| | | Průměr (SD) | Medián (min–max) |
| **Věk při stanovení diagnózy** (roky) | | 32 (16) | 27 (12–76) |
| **Trvání choroby od stanovení diagnózy do operace** (roky) | | 4,6 (5,7) | 2 (0–27) |

GCS (glucocorticosteroids) – kortikosteroidy, AZA (azathioprine) – azathioprin, MTX (methotrexate) – metotrexát, TNF (tumor necrosis factor) - tumor nekrotizující faktor, E-t-E - end to end, S-t-S - side to side

U všech pacientů byl centrální zánětlivý infiltrát pozitivní jak dle klasického histologického vyšetření, tak dle CLE. Dle histologického vyšetření byla u většiny pacientů (72,2 %) negativní resekční linie tlustého i tenkého střeva, u 3 pacientů (8,3 %) byla pozitivní pouze resekční linie tlustého střeva, u 4 pacientů (11,1 %) byla pozitivní pouze resekční linie tenkého střeva a u 3 pacientů (8,3 %) byly pozitivní obě resekční linie. Dle CLE byla negativní resekční linie tlustého i tenkého střeva u 69,4 % pacientů, u 3 pacientů (8,3 %) byla pozitivní pouze resekční linie tlustého střeva, u 5 pacientů (13,9 %) byla pozitivní pouze resekční linie tenkého střeva a u 3 pacientů (8,3 %) byly pozitivní obě resekční linie. V tabulce 4 je pak uvedena základní sumarizace pozitivity resekčních linií z pohledu histologie a CLE.

**Tabulka 4.** Pozitivita resekčních linií u pacientů s CD po ileocekální resekci (n = 36).

| **Pozitivita resekčních linií dle histologie** | | n | % |
|---|---|---|---|
| **Centrální zánětlivý infiltrát** | Negativní | 0 | 0,0 % |
| | Pozitivní | 36 | 100,0 % |
| **Tlusté střevo** | Negativní | 30 | 83,3 % |
| | Pozitivní | 6 | 16,7 % |
| **Tenké střevo** | Negativní | 29 | 80,6 % |
| | Pozitivní | 7 | 19,4 % |
| **Pozitivita celkově** | Pouze centrální infiltrát | 26 | 72,2 % |
| | Centr. inf. + tlusté střevo | 3 | 8,3 % |
| | Centr. inf. + tenké střevo | 4 | 11,1 % |
| | Centr. inf. + tlusté střevo + tenké střevo | 3 | 8,3 % |
| **Pozitivita resekčních linií dle CLE** | | n | % |
| **Centrální zánětlivý infiltrát** | Negativní | 0 | 0,0 % |
| | Pozitivní | 36 | 100,0 % |
| **Tlusté střevo** | Negativní | 30 | 83,3 % |
| | Pozitivní | 6 | 16,7 % |
| **Tenké střevo** | Negativní | 28 | 77,8 % |
| | Pozitivní | 8 | 22,2 % |
| **Pozitivita celkově** | Pouze centrální infiltrát | 25 | 69,4 % |
| | Centr. inf. + tlusté střevo | 3 | 8,3 % |
| | Centr. inf. + tenké střevo | 5 | 13,9 % |
| | Centr. inf. + tlusté střevo + tenké střevo | 3 | 8,3 % |

Výsledky ukazují, že CLE má nižší schopnost určit pacienty s pozitivní resekční linií tlustého střeva (senzitivita 66,7 %) než určit pacienty s pozitivní resekční linií tenkého střeva (senzitivita 85,7 %). Nicméně především kvůli nízkému celkovému počtu pacientů zahrnutých do analýzy (n = 36) a relativně nízkému počtu pacientů s pozitivními resekčními liniemi (dle histologie 6, resp. 7 pacientů) jsou 95% intervaly spolehlivosti zvlášť pro odhad senzitivity experimentální metody velmi široké. To znamená, že odhady mají nízkou přesnost. Neprokázal se statisticky významný rozdíl v pozitivitě resekčních linií mezi jednotlivými vyšetřovacími metodami, což může značit dobrou shodu mezi určením pozitivity resekčních linií mezi oběma metodami, ale rovněž to může být způsobeno i jen relativně nízkým počtem pacientů zahrnutých do analýzy. V případě tlustého střeva (tabulka 5) určily obě metody pozitivitu resekční linie u 6 pacientů, z čehož u 4 pacientů byl výsledek shodný. V případě tenkého střeva (tabulka 6) bylo dle histologie 7 pacientů s pozitivní resekční linií a dle CLE 8 pacientů, shoda v pozitivně resekční linie nastala u 6 pacientů. Tabulky 5 a 6 ukazují vztah mezi určením pozitivity resekčních linií tlustého a tenkého střeva dle histologie (standardní metoda) a dle CLE (experimentální metoda).

**Tabulka 5.** Pozitivita resekčních linií tlustého střeva dle histologie a dle CLE u pacientů s CD – počet (%) pacientů, srovnání pomocí McNemarova testu a základní ukazatele diagnostických testů (n = 36).

| **CLE** (experimentální metoda) | **Histologie** (standardní metoda) | | |
|---|---|---|---|
| | Negativní resekční linie tlustého střeva | Pozitivní resekční linie tlustého střeva | Celkem |
| Negativní resekční linie tlustého střeva | 28 (77,8 %) | 2 (5,6 %) | 30 (83,3 %) |
| Pozitivní resekční linie tlustého střeva | 2 (5,6 %) | 4 (11,1 %) | 6 (16,7 %) |
| Celkem | 30 (83,3 %) | 6 (16,7 %) | 36 (100,0 %) |
| p-hodnota McNemarova testu: | 1,000 | | |
| **Senzitivita** (%, 95% IS): | 66,7 % (22,3–95,7 %) | | |
| **Specificita** (%, 95% IS): | 93,3 % (77,9–99,2 %) | | |
| **Celková správnost** (%, 95% IS): | 88,9 % (73,9–96,9 %) | | |

**Tabulka 6.** Pozitivita resekčních linií tenkého střeva dle histologie a dle CLE u pacientů s CD – počet (%) pacientů, srovnání pomocí McNemarova testu a základní ukazatele diagnostických testů (n = 36).

| **CLE** (experimentální metoda) | **Histologie** (standardní metoda) | | |
|---|---|---|---|
| | Negativní resekční linie tenkého střeva | Pozitivní resekční linie tenkého střeva | Celkem |
| Negativní resekční linie tenkého střeva | 27 (75,0 %) | 1 (2,8 %) | 28 (77,8 %) |
| Pozitivní resekční linie tenkého střeva | 2 (5,6 %) | 6 (16,7 %) | 8 (22,2 %) |
| Celkem | 29 (80,6 %) | 7 (19,4 %) | 36 (100,0 %) |
| p-hodnota McNemarova testu: | 1,000 | | |
| **Senzitivita** (%, 95% IS): | 85,7 % (42,1–99,6 %) | | |
| **Specificita** (%, 95% IS): | 93,1 % (77,2–99,2 %) | | |
| **Celková správnost** (%, 95% IS): | 91,7 % (77,5–98,3 %) | | |

**Závěr:**

Dle našich předběžných výsledků této pilotní studie se zdá, že by peroperační CLE mohla být využitelná k peroperačnímu vyhodnocení mikroskopického zánětu CD v resekční linii.

CLE dosahovalo vyšší schopnosti určit pozitivní resekční linii na tenkém střevu (senzitivita 85,7 %) v porovnání určování pozitivní resekční linie tlustého střeva (senzitivita 66,7 %). Nutno však zdůraznit, že tyto výsledky mohou být méně přesné díky menšímu souboru pacientů.

V současnosti ještě doplňujeme a dokončujeme detailnější analýzu námi provedených záznamů z CLE a jejich korelátů s klasickými histologickými obrazy. Následovat bude finální statistické vyhodnocení. Další studie a vyhodnocení dat na větším souboru pacientů však ještě budou potřeba.

## 4. Závěr a shrnutí habilitační práce:

CD patří mezi chronická zánětlivá onemocnění střev. Dle současných populačních studií je nejvyšší incidence CD ve vyspělých státech světa a prevalence neustále narůstá. Na druhou stranu jsou ale stále objevovány nové diagnostické, prediktivní (miRNA, atd.) a léčebné metody k udržení dlouhodobé remise (jak konzervativní, tak chirurgické léčby).

V diferenciální diagnostice je nutné myslet i na celou řadu jiných onemocnění trávicího traktu (celiakie, náhlá příhoda břišní, atd., ale i raritní onemocnění jako např. MNGIE) nebo také možnou koincidenci s CD (autoimunitní pankreatitida, familiární adenomatózní polypóza).

V případě chirurgického řešení je u pacientů s IBD preferován miniinvazivní přístup. Výhody spočívají především v časné rekonvalescenci, nižší pooperační morbiditě a dosažení lepšího kosmetického efektu.
U pacientů se zánětlivou ileocekální formou CD, po selhání konvenční léčby, se jeví časná laparoskopická ileocekální resekce jako vhodná alternativa léčbě Infliximabem (dokonce se tedy ukazuje, že časná chirurgická léčba přináší určité benefity oproti biologické léčbě).

Kombinace perorální ATB profylaxe s předoperační MBP se zdá být ideální předoperační příprava před střevní resekcí u pacientů s CD k dosažení minimální pooperační morbidity.

U pacientů se dvěma nebo více mutacemi v genu NOD2 byl pozorován agresivnější průběh onemocnění (operace v mladším věku a v krátkém čase od stanovení diagnózy, a navíc resekce ilea byla provedena u všech pacientů). Právě tato skupina pacientů by mohla mít benefit z konzervativní akcelerované step-up léčby nebo časné chirurgické léčby (např. u ileocekální resekce).

Prokázali jsme, že chirurgicky navozená remise u pacientů s CD, zvyšuje pooperační QoL. Stěžejní pro QoL je však udržení dlouhodobé pooperační remise.

Pozitivní mikroskopická zánětlivá aktivita CD v resekční linii u ileocekální resekce má vliv na časnou rekurenci onemocnění v anastomóze. Naše výsledky potvrdila i nedávno publikovaná meta-analýza zahrnující naši práci.
Peroperační CLE by mohla být nápomocná při určování resekční linie a snížit tak časnou rekurenci CD v anastomóze. Další studie s CLE na větších souborech pacientů jsou ale nutné.

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## 6. Seznam zkratek

CD (Crohn's disease) - Crohnova choroba

IBD (inflammatory bowel disease) - idiopatické střevní záněty

UC (ulcerative colitis) - ulcerózní kolitida

NOD2/CARD15 - Nucleotide-binding oligomerization domain 2/ Caspase recruitment domain 15

ECCO - European Crohn’s and Colitis Organisation

miRNA - microRNA

JAMA - Journal of the American Medical Association

MNGIE (Mitochondrial neurogastrointestinal encephalomyopathy) - mitochondriální neurogastrointestinální encefalomyopatie

AIP - Autoimunitní pankreatitida

5-ASA - 5-aminosalicyláty

MBP (mechanical bowel preparation) - ortográdní příprava střeva

QoL (quality of life) - kvalita života

CLE (confocal laser endomicroscopy) - konfokální laserová mikroskopie

SD (standard deviation) - směrodatná odchylka

GCS (glucocorticosteroids) - kortikosteroidy

AZA (azathioprine) - azathioprin

MTX (methotrexate) - metotrexát

TNF (tumor necrosis factor) - tumor nekrotizující faktor

E-t-E - end to end

S-t-S - side to side

## 7. Seznam obrázků

Obr. 17b. (histologie). Klky tenkého střeva nepravidelné stavby, přítomny jsou vícečetné mikroeroze, lamina propria je překrvená, obsahuje zvýšenou lymfoplazmocytázní celulizaci.

Obr. 18a. (CLE). Masivní zánětlivá celulizace, přerušený průběh enterocytů, únik fluoresceinu.

Obr. 18b. (histologie). Sliznice tenkého střeva s poruchou architektoniky klků, přítomna je eroze, lamina propria obsahuje zvýšené množství lymfoplazmocytární celulizace s příměsí neutrofilů.

Obr. 19a. (CLE). Patrná zánětlivá celulizace, četné chaoticky probíhající cévy.

Obr. 19b. (histologie). Spodina ulcerace s patrnou intenzivní lymfoplazmocytární celulizací a tvorbou granulační tkáně.

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**Příloha 1** - Regional Incidence of Inflammatory Bowel Disease in a Czech Pediatric Population: 16 Years of Experience (2002-2017)



OPEN

# Regional Incidence of Inflammatory Bowel Disease in a Czech Pediatric Population: 16 Years of Experience (2002–2017)

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## ABSTRACT

**Objectives:** Inflammatory bowel disease (IBD) is today a global disease, the incidence of which is growing in the pediatric population. This prospective study aims to decipher IBD incidence and its trend in a pediatric population through 16 years in the South Moravian Region of the Czech Republic.

**Methods:** We evaluated data concerning 358 pediatric patients with newly diagnosed IBD at University Hospital Brno, which is a gastroenterology center for the entire pediatric population (0–18 years) and cares for all pediatric IBD patients in the South Moravian Region (1,187,667 inhabitants).

**Results:** The study encompassed 3,488,907 children during 16 years. We diagnosed 192 children (53.6%) with Crohn disease (CD), 123 (34.4%) with ulcerative colitis (UC), and 43 (12.0%) with IBD-unclassified (IBD-U). The incidence of IBD increased from 3.8 (CD 2.9, UC 0.9, and IBD-U 0.0) per 100 000/year in 2002 to 14.7 (CD 9.8, UC 4.0, and IBD-U 0.9) per 100,000/year in 2017 ($P < 0.001$). The overall IBD incidence per 100,000/year was 9.8 (95% confidence interval [CI]: 8.8–10.9). Constituent incidences per 100,000/year were CD 5.2 (95% CI: 4.5–6.0), UC 3.4 (95% CI: 2.8–4.0), and IBD-U 1.2 (95% CI: 0.9–1.6). IBD incidence was projected to reach 18.9 per 100,000/year in 2022.

**Conclusions:** The overall incidence of pediatric IBD in the Czech Republic is increasing, and especially that of CD, whereas trends in UC and IBD-U appear to be constant. These data highlight the need to identify risk factors involved in the rising incidence of IBD.

**Key Words:** children, Crohn disease, Czech Republic, incidence, inflammatory bowel disease, ulcerative colitis

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**What Is Known**

- The incidence of pediatric-onset inflammatory bowel disease shows geographical variability worldwide.
- The incidence and prevalence of childhood-onset inflammatory bowel disease have risen rapidly in recent decades.

**What Is New**

- This research describes an increase in the incidence of inflammatory bowel disease, mainly because of a rise in the incidence of Crohn disease, between 2002 and 2017 in a population of Czech children.
- Prospectively evaluated incidence rates of pediatric inflammatory bowel disease and its subtypes in the Czech Republic are among the highest in the literature.

Inflammatory bowel disease (IBD), consisting of Crohn disease (CD), ulcerative colitis (UC), and inflammatory bowel disease unclassified (IBD-U), is a chronic relapsing inflammatory disorder with a multifactorial etiology. Both genetic aspects and environmental factors are important for IBD pathogenesis (1,2). Approximately 8% of IBD patients have an early onset of the disease in childhood (2). Reviews in the past decade have concluded that the incidence of pediatric-onset IBD has been rising globally, albeit with great geographic variations (3,4). By analyzing studies of IBD incidence and prevalence from around the world, it has been shown that the incidence is rising not only in high-income, but also in low-income and middle-income countries (5). Nevertheless, that incidence remains much lower in the latter countries (6,7). IBD is associated with higher morbidity and decreased quality of life in patients, results in significantly more frequent use of health care resources, and has become a major health concern (8,9). In the case of children, it is key to realize that the forms of the disease are often more aggressive than in adults, as evidenced by higher rates of immunomodulatory drugs and biologic therapies use compared with adults (10).

We have had relatively limited data on the incidence of IBD in Czech children. Therefore, it would be highly desirable to have more precise data in this field, to describe the exact trends in current developments, and to compare these data with those from other regions, especially within Central Europe.

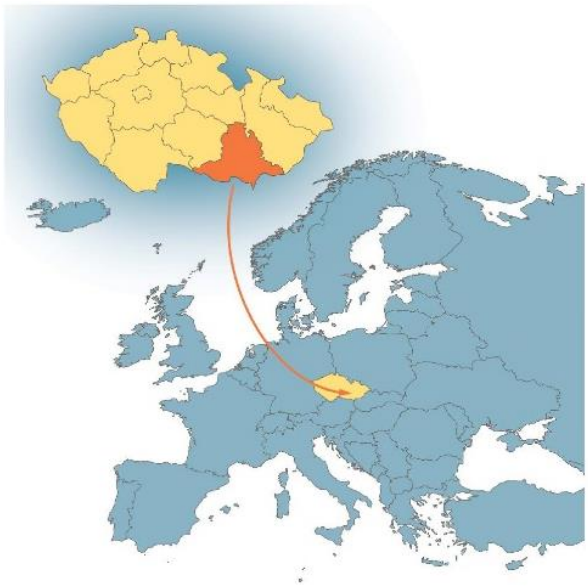

**FIGURE 1.** Location of South Moravian Region (orange) within the Czech Republic (yellow) and Europe (gray).

The aim of our study was to determine the IBD incidence and trends in the Czech pediatric population. The study takes in a 16-year period in the South Moravian Region within the Czech Republic (Fig. 1). It characterizes differences by sex and age, anticipates the incidence of IBD for future years in this region, and, by extension, for the whole of the Czech Republic (11).

## METHODS

### Study Design

We conducted the study in the South Moravian Region, one of the 14 regional administrative units in the Czech Republic. The region has 1,187,667 inhabitants (2018, Czech statistical office), constituting 11% of the Czech Republic's total population. Children account for 19% of this number, or 229,375. The region covers an area of 7188 $km^2$. The health system in the Czech Republic is tax-funded and offers universal access.

The diagnosis and treatment of pediatric patients with IBD in the Czech Republic is limited only to highly specialized centers, which are strategically located and provide comprehensive care to IBD patients. In the South Moravian Region, all regional hospitals are referring pediatric patients for a comprehensive examination to 1 center in the regional capital, University Hospital in Brno. This referral pathway is rigid and has not changed throughout the study period.

Diagnosis of patients under 18 years of age by gastroenterologists serving adults is very unlikely, as in the Czech Republic, this would not be reimbursed by health insurance. The only reason for potential drop-out from our study is diagnosis of a local inhabitant outside of our region. We consider this to be very unlikely, but it does constitute a potential bias in our study. We believe the absolute majority of pediatric IBD patients from the South Moravian region are referred to our center.

The inclusion criteria consisted of children having been diagnosed with IBD according to relevant guidelines (12,13) (clinical history, physical examination, laboratory and serological testing, radiologic findings, and endoscopic appearance with stepwise biopsy for review by clinical pathologists) in a period between January 1, 2002 and December 31, 2017.

All patients underwent upper gastrointestinal endoscopy and ileocolonoscopy, with small bowel imaging (unless typical UC was determined after endoscopy and histology) by magnetic resonance enterography. All children were 0–18 years of age at the time of diagnosis and were resident in the South Moravian Region. The newly diagnosed IBD patients were subdivided into 3 main clinical types: CD, UC, and IBD-U. If a differentiation between UC and CD could not be determined after a complete workup, these patients were designated as IBD-U (11,13). The data were prospectively collected by experienced gastroenterologists into a study database administered by the Institute of Biostatistics and Analyses. Only unequivocal IBD cases were enrolled into the study. The patients without indisputable diagnosis according to the Porto criteria were excluded from further analyses. During the study, data was validated by other experienced gastroenterologists by blindly selecting 10 cases from each year and validating patient records by comparison with original data in the hospital information system. The Institutional Ethical Committee approved the study at University Hospital Brno in accordance with the 1964 Declaration of Helsinki.

### Statistical Methods

Standard statistical methods were adopted for data description. Count data are summarized using absolute and relative frequencies. Median and interquartile range of nonmissing observations are reported for continuous data. Kruskal-Wallis test was used to examine between-group differences for continuous data, whereas Fisher exact test and exact rate ratio test (14), assuming Poisson counts, were applied for count data.

Age-gender adjusted incidence rates are expressed as newly diagnosed children per 100,000 pediatric population per year (100,000/year) and reported with 95% confidence intervals based on a gamma distribution. Data regarding the size of the pediatric population were obtained from the Czech Statistical Office, which counts the number of inhabitants either in actual years or accounts for all regions' redistributions and adjusts past numbers with regard to the regions' present sizes. For this study, we chose to work with figures related to actual years. Incidence trends and future projections were estimated using Poisson regression. All statistical significances were evaluated on a level of $\alpha = 0.05$. The entire analysis was conducted in the statistical software R. Poisson models were estimated using the *glm* function from the built-in *stats* package.

## RESULTS

### Demographics and Inflammatory Bowel Disease Incidence

The basic demographic characteristics of 358 children (<19 years of age) diagnosed for IBD between 2002 and 2017 in the South Moravian Region are shown in Table 1. Over the 16 years, the Czech Statistical Office accounted for 3,488,907 children in the area, and of those diagnosed with IBD, 192 (53.6%) were diagnosed as CD, 123 (34.4%) as UC, and 43 (12.0%) as IBD-U. Among all the IBD cases, 53.1% were boys. The median age of a diagnosed child was 13.9 years (interquartile range: 4.9), the median time between the first symptoms and diagnosis was 4.0 months (interquartile range: 6.3), and no significant differences were found in basic demographic characteristics between diagnoses (all $P > 0.05$).

Incidence rates per 100,000/year for the given period 2002 to 2017 are captured in Figure 2. Except for the year 2015, when CD and UC incidences were comparable, the incidence of CD outgrew those of UC and IBD-U after 2009, which had not been the case prior to

TABLE 1. Demographics of children (0–18 years of age) newly diagnosed with inflammatory bowel disease, Crohn disease, ulcerative colitis, and inflammatory bowel disease-unclassified in the South Moravian Region, 2002 to 2017

| Parameter | IBD | CD | UC | IBD-U |
|---|---|---|---|---|
| Sex, N (%) | | | | |
| N | 358 | 192 | 123 | 43 |
| Male | 190 (53.1%) | 104 (54.2%) | 65 (52.8%) | 21 (48.8%) |
| Female | 168 (46.9%) | 88 (45.8%) | 58 (47.2%) | 22 (51.2%) |
| Age at diagnosis (years) | | | | |
| N | 358 | 192 | 123 | 43 |
| Median (interquartile range) | 13.9 (4.9) | 14.4 (4.7) | 13.6 (4.3) | 12.4 (6.7) |
| Time from first symptoms to diagnosis (months) | | | | |
| N | 301* | 156 | 112 | 33 |
| Median (interquartile range) | 4.0 (6.3) | 4.0 (6.6) | 3.0 (6.2) | 5.0 (6.0) |

CD = Crohn disease; IBD = inflammatory bowel disease; IBD-U = inflammatory bowel disease-unclassified; UC = ulcerative colitis.
*Discrepancy between number of patients and total N is because of missing data.

2009. Before 2009, no obvious predominance of any diagnosis was observable. A rising trend in IBD incidence is nevertheless noticeable for the entire 16-year period. Although in 2002, the IBD incidence was only 3.8 (CD 2.9, UC 0.9, and IBD-U 0.0) per 100,000/year, in 2017 it reached 14.7 (CD 9.8, UC 4.0, and IBD-U 0.9) per 100,000/year. Although there is no significant difference in CD and IBD-U incidences between years 2002 and 2017 (both $P > 0.05$), this is not the case for IBD ($P < 0.001$) and CD ($P = 0.003$). The predominance of the CD diagnosis after 2009 is confirmed by its being significantly higher than the UC and IBD-U incidences ($P = 0.029$ and $P < 0.001$, respectively) in 2017, but its incidence was only higher than that of IBD-U ($P = 0.016$) in 2002.

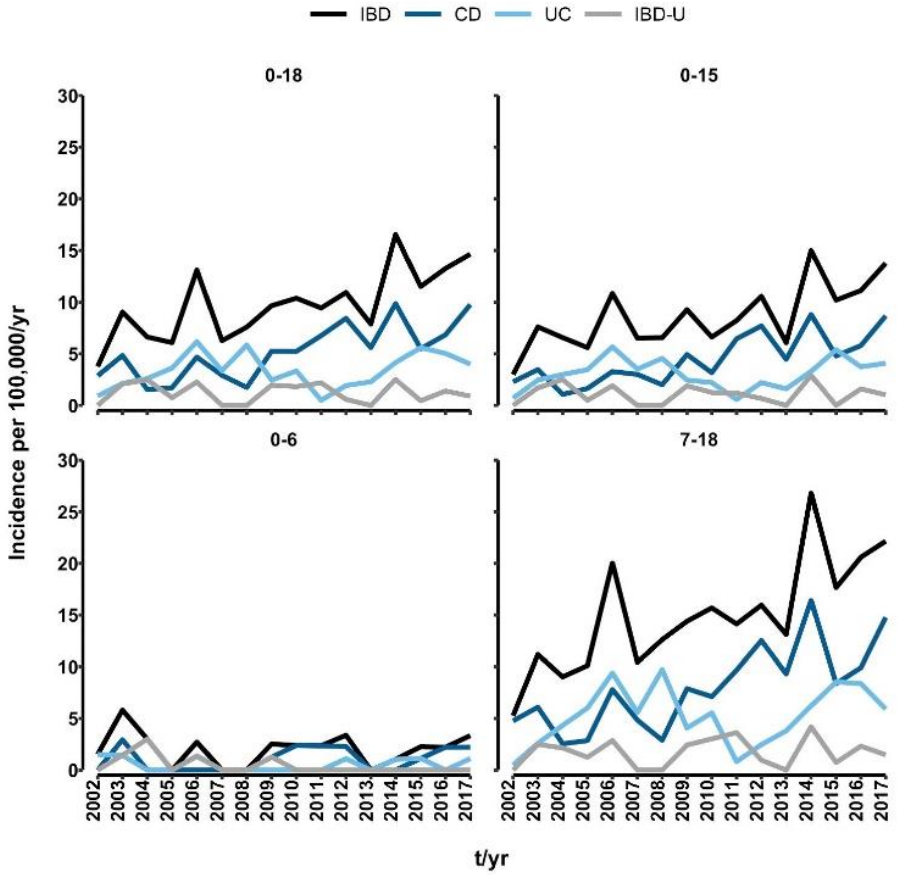


FIGURE 2. Incidence rates per 100,000/year in different age groups of children (0–18, 0–15, 0–6, 7–18 years of age) newly diagnosed with inflammatory bowel disease (IBD), Crohn disease (CD), ulcerative colitis (UC), and inflammatory bowel disease-unclassified (IBD-U) in the South Moravian Region, 2002 to 2017.

TABLE 2. Inflammatory bowel disease incidence by age and sex in newly diagnosed children (0–18 years of age) with inflammatory bowel disease, Crohn disease, ulcerative colitis, and inflammatory bowel disease-unclassified in the South Moravian Region, 2002 to 2017

| Incidence per 100,000/year | IBD | CD | UC | IBD-U |
|---|---|---|---|---|
| Age | | | | |
| 0–18 | | | | |
| N | 358 | 192 | 123 | 43 |
| Mean (95% CI) | 9.8 (8.8–10,9) | 5.2 (4.5–6.0) | 3.4 (2.8–4.0) | 1.2 (0.9–1.6) |
| 0–15 | | | | |
| N | 257 | 135 | 92 | 30 |
| Mean (95% CI) | 8.6 (7.6–9.8) | 4.5 (3.8–5.4) | 3.1 (2.5–3.8) | 1.1 (0.7–1.5) |
| 0–6 | | | | |
| N | 26 | 14 | 7 | 5 |
| Mean (95% CI) | 2.0 (1.3–3.0) | 1.1 (0.6–1.8) | 0.5 (0.2–1.1) | 0.4 (0.1–0.9) |
| 7–18 | | | | |
| N | 332 | 178 | 116 | 38 |
| Mean (95% CI) | 14.7 (13.1–16.3) | 7.8 (6.6–9.0) | 5.2 (4.3–6.2) | 1.7 (1.2–2.3) |
| Gender | | | | |
| Male | | | | |
| N | 190 | 104 | 65 | 21 |
| Mean (95% CI) | 10.1 (8.7–11.7) | 5.5 (4.4–6.7) | 3.4 (2.6–4.4) | 1.2 (0.7–1.8) |
| Female | | | | |
| N | 168 | 88 | 58 | 22 |
| Mean (95% CI) | 9.5 (8.1–11.1) | 4.9 (3.9–6.1) | 3.3 (2.5–4.3) | 1.3 (0.8–1.9) |

CD = Crohn disease; CI = confidence interval; IBD = inflammatory bowel disease; IBD-U = inflammatory bowel disease-unclassified; UC = ulcerative colitis.

A detailed overview of overall incidences by diagnosis, age, and sex is provided in Table 2. The overall IBD incidence per 100,000/year for the 16-year period for children up to 18 years of age was 9.8 (95% CI: 8.8; 10.9), and for children up to 15 years of age, it was 8.6 (95% CI: 7.6–9.8). The overall CD and UC incidences were found to be significantly higher than that of IBD-U (both $P < 0.001$). The difference in CD versus UC incidences also was significant ($P < 0.001$).

## Paris Classification

According to the Paris Classification (15), there were 53 patients (27.6%) in the CD group under 10 years of age (A1a), 115 (59.9%) were between 10 and 17 years of age (A1b), and 28 patients (12.5%) were over 17 years of age (A2). Occurring most frequently was the ileocolic localization (L3) in 134 (69.8%) patients. Upper GIT involvement (L4a and L4b) was found in 28 (14.5%) patients. Most patients (145 [75.5%]), had the nonstricturing and nonpenetrating form of CD (B1), 24 (12.5%) the stricturing form (B2), 16 (8.3%) the penetrating form (B3), and only 1 patient (0.5%) the stricturing and penetrating form (B2, B3). In 6 patients (3.1%) the behavior of the disease could not be validly evaluated. Perianal disease was found in 22 (11.5%) patients. Growth delay at the time of diagnosis was present in 57 (29.7%) CD patients.

Among 123 patients diagnosed with UC, there were 6 (4.9%) patients only with proctitis (E1), 16 (13.0%) with left-sided (distal to splenic flexure) colitis (E2), and 8 (6.5%) with extensive (distal to hepatic flexure) colitis (E3). Pancolitis was present in 90 (73.2%) patients. In 3 patients (2.4%), the extent of the disease could not be validated.

## Inflammatory Bowel Disease by Age

The IBD incidence begins to grow quickly from the age of 8. The peak occurs at 17 years of age, with decrease thereafter. Of those diagnosed with IBD, only 26 (7.3%) were children under 7 years of age, whereas the majority of child patients were at least 7 years of age at diagnosis. Early presentation of CD, UC, and IBD-U at age 6 and earlier occurred in 14 (3.9%), 7 (2.0%), and 5 (1.4%) children, respectively. The overall IBD incidence per 100,000/year for children ages up to 6 years was 2.0 (95% CI: 1.3–3.0), whereas significantly higher ($P < 0.001$) incidence of 14.7 (95% CI: 13.1–16.3) occurred for children aged 7 years and older. Likewise CD, UC, and IBD-U incidences among young children (<7 years) were significantly lower (all $P < 0.001$) than were those for older children (≥ 7 years). No significant between-diagnoses differences were found for patients up to 6 years of age. For patients aged 7 and older, the CD incidence was found to be significantly greater than were those for UC and IBD-U ($P = 0.001$ and $P < 0.001$, respectively), which was true also for incidences of UC vs. IBD-U ($P < 0.001$).

## Inflammatory Bowel Disease by Sex

Of the 358 children diagnosed with IBD, 53.1% were boys (CD 54.2%, UC 52.8%, and IBD-U 48.8%). Overall male and female IBD incidences per 100,000/year were 10.1 (95% CI: 8.7–11.7) and 9.5 (95% CI: 8.1–11.1), respectively, with no statistically significant difference between the 2 ($P = 0.606$). No significant sex-related differences were found between incidences of CD, UC, and IBD-U (all $P > 0.05$). Among both boys and girls, CD and UC incidences were proven to be significantly higher compared with those for IBD-U (all $P < 0.001$) as well as CD vs. UC incidence ($P = 0.005$ and $P = 0.022$ for boys and girls, respectively).

## Trends in Inflammatory Bowel Disease Incidence

Figure 3 shows actual IBD and CD incidences per 100,000/year, an estimated trend over the observed 16 years, 95% CI, and

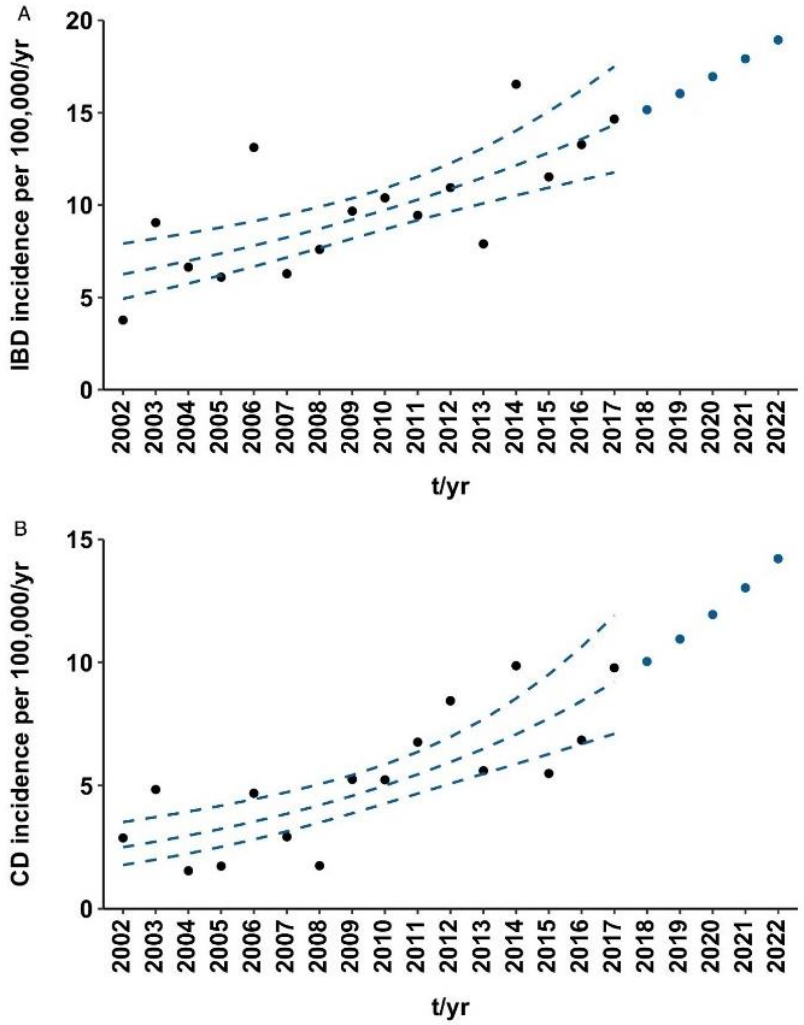


**FIGURE 3.** Incidence rates per 100,000/year among children (0–18 years of age) newly diagnosed with inflammatory bowel disease (IBD) (A) and Crohn disease (CD) (B) in South Moravian Region, 2002 to 2017 and 2018 to 2022. Black points represent actual data. Broken blue lines indicate trend over the observed period based on Poisson regression along with a 95% confidence interval. Blue points are future projections.

future projections for the next 5 years (2018–2022). Overall, the IBD incidence per 100,000/year has risen significantly, with the relative risk (RR) of being diagnosed with IBD increasing by 5.7% each year (RR = 1.057, $P < 0.001$). The rising trend in IBD mainly reflects significant increase in newly diagnosed CD cases (RR = 1.091, $P < 0.001$), whereas neither UC (RR = 1.030, $P = 0.133$) nor IBD-U incidence (RR = 0.988, $P = 0.723$) showed any significant changes. The IBD incidence is projected to reach 18.9 per 100,000/year in 2022 (14.2 for CD).

The relative risk per year of being diagnosed with IBD was 2.7% greater for girls (RR = 1.072, $P < 0.001$) than for boys (RR = 1.045, $P = 0.005$). The difference is substantially smaller for the CD diagnosis, with girls facing relative risk of being diagnosed that is 1.2% higher than in the case of boys (RR = 1.088 [$P < 0.001$], RR = 1.100 [$P < 0.001$] for boys and girls, respectively). There appeared a significant increase in incidence over the 16-year period of girls being diagnosed with UC (RR = 1.065, $P = 0.026$).

## DISCUSSION

We provide a detailed longitudinal data set describing IBD incidence and its trends in pediatric patients through the 16 years between 2002 and 2017 within a well-defined geographical area of the Czech Republic. To our knowledge, this is the most recent and comprehensive study in this field. Our results provide important insights into the high incidence of IBD and its increasing trend, which are due mainly to the rise in rates of CD. The overall IBD incidence per 100,000/year shows IBD incidence in children within the Czech Republic currently to be among the highest in the world (3–6,16,17). These data show considerably higher incidences than were determined from the first Czech national survey conducted about 2 decades earlier by Pozler et al (18). In another, smaller Czech study from the Olomouc Region, an overall increase in the incidence of IBD was also confirmed (19). Schwarz et al recently published a 16-year prospective study of pediatric IBD patients in the Pilsen Region of the Czech Republic showing that a group of 170 pediatric patients (study period 2000–2015) represented an

average incidence of IBD per 100,000/year of 10.0 (6.2 for CD, 2.8 for UC, and 1.0 for IBD-U). That study also projected increasing future incidence (11). Our study is based on data from a region of almost similar size but with more than 2 times the number of pediatric patients with IBD. The incidence of IBD subtypes revealed by our group, and including the proportions among them, is practically identical to the results from the Pilsen Region. Moreover, the incidence trends are very similar. Although acknowledging certain limitations, we therefore, can presume that our findings are potentially similar to incidences to be found in pediatric IBD patients throughout the Czech Republic. We clearly demonstrate an overall increase in IBD incidence within the population of Czech children, with the overall incidence rising more than 3 times when comparing data from the first and final year in our data set. The overall IBD incidence per 100,000/year rose significantly over the study period, that trend reflecting mainly the statistically significant increase in CD incidence even as the UC and IBD-U incidences showed no statistically significant changes. Our future projections put the IBD incidence at 18.9 per 100,000/year in 2022 (14.2 per 100,000/year for CD). In the future, we will be able to compare these projections with real data obtained from our patients. In comparison to neighboring countries in Central and Eastern Europe, our data suggests that the increase in the incidence of IBD is particularly noticeable in Hungary (20,21) and Slovenia (22) whereas it seems to be stable in Germany (23). In Austria, on the other hand, an overall increase was observed from 1997 to 2007 in both CD and UC, primarily in the largest urban areas (24). The overall incidence of IBD cases was surprisingly very low in Poland, at 2.7 per 100,000/year (0.6 for CD, 1.3 for UC, and 0.8 for IBD-U) (6,25). No current data on the incidence of IBD in neighboring Slovakia is known at this time. Globally, CD predominates over UC and IBD-U in areas having high IBD incidence. Recent data indicate higher rates of pediatric CD than UC in Europe and North America, except in northern California (26), Finland (27), Poland (25), and Italy (28), where the incidence of UC exceeds that of CD (6). The reasons for these notable differences remain uncertain (4,6,29). In a recent systematic review, Sykora et al analyzed 140 pediatric incidence studies. They demonstrated substantial increase in the incidence of pediatric IBD as well as great geographic variation. The incidence of IBD remains highest in the northern populations of Europe and America but has remained stable or even decreased. Rising rates of pediatric IBD have been observed in previously low-incidence areas and much of the developing world, as well as among children of immigrants. The incidence rates of CD and UC vary worldwide between 0.2/100,000 and 13.9/100,000 and between 0.1/100,000 and 15/100,000, respectively. In time-trend analyses, 67% of CD and 46% of UC studies have reported significant increases (6). Variation in IBD incidence may reflect differences in the distribution of various environmental triggers for a given disease in specific areas. Rapidly changing IBD incidence in such areas create an opportunity for future studies of genetic-environmental interactions (6,30,31). Exposure to environmental factors in childhood appears to be essential for the later development of IBD. In rapidly developing areas, such as Asia, the food composition of traditional human diets is changing. People are shifting from homemade to processed foods, and lifestyles are changing also in other ways. All this may affect the composition of the human intestinal microbiota and potentially be related to increasing IBD (31–35). We can hypothesize that this reflects a certain similarity to the significant rise in the socioeconomic level within the Czech Republic after the close of the communist era, and thus, an influence on the increase in IBD. One of the prerequisites for developing a proper understanding of IBD's pathogenetic context and next steps in better care for pediatric patients is to find accurate and relevant data, including data for IBD's incidence and prevalence in these patients (36).

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**Příloha 2** - The Emerging Role of Noncoding RNAs in Pediatric Inflammatory Bowel Disease

BASIC SCIENCE REVIEW ARTICLE

# The Emerging Role of Noncoding RNAs in Pediatric Inflammatory Bowel Disease

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Prevalence of inflammatory bowel disease (IBD), a chronic inflammatory disorder of the gut, has been on the rise in recent years—not only in the adult population but also especially in pediatric patients. Despite the absence of curative treatments, current therapeutic options are able to achieve long-term remission in a significant proportion of cases. To this end, however, there is a need for biomarkers enabling accurate diagnosis, prognosis, and prediction of response to therapies to facilitate a more individualized approach to pediatric IBD patients. In recent years, evidence has continued to evolve concerning noncoding RNAs (ncRNAs) and their roles as integral factors in key immune-related cellular pathways. Specific deregulation patterns of ncRNAs have been linked to pathogenesis of various diseases, including pediatric IBD. In this article, we provide an overview of current knowledge on ncRNAs, their altered expression profiles in pediatric IBD patients, and how these are emerging as potentially valuable clinical biomarkers as we enter an era of personalized medicine.

**Key Words:** pediatrics, inflammatory bowel disease, Crohn's disease, ulcerative colitis, noncoding RNA, microRNA

## INTRODUCTION

Inflammatory bowel disease (IBD) is an umbrella term for ulcerative colitis (UC) and Crohn's disease (CD). These chronic inflammatory disorders of the gastrointestinal tract often are diagnosed in adolescence and young adulthood. Some 8%–25% of IBD patients have early onset of the disease in childhood.[1, 2] These cases are more severe,[3] with many extraintestinal issues such as delayed growth and development.[4] The prevalence of these diseases is steadily rising worldwide, and the increase is particularly rapid in the pediatric population.[5–7] Current diagnostic routine includes symptom assessment, endoscopic examination and biopsy, histology, serology, and radiology.[8, 9] No standard diagnostic routine and reliable direct biomarkers are currently available. The biomarkers we have now reflect only general inflammation rather than specific pathogenesis associated with ongoing IBD or a specific subtype of IBD. A time-consuming and often painful diagnostic process eventually leading to surgical intervention is a particularly traumatic experience for young children, but this could very well be avoided by the use of noninvasive or minimally invasive biomarkers for diagnostics and therapeutic disease monitoring.

Although novel therapeutic strategies are effective in managing symptoms and achieving long-term remission, these approaches are not curative, and in some patients, no or only poor response is observed.[10, 11] Early identification of such patients by innovative diagnostic approaches and their redirection to other therapeutic options is therefore essential for improving therapeutic outcomes. Moreover, novel discoveries in IBD pathogenesis are necessary to identify the targets and to develop novel therapeutic strategies. Noncoding RNAs (ncRNAs) are currently being studied intensively in pediatric IBD patients because they constitute a promising, novel class of biomarkers and therapeutic targets.

## NONCODING RNAs, THEIR CLASSIFICATION, FUNCTION, AND BIOGENESIS

After the Human Genome Project revealed that only 1.5% of the genome is protein-coding,[12] it became clear that

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there is more to DNA than mere proteins. Even earlier, there had been some sparse information available about the existence of RNAs untranslated to the proteins, but this was long considered an exception rather than a rule. In addition to transfer and ribosomal RNA, the first observations of small nuclear RNAs (snRNAs) and small nucleolar RNAs (snoRNAs) were made in the 1980s.[13–16] Later, cancer-related deregulation of ncRNAs RNA H19,[17] growth arrest-specific transcript 5 (GAS5),[18] and prostate cancer antigen (PCA3/DD3)[19] pointed to the now well-documented phenomena as to the involvement of noncoding genome in the development of many complex diseases. Only after the discovery of gene expression regulation through RNA interference facilitated by short noncoding RNAs,[20–22] however, did exploration of noncoding genome really begin to take off.

Noncoding RNAs can be divided according to their function into 2 groups: housekeeping ncRNAs (e.g., tRNAs, rRNAs, snRNAs, snoRNAs) and regulatory ncRNAs. The latter of these is historically subdivided into 2 large groups according to the arbitrary dividing line of 200 nucleotides in length. Transcripts shorter than 200 nucleotides are termed short noncoding RNAs (sncRNAs), and transcripts exceeding 200 nucleotides are called long noncoding RNAs (lncRNAs). Both groups are involved in regulating gene expression and operate on several levels depending on the type of ncRNA. The sncRNAs, such as microRNAs (miRNAs), small interfering RNAs (siRNAs), and PIWI-interacting RNAs (piRNAs), are involved mostly in post-transcriptional regulation but also in many other specific processes such as transposon silencing or rRNA maturation.[23] The lncRNAs are much longer by definition and comprise a more diverse group of transcripts. They are known to affect many cellular processes on transcriptional, post-transcriptional, and translational levels. Although both short and long noncoding transcripts usually possess no protein coding capacity, there has been some evidence of cryptic reading frames and translation in to shorter micropeptides in lncRNAs formerly regarded as noncoding.[24–26]

## MicroRNAs

Among all ncRNAs, miRNAs have been studied thoroughly and have claimed the most attention in recent decades. Along with the discovery of RNA interference in the early 2000s, miRNAs were observed first in *Caenorhabditis elegans* as master regulators of developmental timing[20, 21, 27–30] and later in many other species, including humans.[30, 31] Their distinct length of 18 to 25 nucleotides makes them a very specific group of transcripts, currently encompassing about 2000 different mature miRNAs.[32] Naturally produced endogenously, miRNAs constitute a pivotal cellular mechanism for regulating expression in as many as 60% of human genes[31] by complementary binding to their target messenger RNAs (mRNAs). Of the 18 to 25 nucleotides, 8 are essential and make up what is termed the "seed" region, which binds to the 3′ untranslated region of the target, thereby leading to repressed translation of the target mRNA, either by its destabilization or degradation.[33, 34] As the seed region is fairly short, many different mRNAs can contain a complementary sequence and be affected by a single miRNA, thus making it a pleiotropic regulator of several targets.[33] Stemming from either individual miRNA genes or intergenic and intragenic regions of protein-coding genes,[35] miRNAs are canonically transcribed by RNA polymerase II,[36] thereby creating polyadenylated and capped pri-miRNAs.[37, 38] This primary transcript is usually several hundred nucleotides long and contains a future mature miRNA sequence in the stem of the secondary hairpin structures of pri-miRNA. Next, splicing of the pri-miRNA is facilitated by a microprocessor complex consisting of RNase III Drosha[39] and a dimer of DiGeorge critical region 8 (DGCR8).[40, 41] The microprocessor cleaves the pri-miRNA transcript, creating 1 or several hairpin structures—pre-miRNAs—that each contain one future miRNA. Pre-miRNAs are transported by nuclear transporter protein exportin 5[42] to the cytoplasm, where they are processed further. The RNase III–type enzyme Dicer,[43] together with other cooperating proteins (dependant on the species; in humans it is trans-activation-responsive RNA binding protein [TRBP]),[44] cleaves pre-miRNA close to the terminal loop and creates a double-stranded RNA intermediate. One of the strands is recruited into an RNA-induced silencing complex (RISC) with proteins from the Argonaute family (AGO).[44] The strand that is recruited is termed "leading," and the other one, called the "passenger strand," is usually degraded; although in some cases, it also can be recruited into the RISC.[45]

The canonical pathway of miRNA biogenesis can be overcome, as some miRNAs have been observed to be produced alternatively in noncanonical ways that exclude certain steps and also give rise to other types of sncRNAs.[46–49]

## LONG NONCODING RNAs

Long ncRNAs were first regarded as nonfunctional because their roles in the cells have been unknown and their sequences are less conserved than are those of protein-coding genes.[50, 51] In comparison with miRNAs, lncRNAs encompass a much broader group due to their definition by length. Though miRNAs encompass only a specific 18 to 25 nucleotides in length of the spectrum, everything from 200 nucleotides and larger is considered an lncRNA unless it is a coding sequence.[52–56] Next-generation sequencing revealed that lncRNAs originate from more than 59,000 genes.[57] That number was expanded even further by the NONCODE database to more than 96,000 genes producing over 172,000 transcripts.[58] Not many of these, however, have been experimentally validated to date.[59] Nevertheless, structural and functional variability makes it difficult to create a meaningful and useful classification system;[60] currently, several systems are being used based upon localization in the genome in relation to the protein-coding genes, according to their function or depending upon the means of their origin.

Although sharing many similarities with mRNAs, lncRNAs are more tissue- and time-specific and operate in much lower concentrations.[52, 60–62] They are localized both in cell nucleus and in the cytoplasm in 1 or more copies, but nuclear localization, especially close to the chromatin, is their preferential one.[52, 63] Close to the chromatin, they affect gene expression by facilitating chromatin interactions and guiding chromatin-remodeling complexes,[64, 65] thus activating or repressing transcription. Other ways of transcriptional regulation include cooperation with transcription factors,[66, 67] binding to regulatory sequences[68–70] and promoting splicing of mRNAs in complexes with other splicing molecules.[71, 72]

When translocated to the cytoplasm, lncRNAs are involved in post-transcriptional and post-translational regulation of gene expression while acting in cooperation with RNA-binding proteins, or they affect the stability and degradation of such proteins and thus facilitate protein turnover.[73] The mRNA stability is affected by the binding of RNA–protein complexes containing lncRNAs as guiding molecules, which causes either degradation or enhanced translation of the target mRNA.[74, 75] The RNA–protein complexes are also involved in various signaling pathways,[76] fulfill certain roles in cellular organelles, or help transport other molecules into organelles.[77] A separate category of lncRNAs, so-called "competing endogenous RNAs" (ceRNAs), serve as decoys or sponges for miRNAs and so alter the relative availability of miRNAs.[78] Similarly, lncRNAs serve also as protein decoys, averting proteins from binding to other transcripts.[79]

In contrast to the well-described canonical pathway of miRNAs, a general biogenetic pathway for lncRNAs is difficult to trace, as lncRNAs present a diverse group of transcripts produced in several ways. Nevertheless, an initial part of the biogenesis is shared not only among lncRNAs but also by all transcripts. This consists of transcription by polymerase II, polyadenylation, 5′ capping, and chromatin modifications typical for protein-coding sequences.[52, 80] However, lncRNA genes usually contain fewer but longer exons, and their expression is more time- and tissue-specific. Enormous variability exists on the post-transcriptional level, which includes such specific modifications as cleaving of the 3′ end by RNAse P or back-splicing to creating a circular lncRNA (circRNA).[81, 82] There is also some evidence that miRNA transcriptional apparatus is somewhat involved in lncRNA biogenesis. After all, sncRNAs, including for example miRNAs themselves, arise from formerly long primary transcripts classifiable as lncRNAs and only later are processed by specific biogenetic pathways.[83, 84]

## NONCODING RNAs AS BIOMARKERS

Great demand exists for a precise, possibly noninvasive biomarker that can provide a faster, simpler, and more efficient way of characterizing patients and personalizing management of the disease. The ncRNAs have emerged as potential biomarkers for several diseases, as these are generally stable and abundantly present in a variety of clinical specimens, including tissues and bodily fluids; are highly tissue-specific, cell type-specific, and condition-specific; and can be readily detected by routine and inexpensive laboratory techniques.[85, 86]

The majority of the human genome encodes RNAs that do not code for proteins.[20, 21, 87] These ncRNAs affect normal expression of the genes, including genes involved in the immune system, inflammation, and IBD pathogenesis. Although miRNAs are the most studied regulatory ncRNAs to date and miRNA-targeted diagnostics and therapeutics have already reached clinical development,[28, 85, 86, 88] the importance of lncRNAs as potential biomarkers and therapeutic targets is increasingly recognized.[85, 86, 89, 90]

Both short and long ncRNAs function mostly as regulators and fine-tuners of gene expression. Although miRNAs share a simple structure and, in the majority of cases, bind to their target mRNAs through their 8-nucleotide long seed region to post-transcriptionally regulate gene expression,[27] lncRNAs use many different molecular mechanisms depending on the length and structure of a given transcript. This enables a wide variety of functions, spanning from transcription regulation and acting as miRNA sponges to orchestrating epigenetic modifications.[82] Several miRNAs[89, 90] and specific miRNA signatures[91, 92] have been identified in IBD-associated tissues. It has been shown that among many other cellular processes, miRNAs play a significant role in intestinal immunity.[93] Nevertheless, there exists only sparse information on ncRNA profiles and their diagnostic potential in pediatric IBD patients (summarized in Tables 1 and 2). Given that adult and pediatric IBD have some differences in manifestation, etiology, and genetic background,[4] it is expected that ncRNA profiles may reflect these differences. To examine these aspects thoroughly, we searched the PubMed database for relevant studies according to the following strategy: "miRNA" and "pediatric" and ("ulcerative" and "colitis") or ("crohn" and "disease") or "IBD." When we excluded nonclinical studies and chose only studies carried out on pediatric patients, the remaining 11 articles (Tables 1 and 2) were relevant for our discussion.

## NONCODING RNAs IN TISSUES OF PEDIATRIC IBD PATIENTS

The research group of Koukos et al focused on differences in ncRNA expression profiles in pediatric and adult IBD patients and published its study in 2013.[94] In addition to showing that the IL6/STAT3 pathway is a critical factor in the development and progression of IBD, those authors identified 5 miRNAs suppressing activity of STAT3. These are miR-125, miR-101, miR-26, miR-124, and let-7, with miR-124 probably being a central regulator of STAT3 due to its greater than 90% inhibitory effect on STAT3 in human colonocytes.[95] Further investigation using real-time quantitative polymerase chain reaction (RT-qPCR) on adult and pediatric samples revealed that

**TABLE 1.** Summary of Tissue ncRNAs Associated With Various Aspects of Pediatric IBD

| Study | ncRNA | Change in expression (patients) | Compared groups | Number of patients, sample type | Statistical parameters: Best *P*- achieved | Statistical parameters: AUC | Statistical parameters: Sensitivity/ Specificity (%) | Technological platform |
|---|---|---|---|---|---|---|---|---|
| Koukos et al., 2013 [40] | miR-101 | Down | IBD vs. non-IBD | 45 biopsies | — | — | — | MicroRNA-library screen, RT-qPCR |
| | miR-26 | Down | | | — | | | |
| | miR-124 | Down | pUC vs. pCD/non-IBD | | <0.0001/<0.01 | | | |
| Koukos et al., 2015 [42] | miR-4284 | Down | pIBD vs. non-IBD | 37 biopsies | <0.05 | — | — | mirCURY microRNA array, RT-qPCR |
| Zahm et al., 2014 [43] | miR-192 | Down | pUC vs. controls | 50 biopsies | 0.0006 | — | — | nCounter, TaqMan low density array, RT-qPCR |
| | miR-194 | | | | 0.0019 | | | |
| | miR-200b | | | | 0.0056 | | | |
| | miR-375 | | | | 0.0001 | | | |
| | miR-142-3p | Up | | | 0.0048 | — | — | |
| | miR-146a | | | | 0.0027 | | | |
| | miR-21 | | | | 0.0003 | | | |
| | let-7i | | | | 0.0007 | | | |
| | miR-24 | — | pUC vs. pCD | | — | 0.83 | 83.3/85.7 | |
| Béres et al., 2016 [44] | miR-122 | Up | ipCD vs. C/pUC | 28 FF samples, | <0.01 | — | — | RT-qPCR |
| | miR-146a | Up | pUC vs. C | 71 FFPE samples | <0.001 | | | |
| | miR-155 | UP | ipCD vs. C | | <0.001 | | | |
| Szűcs et al., 2016 [45] | miR-146a | Up | ipCD vs. inpCD vs. C | 30 FFPE samples | <0.001 | — | — | RT-qPCR |
| | miR-155 | | | | | | | |
| Béres et al., 2017 [33] | miR-185 | Up | ipCD vs. C | 44 FF samples | <0.05 | 0.81 | 62.5/100 | NGS, RT-qPCR |
| | miR-223 | | | | <0.001 | 1 | 100/100 | |
| | miR-146a | — | pCD vs. pUC | | <0.01 | 0.838 | 80/76.92 | |
| | miR-142–3p | | | | <0.01 | 0.888 | 77.78/90.31 | |
| Tang et al., 2018 [48] | miR-15a | Down | CDre vs. CDac | 54 FF samples | <0.05 | — | — | RT-qPCR |

Abbreviations: AUC, area under the curve; C, control; FFPE, formalin-fixed paraffin-embedded; CDac, active Crohn's disease; CDre, Crohn's disease in remission; FF, fresh frozen tissue; ipCD, histologically intact tissue of pediatric patients with Crohn's disease; inpCD, histologically inflamed tissue of pediatric patients with Crohn's disease; NGS, next-generation sequencing; pCD, pediatric patients with Crohn's disease; pIBD, pediatric patients with inflammatory bowel disease; pUC, pediatric patients with ulcerative colitis; non-IBD, control patients without inflammation typical for IBD; RT-qPCR, real-time quantitative polymerase chain reaction.

**TABLE 2.** Serum ncRNAs With Successfully Validated Biomarker Potential for Various Aspects of Pediatric IBD

| Study | ncRNA | Change in expression (patients) | Compared groups | Number of patients, sample type | Statistical W | | | Technological platform |
|---|---|---|---|---|---|---|---|---|
| | | | | | *P*- achieved | AUC | Sensitivity/ Specificity (%) | |
| Zahm et al., 2011[49] | miR-484<br>miR-16 | Up | pCD vs. control vs. celiac | 102 blood serum samples | <0.0001 | 0.917<br>0.912 | 82.61/84.38<br>73.91/100 | TaqMan human microRNA array, RT-qPCR |
| Zahm et al., 2014[43] | miR-192<br>miR-142–3p<br>miR-21 | Up | pUC vs. control | 47 blood serum samples | 0.0045<br>0.0078<br>— | 0.757<br>0.723<br>0.718 | 79.31/77.78<br>75.86/66.67<br>75.86/66.67 | TaqMan low density array human microRNA panel, RT-qPCR |
| Heier et al., 2016[50] | miR-146a<br>miR-146b<br>miR-320<br>miR-486 | Down | pIBD pharmaco-dynamics | 19 PBMC samples | <0.05<br><0.01<br><0.01<br><0.01 | — | — | RT-qPCR |
| De Iucidibus et al., 2018[51] | miR-29c-3p | Up | pIBD pharmaco-dynamics | 10 PBMC samples | <0.01 | — | — | NGS, RT-qPCR |
| Lucafò et al., 2018[52] | GAS5 | Up | pIBD pharmaco-dynamics | 19 PBMC samples | <0.05 | — | — | RT-qPCR |

Abbreviations: AUC, area under the curve; C, control; GAS5, growth arrest-specific transcript 5; NGS, next-generation sequencing; PBMC, peripheral blood mononuclear cells; pCD, pediatric patients with Crohn's disease; pIBD, pediatric patients with inflammatory bowel disease; pUC, pediatric patients with ulcerative colitis; RT-qPCR, real-time quantitative polymerase chain reaction.

let-7 and miR-125 were downregulated specifically in adult patients, miR-101 and miR-26 in pediatric and adult patients, and miR-124 only in pediatric patients with active UC. Thus, these are potential diagnostic biomarkers depicting disease activity. Downregulation of miR-124 was due to methylation of miR-124 promoter, which provided the first evidence as to a role of epigenetic regulation in pediatric IBDs.[94] The Koukos team continued its research efforts and 2 years later published another study on pediatric IBD patients,[96] again comparing active and inactive disease vs healthy controls and adult UC patients. They discovered a 24-miRNA signature that was deregulated in colonic tissue, with miR-4284 being the most downregulated ncRNA in pediatric UC patients. Its expression was also downregulated in patients with active vs inactive UC. Further in vitro experiments showed that miR-4284 is present in colonic epithelial cells and regulates expression of C-X-C motif chemokine 5 (CXCL5) by binding to its 3′UTR. Correspondingly, CXCL5 levels are increased in pediatric patients with UC due to miR-4284 downregulation.[96] The CXCL5 is known for its expression in colonic epithelial cells, and as a facilitator of neutrophil recruitment, it is one of the major players in the development of UC.[93, 95]

In the study by Zahm et al,[97] tissue expression profiles from rectal biopsies revealed specific miRNA patterns associated with pediatric UC and CD compared with controls. Four miRNAs that were enriched in epithelial cells (miR-192, miR-194, miR-200b, and miR-375) were significantly downregulated in UC patients compared with controls. Contrarily, 4 miRNAs that were overexpressed in inflammatory cells (miR-142–3p, miR-146a, miR-21, and let-7i) were upregulated in UC patients compared with controls. Only miR-375 and miR-21 were significantly altered in pediatric CD patients in comparison with controls. In UC patients receiving the immunomodulator 6-mercaptopurine or methotrexate, significant elevation was observed of miR-375 and miR-192 compared with in UC patients not receiving immunomodulators. A single miRNA, miR-24, was differentially expressed between UC and CD patients and enabled correct classification of 84% of patients, with a sensitivity of 83% and specificity of 86%.[97]

Another study focusing on both pediatric CD and UC came from the group of Béres et al.[98] They selected for their study miR-146a, miR-122, and miR-155, which previously had been shown to play an important role in immune processes and immune-mediated diseases. MiR-146a and miR-155 levels were significantly higher in the inflamed mucosa of children with CD and UC compared with the intact mucosa.[98] Moreover, the authors demonstrated induction of miR-146a and miR-155 after treatment with TNF-α (a potent inflammatory cytokine and effective therapeutic target in IBD)—and hence, their potential involvement in TNF-α proinflammatory signaling. The same team achieved similar results when comparing expression of miR-146a, miR-155, and miR-122 in inflamed duodenal tissue of CD patients, intact duodenal tissue of CD patients, and healthy controls.[99]

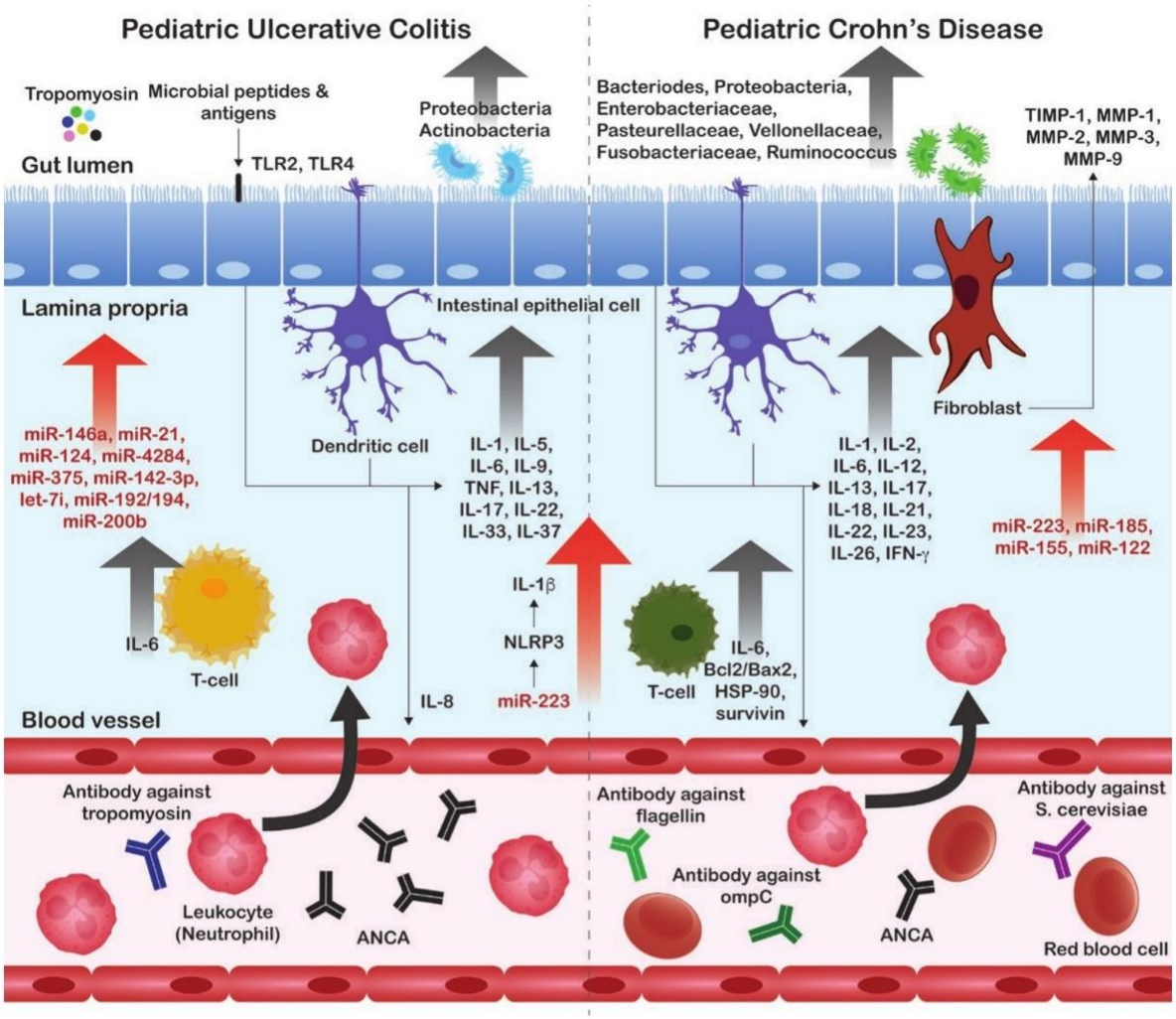


FIGURE 1. Tissue miRNAs involved in the development of pediatric IBD (modified from Park et al., 2017).[107] Abbreviations: TLR, toll-like receptor; TNF, tumor necrosis factor; ANCA, anti-neutrophil cytoplasmic antibodies; IFN, interferon; TIMP, tissue inhibitor of metalloproteinases; MMP, matrix metalloproteinase; Bcl2, B-cell lymphoma 2; BAX, BCL2 associated X; CCL, CC chemokine ligand; CCR, CC chemokine receptor; ompC, outer membrane protein C precursor.

Their follow-up publication describes the most robust biomarker study to date concerning ncRNAs in pediatric IBD patients.[89] Using small RNA sequencing of fresh-frozen tissue biopsies, the authors obtained specific miRNA profiles of CD patients with inflamed and intact histology and also those of healthy controls. The validation phase of the study by Béres et al[89] was conducted not only in CD but also in pediatric UC patients, thereby providing additional information on the discovered miRNAs. The most interesting results from a diagnostic perspective are summarized in Table 1. There was significant overlap between the miRNA expression profiles differentiating CD and UC from healthy patients (upregulation of miR-18a, miR-21, miR-31, miR-99a, miR-99b, miR-125a, miR-126, miR-142-5p, miR-146a, and miR-223 and downregulation of miR-141 and miR-204 in diseased tissue). Nevertheless, there were some miRNAs upregulated in UC compared with CD, namely miR-21, miR-31, miR-125, miR-142-3p, and miR-146a; on the other hand, the expression levels of miR-100, miR-150, and miR-185 were increased in CD patients compared with UC patients. Through combined pathway analysis of miRNAs and their target mRNAs identified in CD, those authors revealed a strong association of these miRNAs and mRNAs with

inflammation, fibrosis, and response to microbiome, in addition to immune and inflammatory response. Five miRNAs differentially expressed in UC patients (miR-20a, miR-126, miR-141, miR-142, and miR-223) were connected to the ABCG2 and ABCB1 efflux transport proteins important in intestinal barrier protection against external stimuli.[89]

It seems that some of these miRNAs are probably not specific for pediatric IBD patients but more likely are important for IBD in general or inflammation as such. Similar profiles have been detected in studies performed on samples from adult IBD patients,[90] and some miRNAs are well-known players in inflammatory processes (eg, miR-146a, miR-155, and miR-21),[100] regardless of whether these are in adult or pediatric patients.

However, there are some examples showing just the opposite. Particularly noteworthy is that miR-223, identified in the Béres study as one of the most significantly upregulated miRNAs in UC and CD (in both inflamed and intact tissue),[89] has been described in adult IBD as a negative regulator of inflammation.[101] Results from Neudecker et al relating to adult IBD patients and an animal model showed that overexpression of miR-223 can attenuate inflammation. Moreover, they observed the release of proinflammatory cytokines and chemokines in myeloid-derived cells through the miR-223–NOD-like receptor 3 (NLRP3)–interleukin-1β (IL-1β) regulatory circuit as a critical component of intestinal inflammation and homeostasis.[101] MiR-223 is probably one of the examples indicating the differences between the underlying IBD pathogenesis in adult and pediatric patients.

The most recent work from Tang et al[102] was focused on miR-15 as a regulator of Cdc4, a potent regulator of the cell cycle. The miR-15 level was quantified in 33 pediatric IBD patients and 21 controls, and moderate increase in miR-15 expression was observed in CD patients. Unfortunately, the variability of miR-15 expression was too high, thus precluding its use as a reliable biomarker of CD. Testing for potential correlation between miR-15 expression and PCDAI score also was unsuccessful.[102]

## NONCODING RNAs IN BODILY FLUIDS OF PEDIATRIC IBD PATIENTS

Concerning ncRNAs in bodily fluids (Table 2), Zahm et al provided initial promising findings.[97, 103] In their early work, these authors revealed that levels of miR-484 and miR-16 were significantly deregulated in blood serum of CD patients compared with healthy controls. Clinical testing achieved 83% sensitivity and 84% specificity for miR-484 and 74% sensitivity and 100% specificity for miR-16; these levels are indisputably higher than those for such laboratory markers currently used, such as C-reactive protein or anti-*Saccharomyces cerevisiae* antibody.[103] In addition to the tissue miRNA profiles from rectal biopsies of pediatric UC and CD patients described previously, they identified in their further work miRNA biomarkers in blood serum. Circulating miR-192, miR-142-3p, and miR-21 were confirmed to be elevated in both UC and CD samples relative to controls, and they correctly classified 79%, 72%, and 72% of IBD patients, respectively. In patients from whom both serum and rectum miRNAs were measured, circulating miRNA levels did not correlate with those of the tissue. There were also no differences in circulating miRNAs that would enable differentiating between CD and UC patients.[97]

Heier et al performed expression profiling of 24 circulating miRNAs involved in inflammation or steroid response to examine their responsiveness to anti-inflammatory treatments (eg, prednisone, infliximab).[104] They identified that 3 miRNAs (miR-146a, miR-146b, and miR-320a) known to be induced by inflammatory signaling were responsive to—or downregulated by—both drugs. A fourth miRNA, miR-486, showed a significant change in response to prednisone but not to infliximab. Together, measuring levels of these miRNAs could potentially help in assessing inflammatory disease and therapeutic response.[104] A similar study evaluated differentially expressed miRNAs during glucocorticoid treatment in blood cells (specifically peripheral blood mononuclear cells [PBMCs]) of pediatric patients with IBD (8 UC, 2 CD) enrolled at diagnosis and followed for the first weeks of steroid therapy.[105] Peripheral blood was obtained at diagnosis (T0) and after 4 weeks of prednisone treatment (T4). Among the 18 miRNAs differentially expressed from T0 to T4, 16 were upregulated and 2 were downregulated. Three miRNAs (miR-144, miR-142, and miR-96) could putatively recognize the 3′UTR of the glucocorticoid receptor gene, and 3 miRNAs (miR-363, miR-96, miR-142) contained glucocorticoid responsive element sequences, thereby potentially enabling direct regulation by the glucocorticoid receptor.[105]

The only study in pediatric IBD patients focusing on lncRNAs thus far was related to glucocorticoid therapy response and GAS5 levels in PBMCs. Clinical activity was assessed using the Pediatric Crohn's Disease Activity Index (PCDAI) for patients with CD and the Pediatric Ulcerative Colitis Activity Index (PUCAI) for patients with UC. Clinical remission was defined as PCDAI <10 or PUCAI <10, whereas clinical improvement was defined as a reduction of at least 15 points from the baseline score for PCDAI and at least 20 points from baseline for PUCAI.[106] Growth arrest-specific 5 levels were measured in PBMCs of 19 pediatric IBD patients at diagnosis and after the first cycle of glucocorticoids. This demonstrated upregulation of the lncRNA in patients with unfavorable steroid response, indicating that GAS5 can be considered a novel pharmacogenomic marker useful for personalizing glucocorticoid therapy.[106]

## CONCLUSION AND FUTURE PERSPECTIVES

Not many studies to date have been focused on ncRNAs in pediatric IBD patients, very little knowledge exists as to the underlying biology of miRNAs involved in pediatric IBD patients (Fig. 1),[107] and the current descriptive observations are

often derived by extrapolation of discoveries from adult IBD experimental studies. Existing results show promise, however, as there is significant overlap in miRNA profiles across independent studies. Specifically, miR-146a, miR-142-3p, and miR-223 seem to be emerging as potential noninvasive biomarkers of pediatric IBD in the near future. Some of these miRNAs are specific for pediatric IBDs when compared with adult counterparts. There also are miRNA biomarkers (eg, miR-24), enabling accurate differentiation between UC and CD cases and tissue miRNA expression changes reflecting successful glucocorticoid treatment. In bodily fluids, miRNAs have been observed to differ by their levels in blood serum of IBD patients and controls. In PBMCs, miRNAs and lncRNA GAS5 have been shown responsive to the anti-inflammatory agents prednisone and infliximab. A variety of study designs are found in the current literature, however. These need to be unified and include independent validation cohorts of patients to provide solid and more convincing results. Also, high-throughput technologies for ncRNA profiling are not as common, and a majority of the studies are based on preselected groups of ncRNA candidates. A higher level of methodological standardization is necessary also to develop reliable clinical-level biomarkers.

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**Příloha 3** - Small bowel adenocarcinoma diagnosed by capsule endoscopy in a patient with celiac disease: a case report and review of literature



# Small bowel adenocarcinoma diagnosed by video capsule endoscopy in a patient with celiac disease: a case report and review of literature

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Celiac disease is an immune mediated entheropathy triggered by gluten in genetically predisposed individuals. Patients with celiac disease are at a higher risk of gastrointestinal malignancies. Diagnosis at an advance stage is one of the factors of an unfavorable prognosis of these complications. Our patient is a woman who was diagnosed with celiac disease at 53 years of age. After two years on a gluten-free diet she developed sideropenic anemia. No source of bleeding was found on the esophagogastroduodenoscopy or colonoscopy. Video capsule endoscopy revealed exulcerated bleeding stenosis in the jejunum, in front of which the capsule lodged. There were no signs of infiltration on simultaneous CT enterography. The patient was operated on and the infiltration of the jejunum was resected. The specimen was evaluated by a histopathologist as a moderately differentiated adenocarcinoma. Due to the risk factors, the patient received adjuvant chemotherapy. The knowledge of the malignant complications of celiac disease, their risk factors and the possibilities of modern enteroscopic methods could help in the early diagnosis and improvement of the prognosis of these diseases. Due to a lack of data and an absence of guidelines, treatment of a small bowel adenocarcinoma is based on an expert agreement and guidelines for colon cancer. Surgical treatment is the only potentially curative option. For stage II with risk factors and stage III adjuvant chemotherapy should be considered.

**Key words:** adenocarcinoma, video capsule endoscopy, celiac disease, small bowel, surgery.

## Adenokarcinom tenkého střeva diagnostikovaný pomocí video kapslové endoskopie u pacientky s celiakií: kazuistika a přehled literatury

Celiakie je imunitně zprostředkovaná enteropatie, rozvíjející se při požití lepku u geneticky predisponovaných osob. Je spojena se zvýšeným rizikem rozvoje malignit trávicího traktu. Tyto komplikace jsou většinou diagnostikovány v pozdním stádiu, což je jedním z faktorů jejich nepříznivé prognózy. Naše kazuistika se týká ženy, jíž byla celiakie diagnostikována v 53 letech. Po 2 letech se u ní náhle rozvinula sideropenická anémie. Esofagogastroduodenoskopie ani kolonoskopie neprokázala krvácení do gastrointestinálnho traktu. Video kapslová endoskopie odhalila exulcerovanou stenózu v jejunu se známkami krvácení, před kterou kapsle retinovala. Na simultánně provedené CT enterografii nebyla infiltrace patrná. Byla provedena operační revize s resekcí infiltrace jejuna. Histologicky byl prokázán adenokarcinom tenkého střeva, vzhledem k rizikovým

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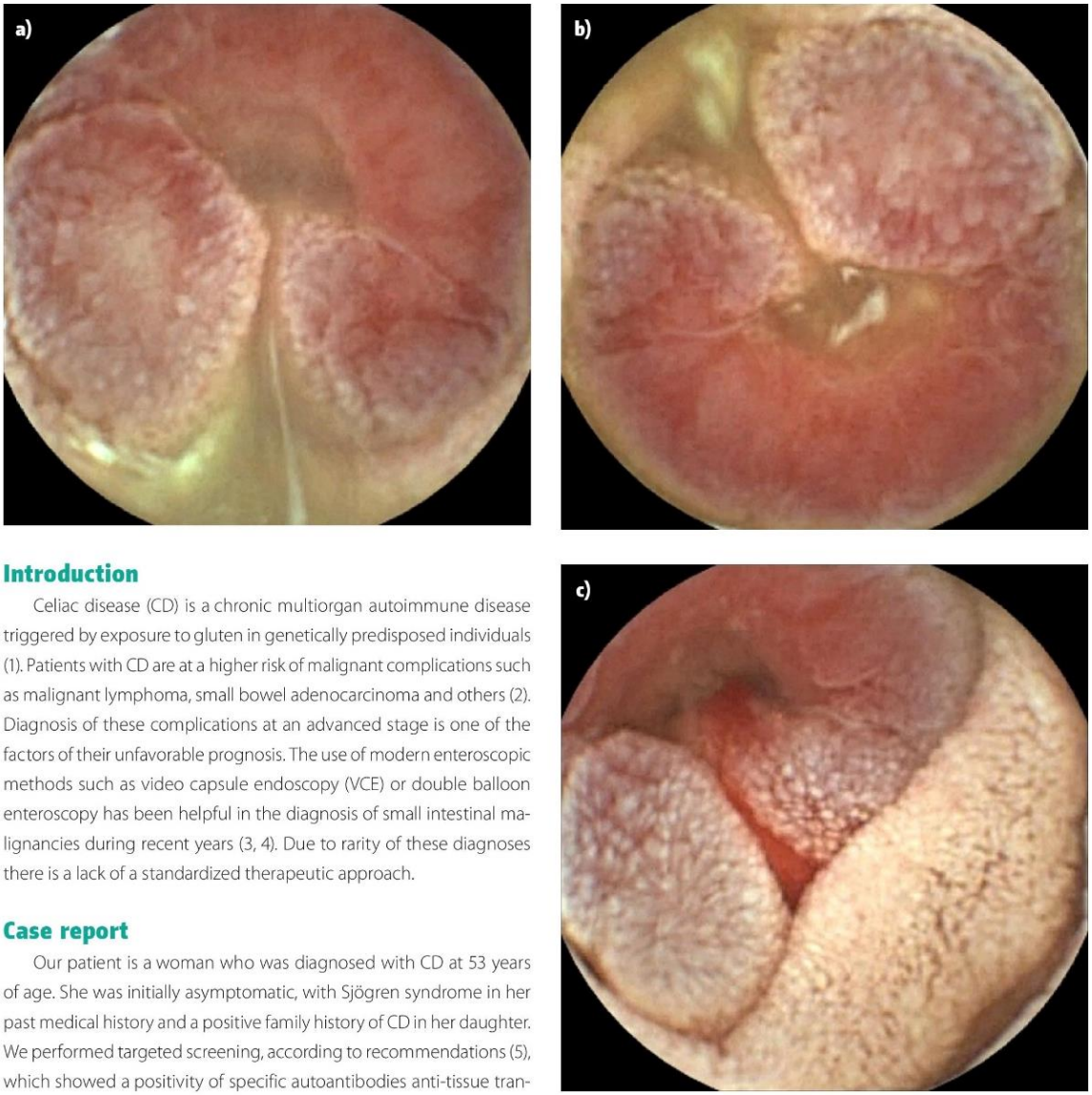
faktorům byla zahájena adjuvantní chemoterapie. Znalost maligních komplikací celiakie, jejich rizikových faktorů a možnosti využití moderních enteroskopických metod může přispět k časné diagnostice a zlepšení prognózy těchto onemocnění. Vzhledem k nedostatku dat a absenci doporučených postupů se léčba adenokarcinomu tenkého střeva řídí názory expertů a doporučenými postupy léčby kolorektálního karcinomu. Chirurgická resekce je jediná potenciálně kurativní léčba. U stádia II s rizikovými faktory a stádia III by měla být zvážena adjuvantní chemoterapie.

**Klíčová slova:** adenokarcinom, celiakie, chirurgie, video kapslová endoskopie, tenké střevo.

**Fig. 1.** *VCE showing malignant tumor of the small bowel (a, b), with apparent bleeding (c)*




## Introduction

Celiac disease (CD) is a chronic multiorgan autoimmune disease triggered by exposure to gluten in genetically predisposed individuals (1). Patients with CD are at a higher risk of malignant complications such as malignant lymphoma, small bowel adenocarcinoma and others (2). Diagnosis of these complications at an advanced stage is one of the factors of their unfavorable prognosis. The use of modern enteroscopic methods such as video capsule endoscopy (VCE) or double balloon enteroscopy has been helpful in the diagnosis of small intestinal malignancies during recent years (3, 4). Due to rarity of these diagnoses there is a lack of a standardized therapeutic approach.

## Case report

Our patient is a woman who was diagnosed with CD at 53 years of age. She was initially asymptomatic, with Sjögren syndrome in her past medical history and a positive family history of CD in her daughter. We performed targeted screening, according to recommendations (5), which showed a positivity of specific autoantibodies anti-tissue transglutaminase (anti-TTG) in IgA and anti-deaminated gliadin peptides (anti-DGP) in IgA and IgG. A biopsy of the distal duodenum showed villous atrophy Marsh 3b according to the Marsh-Oberhuber classification. No anemia was detected at the time of the diagnosis of CD (hemoglobin 125 g/L, MCV 88 fL, ferritin 41.4 µg/L). The patient started a strict gluten-free diet and was in stable condition, without any signs of malnutrition during the follow-up visits. Anti-TTG IgA and anti-DGP IgA decreased to normal levels in seven months with a slight persistent positivity of anti-DGP IgG.

After two years on a gluten-free diet the patient started to suffer from artralgies, for which prednisolone, hydroxychloroquine and non-steroid-anti-inflammatory drugs were prescribed. She experienced slight intermittent epigastric pain and one episode of black stool.

Moderate anemia (hemoglobin 97 g/L, MCV 84 fL, ferritin 22.1 µg/L) was detected on a follow-up visit to rheumatology. We performed an esophagogastroduodenoscopy and colonoscopy in search of bleeding with physiological findings. In accordance with ESGE guidelines (6) VCE was scheduled, an additional push enteroscopy (as required before VCE by the insurance company in our region) with biopsy showed stable findings without villous atrophy (Marsh 1, $CD3^+$ $CD8^-$ as shown by immunohistochemistry). The VCE revealed exulcerated, stenotized infiltration of the small bowel, with signs of bleeding (Fig. 1a, 1b), in front of which the capsule lodged. The capsule was visualized on an abdominal x-ray (Fig. 2). No infiltration was evident on a simultaneously performed CT enterography, only the position of the lodged capsule indicated the site of stenosis (Fig. 3). The patient was operated upon with a finding of infiltration of the jejunum at the mesenterial site, with bilateral lymphadenopathy. A resection of 60 cm of the jejunum (Fig. 4) with side-to-side anastomosis was performed. The patient was discharged 7 days after surgery without any postoperative complications. The specimen was evaluated by a histopathologist as moderately differentiated adenocarcinoma (Grade 2), with angioinvasion and a positive lymph node (1/13), R0 resection, pT3N1M0 (Fig. 5). The patient received adjuvant chemotherapy XELOX (capecitabine plus oxaliplatin) due to risk factors (positive lymph node and angioinvasion).

**Fig. 2.** *A visible capsule on the abdominal x-ray*

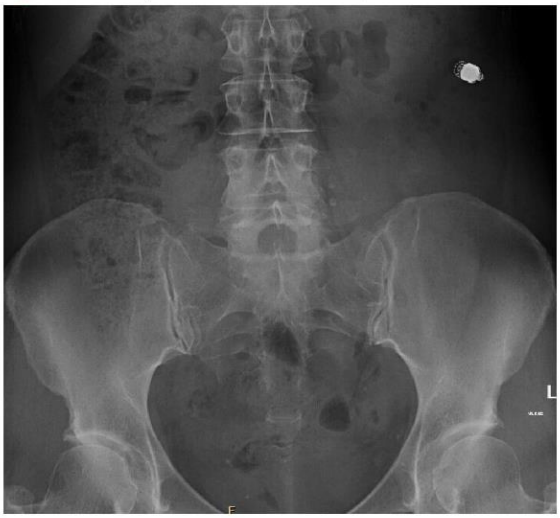
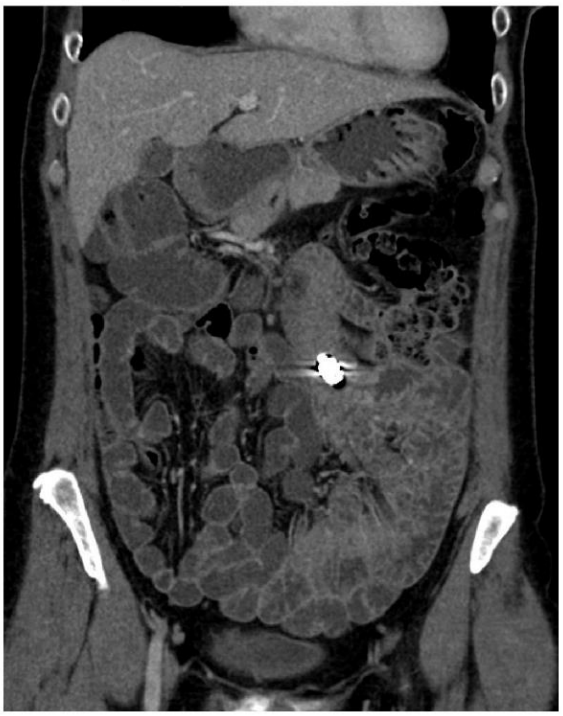


**Fig. 3.** *CT enterography (coronal scan) – VCE lodged in the jejunum with no evident CT signs of tumor infiltration*



## Discussion

Malignant tumors of the small bowel represent only 1–3% of gastrointestinal malignancies. Adenocarcinomas are the most frequent finding (35–50%) followed by carcinoid tumors (30%), lymphomas (15%) and gastrointestinal stromal tumors other than sarcomas (10%) (7–9). Nevertheless, patients with CD are at an increased risk of some of these malignancies. Studies investigating the risk of development of carcinoma in patients with CD bring very different results, ranging from a 10-fold increased risk (2) to an 82.6-fold increased risk (7). Although the relative risk of lymphoma dramatically decreases after one year of gluten-free diet (RR 157.6 to 12.7), the decrease in cases of carcinoma is not so expressed (RR 38.0 to 6.4) and the p-value for the trend doesn't reach statistical significance (10).

Diagnosis of CD at an advanced age, untreated CD and possibly also persisting villous atrophy and male gender were described as risk factors of malignant complication development in celiac patients (11–14), but the number of patients in studies is usually small and the results aren't uniform. Our patient was diagnosed with CD at the age of 53 years. Due to the lack of symptoms it is possible that CD was undiagnosed and untreated for a long time in our patient, highlighting the importance of family screening in such cases. A high turnover of the inflammatory population with mucosal lymphocyte infiltration, an increased permeability to oncogenic factors, a malabsorption of protective substances such as vitamins A and E, or an impaired immune surveillance are considered as pathogenetic mechanisms of cancerogenesis in these settings (14). Another question is the course of development of the carcinoma. A majority of opinions lean toward adenoma-carcinoma evolution sequence (15, 16), but there are some studies which question this approach, providing cases suggestive of dysplasia development in the flat mucosa (3). In contrast to small bowel adenocarcinoma in general, where the duodenum is affected most frequently, carcinomas tend to develop in the jejunum in most cases of CD patients, which corresponds with our case. Vomiting, anemia, weight loss, intestinal bleeding, abdominal mass, and perforation are the most frequent symptoms (17). Unfortunately, a diagnosis is usually made in the advanced stages of the disease (74% in stage III-IV) (14). In most cases the carcinoma isn't accessible to esophagogastroduodenoscopy. CT or MR enterography and PET/CT are used

**Fig. 4.** *Peroperative view of infiltration of jejunum (red arrow) with the lodged capsule which was extracted by enterotomy (green arrow)*

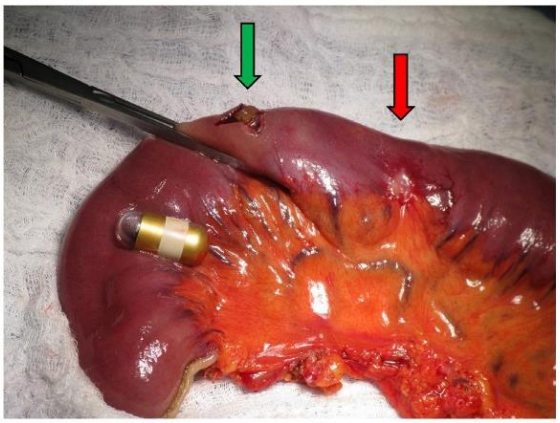
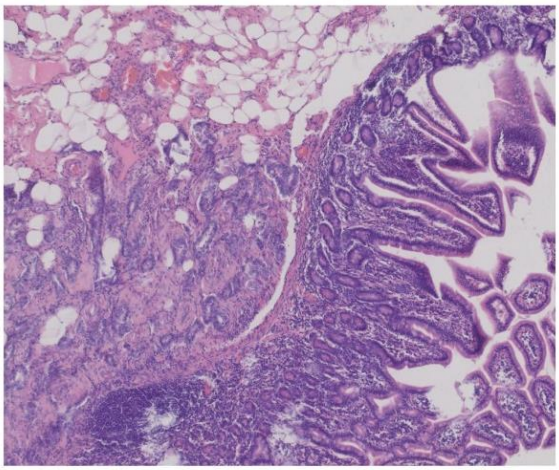


**Fig. 5.** *Histological section: invasive adenocarcinoma infiltrating submucosal tissue, spreading under small intestine epithelium, HE staining, 100×*



in the diagnostic approach. The availability of VCE and device assisted enteroscopy could help in early diagnosis. In our case VCE was the only examination which revealed the infiltration of the jejunum, when even the CT enterography was negative. However, a recent study showed that the diagnostic implementation of new techniques did not yield a significant advantage in terms of an early diagnosis and better outcome, but there is a need for further investigation (18). Due to a lack of data and an absence of guidelines, treatment of a small bowel adenocarcinoma is based on expert agreement and guidelines for colon cancer. A prospective phase III clinical trial PRODIGE 33-BALLAD comparing adjuvant chemotherapy vs observation among patients with small bowel adenocarcinoma with stage I-III is still ongoing. Surgical treatment is the only potentially curative option. However, 40% of patients have a relapse after primary tumor resection. The main prognostic factors are lymph node invasion and localization, with duodenal tumors having a worse prognosis. Five-year survival in cases of lymph node invasion is poor (28–32%) (19–21). For stage II with risk factors (pT4) and stage III (N+) adjuvant chemotherapy should be considered. Regimens are based on fluoropyrimidine in combination with oxaliplatin (22).

## Conclusion

We presented the case of a woman who was diagnosed with atypical CD at the age of 53 years. The disease was complicated by small bowel adenocarcinoma, which was detected by VCE. The patient underwent surgical resection and received adjuvant chemotherapy. The knowledge of the risk factors of CD, malignant complications and the use of modern enteroscopic methods could improve the outcomes of these patients in the future.

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**Příloha 4** - Multiple neuroendocrine tumor of the small bowel: a case report and a review of literature



# Multiple neuroendocrine tumor of the small bowel: a case report and a review of literature

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**Summary**
Primary malignant tumors of small bowel constitute only about 1–2% of all gastrointestinal neoplasms. Although neuroendocrine tumors (NETs) are relatively rare, they still represent the second most common malignancy of the small bowel (after adenocarcinoma). Clinical manifestations include abdominal pain, bowel obstruction, diarrhea, weight loss and bleeding. The differential diagnosis of obscure gastrointestinal bleeding can sometimes be challenging for endoscopy as well as for radiology methods. We present the case of an 80-year-old man suffering from severe hypochromic anemia. Routine endoscopic methods did not show any appropriate pathology. Finally, a single ulcerative infiltration of the ileum was diagnosed by capsule endoscopy (CE). CT enterography did not reveal any other lesions. In accordance with a positive chromogranin A, endoscopic and radiologic methods, a suspicion of NET was expressed. During the surgery, 7 lesions were found and a resection of 120 cm of ileum was performed. The histology confirmed a diagnosis of NET grade 1, with a total number of 15 NET lesions in the specimen. The following octreotide scan did not show any residual infiltration. We present a patient with 15 NET lesions in the ileum diagnosed by CE and successfully cured by surgical resection of the ileum.

**Key words:** capsule endoscopy – carcinoid syndrome – gastrointestinal carcinoids – neuroendocrine tumor – obscure gastrointestinal bleeding – small bowel – surgery

## Mnohočetné postižení tenkého střeva neuroendokrinním tumorem: kazuistika a přehled literatury

**Souhrn**
Maligní tumory tenkého střeva tvoří jen asi 1–2 % ze všech nádorů gastrointestinálního traktu. Ačkoli neuroendokrinní tumory (NETs) jsou relativně vzácné, tak i přesto představují druhou nejčastější malignitu tenkého střeva (hned po adenokarcinomu). Klinicky se projevují bolestí břicha, střevní obstrukcí, průjmy, úbytkem na váze či krvácením. Diferenciální diagnostika skrytého gastrointestinálního krvácení může být někdy výzvou jak pro metody endoskopické, tak radiologické. Prezentujeme případ 80letého pacienta došetřovaného pro těžkou mikrocytární anémii. Základní endoskopické metody neobjasnily zdroj skrytého krvácení. Nakonec pomocí kapslové endoskopie (CE) byla diagnostikována izolovaná ulcerace ilea s navalitými okraji. CT enterografie nezachytila žádnou další lézi. Vzhledem k pozitivním hodnotám chromograninu A, nálezu na endoskopických a zobrazovacích metodách bylo vysloveno podezření na NET tenkého střeva. Během operace bylo zjištěno 7 ložisek NET tenkého střeva a byla provedena resekce 120 cm ilea. Dle definitivní histologie bylo v preparátu nalezeno celkem 15 ložisek NET grade 1. Kontrolní octreoscan neodhalil žádné další reziduální ložisko. Představujeme případ pacienta s celkem 15 ložisky NET tenkého střeva diagnostikovaného pomocí CE s následnou úspěšnou resekcí ilea.

**Klíčová slova:** gastrointestinální karcinoid – chirurgie – kapslová endoskopie – karcinoidový syndrom – neuroendokrinní tumor – skryté krvácení do gastrointestinálního traktu – tenké střevo

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## Introduction

Primary small bowel malignant tumours comprise only 1–2% of all gastrointestinal neoplasms. Neuroendocrine tumours (NETs) represent a relatively rare subgroup of malignant neoplasms. Despite this fact, NETs are the second most common malignant tumours of the small bowel [1–3]. NET can be often asymptomatic for a long time, sometimes can present with obscure gastrointestinal bleeding (OGIT) and the diagnostics can be challenging as for endoscopic as well as radiologic tools [4–7]. An increase of small bowel NETs incidence has been reported recently, not due to a real incidence rise but rather due to better diagnostic methods [6,8,9].

## Case report

Our patient is an 80-year-old polymorbid man investigated for a severe anemia (hemoglobin level of 53 g/L). His case history includes chronic ischemic heart disease, heart attack, aortic valve replacement, cardiac rhythm disturbances, diabetes mellitus and prostatectomy for adenocarcinoma.

Esophagogastroduodenoscopy revealed just a mild erosive gastropathy. During colonoscopy, only diverticulosis of the sigmoid colon was diagnosed, and four small polyps were removed by endoscopic polypectomy (tubular adenomas).

Due to persistent anemia, the patient underwent enteroscopy, where no significant pathology was discovered. Subsequently, capsule endoscopy (CE) was performed, finding a 12 × 6 mm isolated ulceration in the ileum, with thickened edges giving the impression of an exulcerated submucosal formation of 2 cm in total (fig. 1a, 1b).

Due to the positive values of chromogranin A (207.3 µg/L, reference range < 50) and the findings of endoscopic and imaging methods – CT enterography (fig. 2a, 2b),

**Fig. 1a, 1b. CE showing an ulceration with thickened edges of 2 cm in size**

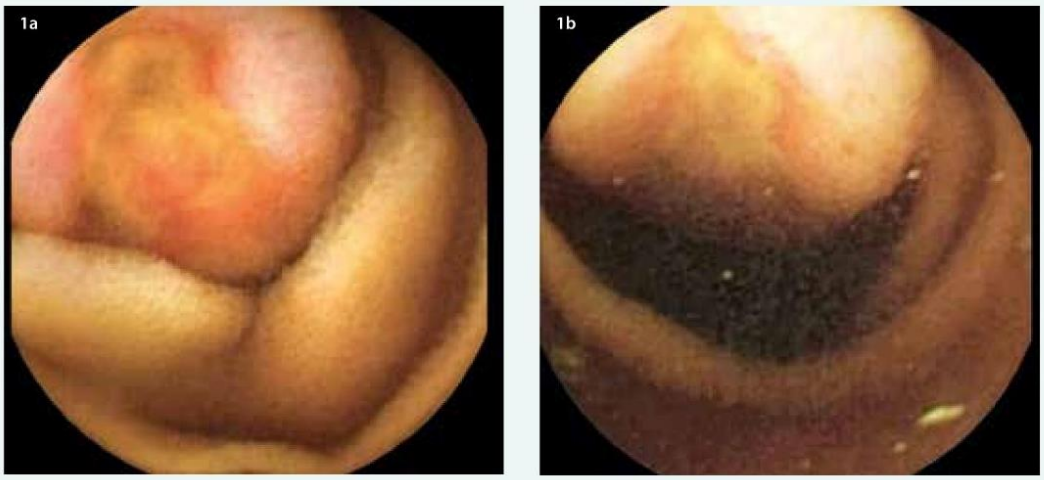
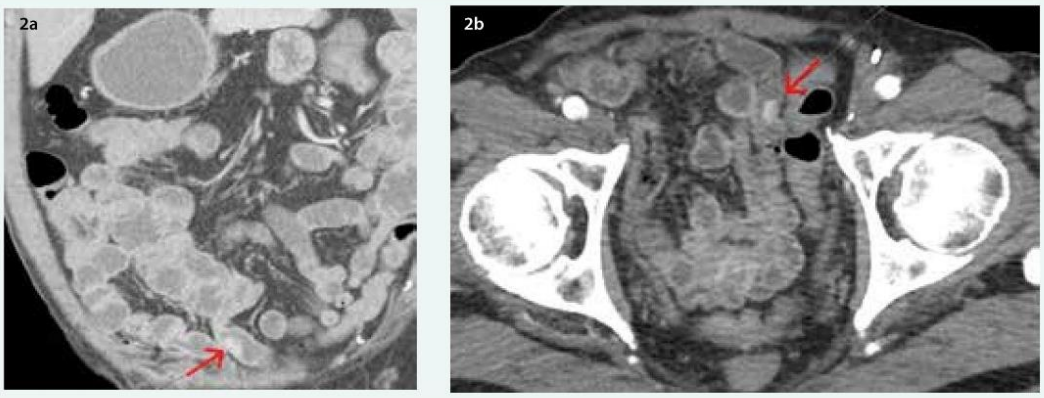



**Fig. 2a, 2b. Contrast enhanced CT: a** (coronal scan) and **b** (transversal scan) **hypervascularised lesion on ileal bowel loop** (red arrow)



we expressed a suspicion of a NET of the small intestine. During surgery (fig. 3), seven suspect rigid small intestine lesions were palpably detected, and a resection of 120 cm of the ileum was performed. According to definitive histology (fig. 4, 5, 6a, 6b), a total of 15 NET grade 1 lesions with the predominance of submucosa and muscularis propria (T3) were found. Metastases were present in 6 regional lymph nodes (total 12 examined lymph nodes). In the postoperative period, a following octreotide scan was performed without residual lesion finding. From an oncological point of view, only observation without subsequent adjuvant oncological treatment will be introduced.

**Fig. 3. Peroperative view of 2 round-shaped lesions**

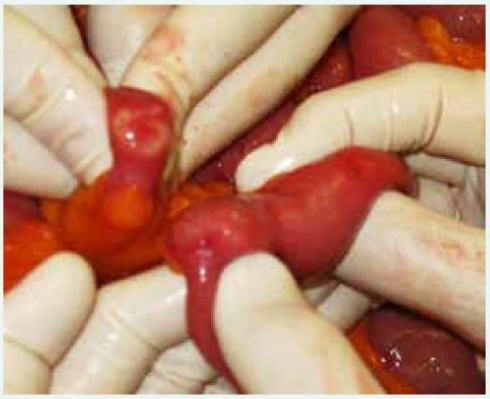
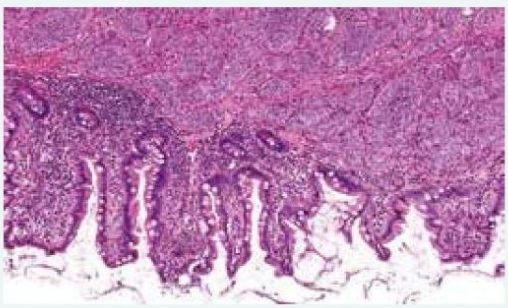


**Fig. 4. Specimen of ileum after fixation in formaldehyde.** Lesions of NET marked by arrows

**Fig. 5. Histological section: NET infiltrating submucosa of the small bowel wall,** HE staining, 200×



## Discussion

NETs located in the duodenum up to 1cm in size can be treated endoscopically and are mostly isolated lesions [10,11]. On the other hand, surgical treatment is recommended for NETs in the jejunoileum. They have a greater propensity to metastasize and NETs in this localization can even form more lesions [2,6,8]. Multiple lesions may be found in up to 40% of cases [8]. Small bowel NETs may initially behave asymptomatically, and even small tumors under 1 cm tend to form lymph node metastases relatively early (in 20–30% of cases). For NETs larger than 2 cm, the risk of metastatic involvement of regional lymph nodes increases to over 80%. With primary tumor size up to 2 cm, the incidence of liver metastases is reported in up to 20% of patients (for sizes greater than 2 cm in more than 40% of patients) [1,5]. The carcinoid syndrome, which occurs in 20–30% of pa-

**Fig. 6a. Histological section: Solid, insular masses of monotonous small round cells positive for chromogranin,** immunohistochemical staining, 200×

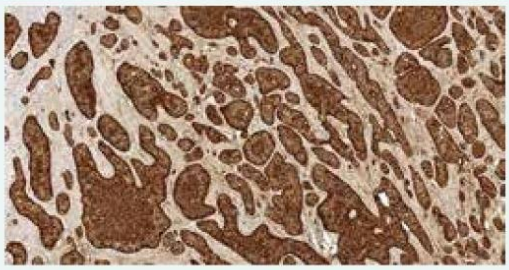
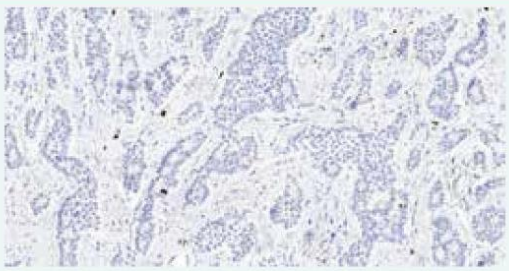


**Fig. 6b. Histological section: Proliferation Ki67 index is less than 2%, 1 mitoses/10 high-power fields,** immunohistochemical staining, 200×



tients with a NET of the small intestine, is almost always (around 95%) associated with the presence of liver metastases [4,6,8].

When diagnosing NETs, their tendency to extraluminal proliferation may be problematic. This was the case with our patient, most of whose lesions tended to infiltrate submucosa and muscularis propria. In the diagnosis of small intestine tumors, CE, double-ballon enteroscopy and CT enterography are usually compared. In comparative studies of these methods in the diagnosis of small intestine tumors, the yield appears to be similar (although in case of NETs, CE has slightly better results) [8,12–15].

On the other hand, a certain disadvantage of CE in the diagnosis of NETs may be their tendency toward extraluminal spreading [5]. The combination of these 3 methods in the diagnosis of OGIB and small intestine tumors [15–19] seems to be ideal. In our case, only one lesion was identically visible on CE and CT enterography. Other lesions were detected by palpation during surgery and from the definitive histology. The following octreotide scan did not reveal any other residual lesions. Therefore there is no indication of systemic treatment.

Even if in our patient one lesion of 2 cm in size and another 14 lesions occurred ranging in size from 0.5 cm to 2 cm, the carcinoide syndrome or liver metastasis were not present. Only positive regional lymph nodes metastases were evaluated in the specimen. There are no data for the adjuvant treatment.

5-year survival rate in patients with NET and the regional lymph node involvement reaches 70–90% after curative surgery with lymphadenectomy [1,4,20].

## Conclusion

We present an 80-year-old man with OGIB. In our rare case, a patient with 15 lesions of NET in the ileum was diagnosed by CE and successfully cured by surgical resection of the ileum.

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**Příloha 5** - Gastric antral vascular ectasia and solitary rectal ulcer syndrome - two rare diagnoses as the cause of anemia in a single patient: case report



# Gastric antral vascular ectasia and solitary rectal ulcer syndrome – two rare diagnoses as the cause of anemia in a single patient: case report

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**Summary**
Gastric antral vascular ectasia (GAVE) and solitary rectal ulcer syndrome (SRUS) are both mentioned in the literature as rare causes of iron deficiency anemia and gastrointestinal (GI) bleeding. GAVE accounts for up to 4 % of upper non-variceal GI bleeding; SRUS is a rare benign disorder that presents with rectal bleeding. We present the case of a 75-year-old patient who was admitted to our facility with anemia. In the same patient, we encountered chronic bleeding from GAVE and SRUS. Both diagnoses were treated endoscopically: GAVE by argon plasma coagulation and a subsequent treatment with proton pump inhibitors and SRUS by adrenaline injection and clipping, consecutively treated with mesalazine enemas. The patient was successfully cured, resulting in a stable level of hemoglobin and no recurrent GI bleeding. We report a unique case of chronic GI bleeding caused by two uncommon diagnoses. The co-occurrence of GAVE and SRUS has not been previously described or published.

**Key words**: anemia – endoscopy – gastric antral vascular ectasia (GAVE) – gastrointestinal bleeding – solitary rectal ulcer syndrome (SRUS)

## Cévní ektázie žaludečního antra a syndrom solitárního rektálního vředu – dvě vzácné diagnózy jako příčina anémie u téhož pacienta: kazuistika

**Souhrn**
Cévní ektázie žaludečního antra (gastric antral vascular ectasia – GAVE) a syndrom solitárního rektálního vředu (solitary rectal ulcer syndrome – SRUS) jsou uváděny v literatuře jako vzácné příčiny způsobující anémii z nedostatku železa a krvácení do gastrointestinálního traktu (GIT). GAVE může způsobovat nevarikózní krvácení z horního GIT do 4 %. V případě SRUS se jedná o vzácné benigní onemocnění, které se nejčastěji projevuje krvácením z konečníku. Prezentujeme případ 75letého pacienta, který byl přijat na naši kliniku pro anémii. U stejného pacienta jsme diagnostikovali chronické krvácení z GAVE a SRUS. Oba nálezy byly ošetřeny endoskopicky: GAVE pomocí argon plazma koagulace s následnou léčbou inhibitory protonových pump a SRUS opichem adrenalinovou injekcí a naložením klipu, poté následovala lokální léčba mesalazinovými klyzmaty. Pacient byl takto úspěšně vyléčen, s výsledným stabilním hemoglobinem a bez dalších známek krvácení do GIT. Prezentujeme ojedinělý případ pacienta s chronickou anémií, jež byla způsobena koincidencí dvou vzácných onemocnění. Koincidence GAVE a SRUS nebyla zatím v literatuře publikována.

**Klíčová slova**: anémie – cévní ektázie žaludečního antra – endoskopie – gastrointestinální krvácení – syndrom solitárního rektálního vředu

## Introduction

**Gastric antral vascular ectasia (GAVE)** is a rare cause of upper gastrointestinal (GI) bleeding. The etiology is still unclear, although there are some theories, including mechanical stress and excess of vasoactive instances [1–3]. GAVE is reported to be the cause up to 4 % of upper non-variceal bleeding [2,3]. This disorder is often linked with other chronic diseases such as autoimmune connective tissue diseases or in 30 % of the patients with liver cirrhosis [3,4]. GAVE has a characteristic endoscopic appear-

ance of linear, red stripes radiating toward the pylorus [5]. A punctate form has also been described, which appears more commonly in patients with liver cirrhosis [6].

**Solitary rectal ulcer syndrome (SRUS)** is also described as an infrequent benign entity that can cause iron deficiency anemia and whose symptoms usually include rectal bleeding. SRUS is often linked with a defecation disorder [7,8]. Its etiology is unknown; it is mostly reported with chronic mucosal and hypoperfusion induced ischemic injury to the rectal mucosa. SRUS is associated with a paradoxical contraction of the pelvic floor, leading to a mucosal prolapse and a pressure necrosis of the rectal mucosa [7]. Endoscopic findings of SRUS can imitate diseases such as inflammatory bowel diseases and neoplasms [7]. Symptoms of SRUS include rectal bleeding, mucus discharge from the rectum, straining during defecation, constipation, rectal prolapse, and lower abdominal pain [7–9].

**Fig. 1A. Characteristic endoscopic view of GAVE stripes in the antrum creating a watermelon stomach**

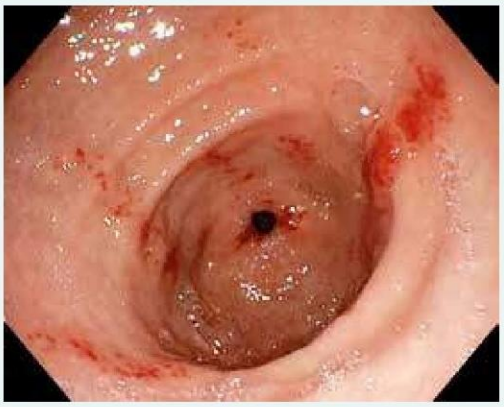
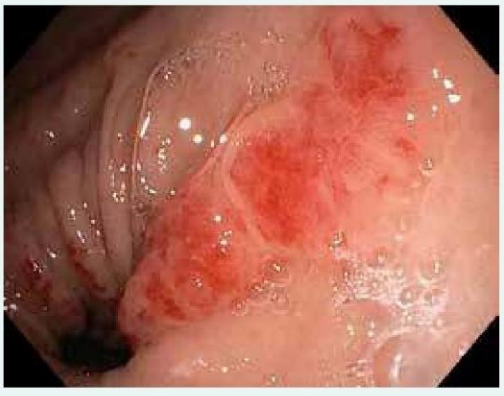


**Fig. 1B. Detail of one of the GAVE stripes with dilated blood vessels**



## Case report

Our patient is a 75-year-old polymorbid man whose case history includes hypertension, diabetes mellitus, dyslipidemia, hyperuricemia, atrial fibrillation for which he was taking anticoagulants, chronic ischemic heart disease, hemorrhoids, diverticulosis of the sigmoid colon, and gastroduodenal ulcer disease. The patient had a history of constipation and occasional episodes of rectal bleeding.

The patient was admitted to our ward for severe sideropenic anemia, with a hemoglobin level of 64 g/L. Dysphagia, vomiting, hematemesis, and melena were not present at the time of admission. The patient was hemodynamically stable. Two blood transfusions were given with no suitable hemoglobin elevation. Esophagogastroduodenoscopy (EGD) and colonoscopy were planned to exclude GI bleeding. EGD showed characteristic findings of GAVE (fig. 1A, 1B), with no signs of acute bleeding. Treatment with argon plasma coagulation (APC) was chosen (fig. 1C) and followed with proton pump inhibitor medication. Diagnosis of GAVE was proved histologically (fig. 2). There was a sudden occurrence of enterorrhagia after a few days, and a colonoscopy was performed; the colonoscopy detected a rectal ulcer 13 cm from the

**Fig. 1C. Endoscopic view after APC treatment**

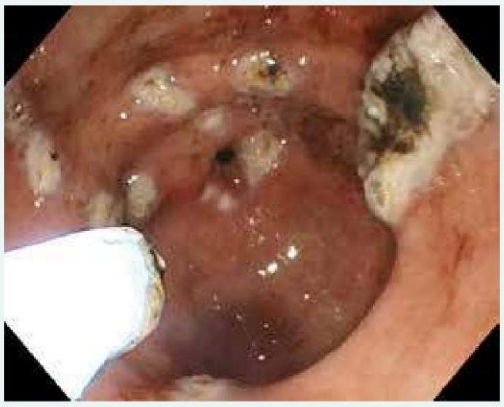
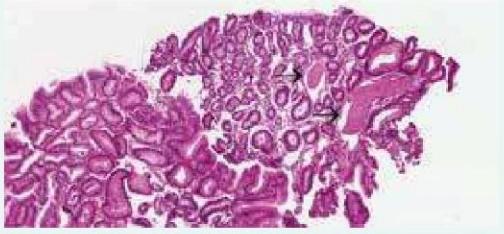


**Fig 2. Gastric antral biopsy:** biopsy showed dilated capillaries (arrows) in the superficial lamina propria with fibrin thrombi and mild foveolar hyperplasia



anal verge, covered by a clot (fig. 3A). Endoscopic treatment of an adrenaline injection and a lining of the clip was performed. Local rectal enema therapy with mesalazine was started. Ten days later, the control colonoscopy showed healing of the rectal ulcer (fig. 3B). The patient seemed to be stable, and his hemoglobin level normal. Liver ultrasound elastography excluded cirrhosis, and EGD excluded esophageal or gastric varices. Transrectal ultrasonography (TRUS) was added, with no signs of infiltration of deeper layers. Finally, histology confirmed the diagnosis of SRUS (fig. 4).

## Discussion

Our patient had several possible causes of GI bleeding in his case history: hemorrhoids, diverticulosis of the sigmoid colon, and gastroduodenal ulcer disease. However, none of them was the cause of the patient's chronic anemia. Two rare entities were shown by endoscopy: GAVE and SRUS.

**Fig. 3A. Endoscopic view of solitary rectal ulcer with a clot 13 cm from the anal verge**

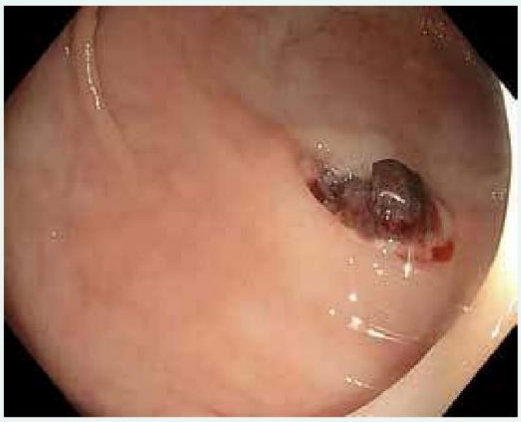
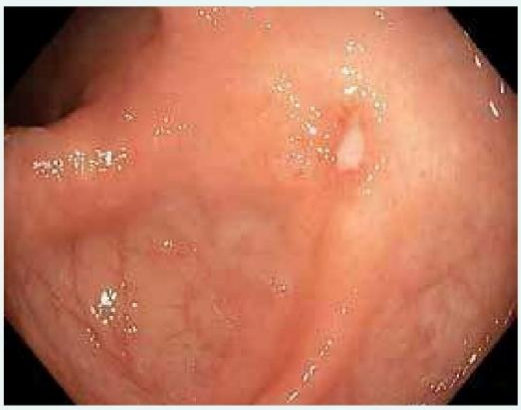


**Fig. 3B. Healing rectal ulcer after 10 days of treatment**



GAVE can be associated with other chronic diseases such as liver cirrhosis, systemic sclerosis, diabetes mellitus, and cardiovascular disease [3,6]. Our patient underwent ultrasound elastography, which excluded liver cirrhosis. Patients with liver cirrhosis and GAVE usually have a punctate form of GAVE instead of the more common linear striped appearance on the endoscope [3,6]. The etiology of GAVE in our patient´s case seems to be cardiovascular.

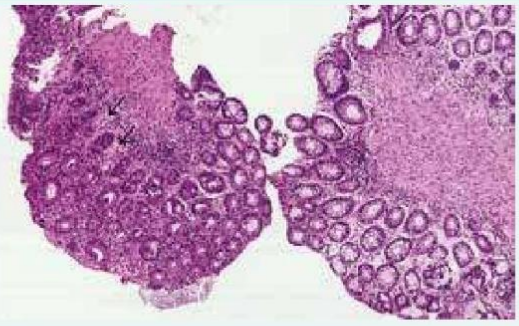
In a differential diagnosis, it is important to distinguish between GAVE and portal hypertensive gastropathy (PHG) or antral gastritis (AG). The treatment of these entities differs from that of GAVE. The treatment of GAVE should be performed endoscopically, whereas PHG treatment is focused on the reduction of portal pressure [1] and AG can be treated by medication.

APC is safe and effective in the treatment of GAVE, but recurrent bleeding occurs and may require more endoscopic sessions [5]. Some authors claim that endoscopic band ligation (EBL) is feasible and effective and should be performed as a method of first choice in GAVE treatment [2,6].

If severe recurrent and refractory bleeding occurs after APC or EBL treatment or endoscopic treatment is not effective, surgery is reserved as an efficacious method. It can, however, be associated with an increased risk of morbidity and mortality [3]. Jin et al published a case of a successfully surgically treated patient with refractory bleeding. In their case, a distal gastrectomy was performed in a hemodynamically unstable patient [4].

Clinical symptoms, endoscopic view, and histological findings constitute the criteria for the diagnosis of SRUS [8,9]. SRUS has been described in three most common endoscopic views. Endoscopic appearances

**Fig. 4. Histopathological section of rectal lesion:** examination of the rectal mucosa adjacent to the ulcer showed non-specific changes: superficial erosion, mixed inflammatory infiltration of the lamina propria mucosa. The following characteristic (traumatic-type) changes were found: starting fibromuscular obliteration of the lamina propria mucosae (arrows) and slight distortion of the crypts



range from erythematous lesions to ulcerative or polypoidal/nodular ones. The most common appearance reported is the ulcerative type [7] that our patient presented with.

Rectal bleeding was the reason to perform colonoscopy in our case. This symptom is reported as most common in SRUS, according to Abid et al [7] in 82 % and Abbasi et al [8] in 56 % of the cases. Constipation, which our patient also presented with, is reported as a less frequent symptom, 23 % in Abid et al [7] but 73 % in Abbasi et al [8]. Giving blood transfusions because of anemia caused by SRUS is uncommon [9]; however, severe anemia and chronic ischemic heart disease were indications for a blood transfusion in our case.

In our sample, the histopathological section confirmed a benign diagnosis. Some authors also recommend TRUS as helpful in ruling out an associated malignancy and recommend performing it routinely as a part of an evaluation in cases of suspected SRUS [10]. Nevertheless, performing a biopsy is mandatory to confirm SRUS and exclude potentially malignant diagnoses.

Hemorrhoids are often the reason for rectal bleeding, but a possible co-occurrence with another disease should not be excluded. Some authors published associated underlying conditions with SRUS. Abid et al [7] reported a slightly increased co-occurrence with hemorrhoids in 6 %. Co-occurrence with ulcerative colitis was present in 2.5 %, hyperplastic polyps in 3.5 %, adenomatous polyps in 2 %, and adenocarcinoma of the colon was observed in 2 % [7].

The treatment of SRUS ranges from a conservative treatment such as topical enemas (5-aminosalicylate or steroid), oral 5-aminosalicylate or sucralfate, biofeedback, followed by endoscopical steroid injections, to surgery (rectopexy, excision of ulcer) [9,11]. In a non-healing SRUS, conservative treatment management, laparoscopic resection rectopexy, and transanal endoscopic microsurgery were reported as safe, feasible, and effective treatment methods [12]. Endoscopy can also be used for the treatment of bleeding SRUS, which we successfully managed endoscopically by an adrenaline injection and clip lining.

## Conclusion

We describe a patient presenting with chronic iron deficiency anemia caused by a combination of two rare diagnoses. Endoscopy was chosen as a first-line treatment, followed by a drug treatment.

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**Příloha 6** - Mitochondrial Neurogastrointestinal Encephalomyopathy Imitating Crohn's Disease: A Rare Cause of Malnutrition

CASE REPORT

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# Mitochondrial Neurogastrointestinal Encephalomyopathy Imitating Crohn's Disease: A Rare Cause of Malnutrition

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## ABSTRACT

Mitochondrial neurogastrointestinal encephalomyopathy (MNGIE) is a rare autosomal recessive disease caused by a mutation in the TYMP gene encoding thymidine phosphorylase. MNGIE causes gastrointestinal and neurological symptoms in homozygous individuals and is often misdiagnosed as anorexia nervosa, inflammatory bowel disease, or celiac disease. We present the case of a 26-year-old female with MNGIE, who was initially diagnosed with anorexia nervosa and Crohn's disease. The diagnosis of MNGIE was established by biochemical confirmation of elevated serum and urine thymidine and deoxyuridine levels after multiple examinations and several years of disease progression and ineffective treatment. Subsequent molecular genetic testing demonstrated a homozygous TYMP gene mutation. MNGIE should be considered in patients with unexplained malnutrition, intestinal dysmotility, and atypical neurological symptoms.

**Key words:** Genetic disease - MNGIE – thymidine phosphorylase – malnutrition – neuropathy – Crohn's disease – anorexia nervosa.

**Abbreviations**: BMI: Body mass index; CD: Crohn's disease; CT: Computed tomography; GI: Gastrointestinal; MNGIE: Mitochondrial neurogastrointestinal encephalomyopathy; MRI: Magnetic resonance imaging; PEG: Percutaneous endoscopic gastrostomy; TP: Thymidine phosphorylase.

## INTRODUCTION

Mitochondrial neurogastrointestinal encephalomyopathy (MNGIE) is a rare autosomal recessive disease caused by a mutation in the TYMP gene encoding thymidine phosphorylase. Although the prevalence of MNGIE has not been determined, approximately 200 cases have been described worldwide [1]. Clinical manifestations, including gastrointestinal (GI) and neurological symptoms, first appear in the second decade of life [2] and may lead to a misdiagnosis of anorexia nervosa, inflammatory bowel disease, celiac disease, or Charcot-Marie-Tooth disease. A definitive diagnosis requires detection of biallelic pathogenic TYMP gene variants with reduced levels of thymidine phosphorylase enzyme activity in peripheral leukocytes and elevated plasma and urine thymidine and deoxyuridine concentrations [3].

## CASE REPORT

A 26-year-old female presented with an 8-year history of intermittent diarrhea, abdominal cramping, early satiety, and weight loss for which she had received neither specific diagnosis nor treatment. The patient was 170 cm tall, weighted 40 kg, and her body mass index (BMI) was only 14 kg/m$^2$. Anemia, lymphocytopenia, hypoalbuminemia, and coagulopathy confirmed a malabsorption syndrome. Gastrointestinal infections and parasites were excluded. An abdominal ultrasound revealed small intestinal malabsorption syndrome, abdominal lymphadenopathy, and hepatopathy. Endosonography of the pancreas and fecal elastase level were normal. An enteroscopic examination detected jejunal and ileal diverticulosis. Celiac disease, lactase deficiency, and Whipple's disease were histologically excluded. A colonoscopy revealed terminal ileum inflammation consistent with Crohn's disease (CD). Amyloidosis was excluded by rectal biopsy. We ruled out immunodeficiency diseases including human immunodeficiency virus. The patient underwent

capsule endoscopy, which was complicated by a small bowel obstruction (Fig. 1) necessitating acute surgical intervention. Intraoperative findings included a pathologically convoluted and structurally altered ileum and the impacted endoscopy capsule. A surgical biopsy showed only reactive inflammatory changes. Subsequently, magnetic resonance (MR) enterography revealed jejunal spasticity, terminal ileum stenosis with prestenotic dilation, lymphadenopathy, an elongated stomach, and hepatomegaly (Figs. 2, 3). Based on the above findings, we diagnosed the patient with CD and prescribed corticosteroid therapy. However, the patient refused this treatment, failed to return for her regular appointments, and was lost to follow-up until she returned to our outpatient clinic three years later. During the interval, she had been diagnosed with anorexia nervosa at an outside gastroenterology clinic. Although she had undergone percutaneous endoscopic gastrostomy (PEG) tube placement for delivery of enteral nutrition, the patient was severely malnourished (weight, 34.2 kg; BMI, 11 kg/m$^2$). Her condition gradually worsened over the next year, and we performed a second complete workup.

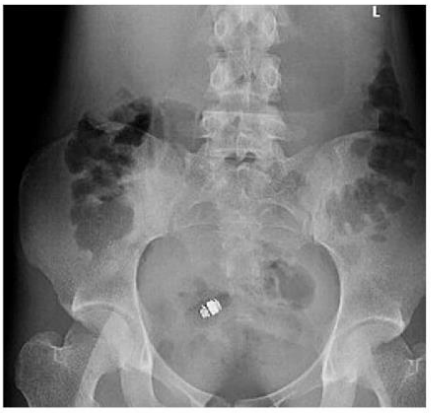

**Fig.1**. Abdominal x-ray showing an impacted endoscopy capsule in the patient with mitochondrial neurogastrointestinal encephalomyopathy (MNGIE).

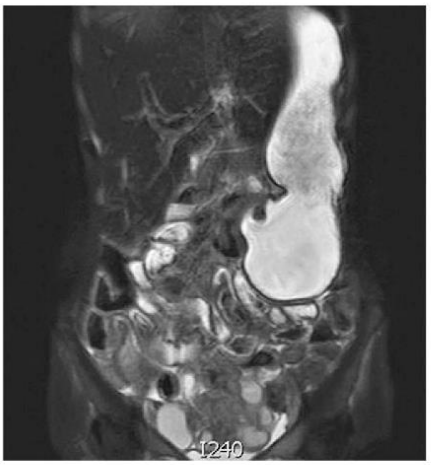

**Fig. 2.** CT enterography showing gastrectasia in our patient.

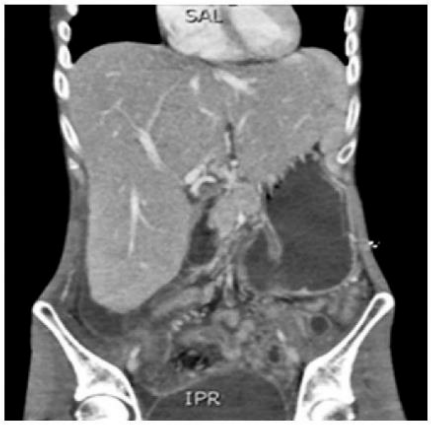


**Fig. 3.** Abdominal CT reveals hepatomegaly in the patient.

Gastroscopy and colonoscopy showed normal macroscopic findings, but histological examination of random colonic biopsies revealed eosinophilic infiltration. MR enterography confirmed an elongated stomach. A colon transit study recorded a very low bowel motility rate. A high positive level of fecal calprotectin (about 1800 IU) was repeatedly recorded. Immunological and endocrine laboratory test results were within normal limits. We continued enteral nutrition via the PEG tube.

A few months later, the patient was hospitalized with an ileus. Laboratory tests at that time revealed microcytic anemia, coagulopathy, hepatopathy, and severe malnutrition. An ultrasound examination showed intestinal malabsorption. Abdominal computed tomography (CT), CT enterography, and x-ray enteroclysis showed hepatomegaly and a convoluted ileal loop (Fig. 4). These findings and the elevated fecal calprotectin were considered consistent with active CD. Total parenteral nutrition, complete bowel rest, and intravenous corticosteroid therapy were initiated. We ordered a neurological evaluation due to the onset of peripheral neuropathy with atypical sensation in the feet (Fig. 5) and blepharoptosis. Electromyography detected a small fiber neuropathy highly suspicious for Charcot-Marie-Tooth disease (later ruled out by genetic testing). MR imaging (MRI) of the brain revealed extensive symmetric changes within the white matter bilaterally and discrete areas of restricted diffusion in the splenium of the corpus callosum (Fig. 6). Corticosteroid treatment was ineffective. The patient experienced nausea and vomiting due to intestinal stagnation. At that point, we performed a laparotomy and found abdominal ascites (approximately 1000 mL), hepatic cirrhosis, and a convoluted ileal segment (length, 120 cm) with stenosis and no apparent peristalsis. We performed a strictureplasty and terminal ileum resection (length, 30 cm) with an ileal-ascending colon anastomosis and protective ileostomy. The intraoperative liver biopsy showed micronodular hepatic cirrhosis. However, postoperatively, the patient still had problems due to GI dysmotility, and her nutritional status continued to decline. Finally, we implanted a Broviac catheter for long-term parenteral nutrition.

We expected a rare disease because the patient had prolonged and progressive atypical GI and neurological

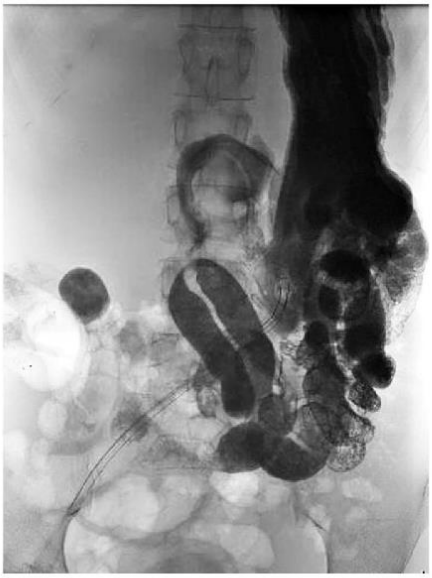

**Fig. 4.** X-ray enteroclysis: gastrectasia and a convoluted ileal loop.

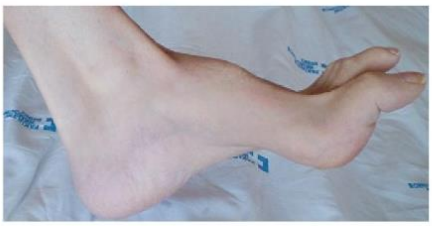

**Fig. 5.** Pes cavus in the 26-year-old patient with MNGIE.

symptoms of unknown etiology. Our suspicion on the diagnosis of MNGIE was confirmed. We assessed serum and urine levels of purines and pyrimidines. The results confirmed a thymidine phosphorylase deficiency. The patient's serum deoxyuridine and thymidine concentrations were elevated to 7.2 μmol/L (reference range up to 0.05 μmol/L) and 3.6 μmol/L (reference range up to 0,05 μmol/L), respectively, and thymine was not detected. Urine levels of deoxyuridine (36.9 mmol/mol creatinine), thymidine (18.4 mmol/mol creatinine), thymine (7.02 mmol/mol creatinine), and uracil (23.0 mmol/mol creatinine) were elevated. Molecular genetic analysis of the TYMP gene (nine exons and the adjacent introns) revealed a homozygous mutation, c.647C>T (Ala216Val), in exon 6. Genetic testing of the patient's parents identified a heterozygous pathogenic TYMP gene mutation (c.647C>T) in both, establishing them as healthy carriers of MNGIE. We ordered a re-examination of the small intestinal biopsy sample obtained during the patient's first presentation. The histologic findings were chronic enteritis with ulceration and focal diverticulitis, compatible with the diagnosis of MNGIE (Fig. 7 a, b). A radiologist confirmed that the changes noted in the patient's brain MRI were typical of MNGIE.

At the time of this report, the patient is receiving symptomatic care including parenteral nutrition through a Broviac catheter with enteral dietary supplements. The protective ileostomy is still maintained, due to depressed rectal sphincter tone. Presently, she does not require liver transplantation as her liver function is stable. She leads a relatively normal life that includes travelling and is followed by our outpatient nutrition services department. Prospectively, there is hope for gene therapy for our patient, a technique under research and still unavailable.

## DISCUSSION

Mitochondrial neurogastrointestinal encephalomyopathy is a rare autosomal recessive disease caused by a mutation in the TYMP gene (previously known as ECGF1) located on chromosome 22q13.32-qter [4] that encodes thymidine phosphorylase. Thymidine phosphorylase is an enzyme that normally catalyzes the degradation of thymidine to thymine [5]. Consequently, MNGIE results in increased cellular thymidine concentration and high serum thymidine levels [3]. The disease is associated with errors and multiple deletions of mitochondrial DNA in the skeletal muscle resulting from miscommunication between nuclear and mitochondrial genomes [6]. Homozygous individuals suffer from multiple symptoms including GI dysmotility with pseudo-obstruction manifested as cachexia, abdominal pain, diarrhea, vomiting, borborygmi, and early satiety. Patients are typically unable to gain weight or increase their body fat percentage in late

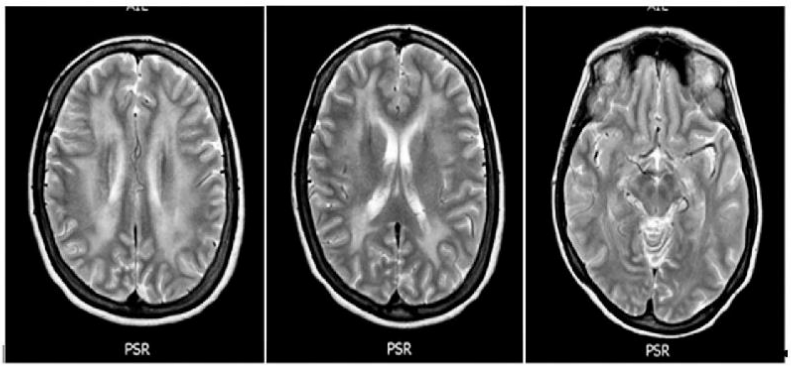


**Fig. 6.** T2-weighted magnetic resonance imaging of the brain showing diffuse cerebral white matter hyperintensity .

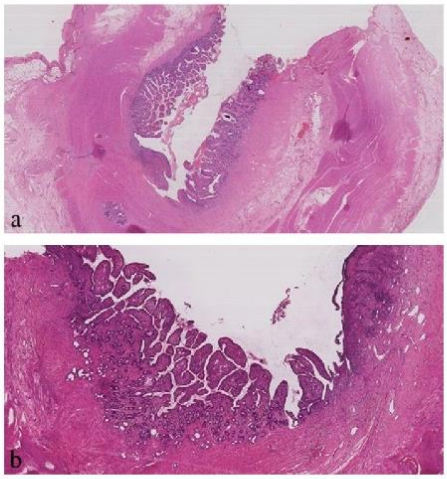


**Fig. 7.** Histologic evaluation of the small intestinal biopsy: (a) mucosal and submucosal ulcer with granulation tissue at the base of the defect and muscular layer diverticulum; (b) mucosal ulcer with granulation tissue at the base of the defect.

childhood. Diverticulosis, especially atypical small intestinal diverticulosis, can be found in about 67% of patients [3] and may result in intestinal perforation with peritonitis. Radiological studies (x-ray, ultrasound, CT) usually show gastrectasia and intestinal dilation with signs of possible bowel obstruction. Decelerated transit time can be recorded within the GI tract. An endoscopic examination usually determines no macroscopic GI mucosal pathology. Histopathological examination of a biopsy specimen can confirm submucosal ganglion cell eosinophilic cytoplasmic inclusions with abnormal mitochondria, especially in the colorectal mucosa [7]. An upper GI biopsy can verify focal smooth muscle cell atrophy, serosal granulomas, and focal loss and fibrosis of Auerbach's plexus [8]. Typical neurological features are peripheral neuropathy with demyelination of sensory and motor nerves and myopathy causing paresthesia, weakness, and a stocking-glove pattern of sensory loss [4]. A foot deformity (pes cavus) with a high longitudinal arch is frequently found. MNGIE tends to be misinterpreted by neurologists as Charcot-Marie-Tooth disease, but genetic testing rules out this diagnosis. MRI demonstrates diffuse changes within the white matter except for the corpus callosum, confirming brain leukoencephalopathy. Although these changes usually cause no symptoms, the patient may experience blepharoptosis and ophthalmoplegia. Other clinical manifestations can include active hepatic macrovesicular steatosis or cirrhosis with increased liver enzymes. Hepatomegaly is often apparent, and cardiomyopathy occurs in rare cases.

Treatment is primarily symptomatic and supportive; the aim is augment the patient's nutritional intake with enteral or parenteral feeding, and a PEG tube is often needed. Symptomatic treatment of nausea and vomiting is required as these medications control neuropathic symptoms. Management of dysphagia and airway protection are essential measures in severe cases of MNGIE [4]. The clinician should take steps to avoid bacterial overgrowth and infectious complications, and psychological or psychiatric intervention might also be considered. Currently, there are no proven causal treatments for MNGIE although several novel treatments are under investigation. Allogeneic hematopoietic stem cell transplantation can restore thymidine phosphorylase and improve the clinical condition of patients with MNGIE [9]. However, the relatively high mortality rate associated with this procedure is a prominent drawback. Liver transplantation has also been proposed as a treatment for MNGIE due to the high hepatic thymidine phosphorylase expression that could normalize thymidine levels and decrease serum levels of toxic nucleotides [10]. Other published studies utilized hemodialysis or peritoneal dialysis [11, 12]. Current gene therapy research employs a generated vector containing the coding sequence of the human TYMP gene under the control of a liver-specific thyroxine-binding globulin promoter [13].

## CONCLUSION

We presented the case of a patient with MNGIE who exhibited typical features of the disease. MNGIE should be considered in patients with unexplained malnutrition, intestinal dysmotility, and atypical neurological symptoms. The prognosis of patients with MNGIE is poor.

**Conflicts of interest**: The authors declare that they have nothing to disclose.

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**Authors contributions**: L.Kucerova: manuscript writing; L.Kucerova, M.D. and L.Kunovsky.: conception and design of the work; L.Kucerova, T.H. and L.Kunovsky.: literature search; J.D., M.D. T.H., and L.Kunovsky: consultants, text editors; D.B.: imaging investigations; J.M.: histological examination. All authors read and approved the final manuscript.

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**Příloha 7** - Zobrazovací metody u neúrazových náhlých příhod břišních

Klinická a experimentální gastroenterologie: přehledová práce

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# Zobrazovací metody u neúrazových náhlých příhod břišních

## Imaging methods in non-traumatic acute abdomen

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**Souhrn:** Náhlé příhody břišní jsou urgentní stavy, které vyžadují rychlou diagnostiku i léčbu. V dnešní době změnily ultrasonografie (USG) a výpočetní tomografie (CT – computed tomography) v některých případech pohled na využití prostého snímku břicha. USG je dnes plně dostupnou metodou, která je schopna u některých stavů poskytnout „finální" diagnózu. Častější využití CT vyšetření v diagnostice náhlých příhod břišních je v dnešní době evidentní. CT vyšetření sice znamená pro nemocného poměrně velkou radiační zátěž, ta je však kompenzována její vysokou senzitivitou i specificitou v detekci příčin urgentních stavů. O protokolu CT vyšetření rozhoduje radiolog.

**Klíčová slova:** náhlé příhody břišní – zobrazovací metody – prostý snímek břicha – ultrasonografie – výpočetní tomografie

**Summary:** An acute abdomen is an urgent condition requiring rapid diagnosis and treatment. Nowadays, with the new developments and progression in ultrasonography (US) and computed tomography (CT), these methods have become a far better alternative to plain abdominal radiography. US is now an available and proven method used to provide a "final" diagnosis in various conditions. The frequency for CT examination for the diagnosis of acute abdomen has increased. A disadvantage of using CT examination includes high doses of radiation for the patient. Fortunately, this disadvantage is outweighed by the multitude of advantages. The advantages include high sensitivity and specificity in the detection of causes in urgent conditions. The CT protocol of examination is primarily lead by the radiologist.

**Key words:** acute abdomen – imaging methods – plain abdominal radiography – ultrasonography – computed tomography

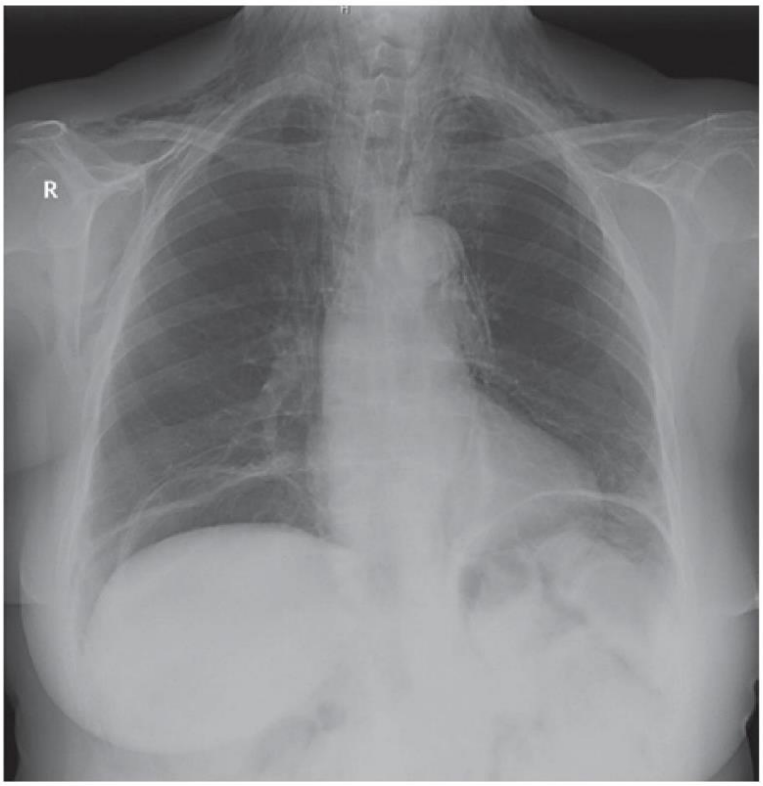
## Úvod

Náhlé příhody břišní (NPB) jsou charakteristické náhlým vznikem (postihují většinou jedince z pocitu plného zdraví) a svým rychlým průběhem. Tito pacienti se mnohdy objevují na ambulancích v nočních, resp. pohotovostních hodinách. Pro radiologa, a tím i pro kvalitní diagnostiku je velice výhodné, ba přímo nutné znát základní klinické údaje. Pokud není v těchto případech jasná klinická otázka, omezuje se vyšetření většinou na hledání „nějaké patologie, která by vysvětlovala dané potíže" v celé břišní dutině a retroperitoneu. Nelze též opomenout možnost propagace potíží do dutiny břišní z hrudníku při postižení pleury či plic. Mezi základní zobrazovací metody u pacientů s podezřením na NPB stále patří prostý snímek břicha, event. i hrudníku, a ultrasonografie (USG) břicha a malé pánve. V dnešní době je však stále více využíváno vyšetření výpočetní tomografií (CT – computed tomography).

Jak při traumatické, tak při netraumatické příčině NPB zajímají chirurga, resp. klinika některé zásadní skutečnosti, na které by radiolog měl být schopen odpovědět. Při těchto akutních stavech máme ze zobrazovacích metod k disposici rentgen (RTG), USG a CT. Volba optimální diagnostické metody by měla záviset na klinickém a laboratorním stavu pacienta. V některých případech správná indikace CT může nahradit jak RTG, tak USG. Nedochází k časové prodlevě a většinou je stanovena „finální" diagnóza (např. střevní ischemie). Mezi základní otázky, na které se nejčastěji klinik ptá a které mají pro další léčebnou strategii zásadní důležitost, patří:

1. Je přítomen volný plyn v dutině břišní? – perforace gastrointestinálního traktu (GIT)?
2. Je přítomna volná tekutina či ohraničené kolekce tekutiny? – hemoperitoneum, ascites, uroretroperitoneum, střevní obsah, ohraničené kolekce, absces, lokalizace?
3. Jsou známky poruchy střevní pasáže? Pokud ano, o jaký typ poruchy se jedná a zda je porucha mechanická či funkční. V případě obstrukčního ileu je důležité stanovení místa, popřípadě i charakter překážky.
4. Jsou zánětlivé změny na parenchymatózních orgánech či trávicí trubici?

Kvalitní předoperační diagnostika a moderní možnosti monitorování pacientů umožňují v některých případech




**Obr. 1. Prostý snímek hrudníku, masivní pneumoperitoneum, oboustranné podbrániční srpkovité kolekce volného plynu – perforovaný vřed žaludku.**
Fig. 1. Plain X-ray of the chest, with a massive pneumoperitoneum, and a bilateral diaphragm sickle-shaped collection of free gas – perforated gastric ulcer.

postupovat méně razantně a pokud možno konzervativně. Tomu napomáhá i rozvoj nechirurgických terapeutických modalit (radiologické intervenční výkony, endoskopické výkony). Tyto techniky mohou modifikovat akutní péči o pacienta a samotný chirurgický výkon provést v odložené, příhodnější době (např. perkutánní drenáž abscesů, embolizace při poranění jater atd.).

## Zobrazovací metody u náhlých příhod břišních

### Prostý rentgenový snímek břicha

Prostý snímek břicha je stále využívaný při vyšetření nemocných s NPB. Chirurgy je oblíben a i v dnešní době na něj mnohdy pohlížejí jako na zlatý standard u NPB. Ne každá chirurgická ambulance má k dispozici CT, v některých zařízeních nemusí být neustále k dispozici USG, většina ambulancí má však RTG pracoviště. Prostý snímek břicha má význam při podezření na střevní obstrukci, perforaci trávicí trubice či fulminantní střevní zánět. Vyšetření je možné provést i u lůžka pacienta pojízdným RTG přístrojem. RTG snímek břicha má význam i pro hodnocení polohy drénů [1–3]. Využití prostého snímku břicha se s rozvojem a dostupností CT u některých stavů snižuje. Specificita prostého snímku břicha u pacientů s podezřením na NPB je ve srovnání s CT vyšetřením malá, byť je jeho senzitivita např. v případě většího množství volného vzduchu v dutině břišní velká. Pokud u nemocných s NPB provádíme prostý snímek břicha, pak k základním projekcím patří:

1. snímek břicha vleže na zádech;
2. zadopřední snímek hrudníku vestoje;
3. snímek břicha vestoje a v některých případech lze zhotovit i snímek horizontálně probíhajícím paprskem vleže na boku.

Snímek břicha vleže na zádech mnohdy poskytuje více informací než snímek vestoje. Přesněji můžeme posoudit šířku lumen tenkého i tlustého střeva. Vzduch tvoří negativní kontrast, který umožní částečně hodnotit i šíři střevní stěny i řas. Lépe než u snímku vestoje může být zhodnoceno rozložení plynaté náplně střev, a tím i stanovení lokalizace přechodové zóny.

Podezření na pneumoperitoneum bývá častou indikací k provedení prostého snímku břicha. Volný vzduch v peritoneální dutině je známkou patologické komunikace trávicí trubice s volnou dutinou břišní. Můžeme ho však pravidelně detekovat u nemocných po laparoskopii a po některých dalších chirurgických výkonech.

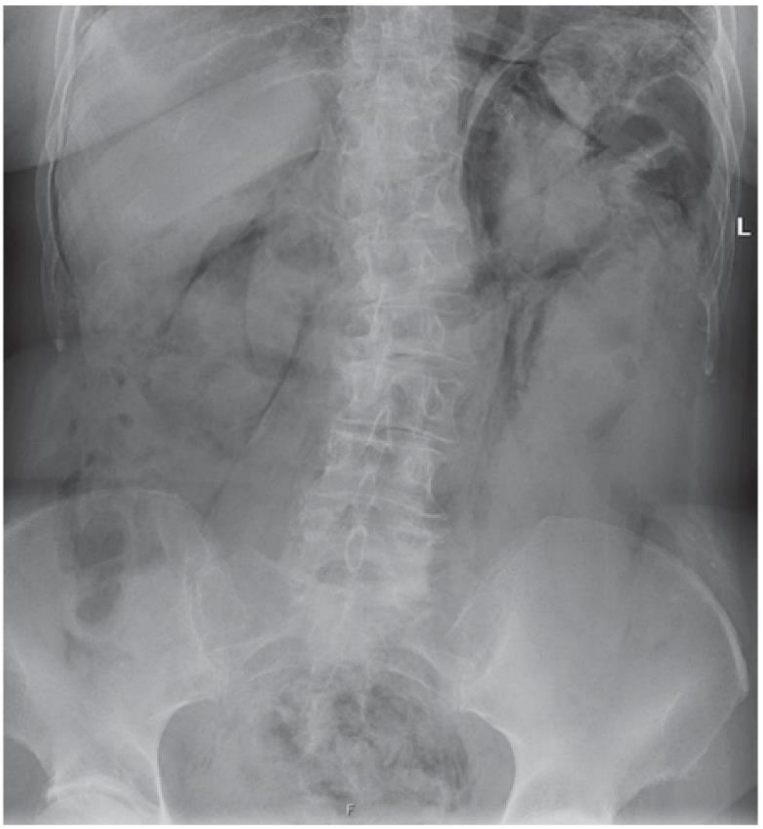
U prostého snímku břicha vestoje je centrální paprsek zaměřen do středu spojnice hřebenů lopat kyčelních, a subdiafragmatický prostor je tak zobrazen zespodu, šikmo a ne tangenciálně. Výsledek je jednak sumace této oblasti s masou celých jater a dále sumace především s dorzálním diafragmatickým recesem vyplněným vzdušnou plicní tkání. Větší diagnostický význam při detekci vzduchu pod bránicí má proto prostý snímek hrudníku vestoje (obr. 1) [1]. Snímek plic patří k základnímu vyšetření nemocných s NPB i proto, že u některých pacientů může být příčinou potíží patologický proces v dutině hrudní.

Volný plyn může být detekovatelný i na snímku břicha vleže na zádech (double wall sign) (obr. 2). Malé množství volného plynu v dutině břišní je však takto nezobrazitelné. Také srůsty mohou bránit migraci plynu do podbráničních prostor, a tím zvyšovat falešnou negativitu vyšetření. Kryté perforace prakticky detekovatelné nejsou. Nejčastějšími příčinami pneumoperitonea jsou perforující vřed gastroduodena a komplikovaná divertikulitida.

Dalším častým požadavkem klinika je hodnocení přítomnosti hladinek. Tzv. hydroérický fenomén neboli hranice tekutina/plyn můžeme vídat někdy i u zdravých jedinců, pacientů s malabsorpčním syndromem či u pacientů s paralytickým ileem. Snižováním aktivity střeva se tekutina a vzduch kumulují, dochází k distenzi trávicí trubice a na snímku vestoje se tvoří typický obraz hladinek (obr. 3). V některých případech, dle charakteru a lokalizace hladinek, lze z prostého snímku odhadnout předpokládané místo mechanické překážky.

Dále hodnotíme na prostém snímku břicha též struktury retroperitonea (přítomnost možné urolitiázy, kalcifikace v různých lokalizacích, kontury psoatů aj.) [4–6].

Při indikaci prostého snímku břicha je nutné z výše uvedeného vycházet. Indikující lékař si musí uvědomit, že CT a USG vyšetření změnila pohled na využití prostého RTG snímku břicha. Pokud se rozhodne indikovat prostý snímek břicha, nemělo by to být z důvodů, že je tato metoda nejvíce dostupná a „cesta nejmenšího odporu", ale proto, že v dané situaci považuje provedení RTG snímku břicha za indikované. Typickým příkladem jsou subileózní pacienti, u kterých lze pomocí akutního RTG snímku břicha sledovat vývoj množství plynu v kličkách tenkého střeva. Stejně tak jsou indikací kontrolní snímky po zavedení drénů. U skutečně akutních pacientů má však prostý snímek břicha oproti možnostem CT malý význam. V případě pozitivního nálezu je obvykle nutné tak jako tak provést CT břicha, v případě negativního nálezu je pak vhodné provést buď USG břicha, nebo též CT vyšetření břicha. Obecně je uváděna senzitivita a specificita prostého snímku břicha u NPB 28 a 91 %, senzitivita se u obstrukcí tenkého střeva zvyšuje na 80 %. U USG se hodnoty pohybují kolem 62, resp. 98 %. Senzitivita u provedených CT vyšetření je 88 %, se specificitou 93 % [7]. Lze tedy shrnout – prostý RTG snímek břicha je v dnešní době v diagnostice NPB stále poměrně hojně využíván i přes jeho poměrně nízkou citlivost. V některých případech, na základě zhodnocení klinického či laboratorního stavu pacienta, je však racionální provést CT vyšetření jako zobrazovací metodu první volby.

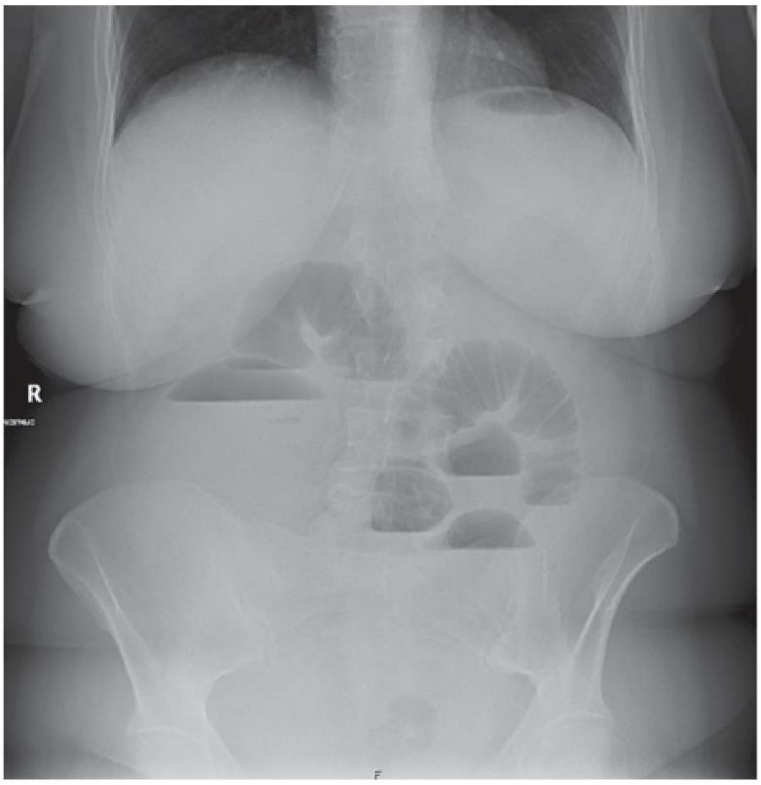



**Obr. 2. Prostý snímek břicha vleže – masivní pneumoperitoneum po koloskopii.**
Fig. 2. Plain X-ray of the abdomen, prone – with a massive pneumoperitoneum after colonoscopy.

## Ultrasonografické vyšetření

USG je dnes v medicíně široce využívanou metodou. Je považována za metodu bezpečnou stran možných nežádoucích účinků, metodu rychlou, levnou a dostupnou. Vyšetření USG je u nemocných s NPB, spolu s prostým RTG snímkem břicha, často metodou první volby. Mezi základní indikace k urgentnímu vyšetření dutiny břišní patří podezření na postižení žlučníku a žlučových cest, parenchymu jater a sleziny, detekce volné tekutiny a kolekcí v dutině břišní. Dnes je již samozřejmostí vyšetření appendixu, ileocékální krajiny [3] a tlustého střeva. Posouzení dilatace střevních kliček patří spolu s RTG snímkem k základním metodám k hodnocení ileózního stavu. Je možno vyšetřit cévy a hodnotit jejich akutní uzávěr či stenózy.

Na střevních kličkách můžeme hodnotit šířku a echogenitu střevní stěny, postižení jejich jednotlivých vrstev, dilataci kliček, patologické změny v okolí střeva (změněné uzliny, postižení mezenteria, volnou tekutinu aj.) a komplikace zánětlivých procesů (absces, pseudotumor, píštěle, konvolut střevních kliček apod.). V dopplerovském záznamu můžeme posoudit vaskularizaci stěny střevní, uzlin aj. a tímto posoudit i aktivitu postižení. Sledování dynamiky procesu a opakované kontroly přitom pacienta nepo-




**Obr. 3. Prostý snímek břicha vstoje horizontálním paprskem, vícečetné hladinky na kličkách jejuna, dilatace, edém řas – operační nález adheze ilea.**
Fig. 3. Plain X-ray of the abdomen standing using a horizontal beam, with multiple levels on the loops of the jejunum, dilatation, edema of the mucosa – surgical finding of adhesion of the ileum.

škozují radiační zátěží. Pacient nemusí být nijak speciálně připravován, nemusí být lačný a vyšetření lze libovolně opakovat [3]. Je třeba si uvědomit, že vzhledem k rušivým artefaktům, které vytváří přítomnost vzduchu v lumen, nelze dostatečně posoudit dorzální stěnu střevní kličky. Orientace v dutině břišní u nemocných s plynatou distenzí střev může být velice obtížná. Také orientace po resekčních výkonech na střevech s různým typem anastomóz je někdy problémem i pro zkušeného vyšetřujícího. Šířka stěny zdravé trávicí trubice se v USG obraze pohybuje od 2 do 3 mm. Každý patologický proces vede k rozšíření stěny střevní, jednotlivé procesy různou měrou. Dnes prakticky každý sonografista, který se věnuje abdominální sonografii, by měl umět zhodnotit appendix, ileocékální oblast, tlusté střevo, především esovitou kličku k posouzení divertikulitidy. Důležité je posouzení dalších, i nepřímých USG známek NPB.

Sonografie pacienta nezatěžuje zářením. I tak by ale mělo být USG vyšetření břicha u nemocných s NPB prováděno cíleně, s jasně formulovanou užší otázkou. Indikace „USG vyšetření břicha – bolesti břicha" je naprosto nesmyslná. USG vyšetření břicha u nemocných s NPB je indikováno především k posouzení žlučníku (má větší přesnost než CT) [8], appendixu (k průkazu postižení, CT má smysl doplňovat jen při nejasném nálezu), u divertikulitidy (při pozitivním nálezu je většinou nutné doplnit CT k přesnému stanovení závažnosti divertikulitidy a jejím komplikacím), u podezření na kolitidu, Crohnovu chorobu (CD – Crohn's disease), při ileu a při podezření na volnou tekutinu v dutině břišní. U pacientů s renální kolikou, při podezření na pankreatitidu nebo obstrukční ileus je vhodné provést CT vyšetření. Totéž se týká neurčitých bolestí břicha u klinicky či laboratorně jasně nemocných akutních pacientů.

## Výpočetní tomografie

CT je u nemocných s NPB stále častěji metodou první volby. Vyšetření je standardizováno. Provádí se jako necílené vyšetření břicha a pánve anebo jako vyšetření cílené na určitou oblast či orgán (např. CT jater, pankreatu, střev). Samotný protokol vyšetření je určován stavem pacienta a mnohdy je závislý na položené klinické otázce. Známou nevýhodou CT vyšetření je radiační zátěž. Typická efektivní dávka pro CT vyšetření břicha se pohybuje kolem 7–10 mSv. Pro představu, dávka u RTG hrudníku je 0,02 mSv, RTG břicha asi 1,5 mSv. V posledních letech dochází obecně k nárůstu CT vyšetření, což však významně zvyšuje kolektivní dávku z lékařského ozáření v populaci. V indikaci k CT vyšetření musíme zohledňovat stav pacienta a možnosti ostatních vyšetřovacích modalit.

S ohledem na klinickou diagnózu a stav pacienta je samotné CT vyšetření prováděno podle různých protokolů. Ve většině případů je nutná nitrožilní aplikace kontrastní látky (k. l.). Pokud je však požadavkem vyloučení pneumoperitonea (např. při klinické suspekci na perforaci gastroduodenálního vředu), postačuje obvykle jen nativní vyšetření, prakticky se 100% senzitivitou i specificitou v detekci volného plynu (obr. 4) [1,9]. Obdobná situace může být v hodnocení kryté perforace. Jiný protokol je při podezření na střevní ischemii, kde je nutné provedení nativní, arteriální i portovenózní fáze. K prokázání krvácení do trávicí trubice využíváme i opožděnou fázi za 300 s. Při podezření na divertikulitidu colon sigmoideum obvykle stačí nativní CT břicha a malé pánve a postkontrastní fáze jen na oblast malé pánve. Z toho vy-

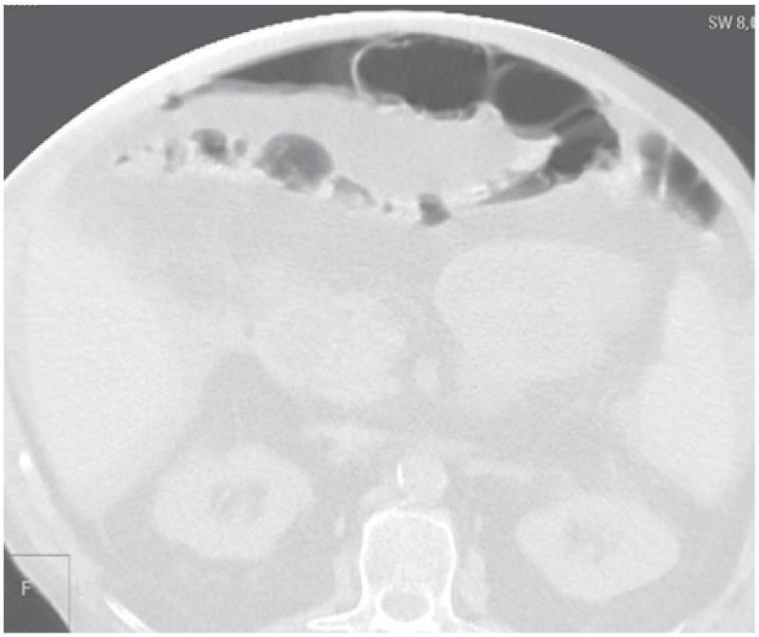
plývá opravdu potřeba kvalitních informací od klinika a i zohlednění výsledků předešlých vyšetření. Při aplikaci jodových k. l. intravenózně je nutné zohlednit renální parametry a alergie pacienta v souladu s Metodickým listem intravaskulárního podávání jodových k. l., vydaného Radiologickou společností.

Mimo hodnocení parenchymových orgánů a volné tekutiny v dutině břišní můžeme pomocí CT zobrazit postižení samotné střevní stěny a rovněž změny v okolí trávicí trubice (kolekce zánětlivé tekutiny – absces, zánětlivý infiltrát, postižení mezenteria, píštěle, fibrózní lipomatózu, desmoplastické reakce atd.). Hodnocení přechodové zóny a event. její příčiny je velkou předností CT vyšetření při ileózních stavech. Běžně je dnes využívána CT angiografie k hodnocení cév v dutině břišní, což je stěžejní při podezření na střevní ischemii.

Vyšetření CT znamená pro nemocného relativně velkou radiační zátěž. Ta je však kompenzována vysokou senzitivitou i specificitou pro řadu patologických stavů. To nic nemění na tom, že na žádance musí být především jasně formulovány otázky, na které má toto vyšetření najít odpovědi. Tyto odpovědi se pak musí objevit v popisu, resp. v závěru vyšetření. V některých případech u nemocných s NPB postačí nativní CT vyšetření bez perorálního či intravenózního podání k. l. Tak lze opět snížit radiační zátěž i riziko komplikací spojených s intravenózním podáním k. l. O protokolu vyšetření rozhoduje radiolog. Výhodná může být i kooperace s klinikem, podle očekávaného přínosu vyšetření.

### Digitální subtrakční angiografie

Význam angiografického vyšetření jako diagnostické metody u nemocných s NPB ustoupil do pozadí. V naprosté většině při podezření na krvácení v dutině břišní je metodou první volby CT angiografie, jelikož má vysokou senzitivitu. Digitální subtrakční angiografii (DSA) dnes provádíme především u nemocných s krvácením do GIT jako součást intervenčního výkonu (např. embolizace pseudoaneuryzmat aj.). Před každou indikací k provedení angiografického výkonu je nezbytné si uvědomit, že se jedná o výkon invazivní, a tedy spojený s různě vysokými riziky pro nemocného. U diagnostických výkonů jej tedy zásadně volíme až po vyčerpání všech vhodných neinvazivních metod.



**Obr. 4. CT vyšetření břicha, pneumoperitoneum, volný plyn pod břišní stěnou.**
Fig. 4. CT image of the abdomen, with a pneumoperitoneum, and free gas under the abdominal wall.

### Magnetická rezonance

Díky technickým pokrokům se sice rozsah indikací pro magnetické rezonanční (MR) zobrazování břišní oblasti stále rozšiřuje, nicméně u urgentních stavů vystupují do popředí limitace tohoto vyšetření (dostupnost v dané chvíli, nutnost spolupráce pacienta u vyšetření, délka vyšetření atd.). U těhotných žen ve 2. a 3. trimestru těhotenství je vyšetření obecně považováno za bezpečné [10].

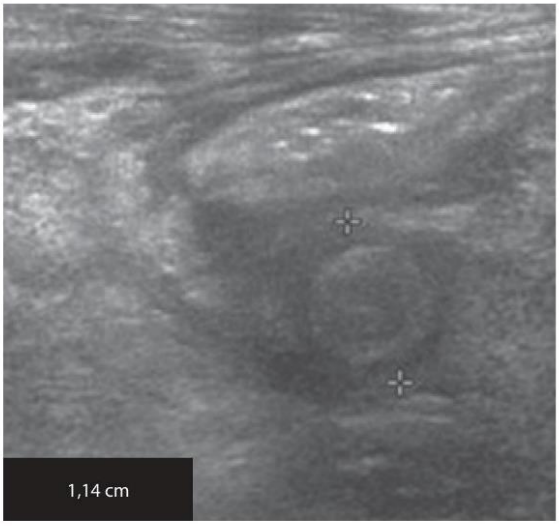
V 1. trimestru těhotenství se doporučuje provádět MR vyšetření se zvýšenou obezřetností a v tomto období pečlivě zvážit jeho diagnostický přínos [11]. Prakticky kontraindikováno je podání k. l. během celého těhotenství [12].

Využití MR u NPB je spíše raritní. Závisí většinou na zvyklostech jednotlivých pracovišť, klinickém stavu pacienta a výsledcích předešlých vyšetření.

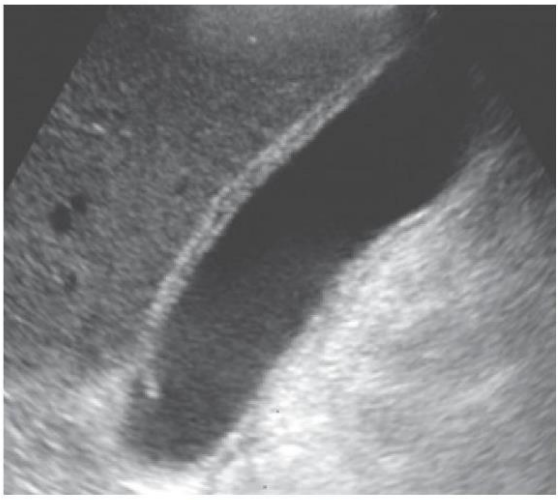
## Vybrané kapitoly z neúrazových náhlých příhod břišních u dospělých

### Akutní appendicitida

Akutní appendicitida je řazena mezi nejčastější příčiny urgentní abdominální chirurgie, a to jak u dětí, tak u dospělých. Správná a včasná diagnostika a léčba je pro osud nemocného rozhodující [1,13]. Klinická diagnóza je postavena na anamnéze, typických příznacích, fyzikálním nálezu a elevaci zánětlivých parametrů. Akutní appendicitidu však mohou svými symptomy napodobit rozličná onemocnění orgánů v okolí, vzácně i některé chorobné procesy v jiných lokalizacích dutiny břišní, event. i hrudníku. Zvláště v těchto případech, kdy i klinický obraz je atypický, je USG v rámci využití zobrazovacích metod jednoznačně metodou první volby [13,14]. Vyšetření umožňuje posouzení samotného appendixu, jeho




**Obr. 5. Ultrasonografie pravé jámy kyčelní, detekce zesílené stěny appendixu, edém stěny, prosáknutí v okolí, jemné tekutinové lemy – operační nález akutní apendicitidy.**
Fig. 5. Ultrasonography of the right illiac fossa, showing a thickened appendix wall, a wall edema, leakage in the surroundings, fine fluid margins – surgical finding of acute appendicitis.



**Obr. 6. Ultrasonografie hepatobiliárního systému, detekce zvětšeného žlučníku s drobnou lithiázou, lehce zesílenou, stratifikovanou stěnou, při dózované kompresi výrazná citlivost – obraz lehké akutní cholecystitidy.**
Fig. 6. Ultrasonography of the hepatobiliary system, showing an enlarged gallbladder with a small presence of lithiasis, a slightly thickened, stratified wall, and significant sensitivity during dosed compression – image of mild acute cholecystitis.

uložení, délku, celkovou šířku, šířku stěny a charakter jednotlivých vrstev, přítomnost koprolitu. Je možné posoudit změny v okolí, a tím ozřejmit charakter zánětlivého procesu (katarální, flegmonózní, gangrenózní appendicitida) (obr. 5) [14]. Je možné diferencovat komplikace v podobě abscesu, píštělí, zánětlivého pseudotumoru. Samozřejmostí by mělo být i posouzení přilehlých střevních kliček, zvláště terminálního ilea a céka (CD). Senzitivita USG v diagnostice appendicitidy se pohybuje od 80 do 93 % a specificita dosahuje 94 % [13–17]. Při USG nálezu normálního appendixu (šíře stěny do 3 mm, celková šíře appendixu do 8 mm, normální rozvrstvení stěny, bez reaktivních změn v okolí) se můžeme pokusit o stanovení alternativní diagnózy – tedy vyloučit postižení okolních orgánů, nejčastěji gynekologických orgánů, urolitiázy, afekci žlučových cest, terminální ileitidu aj. [3,13,14].

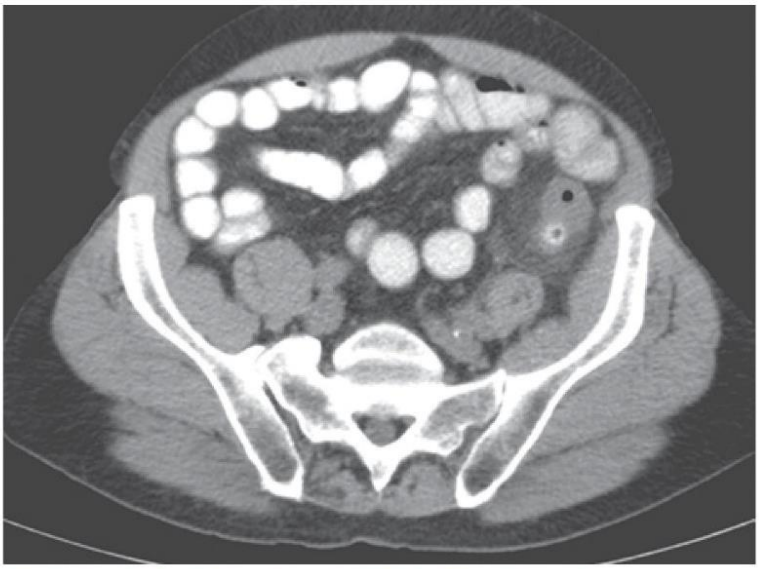
## Určení polohy appendixu

Určení polohy appendixu je výhodné u těch případů, kdy je bolestivost lokalizována do atypické oblasti. Uložení appendixu je určeno primárně lokalizací céka. Typická poloha céka je v pravé jámě kyčelní a při tomto uložení rozeznáváme několik základních poloh appendixu, vyskytujících se v populaci s určitou četností. Nejčastější poloha je pelvická (subcékální) (40 %), kdy se appendix při své určité délce dostává do blízkosti rekta, močového měchýře a gynekologických orgánů. Další častou polohou je mediocékální uložení (15 %). Appendix probíhá kolem terminálního ilea a končí opět dle své délky mezi tenkými kličkami mediálně od céka. Laterocékální uložení appendixu (2–15 %) odpovídá poloze mezi laterální stěnou céka a stěnou břišní. Dosti zrádná jak v USG diagnostice, tak i v klinickém hodnocení je retrocékální poloha (10–30 %), kdy appendix může být uložen částečně či úplně extraperitoneálně, a tím způsobovat poněkud atypický klinický obraz. Plyn obsažený v céku znemožňuje posoudit retrocékální prostor. Vzácná je poloha precékální [1]. Mimo typickou polohu céka v pravé jámě kyčelní je nutno zmínit ještě polohu při situs inversus intestini a zvláště kraniální dystopii céka uloženého v podjaterní krajině, který může svými klinickými projevy imitovat postižení žlučníku či duodena. Někdy tedy mohou být překvapivé nálezy akutní appendicitidy v subhepatální krajině při klinickém podezření na akutní cholecystitidu.

Při nejasném nálezu na USG či při komplikacích appendicitidy (zánětlivý pseudotumor, podezření na absces, ileus, aj.) bývá indikováno CT vyšetření [15,16,18]. Pro detekci samotného appendixu a zhodnocení, zda se jedná o zánětlivé změny, někdy postačuje nativní vyšetření. Pro aplikaci k. l. intravenózně (i.v.) se rozhodujeme, pokud je nativní obraz nejasný, či k ozřejmění komplikací. Oproti USG můžeme detekovat lépe zánětlivý pseudotumor, absces či perforaci. Detailní hodnocení komplikací může mít vliv na adekvátní terapii a event. i na načasování operačního výkonu. Při příznivých anatomických pod-

mínkách lze perkutánně pod CT drénovat absces či provést aspiraci obsahu ke kultivaci, pokud to stav nemocného vyžaduje. Obecně platí, že význam CT vyšetření je u těchto nemocných především v případě komplikovaných USG nálezů, u obézních pacientů a v případě jasného klinického nálezu, když se na USG nepodaří appendix najít. Indikace k MR je především u těhotných.

Diferenciálně diagnosticky je především u nemocných s klinickým podezřením na akutní appendicitidu nutno zvažovat možný zánět appendices epiploicae. Tyto tukové výběžky lokalizované kolem tlustého střeva jsou dobře detekovatelné při CT vyšetření, nicméně je lze zachytit i při USG střeva. Metodou volby při hodnocení možné patologie appendices epiploicae je tedy CT či USG, s obdobným nálezem perifokálního zánětu jako při typické divertikulitidě.



**Obr. 7. CT vyšetření břicha, obraz ojedinělého divertiklu na přechodu sigmoideum-descendens, s jemným prosáknutím tuku v okolí, bez dalších komplikací – lehká divertikulitida.**
Fig. 7. CT examination of the abdomen, imaging a single diverticulum at the sigmoideum-descendens junction, with a fine leakage of fat into the surroundings, without other complications – mild diverticulitis.

## Akutní cholecystitida

Akutní zánět žlučníku patří mezi další zánětlivé jednotky, které se mohou projevovat náhlou příhodou břišní. Až v 95 % bývá následkem obstrukce vývodu žlučníku konkrementem. Zbylá procenta jsou pod obrazem tzv. akalkulózní cholecystitidy, v rámci ischemie či sekundárního zánětu. Klinická diagnóza je zvykle postavena na anamnéze a většinou typických klinických příznacích. Pro potvrzení diagnózy je metodou první volby USG.

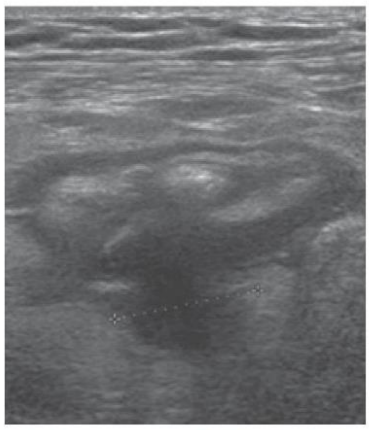
Při USG detekujeme u nekomplikovaného zánětu celkové zvětšení žlučníku, obvykle v příčném průmětu > 5 cm. Žlučník obsahuje zahuštěný obsah (zvláště při empyému) a můžeme detekovat hyperechogenní konkrementy ve žlučníku, v duktus cystikus, event. i v dalších partiích žlučových cest. Stěna žlučníku je zesílená na více než 4 mm, edém způsobuje tzv. vrstvení stěny, v lůžku žlučníku může být prosáknutí (obr. 6). Důležitou známkou je i výrazná palpační citlivost v krajině žlučníku (Murphyho znamení). Při komplikovaném průběhu akutní cholecystitidy se objevuje v lůžku žlučníku volná tekutina, někdy i drobné abscesy ve stěně či v lůžku. Při šíření zánětu do okolí je prosáklý okolní tuk, perihepaticky je přítomna volná tekutina a při propagaci zánětu do okolního jaterního parenchymu se může utvářet absces jater. Při podezření na tyto komplikace je někdy výhodné provést i dynamickou kontrastní ultrasonografii (CEUS – contrast enhanced ultrasonography), při které může být lépe vizualizován tvořící se absces v přilehlém parenchymu jater.

Vyšetření CT je většinou indikováno u komplikovaných forem zánětu, pro potvrzení diagnózy provedeného USG vyšetření a k vyloučení dalších možných komplikací [8]. Vyšetření je prováděno nativně a po aplikaci k. l. i.v. Detekovány jsou obdobné změny jako při USG vyšetření. Objemný žlučník, stratifikace rozšířené stěny žlučníku, její postkontrastní sycení, prosáknutí či volná tekutina v lůžku či perihepaticky. Na intramurální či pericholecystický absces můžeme usuzovat z asymetrického zesílení stěny žlučníku tak jako na USG vyšetření. Zde nesmíme opomenout i obdobný nález např. u tumoru žlučníku. Cholesterolové konkrementy žlučníku obvykle na CT nevidíme. Při nekróze stěny mohou být detekovány drobné bublinky plynu ve stěně či v lůžku žlučníku či v okolí. Při pokročilejších zánětlivých procesech detekujeme i perforaci žlučníku s možnou dislokací žlučníkového konkrementu do duodena, někdy se známkami kryté perforace, či detekujeme volný plyn v břišní dutině. Ve většině případů tedy platí, že význam CT vyšetření je u těchto nemocných minimální a v případě negativního nálezu na USG vyšetření nemá smysl CT vyšetření doplňovat.

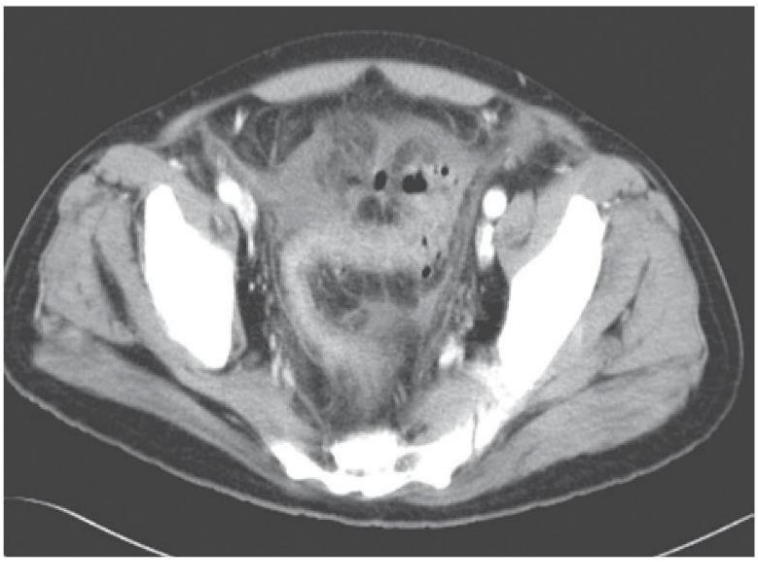
V diferenciální diagnostice je nutno vyloučit procesy v oblasti hepatální flexury tlustého střeva (divertikulitida, segmentární záněty, komplikovaný tumor colon aj.), akutní pankreatitidu, absces jater, vředovou chorobu gastroduodena a její komplikace či appendicitidu při subhepatální lokalizaci appendixu.

## Akutní divertikulitida tlustého střeva

Divertikulóza tlustého střeva se definuje jako výskyt obvykle mnohočetných



**Obr. 8. Ultrasonografické vyšetření břicha, obraz divertiklu na colon sigmoideum, s jemným prosáknutím tuku v okolí, lehce zesílenou stěnou segmentu sigmoidea, bez dalších komplikací – lehká divertikulitida.**
Fig. 8. Ultrasonographic examination of the abdomen, imaging a diverticulum on the sigmoid colon, with a fine infiltration of fat into the surroundings, and a slightly thickened wall of the sigmoid segment, without any other complications – mild diverticulitis.



**Obr. 9. CT vyšetření břicha, axiální rovina (ze sonografie komplikovaná divertikulitida colon sigmoideum). CT potvrzuje edematózní stěnu colon sigmoideum, četné divertikly, krytou perforaci, tekutinové lemy, toho času bez ohraničené kolekce tekutiny či jasného abscesu.**
Fig. 9. CT examination of the abdomen, in the axial plane (from a sonograph of complicated diverticulitis of the sigmoid colon). The CT confirms the edematous wall of the sigmoid colon, numerous diverticula, a covered perforation, fluid margins, at that time without a contained collection of fluid or obvious abscess.

divertiklů v různých částech tlustého střeva. Nejčastěji se vyskytují divertikly v colon sigmoideum (95 %), až u třetiny pacientů se vyskytují divertikly i na jiné části tlustého střeva a asi u 7 % pacientů mluvíme o pankolickém postižení [19–21]. Jednou z možných komplikací divertikulární choroby tračníku jsou zánětlivé změny s různě rozsáhlou propagací do okolí (obr. 7). Jako komplikovaná divertikulitida se označuje vznik abscesu, píštěle či perforace. Další možnou komplikací je krvácení. Při klinickém podezření na akutní divertikulitidu je metodou první volby USG. Hlavními USG známkami jsou zesílení stěny postiženého segmentu tlustého střeva (> 4 mm) a edém stěny střevní. Samotné divertikly jsou se zneostřenou stěnou a okolní tuk je zvýrazněný a prosáklý (obr. 8). Lemy volné tekutiny v okolí, ohraničené kolekce v okolí, signalizují těžkou, komplikovanou formu divertikulitidy. Pacient obvykle při dózované kompresi sondou přesně topizuje místo zánětu, a tím „navádí" vyšetřujícího na oblast zájmu. Samozřejmě je nutné si uvědomovat limitace USG (habitus pacienta, zkušenosti vyšetřujícího, nevhodné anatomické poměry, stav po střevních resekcích atd.). Citlivost USG v detekci abdominálních abscesů je udávána v rozmezí 81–100 %, se specificitou 90–100 % [22]. Pokud je tedy z USG vyšetření či dle klinického stavu a laboratorních hodnot podezření na těžkou, komplikovanou divertikulitidu, je indikováno vyšetření CT.

Vyšetření CT je prováděno nativně, v rozsahu base hrudníku až do malé pánve (vyloučení pneumoperitonea, detekce postiženého segmentu střeva). Dle nativního obrazu je většinou doplňováno vyšetření s k.l. i.v. Při příznivém, resp. jasném nativním obraze však není podmínkou. Vyšetření je schopné detekce výše uvedených změn tak jako na USG. Lépe však hodnotí komplikace zánětlivých změn, zvláště pak je suverénní v detekci volného plynu v dutině břišní (obr. 9). Senzitivita a specificita CT vyšetření pro komplikovanou divertikulitidu je uváděna v rozmezí 75–98 %, resp. 75–100 %. Problémem mohou být drobné kryté perforace [23]. Dobře je stanovitelná délka segmentu střevního, který má zesílenou stěnu, prosáknutí okolního tuku, volná tekutina, ohraničené kolekce tekutiny perikolicky a v malé pánvi či možné komunikace s okolními orgány při komplikované divertikulitidě. V indikovaných případech je možná i perkutánní drenáž perikolického abscesu pod CT kontrolou. Přesné morfologické změny při divertikulitidě, a tím i indikace adekvátní terapie dávají různé modifikované klasifikace dle Hinchey et al [24,25].

## Ileózní stav

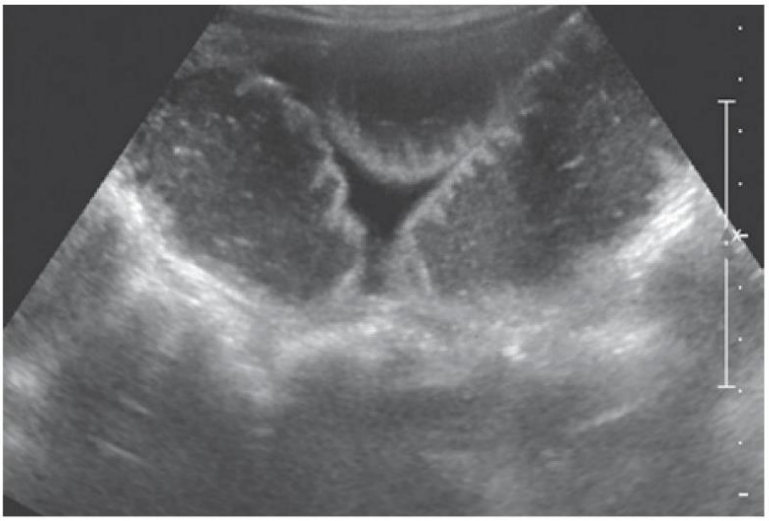
Porucha střevní pasáže patří mezi velmi závažná onemocnění a stav pacienta mnohdy vyžaduje urgentní chirurgický zákrok. V 60–80 % případů je postižení

na tenkém střevě [1,26]. Vyšetření se většinou omezuje na snímek břicha vestoje horizontálním paprskem. Radiologický popis informuje indikujícího lékaře o počtu a lokalizaci hladinek, a pokud je distenze střevní, tak o kalibru dilatovaných kliček [5]. I když jsou možnosti hodnocení z prostého snímku břicha omezené, měl by dávat odpovědi na základní otázky: stran přítomnosti dilatace střev, charakter střevní poruchy (obstrukční/mechanický ileus nebo adynamický/paralytický/neobstrukční ileus), lokalizaci přechodové zóny a hodnocení dalších možných komplikací.

V diagnostice ileózního stavu se vedle nativního snímku břicha, který je diagnostický v 50–60 % případů [1,4,5], uplatňuje dále USG (obr. 10) a CT [27,28]. V indikovaných případech lze využít MR. Zcela vymizelo využití RTG kontrastních metod i aplikace k. l. při těchto akutních stavech. Je potřeba si uvědomit, že hypertonické jodové, ve vodě rozpustné látky zvětšují objem tekutiny v lumen střevním, zvyšují edém stěny a u mechanické obstrukce tímto mechanizmem zhoršují stav nemocného. Pro lokalizaci přechodové zóny, a tím zvýšení senzitivity i specificity všech těchto metod je výhodné, pokud se dělají ještě před event. zavedením nazogastrické sondy (aby nedošlo k dekompresi trávicí trubice a následnému zkreslení hodnocení přechodové zóny).

U cca 50 % nemocných s obstrukcí tenkého střeva jsou příčinou adheze. Bývají zpravidla důsledkem chirurgické intervence a mohou se objevit již do týdne po výkonu [3]. Dalšími příčinami jsou v 15 % tumory, metastázy, dalších 15 % tvoří hernie a zbylých 20 % je způsobeno jinými příčinami, jako jsou např. biliární konkrementy, zánětlivá střevní onemocnění, volvulus či invaginace [3,29–32].

Při chronické idiopatické pseudoobstrukci (CHIP) má tenké střevo oslabenou či vymizelou propulzní peristaltiku a rozšířené lumen bez definovatelné příčiny. CHIP se vyskytuje v každém věku a stejně často u obou pohlaví. Charakteristické jsou rekurentní ataky abdominální distenze, periumbilikální bolest, nauzea, zvracení, zácpa. CHIP provází dilatace jícnu s hypoperistaltikou dolní třetiny jícnu, dilatace duodena a proximálního tenkého střeva bez přítomnosti plynu v tenkém střevě. Příčinou obstrukce tlustého střeva je v 50 % tumor, nejčastěji v colon sigmoideum.



**Obr. 10. Ultrasonografické vyšetření břicha, konvexní, nízkofrekvenční sonda, dilatované kličky ilea, edém řas, volná tekutina mezikličkově, ileus – operační nález adheze.**

Fig. 10. Ultrasonographic examination of the abdomen, convex, using a low-frequency probe, dilated loops of the ileum, edema of the mucosa, free fluid between the intercellular, ileus – surgical finding of adhesion.

Při akutní pseudoobstrukci tlustého střeva (Ogilvieho syndrom) dochází k progresivní dilataci tlustého střeva bez přítomnosti mechanické obstrukce. Jako etiologický faktor se předpokládá porušení parasympatické inervace. Akutní abdominální distenze se objevuje během 10 dní po vyvolávajícím podnětu (trauma, rozsáhlé břišní a pánevní operace, intraabdominální zánět, alkoholizmus, choroby srdce, zvracení, retroperitoneální choroba, těhotenství či porod) [30,33].

Obecně při ileózním stavu dochází k postupnému snižování aktivity střeva. Tekutina a vzduch se akumulují v jeho lumen, které se tak rozšiřuje. K distenzi trávicí trubice dochází orálně od místa obstrukce. Rozložení plynu v tenkém střevě může být rozličné. U některých pacientů vytváří obraz štaflí, jindy se může většina vzduchu resorbovat, čímž vzniká obraz šňůry perel (malé kolekce vzduchu mezi řasami), znamení kávového zrna (uzávěr kličky tenkého střeva na dvou místech) či obraz pseudotumoru (klička tenkého střeva naplněná tekutinou, která se jeví jako měkká, oválná, intraabdominální masa).

Falešně pozitivní a negativní nálezy z prostého snímku břicha jsou při obstrukčním ileu až u 20 % nemocných. Ke zpřesnění diagnostiky přispívá především znalost kliniky, poslechového nálezu a kontrolní snímek za 12–24 hod či provedení akutního CT vyšetření (vše na základě vývoje klinického obrazu).

Vyšetření USG bývá u ileózních stavů další z metod volby. Nicméně je třeba si uvědomit, že jednou z nevýhod USG je, že neprochází plynem. Orientace v dutině břišní při plynaté distenzi střev může být ztížená. I tak je však možné posoudit míru dilatace tenkých kliček, které jsou vyplněné tekutinou, a posoudit, zda je přítomen edém řas či je přítomna volná tekutina v dutině břišní. To vše jsou nepřímé známky stavu, nicméně snahou

vyšetření by mělo být i zjištění příčiny dilatace střevních kliček. USG je za příznivých podmínek schopna detekovat patologii, která dilataci střev způsobuje (např. postižení střevního segmentu u CD, postižení ileocékální při komplikované appendicitidě, zánětlivý pseudotumor, divertikulitidu colon sigmoideum, expanzi v dutině břišní aj.) [31,34].

Hlavní předností CT vyšetření je komplexní zhodnocení břišní dutiny a rychlost vyšetření. Vedle diagnózy střevní obstrukce a určení její lokalizace je to zejména i možnost zachycení porušené vitality střevní stěny. Toto vyšetření lze rovněž použít k odlišení pooperačního paralytického ileu od mechanické obstrukce [23]. Udávaná senzitivita CT u akutní střevní obstrukce je 90–96 %, specificita 96 % a přesnost 95 % [6,27,28], objasnit příčinu se při CT vyšetření podaří v 73–95 % případů [1].

Samotné CT vyšetření provádíme vzhledem k akutnosti stavu bez předchozí přípravy. Je však nutno zohlednit renální parametry, alergie a zda neužívá pacient metformin. Vyšetření, rozsahem nejčastěji od bránice až do malé pánve, provádíme iniciálně nativně a následně na ozřejmění vitality střevní stěny doplňujeme kontrastní vyšetření s aplikaci k. l. i.v. Stagnující tekutý obsah v kličkách střevních poskytuje dobrý negativní kontrast, perorální podání k. l. proto považujeme za neopodstatněné. Navíc podání k. l. zhoršuje hodnocení opacifikace střevní stěny.

Pro diagnózu střevní obstrukce je zásadní detekce tzv. přechodové zóny, tedy místa, ve kterém se náhle mění průsvit střevní z dilatovaného na normální či kolabovaný. V případě paralytického ileu přechodovou zónu nenalézáme, většinou je dilatováno jak tenké, tak tlusté střevo. O dilataci tenkého střeva při CT vyšetření uvažujeme, pokud průměr kliček přesahuje 2,5 cm [1,6]. K určení příčiny obstrukce je nezbytná pečlivá analýza skenů v oblasti přechodové zóny. Výhodné je využití multiplanárních zobrazení, v koronární a sagitální rovině. Diagnózu adhezivního ileu stanovíme nepřímo, vlastní srůsty totiž nebývají detekovatelné, a tak, pokud na CT skenech nezobrazíme přímo příčinu obstrukce, je velké podezření, že stav je způsoben právě adhezemi.

Ostatní příčiny lze přímo vizualizovat. Tumory se zobrazí jako solidní léze mající vztah k místu obstrukce. Polypoidní tumory mohou být příčinou invaginace [31]. Zánětlivé stenózy (nejčastěji u CD) a postiradiační stenózy mají obdobný vzhled zpravidla v delším úseku cirkulárně zesílené stěny způsobující těsnou stenózu s prestenotickou dilatací [3,29,35]. Zevní kýly jsou snadno detekovatelné, zatímco odhalení vnitřní hernie může být problematické [26]. Volvulus má typický vzhled víru, způsobený otočením mezenteria s radiálním uspořádáním střevních kliček [1].

Strangulace je komplikací mechanické obstrukce, nejčastěji se objevuje u adhezivního ilea, při uskřinutí v kýlní brance či při volvulu. Strangulaci představuje při CT vyšetření obraz closed loop, střevní klička tvaru U, C nebo tvaru zobáku, někdy se může objevit neobvyklý průběh mezenteriálních cév, kdy nacházíme obrácenou pozici horní mezenterické tepny a žíly, příznak víru nebo cévy konvergují do jednoho místa. Vlivem strangulace dochází nejprve k obstrukci žilní drenáže a posléze k přerušení toku i v přívodných mezenteriálních tepnách a ke vzniku ischemie střevní.

## Střevní ischemie

Akutní střevní ischemie je závažný stav s vysokou mortalitou. Nejčastěji vzniká embolizací či akutní trombózou horní mezenterické tepny. Embolizace do viscerálních tepen může být sdružena i s embolizací jiných orgánů (slezina, ledviny, dolní končetiny). Trombóza mezenterických žil má většinou pomalejší klinický rozvoj vzhledem k bohatému kolaterálnímu řečišti. Další jednotkou je nonokluzivní ischemie střevní, bez prokazatelného uzávěru tepenného či žilního. Zde se jedná např. o pacienty v šokovém stavu spojeném s poklesem krevního tlaku v kombinaci s poklesem hematokritu po krevních ztrátách.

Při klinickém podezření na akutní střevní ischemii je metodou první volby provedení CT. Nicméně řada případů není typických a obvykle se vylučují i jiné možné příčiny NPB. I zde bývá indikován prostý snímek břicha, kde je možno detekovat ileózní stav s edémem řas tenkého střeva a v pokročilejších stadiích i obraz plynu ve stěně střevní (pneumatosis intestinalis). Doplnění USG vyšetření může zobrazit zesílení stěny, edém stěny, změny vaskularizace stěny střevní, prosáknutí mezenteriálního tuku a více či méně volné tekutiny. V dopplerovském záznamu můžeme vylučovat aneuryzma či disekci aorty a průchodnost odstupujících viscerálních tepen. Celkově je diagnostika ischemie střevní na USG dosti iluzorní i vzhledem k obvyklému habitu těchto pacientů.

Vyšetření CT vykazuje vyšší senzitivitu i specificitu v hodnocení změn při akutní střevní ischemii. Detailně je možno hodnotit abdominální aortu a přítomnost disekce. Typickým nálezem bývá absence vysycení mezenterických tepen k. l., které se objevuje v jejich průběhu. Ischemická střevní stěna bývá cirkulárně edematózně zbytnělá, přičemž lze někdy diferencovat její vrstvy. Tento nález, spolu s tekutinovým obsahem v lumen, vytváří na příčném řezu obraz terče. Nepravidelné hyperdenzní zóny ve stěně střevní odpovídají krvácení.

Typické je i prosáknutí okolního mezenteria a lemy volné tekutiny (obr. 11) [36]. V pokročilých fázích je plyn ve stěně střeva nebo plyn v mezenteriálním a portálním řečišti, což představuje ireverzibilní změny a je projevem nekrózy střevní stěny. Postupně se rozvíjí paralytický ileus.

Chronická ischemie bývá spojena s hemodynamicky významnou stenózou alespoň dvou tepen podílejících se na zásobení střevních kliček (truncus celiacus, arteria mesenterika superior, arteria mesenterika inferior). Základní vyšetřovací metodou k potvrzení stenózy je dnes USG a CT angiografie.

Při správné indikaci je možné využít možností endovaskulárního řešení těchto okluzivních stavů. Při trombóze na podkladě přítomnosti aterosklerotického plátu je možné provedení angioplastiky, většinou s implantací stentu. Při embolizacích je možné se pokusit o aspiraci, mechanickou trombektomii či farmakologickou intrarteriální trombolýzu mezenterického řečiště.

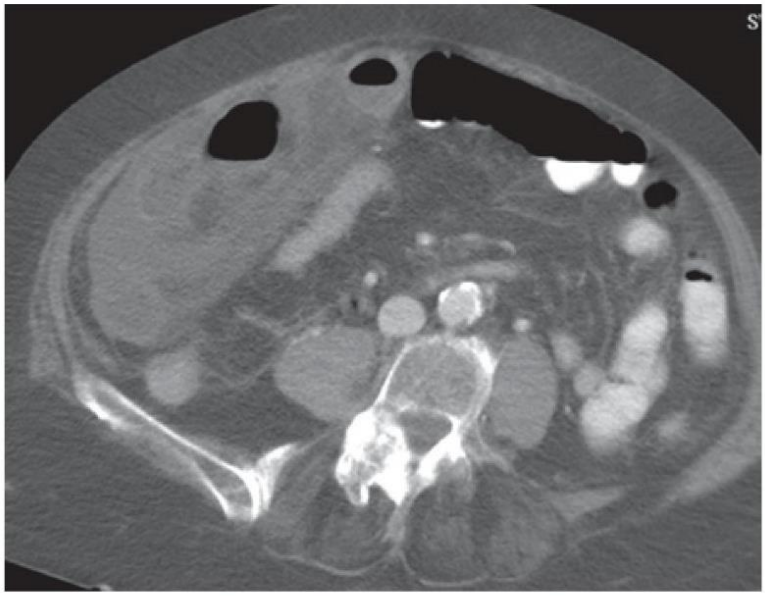
### Krvácení do trávicí trubice

Základní diagnostickou metodou v případě krvácení z horní i dolní části trávicí trubice, a to jak u akutního, tak chronického krvácení, je endoskopie. Pokud jsou v detekci zdroje krvácení endoskopické metody neúspěšné, je indikováno CT vyšetření nebo chirurgická intervence [37]. Vyšetření je vhodné provést vč. tzv. odložené fáze. Zde je větší šance na detekci i.v. podané k. l. intraluminálně, což potvrzuje krvácení. Někdy detekujeme přímo leak k. l. při arteriální fázi vyšetření. CT vyšetření může detekovat možný zdroj tohoto krvácení (např. nádory, ischemie střevní, divertikly, aortoduodenální píštěl atd.).

DSA provádíme spíše jen na podkladě pozitivního CT nálezu v rámci event. endovaskulárního řešení (embolizace) či při nejasném CT obraze a neutěšeném klinickém stavu pacienta. DSA provádíme přehledným nástřikem abdominální aorty a selektivním nástřikem truncus celiacus a mezenterických větví. Alternativou standardně provedené angiografie s pozitivní jodovou k. l. je využití negativního kontrastu, kterým je oxid uhličitý. Jeho nízká viskozita usnadňuje únik k. l. mimo cévní systém a jeho následné rozpínání zvýrazňuje nález. Samotné hodnocení může být obtížnější a vyžaduje zkušenost vyšetřujícího s touto technikou.

### Akutní pankreatitida

Jedná se o závažné onemocnění s akutním průběhem, které může probíhat pod obrazem NPB. Tito pacienti mohou být v počátcích diagnosticky a diferenciálně diagnosticky problémem. Radiologie má nezastupitelnou roli jak v diagnostice a sledování průběhu léčby, tak i v řešení možných urgentních komplikací akutní pankreatitidy (např. embolizace pseudoaneuryzmat aj.).



**Obr. 11. CT vyšetření břicha, axiální rovina, volvulus tenkého střeva s nevysycující se stěnou střevní po aplikaci kontrastní látky intravenózně – ischemie střevní.**

Fig. 11. CT examination of the abdomen, in the axial plane, showing a volvulus of the small intestine with a non-enhancing intestinal wall after application of an intravenous contrast agent – intestinal ischemia.

Při provedeném prostém snímku břicha můžeme na akutní pankreatitidu pomýšlet při příznaku tzv. strážní kličky. Jedná se o plynem distendovanou kličku jejuna v oblasti středního či levého mezogastria, s hydroérickým fenoménem a edémem řas. Někdy můžeme zachytit neostrou levou bránici nebo i drobný pleurální výpotek vlevo. Pozorujeme též chudou pneumatózu střevních kliček.

Další indikovanou metodou bývá USG. Je nutné posoudit především žlučové cesty na přítomnost konkrementů k vyloučení biliární etiologie. Samotný pankreas a peripankreatická oblast nemusí být na sonografii dostatečně přehledné. V závislosti na vývoji zánětlivých změn detekujeme edematózně zvětšenou žlázu, prosáknutí či kolekce v okolí.

Základní význam má CT, které je vedle vlastní diagnostiky považováno za metodu nejlepšího skórovacího systému těchto nemocných (např. CT severity index (CTSI) či jiné modifikované indexy) [38,39]. Na základě CT vyšetření po i.v. podání k. l. můžeme hodnotit zvětšení a edém žlázy, přítomnost nekrózy a její rozsah a charakterizovat přítomnost, rozsah, homogenitu a lokalizaci peripankreatických či pankreatických kolekcí tekutiny. K určení tíže akutní pankreatitidy a k vyloučení komplikací je tedy ideální odstup 48–72 hod od začátku onemocnění [40]. Akutní CT vyšetření provádíme ihned v případě, pokud pomýšlíme na jinou NPB, např. perforaci, která vyžaduje chirurgické řešení.

Z CT vyšetření lze posoudit ev. extrapankreatický nález (cholecystolitiáza, choledocholitiáza, trombóza žil, pseudoaneuryzmata, ascites atd.) či další abnormality v dutině břišní.

## Závěr

NPB vyžadují rychlou a správnou diagnostiku. Využití a možnosti jednotlivých zobrazovacích metod závisí

mnohdy na zvyklostech jednotlivých pracovišť. Zřejmý je v dnešní době nárůst CT vyšetření. Dnešní možnosti zobrazovacích metod umožňují nejen zodpovězení základních otázek, se kterými chirurg k vyšetření přistupuje (pneumoperitoneum, ileózní stav, volná tekutina v dutině břišní, postižení parenchymatózních orgánů aj.), ale zvláště CT je schopno detailnější charakteristiky jednotlivých patologických stavů (předpokládané místo perforace, lokalizace a povaha překážky, lokalizace krvácení atd.). V některých akutních stavech je dnes také možné využít výkonů v rámci intervenční radiologie.

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**Příloha 8** - Rare cases imitating acute appendicitis: Three case reports and a review of literature

Case report

# Rare cases imitating acute appendicitis: Three case reports and a review of literature

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**Summary**
Acute appendicitis with its characteristic clinical course is one of the most common diagnoses that require urgent surgery. The following three case reports present patients with symptoms typical of acute appendicitis which was, however, not confirmed intraoperatively. Preoperative CT or MRI were not requested because symptoms clearly indicated acute appendicitis. The first case describes a male patient with right-sided diverticulitis, the second case report involves a pregnant woman in 33rd week of gestation with right adnexal torsion due to a dermoid cyst, and in the last report, a case of spontaneous perforation of appendiceal mucinous neoplasm is presented.
**Key words:** right-sided diverticulitis – dermoid cyst – adnexal torsion – mucinous neoplasm – pseudomyxoma peritonei – appendicitis

**Souhrn**
**Vzácné případy napodobující akutní apendicitidu: tři kazuistiky a přehled literatury**
**L. Kunovský, Z. Kala, L. Mitáš, V. Čan , J. Dolina, E. Němcová, L. Klvačová, T. Gajdošová, I. Penka**

Akutní apendicitida, se svým typickým klinickým průběhem, je jedna z nejčastějších diagnóz vyžadující akutní operaci. V těchto třech kazuistikách prezentujeme pacienty, jež měli typický klinický průběh svědčící pro akutní apendicitidu, která se však během operace nepotvrdila. CT nebo MR nebyly předoperačně provedeny vzhledem k typických příznakům akutní apendicitidy. V první kazuistice je popsán pacient s pravostrannou divertikulitidou, v druhé kazuistice gravidní pacientka ve 33. týdnu těhotenství s torzí pravého ovária a v poslední popisujeme spontánní perforaci apendikální mucinózní neoplazie.
***Klíčová slova*:** pravostranná divertikulitida – dermoidní cysta – mucinózní neoplazie – pseudomyxom peritonea – apendicitida

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## INTRODUCTION

Acute appendicitis (AA) is one of the most common causes for urgent surgery.

The lifetime incidence of AA is approximately 7% [1,2]. In recent studies, a decreasing rate in most countries worldwide has been reported [3–6]. The annual incidence varies from 75/100,000 in Ontario (Canada) [4], 94/100,000 in USA [7], 98/100,000 in Finland [5] to 107/100,000 in Taiwan [6].

The first-line treatment for AA is prompt surgical intervention. Therefore, surgery is sometimes performed for presumed appendicitis and a non-appendiceal and less common diagnosis is finally revealed.

Differential diagnosis of right iliac fossa pain includes a wide variety of conditions. Apart from AA, problems of gynaecological or urological origin, mesenteric lymphadenitis, infectious gastroenteritis, inflammatory bowel disease, cecal tumours etc. can be considered.

In differential diagnosis of right lower quadrant pain, we have recently encountered the following infrequent cases at our department: right-sided diverticulitis, adnexal torsion in late pregnancy and spontaneous perforation of an appendiceal mucinous neoplasm.

Right-sided diverticular disease is rare in the Western world with incidence being approximately 1–2% of all cases of colonic diverticulosis. However, the disease is more common in Asia where the incidence varies between 50–70% [8–11]. Preoperative diagnostics of acute right-sided diverticulitis (RSD) is challenging and the success rate is usually as low as 0–23% [12] due to symptoms similar to AA. Most diagnoses of RSD (70–90%) are made during surgery [12,13].

Right adnexal pathology can often mimic symptoms of AA. A clear distinction based on clinical examination or ultrasound is difficult. Moreover, pregnancy, particularly in its later stages, can make differential diagnosis of right iliac fossa pain even more demanding.

Dermoid cysts represent 20–40% of ovarian neoplasms discovered during pregnancies and can cause serious complications such as rupture, torsion, bleeding, infection, malignancy or obstructed labour [14–16]. The highest number of torsions occurs in the first, occasionally in the second and very rarely in the third trimester [16].

Appendiceal tumours are rare and can be found in less than 1% of the performed appendectomies [17,18]. Of these, low-grade appendiceal mucinous neoplasms (LAMN) represent only a minor subgroup [18]. Pseudomyxoma peritonei (PMP) is described as mucinous ascites or intraperitoneal mucin deposits containing variable numbers of neoplastic epithelial cells [19]. PMP mostly arise from appendiceal mucinous neoplasms [19,20].

## CASE REPORT 1

### Right-sided diverticulitis

A 39-year-old man was referred to our outpatient department with a two-day history of right iliac fossa pain without nausea or vomiting. The patient was known to have diabetes mellitus and had undergone left inguinal hernia repair. Clinical examination revealed signs of peritonitis in right lower quadrant and blood tests showed elevated inflammatory markers (CRP: 69 mg/l, WBC count: $12\times10^9$/l). An ultrasound scan proved a thickened appendix wall as well as mild inflammatory changes in the caecum and ascending colon. The patient was admitted for a high suspicion of AA and laparoscopy was performed, however, with surprising findings. The appendix showed no inflammatory changes. On the contrary, initial stage of cecal diverticulitis was diagnosed (Fig. 1a, 1b). No severe complications were observed and therefore laparoscopic appendectomy was performed. During hospital stay, antibiotic therapy was administered and CT scans were done (Fig. 2a). The patient was discharged on the 6$^{th}$ postoperative day with appropriate instructions and scheduled follow-up. Three months later, the patient was readmitted for abdominal pain with a WBC count of $17\text{x}10^9$/l and CRP of 250 mg/l. A repeat CT scan showed extensive diverticulitis of the caecum and the ascending colon with a forming abscess (fluid collection) (Fig. 2b). Laparoscopic revision was carried out and pericecal abscess, distant abscess in small pelvis and inflammatory

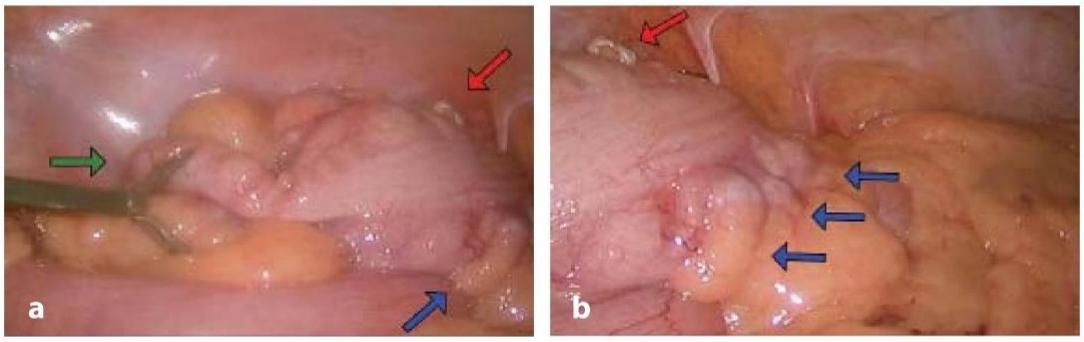


**Fig. 1a, 1b: Laparoscopic view – no inflammatory changes of the appendix (green arrow), diverticula with infiltrate (red arrow), other mildly inflamed diverticula in the caecum and ascending colon (blue arrows)**

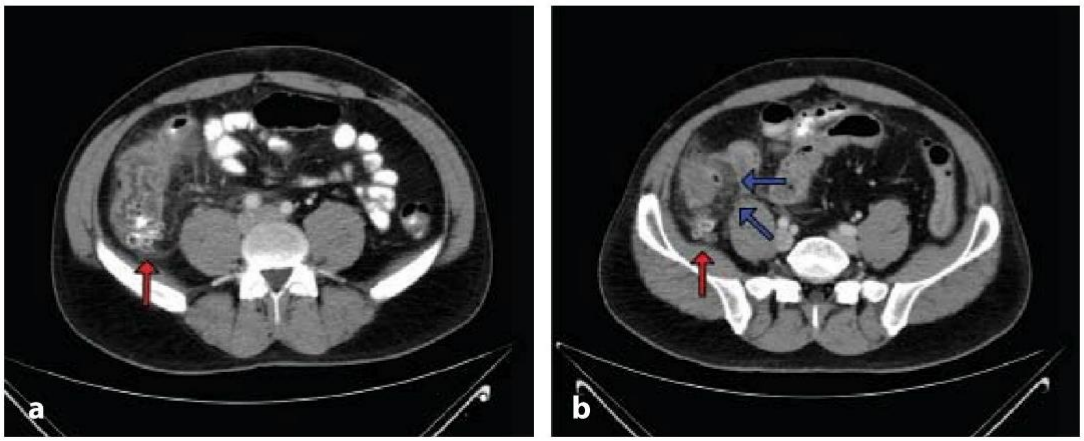


**Fig. 2a: CT scan – image of the initial stage of cecal diverticulitis (red arrow – diverticula)**

**Fig. 2b: CT scan – image of extensive diverticulitis affecting caecum and ascending colon with a forming abscess (fluid collection) (red arrow – diverticula, blue arrows – forming abscess)**

adhesions between terminal ileum and caecum were found. All pus was aspirated, thorough lavage was performed and two drains were placed into the abdominal cavity (pericaecally and into the small pelvis). Parenteral nutrition and intravenous antibiotic therapy was given. The patient was discharged on day 9 after surgery and scheduled for elective right hemicolectomy in 2 months' time.

## CASE REPORT 2

**Adnexal torsion due to a dermoid cyst in the 3rd trimester of pregnancy**

A 35-year-old woman in the 33rd week of her second pregnancy suffered from diffuse abdominal pain that lasted for 24 hours and later progressed into the right lower abdomen. The pain was accompanied by nausea and occasional vomiting. The patient was known to have Crohn's disease affecting terminal ileum, in remission at that point, and a solitary gallbladder stone. Gynaecological examination was unremarkable – normal gestation. Blood tests showed elevated inflammatory markers (CRP: 59 mg/l, WBC count: $11\times10^9$/l) and signs of peritoneal irritation were present in the right lower quadrant during physical examination. Abdominal ultrasound study was limited due to patient's late pregnancy and the appendix was not visualized although indirect signs of AA were reported. There were no signs of acute cholecystitis or active inflammatory changes in the terminal ileum. The patient was admitted for typical signs of AA and, because of her advanced pregnancy, Mc Burney's laparotomy was performed. Surprisingly, a normal appendix was found together with dermoid cyst 5×3 cm in size causing ovarian torsion on the right side (rotated three times around the axis) (Fig. 3). Detorsion of the ovary and resection of the dermoid cyst was performed. Appendectomy was not indicated due to the absence of inflammatory changes. The patient was discharged 5 days after surgery. She vaginally delivered in the 39th week of gestation. The weight of the newborn was 2100 g. The diagnosis of dermoid cyst was confirmed by histology (Fig. 4).

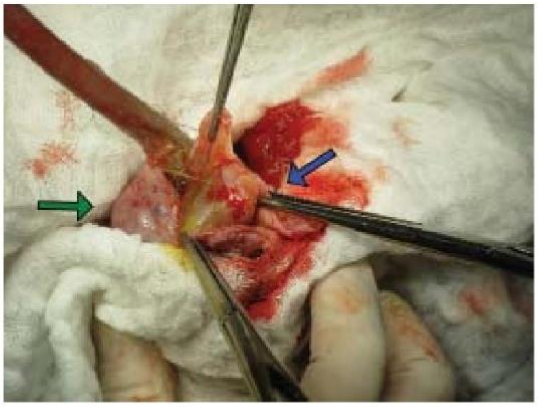

**Fig. 3: Intraoperative findings showing hairs and sebum characteristic for dermoid cyst (green arrow – ovary, blue arrow – part of the dermoid cyst)**

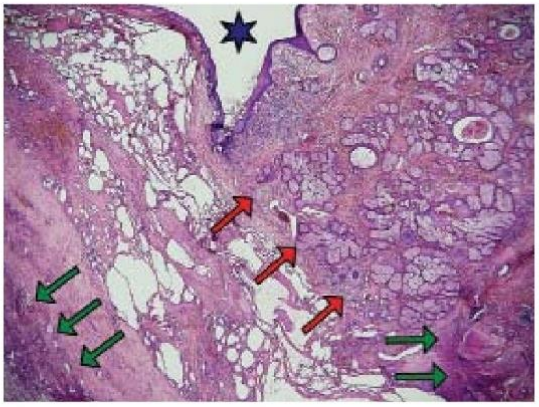

**Fig. 4: Histological section of the dermoid cyst – epidermis with sebaceous glands and hair follicles (red arrows), lumen of the dermoid cyst (star), residual ovarian stroma (green arrows)**

## CASE REPORT 3

**Spontaneous perforation of an appendiceal mucinous neoplasm**

A 66-year-old woman presented with intermittent pain in the hypogastrium. A CT was done showing only

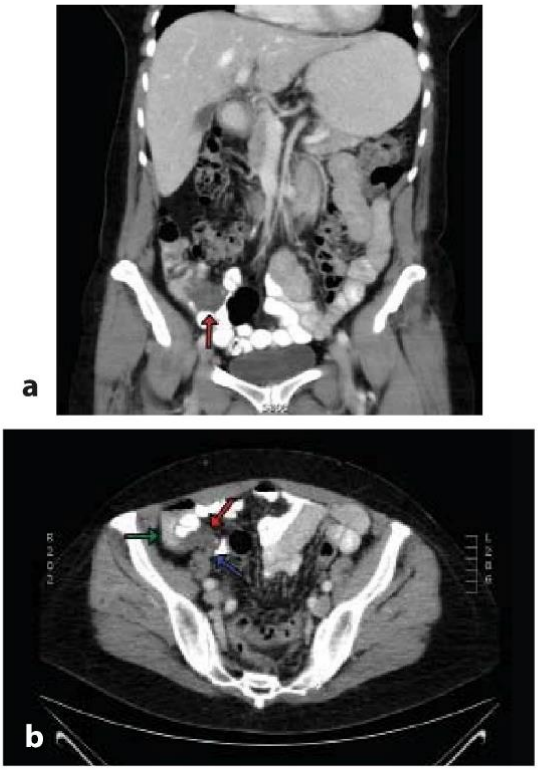


**Fig. 5a, 5b: CT scan – dilated appendix in its base, filled with mucus (red arrow), unextended part of the appendix in medial-dorsal position (blue arrow), the caecum (green arrow)**

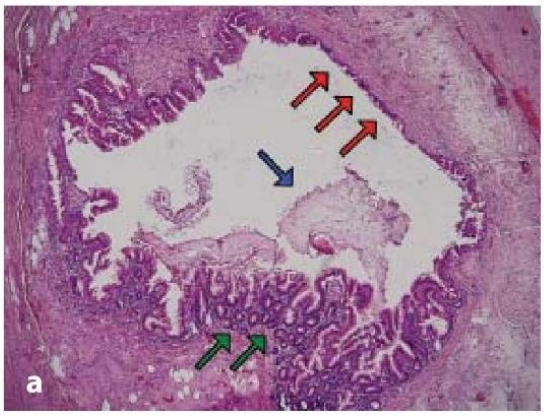


**Fig. 6a: Histological section – low-grade appendiceal mucinous neoplasm (red arrows – undulating epithelium with low-grade dysplasia which rests on fibrous stroma; there is no lamina propria, blue arrow – mucin, green arrows – normal non-dysplastic epithelium)**

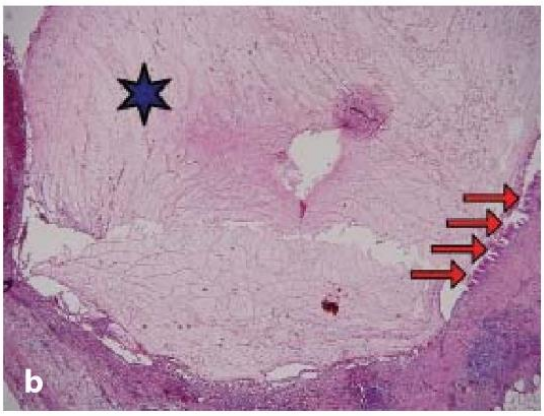


**Fig. 6b: Histological section through dilated base of the appendix, lumen filled with mucin (star), (red arrows – undulating epithelium with low-grade dysplasia)**

a dilated base of the appendix (Fig. 5a, 5b). The scan was reported as postinflammatory changes. The patient refused any further investigations at that point.

One year later, she was admitted for 2-day history of right hypogastrium pain without vomiting, nausea or dysuria. The patient's surgical history was significant for hysterectomy performed for uterus prolapse with no other comorbidities reported. Blood test showed altered inflammatory markers. Given the suspicion of AA reported by ultrasound scan together with tenderness in the right lower quadrant, diagnostic laparoscopy was indicated. The procedure was converted to open due to unclear findings in the area of appendix. The appendix was found in the medial-dorsal position, with no inflammatory changes, however, dilated at the base and full of mucinous tissue with signs of spontaneous perforation. Standard appendectomy was performed. The patient's recovery was uneventful and she was discharged on the 7$^{th}$ postoperative day. The specimen was reported as a low-grade appendiceal mucinous neoplasm (Fig. 6a, 6b). In accordance with oncologists, no further surgical intervention was indicated and patient will proceed with clinical follow-up including a surveillance CT scan in 6 months' time and a colonoscopy.

## DISCUSSION

Differential diagnosis of right lower quadrant pain remains a challenge surgeons frequently face in their clinical practice. The spectrum of organs and potential conditions to be considered is wide and therefore, it is often difficult to reach the right conclusion. Particular case history and physical examination may not raise suspicion of a certain disease. Moreover, ultrasound study or blood test do not always correlate with the clinical findings and do not necessarily reveal the cause of the pain. Three cases were presented in which the only common lead for the surgeon was right iliac fossa pain. Neither ultrasound nor laboratory tests contributed to the right diagnosis.

The treatment of RSD remains controversial and varies from antibiotic therapy only, through prophylactic appendectomy, diverticulectomy, up to radical resection. Despite the controversies, most authors recommend performing a prophylactic appendectomy followed by antibiotic therapy in non-complicated diverticulitis when diagnosed intraoperatively [10,13,21]. The management of RSD depends on the disease stage and should be treated similarly as left-sided diverticulitis [22]. In complicated diverticulitis (stage Ib or higher according to modified Hinchey classification [23]), surgical intervention should be considered [13,21].

For recurrent disease, elective surgical resection should be preferred [13,21]. The early stage of complicated diverticulitis (stage Ib) can be treated conservatively or with CT-guided percutaneous drainage. In Hinchey stage II, CT-guided drainage should be preferred to urgent radical surgery [24]. Laparoscopic peritoneal lavage and drainage (LLD) are also suitable options at this stage. In case of peritonitis (stage III or IV), laparoscopic Hartman's procedure (LHP) or LLD is indicated according to Liang et al. [25]. In their study, both methods were reported as safe and effective in management of severe diverticulitis. Liang claims that LLD does not treat completely the source of infection, but avoids stoma and has better short- and long-term outcomes than LHP. Gentile et al. [26] published similar results suggesting that LLD is safe and effective, but only for Hinchey stage III. Open Hartmann's procedure remains the golden standard in the management of stage IV diverticulitis, however, the surgery is associated with a high morbidity and mortality. LLD should be indicated based on individual, complex patient assessment as well as on the department's experience [27].

In our case, the first attack of diverticulitis was treated with appendectomy followed by antibiotic therapy.

The second attack with pericecal abscess was managed by surgery – abscess evacuation and drainage. Given two subsequent episodes of diverticulitis and the fact the second one was classified as complicated, the decision was made to proceed with elective right hemicolectomy.

The incidence of adnexal torsion is approximately 5 per 10 000 spontaneous pregnancies [28,29] and is more frequent in the first and second trimester [15,16]. The onset peaks between 8th and 16th week of gestation when uterus grows faster [15], in contrast to the third trimester when the uterus fills out most of the abdominal cavity and the incidence of torsions is rather sporadic.

Dermoid cysts measuring 5 cm and less with benign ultrasound appearance can be treated conservatively during pregnancy [14,30]. Resection should be performed in the cysts larger than 10 cm because of an increased risk of malignancy, rupture or torsion [14,29,30]. The management of cysts 5–10 cm in size remains controversial. Caspi et al. [31] advocate conservative management of adnexal masses with <6 cm in diameter. Masses of 6–10 cm in size require careful evaluation by ultrasound or MRI imaging. If multilocular, thick-walled, semi-solid cysts or cysts with papillary excrescences are detected, resection is recommended [16,29,30]. Some authors claim that if a dermoid cyst larger than 6 cm in diameter is detected by ultrasound or MRI scan in gravidity, elective resection should be performed to prevent surgical emergency [14,16,30].

If elective surgery is indicated during pregnancy, it should be scheduled between the 16th and 20th week when the fetus is securely implanted. Moreover, some types of cysts (e.g. functional cysts) can resolve spontaneously by the 16th week of gestation [14,29]. Patients who underwent surgery due to adnexal torsion or any laparotomy after 23rd week of gestation are in a significantly higher risk of adverse pregnancy outcomes compared to patients who had the operation in earlier stages of pregnancy [16,30]. This has been also documented in our case report (newborn hypotrophy – 2100 g).

In the first two trimesters, laparoscopy should be preferred, in contrast to the third trimester where open approach is usually indicated due to uterus size. This decision has also been taken in our patient in the 33rd week of pregnancy. Most current studies have proven that the laparoscopic approach, when compared to open, has similar risks for the fetus. Laparoscopy in pregnancy is considered to be a safe and feasible procedure and the risks of complications are mostly associated with the underlying disease combined with other maternal factors rather than with the type of surgical approach [14,32].

In our case of LAMN, the appendectomy was radical enough because no infiltration of the surrounding colon or mesocolon was present. Nevertheless, careful follow-up is needed including control CT scan after half a year to rule out intraabdominal relapse as well as colonoscopy because the appendiceal neoplasia can be associated with colorectal cancer [17,33]. Patients with mucin limited to the appendix (without any free mucin on the appendix serosa) are at a very low risk of developing PMP and appendectomy is a sufficiently radical procedure. If mucin occurs in the appendix serosa, the risk of PMP has to be considered. Even though, in our case the risk of relapse and PMP had to be considered due to spontaneous perforation, more extended procedure was not indicated from our point of view. The extra-appendiceal mucin was reported by a pathologist as acellular (no neoplastic epithelial cells present). If cellular mucin (with neoplastic epithelial cells) occurred on the appendiceal serosa, the patient would be at a higher risk of developing PMP [18,19,34].

Some authors claim cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) should be considered in patients with a high risk of PMP [18]. More studies focused on the efficacy of CRS and HIPEC should be conducted before these approaches become the method of choice in high-risk patients as they are very difficult to organize and carried out in a limited number of departments; better data about their benefits, effectiveness and significance in the prevention of disease recurrence should therefore be available.

In consensus with oncologists, it has been taken into account that neoplastic epithelial cells had not been detected in the extra-appendiceal mucin and therefore conservative treatment with clinical follow-up was indicated as mentioned previously.

## CONCLUSION

AA usually has a typical clinical course requiring prompt surgery. In this article, three cases are presented where the diagnosis of AA has not been confirmed intraoperatively, nevertheless, in all cases the surgical intervention was indicated. Less common conditions need to be considered in differential diagnosis of right iliac fossa pain. Despite the availability of modern imaging, the indication for surgery should be based on clinical examination and, if any doubts (for example unclear CT or MRI findings), at least a diagnostic laparoscopy should be performed.

**Abbreviations:**

| | |
|---|---|
| AA | – acute appendicitis |
| RSD | – right-side diverticulitis |
| LAMN | – low-grade appendiceal mucinous neoplasm |
| PMP | – pseudomyxoma peritonei |
| LLD | – laparoscopic peritoneal lavage and drainage |
| LHP | – laparoscopic Hartman's procedure |
| CRS | – cytoreductive surgery |
| HIPEC | – hyperthermic intraperitonal chemotherapy |
| CRP | – c-reactive protein |
| WBC | – white blood cells |

*Conflict of Interests*

*The authors declare that they have not conflict of interest in connection with the emergence of and that the article was not published in any other journal.*

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**Příloha 9** - Crohn disease and pregnancy: a case report of an acute abdomen

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LETTER TO THE EDITOR

# Crohn disease and pregnancy: a case report of an acute abdomen

**Lumir Kunovsky[1] · Beata Hemmelova[1] · Zdenek Kala[1] · Jiri Dolina[2] · Stefan Konecny[2] · Igor Penka[1]**

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Dear Editor:

Crohn disease (CD) as a chronic inflammatory disease with heterogeneous clinical features has a fluctuating progress with periods of remission and relapses.

It has been reported that pregnancy does not worsen the course of CD and that tendencies for relapses of disease in pregnancy are rare. In our case, we report a 29-year-old woman with CD in the 12th week of gravidity where conservative therapy failed and the patient had to undergo a surgical procedure.

The incidence of CD is increasing worldwide. Nowadays, the highest incidence is in North America (20/100,000) and Australia (16–17/100,000), followed by Western Europe (9–13/100,000). In the Middle East and other Asian countries, the incidence is lower and varies (0.2–5/100,000), nevertheless an increase due to globalization is apparent.

CD manifestation usually occurs in younger age and half of the patients are already diagnosed with CD before or at the age of 30. A considerable part of women with CD know the diagnosis before pregnancy and are afraid of an exacerbation of CD due to gravidity even though it has been reported that pregnancy does not affect the course of the disease in the means of more severe course or relapses of CD.

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## Case report

We present a 29-year-old patient with Crohn disease diagnosed in 2009 who underwent right side hemicolectomy in January 2014 (because of a stenosis of caecum and ascending colon). Side to side anastomosis was performed. The control colonoscopy did not show signs of CD recurrence, there were only three aphthous lesions near the base of the colon. Rutgeerts score was i1, so the step-up therapy was not indicated. After the procedure, the patient remained in remission on a conservative treatment using azathioprine. The patient is a non-smoker since 2010, before that she used to smoke five cigarettes per day and before conception she used per oral contraception for 8 years until August 2014. Because of the remission of CD and after a consensus with a gastroenterologist, the first pregnancy was planned. During the pregnancy, the medication remained on azathioprine.

In February 2015, when the patient was in the 12th week of gravidity, abdominal pain occurred and the patient had to be admitted to the surgical ward. The clinical examination demonstrated painful palpation in both hypogastrium. On the day of admission, the inflammatory markers in the blood test were elevated (CRP 141 mg/l, Leukocytes $17 \times 10^9$/l). Ultrasound showed only discreet peritoneal cavity fluid, mostly in the small pelvis, a slight thickening of the ileum wall in the length of 10 cm in the right lower abdominal quadrant and an effusion of the mesentery. The exacerbation of CD was not clear from the beginning. Infectious gastroenteritis was considered in differential diagnosis as well, due to fevers and diarrhea. Even a gastroenterologist did not presume an exacerbation of the disease. Despite the antibiotic therapy, the markers of inflammation in the blood tests increased and the clinical condition worsened. The signs of peritoneal irritation were present. A surgical

revision had to be performed. A diagnostic laparoscopy was carried out first. Because of the present findings—purulent peritonitis and inflammatory convoluted part of neo-terminal ileum (possible signs of active Crohn disease)—the decision about a conversion was made. The reason of the peritonitis was a perforated fistula going from the ileum to the mesentery. The perforated fistula was found 10 cm before the anastomosis. No stenosis was present in the anastomosis. A resection of the affected part of the neo-terminal ileum including the anastomosis, blind closure of transverse colon, and terminal ileostomy was performed. An anastomosis was not constructed because of severe inflammatory findings and the risk of anastomotic leak. Postoperative course was without any complications. The pregnancy was checked by a gynecologist and was untouched. The patient was dismissed on the 13th day after the surgical procedure. Azathioprine was changed postoperatively for anti-TNF, because of the previous failure of treatment. During the postoperative period, the patient had to be admitted twice to the surgical department for vomiting and abdominal pain, but this was solved by conservative therapy. Consequently (to prevent bowel obstruction), the patient was on liquid aliment and nutritive drinks. During the pregnancy, there were no signs of malnutrition of the fetus. The childbirth was in term by vaginal delivery. The newborn had normal weight and size with no malformations. Following an agreement with the patient, breast-feeding was stopped due to anti-TNF therapy. After puerperium, the patient underwent a reinvestigation of the disease and 6 months after childbirth, the restoration of the gastrointestinal tract (ileotransverse anastomosis) was successfully performed.

## Discussion

Several published studies proved that pregnancy does not adverse the course of CD. Despite the preserved medication with azathioprine during pregnancy, an acute exacerbation of the disease was presented in this case report. After the surgical procedure, the medicament therapy was intensified by anti-TNF. Topical studies describe no evidence for contraindication of medicament therapy for CD patients during pregnancy, except for methotrexate and thalidomide, and the medicament therapy should not be discontinued.

Smoking and contraceptives are commonly considered as significant risk factors causing more severe courses of CD. Our patient has both in case history, even though smoking occurred in the past.

In spite of a previous surgical procedure in her case history in 2014, we decided to start the operation laparoscopically. The conversion for an open procedure had to be done because of purulent peritonitis and a convoluted part of the neo-terminal ileum. Laparoscopy due to acute abdomen during pregnancy is safe and has similar risks (abortion, preterm birth, or low birth weight) as open surgery; diagnostic laparoscopy should be preferred instead of open surgery. If a difficult surgery occurs (adhesions, peritonitis, etc.) conversion should be performed.

The ileostomy was led out more cranially than usual to avoid obstruction caused by the growing uterus in the late stages of pregnancy. If ileostomy obstruction occurs, MRI should be done to distinguish if the reason of ileus is because of adhesions (caused by previous operation) or compression of growing uterus. Suspicion for adhesions should be an indication for surgical treatment, compression by the growing uterus can be treated conservatively.

In 17 years' experience of our stoma nurse care, three patients with ileostomy gave childbirth. In all cases, vaginal delivery was performed, with no complication during pregnancy. Only a few cases of childbirth with ileostomy were published, vaginal delivery should be preferred and caesarean section is reserved if rectovaginal fistula or bowel obstruction appears.

Our patient gave birth in term, although CD (especially if active disease course occurs) is a risk factor for preterm birth. No congenital malformation or lower birth weight as has been already published in relation to CD was present.

Current studies show that breast-feeding during anti-TNF therapy seems to be safe, but a miniscule part of anti-TNF is transferred into breast milk; therefore, a deleterious effect on the neonate cannot be excluded and long-term data are still missing. The application of live virus vaccines in infants who had been exposed to biological therapy in utero should be delayed until biological molecules are no longer detectible in the child's blood. That can require several months and use of these vaccines should be avoided during this period of time (usually 6 months).

## Conclusion

We describe a rare case of a pregnant patient who developed an acute abdomen due to an exacerbation of her underlying Crohn disease.

**Compliance with ethical standards**

**Conflict of interest** The authors declare that they have no conflict of interest.

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**Příloha 10** - Náhlé příhody břišní u pacientů s Crohnovou chorobou – kazuistiky

Kazuistika

# Náhlé příhody břišní u pacientů s Crohnovou chorobou – kazuistiky

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**Souhrn**

*Úvod:* Crohnova choroba (CD – Crohn's disease) jako chronické zánětlivé onemocnění může postihovat celý trávicí trakt, a tudíž zahrnuje velkou škálu příznaků a obtíží. Často imituje jiná onemocnění trávicího traktu. V případě náhlé příhody břišní u pacienta s CD je potřeba přistupovat individuálně ve spolupráci s gastroenterologem za účelem zmenšení rozsahu resekce a zajištění méněnádobých resekcí.
*Kazuistiky:* V našich dvou kazuistikách předkládáme pacienty s ileózní a zánětlivou náhlou příhodou břišní. První pacient profituje z konzervativní léčby i přes přítomnost ileózního stavu (vzniklého na zánětlivém podkladě) před následným operačním řešením. Představuje tak relativně častou a typickou akutní komplikaci CD. Další pacientka i přes probíhající graviditu a nemožnost adekvátního došetření zobrazovacími metodami dospěje na základě klinického stavu k akutnímu operačnímu řešení pro nepříliš častou perforaci do volné dutiny břišní.
***Klíčová slova:*** Crohnova nemoc – chirurgie – náhlá příhoda břišní – ileus – peritonitida

**Summary**

**Acute abdomen in patients with Crohn's disease – case reports**

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*Introduction:* Crohn's disease (CD) as a chronic inflammatory disease can affect the entire digestive tract and therefore involves a wide range of symptoms and health problems. It often mimics other diseases of the digestive tract. In the case of acute abdomen in a patient with CD, it is necessary to approach it individually in cooperation with a gastroenterologist in order to reduce the extent of resection and to ensure fewer resections.
*Case reports:* In our two case reports, we present patients with bowel obstruction and inflammatory acute abdomen. The first patient benefits from conservative treatment despite the presence of a bowel obstruction (resulting from inflammation) before subsequent surgical treatment. It is a relatively common acute complication of CD. The second patient, despite her ongoing pregnancy and the impossibility of using appropriate imaging techniques in the follow-up treatment, with regard to her clinical condition, requires an urgent surgical solution due to a fairly rare perforation to abdominal cavity.
***Key words:*** Crohn's disease – surgery – acute abdomen – bowel obstruction – peritonitis

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## ÚVOD

Přestože nastal značný pokrok v medikamentózní terapii (rozvoj biologické léčby) u pacientů s Crohnovou chorobou (CD – Crohn's disease), ukazuje se, že k významnému snížení počtu operačních výkonů nedošlo a chirurgická léčba má nadále důležitou roli v terapii CD [1–3].

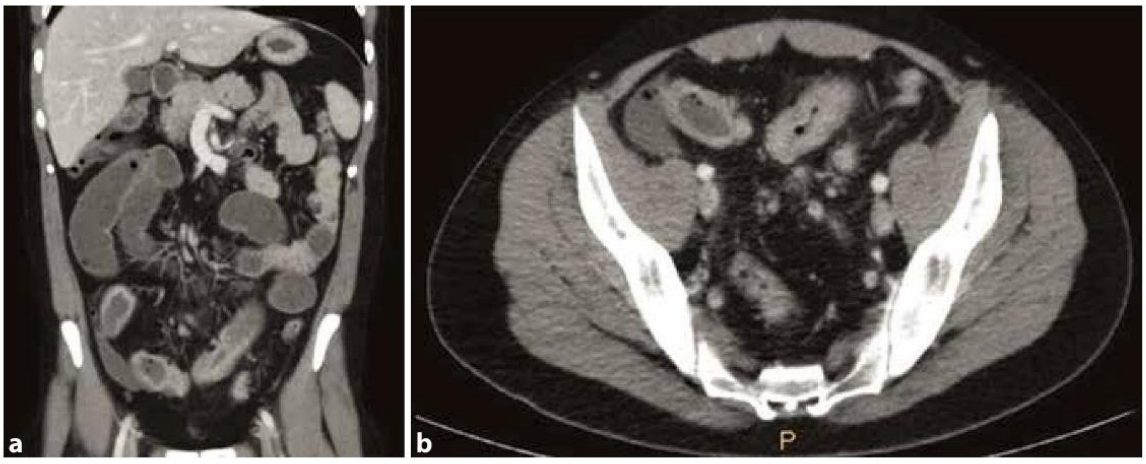
Většina pacientů s CD podstoupí během svého života alespoň jedno operační řešení kvůli tomuto onemocnění, konkrétně 70–90 % pacientů vyžaduje chirurgickou léčbu [4–6].

Vzhledem k charakteru choroby postihující kteroukoliv část trávicí trubice je škála elektivních i akutních operačních výkonů široká.

Střevní obstrukce je velmi častým příznakem postižení tenkého střeva CD [7–9]. Může být zapříčiněna primární stenózou nebo aktivitou choroby při selhání medikamentózní terapie. Příčinou bývají často zánětlivé pseudotumory, mnohokrát ve spojení s fistulacemi, vzácněji se může jednat o perforaci.

## KAZUISTIKA 1

Prezentujeme kazuistiku 28letého pacienta americké národnosti studujícího dlouhodobě v Estonsku a následně v České republice. CD byla u pacienta diagnostikována v roce 2015 v ileocekální oblasti a segmentálně v oblasti kolon sigmoideum. Koncem roku 2016 došlo k relapsu onemocnění s nutností kortikoterapie a převedení na imunosupresivní terapii azathioprinem. Poté si sám ukončil medikamentózní léčbu. Pacient se dostavil v říjnu 2017 pro asi 6 dní trvající bolesti břicha v oblasti pupku vystřelující do zad, vzedmutí břicha a intermitentní zvracení. Uváděl celkově velkou únavu a slabost. Klinicky byla difuzní palpační bolestivost s maximem v oblasti pupku, meteorismus, bez peritoneální iritace. V laboratoři byla elevace leukocytů na $15x10^9$/l, CRP 115 mg/l. RTG vyšetření břicha ukázalo obraz ileózního stavu tenkých kliček, na ultrazvuku břicha byl nález postižení cca 30 cm terminálního ilea se stenózou lumen a známkami aktivity zánětu. Vzhledem ke klinickým obtížím pacienta a paraklinickým




**Obr. 1a, b: CT nález ileózního stavu se stenotizací a zánětlivým postižením 25 cm terminálního ilea s mezikličkovou fistulací**
**Fig. 1a, b: CT showing bowel obstruction with stenosis and inflammation of terminal ileum in the length of 25 cm with intestinal fistula**

vyšetřením jsme provedli akutní ambulantní CT břicha (Obr. 1a, 1b). Patrné bylo postižení cca 20–25 cm terminálního/aborálního ilea se sytící se zesílenou stěnou se stenotizací. Dorzálně od postiženého úseku na mezenteriu byl pruhovitý zánětlivý infiltrát velikosti kolem 65x15 mm, do kterého byl zavzatý i zánětlivě změněný apendix. Dále byly patrné fistulace mezi postiženým úsekem terminálního ilea a zánětlivým infiltrátem až ke kličce kolon sigmoideum. Bez detekce patologické kolekce charakteru abscesu. V oblasti orálního konce postiženého úseku terminálního ilea v levém hypogastriu byla přechodová zóna, nad kterou byla dilatace tenkých kliček ilea až k 5 cm. Vzhledem k poruše pasáže gastroenterolog neindikoval převzetí do péče, pacient byl přijat na Chirurgickou kliniku FN Brno, nasazen „bowel rest" (střevní klid) s plnou parenterální výživou, antibiotická terapie (Unasyn a Metronidazol), zavedena nasogastrická sonda. Pro suspekci na ileokolickou píštěl terapie kortikoidy nebyla indikována. Vzhledem k ileóznímu stavu a zánětlivému postižení rozsáhlého úseku tenkého střeva s fistulací mezikličkově a do kolon sigmoideum jsme volili dle doporučení ECCO (European Crohn's and Colitis Organisation) a po konsenzu s gastroenterology konzervativní postup s odloženým operačním řešením za účelem provedení limitované resekce s možností primární anastomózy. Po zavedení terapie došlo postupně k poklesu zánětlivých parametrů a po snížení odpadů ze žaludeční sondy došlo k obnovení střevní průchodnosti. Pacient byl předán na metabolickou interní JIP k další terapii. V mezidobí byl pacient stabilizován, došlo k úpravě nutričních parametrů s nízkou hodnotou zánětlivých ukazatelů. Stav byl komplikován trombózou vena jugularis vpravo po zavedení centrálního žilního katétru s následnou nutností navýšení dávky nízkomolekulárního heparinu. Po 5 týdnech byla provedena kontrolní vyšetření ke zhodnocení efektu léčby základní choroby, kde na UZ bylo popsané chronické zánětlivé postižení 25 cm terminálního ilea se suspektní mezenteriální píštělí. Koloskopicky byla patrna jen mírně edematózní sliznice kolon sigmoideum se setřelou cévní kresbou, jinak normální nález na tračníku a klidový slizniční nález na Bauhinské chlopni a 10 cm terminálního ilea. Pacient byl tedy po 6 týdnech „bowel restu" a antibiotické terapii indikován k operačnímu řešení. Provedli jsme laparoskopickou revizi a resekci postiženého úseku. Peroperační nález postižení terminálního ilea odpovídal předoperačnímu CT vyšetření. Infiltrát byl přitažený ke kolon sigmoideum, vlastní fistulace ale nebyla prokázána. Provedli jsme laparoskopickou ileocekální resekci s izoperistaltickou anastomózou stranou ke straně pokračujícím extramukózním stehem. Pooperační průběh byl bez komplikací. Histologicky byl potvrzen granulomatózní zánět typu CD s intaktními resekčními okraji. Pacient je poté postupně realimentován po dlouhodobém „bowel restu" za hospitalizace na gastroenterologii. Pooperačně byla následně nasazena konvenční imunoterapie thiopuriny. Pacient po zhojení laparotomie odjel k další ambulantní léčbě do Estonska.

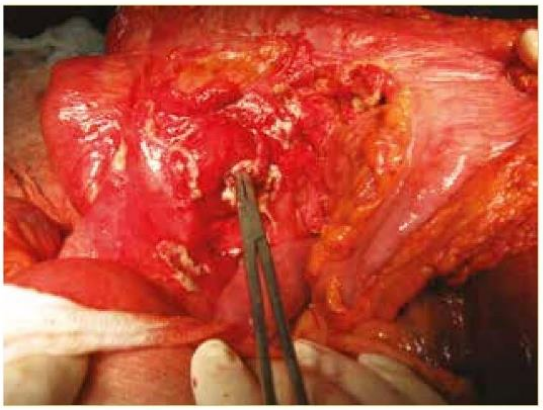
## KAZUISTIKA 2

Prezentujeme 29letou pacientku s CD diagnostikovanou v roce 2009, primárně s postižením céka a 10 cm terminálního ilea. Terapie byla postupně eskalována na biologickou terapii. Pro fibrózní stenotizaci terminálního ilea, céka a vzestupného tračníku s počínající predilatací byla provedena elektivní pravostranná hemikolektomie s anastomózou stranou ke straně. Pooperační průběh byl bez komplikací. V rámci endoskopické dispenzarizace za 6 měsíců od operace byla provedena kontrolní koloskopie bez nálezu rekurence CD v anastomóze. Pooperačně byla u pacientky nasazena imunoprofylaxe azathioprinem a po konsenzu s gastroenterologem byla plánována gravidita. V 2/2015 byla pacientka ve 12. týdnu gravidity přeložena z okresního chirurgického pracoviště na Chirurgickou kliniku FN

Brno pro přetrvávající bolesti břicha k další terapii. Při překladu byla hodnota CRP 141 mg/l, leukocyty 5x10$^9$/l, dle UZ břicha byly zesílené střevní kličky v pravém podbřišku, minimální lemy tekutiny zejména v malé pánvi. Vzhledem ke graviditě CT břicha nebylo možné provést. Pacientka byla afebrilní, klinicky bylo břicho palpačně lehce citlivé v pravém mezogastriu. Byla nasazena antibiotická terapie, parenterální nutrice a „bowel rest". Dle konzultace gastroenterologa se nezdála být zcela jednoznačná reaktivace základního onemocnění. Pro současnou přítomnost teplot a průjmů jsme v rámci diferenciální diagnostiky zvažovali možnost infekční gastroenteritidy. Do dalšího dne došlo k nárůstu CRP na 308 mg/l, leukocyty na 14x10$^9$/l, na UZ břicha byl pouze nález minimální progrese volné tekutiny. Docházelo postupně ke zhoršování bolestí břicha, klinicky byla palpační bolestivost v pravé polovině břicha až s naznačeným peritoneálním drážděním. Indikovali jsme operační revizi, která byla zahájena diagnostickou laparoskopií s nálezem difuzní peritonitidy s perforací tenké kličky do mezenteria a následně do volné dutiny břišní ve vzdálenosti 10 cm před původní anastomózou po pravostranné hemikolektomii. Vzhledem k peroperačnímu nálezu jsme konvertovali na otevřenou laparotomii (Obr. 2), provedli resekci postiženého úseku i s původní anastomózou, slepý uzávěr kolon transversum a vyvedení terminální ileostomie. Pro nález difuzní peritonitidy při zánětlivě změněném infiltrátu s perforací jsme primární anastomózu neprovedli. Pooperační průběh byl bez komplikací, gravidita intaktní. Pacientka byla předána k další léčbě na Interní gastroenterologickou kliniku, kde byla zahájena eskalace medikace na anti-TNF terapii pro neefektivitu thiopurinů. Průběh gravidity byl komplikován rozvojem subileózního stavu v 5/2015 a 6/2015 diagnostikovaným na základě klinického stavu pacientky a UZ nálezu. V obou případech byl stav zvládnutý konzervativně. Pacientka porodila v 38. t.g. fyziologicky bez komplikací v 8/2015. Pro klinickou i morfologickou remisi v 1/2016 bylo provedeno elektivní obnovení kontinuity ileotransverso anastomózou stranou ke straně, pooperační průběh byl bez komplikací. I přes nutnou modifikaci dávek anti-TNF terapie přetrvává klinická i endoskopická remise onemocnění a pacientka je v současnosti v průběhu druhé gravidity.

## DISKUZE

CD spolu s ulcerózní kolitidou (UC – ulcerative colitis) patří do skupiny idiopatických střevních zánětlivých onemocnění (IBD – inflammatory bowel disease). CD na rozdíl od UC postihuje zánětem trávicí trubici od úst až do oblasti anu v celé jeho vrstvě. Nejčastěji jde o postižení terminálního ilea. Vyskytuje se shodně u mužského i ženského pohlaví ve všech věkových kategoriích s predilekcí ve druhé a třetí dekádě věku pacientů [10–12]. CD se velmi často manifestuje bolestí a křečemi, často bývá doprovázena četnými průjmovitými stolicemi s příměsí hlenů a krve. U některých pacientů bývají přítomny dlouhotrvající subfebrilie, nauzea a zvracení. Neméně časté jsou i extraintestinální příznaky [13].



**Obr. 2: Peroperační nález s fistulací jdoucí z ilea do mezenteria**
Fistulace byla lokalizovaná 10 cm před anastomózou. Do fistulace zaveden peán.
**Fig. 2: Intraoperative findings showing fistula going from the ileum to mesentery**
The fistula was located 10 cm before the anastomosis. A pean is inserted into the fistula.

Pro CD není zcela typická manifestace formou náhlé příhody břišní. Relativně častou bývá střevní obstrukce u střevních stenóz. Perforace do volné dutiny břišní je velmi vzácnou komplikací a je vzhledem k rozvoji peritonitidy indikací k akutní operaci. Masivní krvácení u pacientů s CD se objevuje také relativně vzácně, uvádí se v rozmezí 0–6 % [14]. Existuje mnoho zobrazovacích modalit k diagnostice a další dispenzarizaci pacientů s CD, jako jsou UZ střev, koloskopie, gastroskopie, enteroskopie, CT či MR enterografie a také kapslová endoskopie. Dle posledních doporučení není žádná z těchto metod stanovená jako zlatý standard a velmi často se tyto metody vzájemně kombinují. Omezeni jsme zejména u gravidních pacientek [15,16].

Pacienti s CD velmi často před operací vyžadují multidisciplinární přípravu vzhledem k často přítomné malnutrici, imunosupresivní terapii či užívání vysokých dávek kortikoidů. Je vhodné takto komplikované pacienty probírat na multioborovém semináři za účasti chirurga, gastroenterologa a radiologa. U akutních stavů může být kombinace obstrukce na podkladě dekompenzace chronické stenózy se zánětlivým postižením v mnoha možných variantách. Často jde o mladé pacienty, pro které je kosmetický efekt důležitou složkou kvality života, stejně jako zachování sexuálních funkcí a snaha o provedení kontinentní operace [17]. Léčba těchto pacientů je specifická jak u elektivních pacientů, tak zejména u pacientů s akutní symptomatikou, kde je důležité načasování operace. Správný management léčby má vliv na rozsah resekčního zákroku, nutnost založení stomie a také na rekurenci onemocnění po resekčním zákroku.

V lednu 2018 bylo publikováno kolektivem autorů ECCO doporučení k chirurgické léčbě CD [18]. Prohlášení 2A zahrnuje indikaci k akutnímu operačnímu řešení u pacientů s perforací do volné dutiny břišní s rozvojem peritonitidy. Součástí doporučení je resekční zákrok s anastomózou či bez dle lokálního a celkového nálezu. Při rozvoji sepse je doporučena tekutinová terapie s antibiotiky a nutriční podporou. Ke zvážení je i zavedení permanentního močového katétru a zajištění centrální žíly. Naopak prohlášení 2C zahrnuje chirurgickou léčbu akutní střevní obstrukce způsobenou dekompenzací chronické stenózy či akutní exacerbaci CD. U těchto případů je doporučeno postupovat konzervativně, jak je prezentováno v naší kazuistice. Indikací pro akutní operaci je úplná obstrukce nereagující na konzervativní terapii či podezření na střevní ischemii. V případě neúplné obstrukce by měla chirurgická léčba následovat až po optimalizaci stavu pacienta ve smyslu potlačení zánětlivého postižení, odeznění ileózních obtíží a nutriční stabilizaci pacienta. Doporučení zahrnuje zavedení nasogastrické sondy, „bowel rest" a parenterální výživu. V případě konkomitantní fistulace také antibiotickou terapii. U abscesu doprovázejícího fistulaci jsou ke zvážení perkutánní drenáž či punkce.

## ZÁVĚR

Při rozvoji náhlé příhody břišní u pacientů s CD je vhodné postupovat individuálně a také za těsné spolupráce chirurga, gastroenterologa a radiologa s cílem snížení rozsahu případného resekčního výkonu. Představujeme 2 kazuistiky. První pacient s ileózním stavem (na zánětlivém podkladě) je primárně léčen konzervativně s následným jednodobým elektivním laparoskopickým výkonem. Na rozdíl u druhé gravidní pacientky vzhledem ke zhoršujícímu se klinickému stavu byla indikována akutní operační revize s nálezem perforující píštěle do mezenteria a následně do volné dutiny břišní. Při progresi klinického stavu pacienta a nemožnosti provedení CT břicha nebo jeho nejasného nálezu by měla být zvažována diagnostická laparoskopie.

Seznam zkratek

CD – Crohn's disease – Crohnova choroba
CT – computed tomography – výpočetní tomografie
MR – magnetická rezonance
UZ – ultrazvuk
CRP – C-reaktivní protein
Anti-TNF – anti-tumor necrosis factor
ECCO – European Crohn's and Colitis Organisation
UC – ulcerative colitis – ulcerózní kolitida
IBD – inflammatory bowel disease – idiopatické střevní záněty

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**Příloha 11** - Autoimmune pancreatitis – An ongoing challenge

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Review article

# Autoimmune pancreatitis – An ongoing challenge

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ABSTRACT

Autoimmune pancreatitis is a rare form of chronic pancreatitis. The first descriptions of the disease date back to the 1990s. Etiology is multifactorial, with the use of genetic, environmental and complex immunological mechanisms. It is classified into two subtypes. Type 1 is part of a group of diseases called IgG4-related disease. Clinically is autoimmune pancreatitis manifested by icterus and abdominal discomfort. It can rarely present as acute pancreatitis. There is also a completely asymptomatic form of the disease. The diagnosis is based on abnormalities in histology, imaging methods, serology, the involvement of other organs in relation to IgG4-related disease, and a significant positive response to corticosteroid therapy. Differential diagnosis between the focal form of autoimmune pancreatitis and pancreatic cancer can be complicated, with endosonography playing an important role. In the treatment, we use corticosteroids and other immunosuppressants including biological therapy. Patients with the asymptomatic disease should also be treated to prevent late complications and exocrine and endocrine insufficiency. In addition to drug treatment, endoscopic and/or surgical treatment may be necessary. Even after recovery, the disease can relapse. The relationship between autoimmune pancreatitis and malignancies has not been clearly confirmed. The goal of this review is to provide a comprehensive look at autoimmune pancreatitis and translate latest scientific knowledge into clinical practice.

## 1. Introduction

Autoimmune pancreatitis (AIP) is a rare form of chronic pancreatitis characterized by the clinical symptomatology of the obstructive icterus, lymphoplasmacytic infiltration with marked storiform pancreatic parenchyma fibrosis, and a response to corticosteroid therapy [1]. The first description of chronic pancreatitis with autoimmune abnormalities was provided in 1995 by Yoshida et al. [2], who also found a therapeutic response to corticosteroid administration. In 2001, Hamano et al. [3] for the first time reported an increase in the serum levels of immunoglobulin G4 (IgG4) in subjects with chronic autoimmune pancreatitis and laid the basis for identifying other conditions associated with IgG4 elevation, now referred to as IgG4-related disease (IgG4-RD). Two years later, Kamisawa et al. [4] described the abundant infiltration of IgG4-positive plasma cells not only of the pancreas, but also of other organs and designated AIP as one of the forms of IgG4-RD.

## 2. Review

### 2.1. Pathogenesis

In the AIP pathogenesis, the multifactorial nature of the process is characteristic. There are genetic, environmental and immunological factors. Recent studies show that in addition to the known fact that AIP/IgG4-RD is associated with high IgG4 plasma levels and both the pancreas and some other parenchymatous organs are massively infiltrated with IgG4-containing plasma cells, the disease is closely linked to the increase in Interferon type I (IFN-I) produced by plasmacytoid dendritic cells. AIP/IgG4-RD has been shown to be characterized by the increased production of IFN-I dependent Interleukin 33 (IL-33). This can be included as a factor participating in the induction of inflammatory and fibrotic changes characterizing these diseases [5]. The abnormal production of INF-I is undoubtedly a novel factor in the pathogenesis of AIP/IgG4-RD. In addition to this disease, IFN-I (usually

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alpha type or beta type) is a significant factor in the development of other autoimmune diseases, e.g. systemic lupus erythematosus [6].

Attention is also paid to the role of genetic and immunological factors. Two genes in the HLA region (*HLA-DRB1* and *ABCF1*) are associated with the susceptibility to AIP [7,8]. Patients with AIP have a high level of multiple antibody positivity: in 40% positive antinuclear antibodies, in 55% *anti*-carbonic anhydrase II or pancreatic secretory trypsin inhibitor (PSTI) antibodies, and even in 75% *anti*-lactoferrin antibodies are found [9]. Löhr et al. [10], found a higher titer of autoantibodies to trypsinogens PRSS1 and PRSS2 but a non-elevated value for PRSS3 in AIP patients. This explains why pancreatic acini are more damaged than the cells of the ducts in the inflammatory affections of the pancreas. Some of the above-mentioned antibodies are not specific for AIP, but they are also positive for other conditions, e.g. Sjogren's syndrome [11].

There is an interesting hypothesis about the molecular mimicry of *Helicobacter pylori* (*H. pylori*) bacteria and the pathogenesis of AIP, where human carbonic anhydrase II is equivalent to the alpha-carbonic anhydrase found in *H. pylori*. A similarity was also found between the plasminogen-binding protein of *H. pylori* and the enzyme produced by acinar pancreatic cells – ubiquitin-protein ligase E3 component n-recognin 2. Thus, it was speculated that *H. pylori* infection may be the trigger mechanism for an autoimmune response against pancreatic acini via molecular mimicry. However, to date, there has been no validation of these findings [12–14].

The role of environmental factors has been monitored from the perspective of whether repeated exposure to different antigens may result in changes in IgG4 concentration in the blood serum. The long-term exposure of workers to certain substances such as mineral oils, solvents, industrial or metal dusts could actually be the cause [15].

A histologically significant finding in IgG4-RD subjects is the massive infiltration of IgG4-positive plasma cells. However, it is still unclear whether IgG4 antibodies are a reflection of overexpression caused by an unknown inflammatory stimulus, or whether they are autoantibodies referred to as destructive antibodies [16,17]. The study by Mattoo et al. [18] demonstrated that recombinant immunoglobulins obtained from the most commonly identified IgG4 clone of IgG4-RD subjects' plasma cells are self-reactive, which may be a significant factor involved in the pathogenesis of IgG4-RD.

### 2.2. Classification of autoimmune pancreatitis

Based on the nomenclature published in 2012 [19], AIP is divided into two types. Type 1 was originally referred to as lymphoplasmacytic sclerosing pancreatitis (LPSP). It is now clearly accepted that this AIP type is part of a group of diseases called IgG4-RD. Therefore, this AIP type is now referred to as IgG4-related pancreatitis (IgG4-RP). Type 2 is not associated with IgG4-RD and is called idiopathic duct-centric pancreatitis (IDCP). Table 1 shows the characteristics and differences between both types of AIP (Table 1).

### 2.3. Epidemiology

The epidemiological data of AIP are not very frequent. The diagnosis of AIP is low in the general population. At the same time, type 2 AIP has a significantly lower prevalence than type 1. The disease more often affects older men. A representative study from Japan [21], found a prevalence of 4.6 per 100,000 inhabitants and an incidence of 1.4 per 100,000 inhabitants. The male to female ratio was 3.2 at the average age of 66 at the time of diagnosis. The problem with sparse epidemiological studies is that different diagnostic criteria have been used. The first and thus far the only work using internationally accepted criteria for diagnostic consensus [1] is a German study published in 2017 [22]. The authors demonstrate, in comparison with all previously reported studies, a high prevalence of AIP – 9% in the group of people with non-alcoholic pancreatitis. AIP was not found in alcoholic pancreatitis. The overall incidence of AIP in Germany is less than 1 per 100,000 inhabitants.

**Table 1**
Characteristics and fundamental differences of Type 1 and Type 2 AIP (according to Webster [20]).

| | Type 1 (LPSP) | Type 2 (IDCP) |
|---|---|---|
| IGg4-RD | Yes | No |
| Prevalence | Asia > USA/Europe | USA/Europe > Asia |
| Sex | M > F | M = F |
| Worldwide percentage | > 90 | < 10 |
| Age predominance | > 50 | 30–50 |
| Initial icterus | > 60 | < 30 |
| Acute abdominal pain | < 30 | > 60 |
| Elevated serum IgG4 | > 70 | < 10 |
| Histopathology | Storiform fibrosis, LPSP, Obliterative phlebitis | IDCP, GEL |
| Affection of other organs | Yes | No |
| Association with IBD in % | < 10 | > 40 |
| Steroid response | > 90 | > 90 |
| Relapse after steroid therapy | > 40 | < 10 |

Abbreviations: AIP, Autoimmune pancreatitis; IgG4-RD, IgG4-related disease; LPSP, lymphoplasmacytic sclerosing pancreatitis; IDCP, idiopathic duct centric pancreatitis; GEL, granulocytic epithelial lesions; IBD, inflammatory bowel disease

### 2.4. Clinical symptomatology

The most common initial clinical symptoms are obstructive icterus in 60–70% of patients, focal gland enlargement, abdominal pain or abdominal discomfort. Signs of acute pancreatitis are rarely present. There is also a completely asymptomatic form of AIP. In general, AIP is rarely the cause of idiopathic recurrent pancreatitis. In a clinical presentation, we must not overlook the symptoms resulting from the involvement of other organs in IgG4-RD [23].

### 2.5. Diagnostic features of autoimmune pancreatitis

Several criteria for AIP diagnosis have been published. The first set of criteria was established in 2002 by Japanese Pancreatic Society with revision in 2006 [24]. These consisted of three main findings: imaging, serology and pathology. The HISORt criteria published by Mayo Clinic added other organ involvement and response to steroid therapy [25]. The need for uniform international diagnostic criteria resulted in publication of International Consensus Diagnostic Criteria (ICDC) [1]. The ICDC, along with the Japanese amendment that makes them more applicable for general internists, are currently preferred [26]. The demonstration of the following 5 main features is essential for diagnosis:

a) pancreatic histomorphology.
b) changes in pancreatic parenchyma and biliary tree using imaging methods.
c) serology.
d) presence of other organ involvement.
e) positive response to corticosteroids.

### 2.6. Histology

A histopathological feature of type 1 AIP is a picture of LPSP without granulocytic epithelial lesions (GELs). Other signs are storiform fibrosis, obliterative phlebitis and abundant infiltration by IgG4 positive plasma cells (more than 10 per high power field). To confirm the diagnosis of type 2 AIP, the detection of the duct wall granulocytic infiltration (GEL positivity) omitting pancreatic lobules and the

minimal or no positivity of IgG4 positive cells in the pancreatic tissue is important. The most usual way of obtaining tissue sample from pancreas is via endoscopic ultrasound (EUS). Endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) is a well-established method used in the diagnosis of pancreatic cancer. However, specimens acquired with this technique may be insufficient for diagnosis of AIP, because the evaluation of tissue architecture and immunostaining usually require larger samples. Thus, pancreatic core cut biopsy using either a larger caliber needle or other specially designed needles may be necessary [27,28]. Even with these needles, definitive histological verification cannot be achieved in a significant number of patients. That is, in the type 1 AIP, not all four histological features mentioned above may be present, and in the type 2 AIP, rather than duct wall granulocytic infiltration, granulocytic acinar inflammation is described with absent or scant IgG4 positive cells. Softened criteria may rely on the presence of lymphoplasmacytic infiltrate alone without the need for the infiltrate to be in periductal location and lower level of preservation of arterioles, venules and ductules in specimen [29,30]. Softening of diagnostic criteria may improve diagnostic sensitivity in expense of specificity. This is problematic mainly in the differential diagnosis between AIP and pancreatic cancer, which is often associated with lymphoplasmacytic infiltrate.

### 2.7. Imaging methods

Imaging methods play an important role in the AIP diagnostic algorithm. They can be used to identify whether changes are diffuse or focal. From the perspective of differential diagnosis, focal changes are unsolvable without the use of imaging methods [31]. It can be said that all imaging methods have a benefit in the diagnosis and differential diagnosis of AIP – i.e. abdominal ultrasound, computed tomography (CT), magnetic resonance (MR), magnetic resonance cholangio-pancreatography (MRCP), EUS as well as traditional endoscopic retrograde cholangio-pancreatography (ERCP) [1,32–37]. Abdominal ultrasound is the most available method used in the examination of pancreas. It is usually the first method used in differential diagnosis of abdominal pain or jaundice. Its benefits include the lack of radiation exposure, non-invasiveness and cost effectiveness compared with aforementioned procedures. Contrast enhanced abdominal ultrasound might be beneficial in differentiating focal form of AIP from pancreatic cancer [38]. On the contrary, abdominal ultrasound remains an operator dependent examination and, in some patients, visualization of pancreas may be very poor, or pancreas may not be visualized at all.

Some of the images may be more characteristic of AIP – such as sausage-shaped pancreas enlargement in an ultrasound examination, or the identification of brightening under the pancreatic capsule during CT – the so-called rim. The rim reflects fibroinflammatory changes involving the peripancreatic adipose tissue. This finding is highly specific for type 1 AIP [39]. Other changes are less specific in terms of the diffuse, focal or segmental enlargement of the gland. While the pancreatic duct is unidentifiable at the diffuse pancreatic enlargement, evidence of pancreatic duct dilatation may be associated with both malignancy and AIP in the case of a focal pancreatic lesion finding. Typical features in MRCP (similar to ERCP) are long, smooth and tight pancreatic duct stenosis without dilation before stenosis. EUS shows hypoechogenic pancreatic enlargement in more than 50% of AIP subjects and hypoechogenic foci placed irregularly in the pancreas in about 40% of subjects [40]. EUS plays an important role in differential diagnosis distinguishing between pancreatic cancer and AIP. An indisputable advantage of EUS is the possibility of performing a targeted gland biopsy. MR is superior over CT in differentiating non-diffuse type AIP from pancreatic ductal adenocarcinoma [41]. Invasive ERP is certainly not a basic investigative method, but for the sake of completeness, it should be noted that there are also changes, especially multiple stenoses of the pancreatic duct and its secondary branches, which can be typical for AIP. The finding of biliary tree stenoses requires the examination of the patient from the perspective of differential diagnosis – primary sclerosing cholangitis, cholangiocarcinoma, but also IgG4-associated cholangitis.

### 2.8. Serology

Serological diagnostic criterion is the determination of the IgG4 level. The upper limit of the standard is reported to be between 135.0 mg/dl and 140.0 mg/dl [42]. It is generally accepted that an increase of more than double the standard is a diagnostic valid marker for AIP. An increase in the IgG4 serum level above the limit of 135.0 mg/dl is specific not only to AIP but has also been found in 10% of pancreatic carcinoma patients. However, in only 1% of pancreatic carcinoma patients was the IgG4 serum level above 280 mg/dl [3]. An increase in the IgG4 above the standard can be identified not only in pancreatic cancer but also in patients with chronic pancreatitis, primary biliary cirrhosis, primary sclerosing cholangitis or Sjogren's syndrome. Differential diagnosis between AIP and pancreatic carcinoma with the simultaneous elevation of the IgG4 in the blood serum is often very difficult. Some initially promising markers such as carbonic anhydrase II antibodies, plasminogen-binding protein antibodies, or lactoferrin antibodies have not been shown to be beneficial [13,43]. In our own study, we examined a group of 106 subjects with histologically verified pancreatic carcinoma and found elevated IgG4 levels in 11 of them. In 6 of these 11 subjects, the IgG4 levels were more than twice the standard. We also found 1 patient with an AIP histological picture and pancreatic carcinoma in this terrain [44]. Serum IgG4 level is an important diagnostic criterion, but whether it predicts the disease progression is unclear. According to Tsang et al. [45], raised serum IgG4 level twice above the upper normal limit was significantly associated with disease relapse and pancreatic exocrine insufficiency in patients with IgG4-RP.

In the recent years, cases of type 1 AIP with histologically typical findings of LPSP with no serum IgG4 level elevation or histologically detectable IgG4 positive cells have been described [46,47]. IgG4 is not an absolute criterion for the diagnosis of type 1 AIP.

### 2.9. Other organ involvement

Fujinaga et al. [48] published a representative study diagnosing extrapancreatic lesions in patients with AIP. The most common extrapancreatic manifestation of AIP is the enlargement of the lacrimal and salivary glands and retroperitoneal fibrosis; other frequent findings are changes in the biliary system, referred to as IgG4-associated sclerosing cholangitis or autoimmune cholangitis. A less common extrapancreatic sign is kidney or prostate involvement [49]. In contrast to frequent extrapancreatic manifestations in type 1 AIP, the extrapancreatic disease is rare in type 2 AIP. A very strong relationship has been reported between type 2 AIP and inflammatory bowel disease (IBD), whereas the presence of IBD in type 1 AIP patients is uncommon [50].

### 2.10. Therapy

After excluding malignancy, the basic drugs used are corticosteroids and immunosuppressants. In the recent years, there has been a significant change in the way the patients diagnosed with AIP are treated. In addition to those with symptomatic AIP, patients with the asymptomatic disease should also be treated. The therapy can prevent progression of fibrotic changes in the gland, biliary strictures, as well as the induction of exocrine and endocrine pancreatic insufficiency or risks of relapses [51–53].

There are various patterns of corticosteroid dosing. The most commonly used and recommended schedule is administering prednisolone in the dose of 30–40 mg/day for 2–4 weeks. The dose is then reduced by 5 mg every 1–2 weeks to a maintenance dose of 5.0–7.5 mg/day. The maintenance treatment period varies, usually 12 weeks to 6 months. The above-mentioned system is used in Europe and the USA. Another

scheme is recommended in Asian countries where a dose of 0.6–1.0 mg/kg/day is administered for 2–4 weeks. In addition, in this scheme the dose is reduced by 5 mg at intervals of 1–2 weeks. However, the recommendation about the maintenance treatment period is different: 6 months to 3 years [54]. The authors of the systematic review and meta-analysis about the rate of relapse of AIP after initial remission after steroid treatment found that a large proportion of patients with AIP treated successfully with steroid induction therapy had relapse in 33% - particularly patients with type 1 AIP – 37.5%. The group of patients with type 2 AIP had relapse in 15.9%. Maintenance steroid therapy lasting longer than one year could reduce the risk of relapse [55].

If corticosteroid therapy is unsuccessful, azathioprine, 6-mercaptopurine or mycophenolate may be administered. Azathioprine is a convenient treatment, especially where a relapse has occurred during steroid therapy [56]. The most frequently recommended treatment for AIP relapse is the re-introduction of corticosteroids. The other drugs mentioned above are also an alternative [57]. Rituximab with the induction of complete remission in up to 83% of patients is an effective drug for the treatment of a relapse and in corticosteroid-intolerant patients [58].

The effectiveness of therapy is evaluated by monitoring the dynamics of changes using imaging methods and serological examination [59].

In our opinion and clinical practice measuring the levels of IgG4 antibodies in the blood serum should be a part of follow-up. In the absence of clinical or imaging correlate, we do not treat just elevated levels of these antibodies. However, one must stay very cautious as gradual increase in IgG4, especially three times above the upper limit of standard, oftentimes precedes the disease relapse.

In addition to drug treatment, endoscopic procedures are sometimes indicated in the case of insufficient initial drug effect for the treatment of patients with obstructive icterus. Surgical therapy is rarely used. The indication is the inability to accurately differentiate benign from malignant pancreatic expansion, extensive extrapancreatic fibrosis therapy, or where endoscopic biliary drainage could not be performed.

### *2.11. Autoimmune pancreatitis and exocrine and endocrine insufficiency*

Frulloni et al. [60], examined a group of 21 patients with AIP before and after corticosteroid use. Exocrine pancreatic secretion was assessed by fecal elastase-1 (FE-1), and endocrine function by morning blood glucose. In AIP subjects, where no therapy had been applied, the average FE-1 was 107–126 μg/g of feces. At a cut-off limit < 100 μg/g, exocrine pancreatic insufficiency was found in 62% of the examined patients; the so-called grey zone, interpreted by the authors as mild exocrine insufficiency, determined in the range of 100–200 μg/g of feces, was found in 19% of patients. After the corticosteroid therapy was applied, the FE-1 value increased to an average of 237 μg/g of feces. Diabetes mellitus was identified in 5 subjects (24%) prior to therapy. At the same time, all patients with diabetes had an extremely low FE-1 value with an average < 19 μg/g of feces. After the deployment of corticosteroids, glycemia levels normalized in all subjects. From this study, it is evident that AIP often has a significant exocrine, or endocrine pancreatic insufficiency.

### *2.12. Autoimmune pancreatitis and cancer*

The study by Yamamoto et al. [61] monitored the incidence of malignant diseases in patients with IgG4-RD. Of the 106 patients with this diagnosis in the 3-year monitoring period, malignancy was detected in 11 subjects (10.4%). These were lung cancer, colorectal cancer, prostate and ovarian cancer, and MALT lymphoma [62]. Surprisingly, pancreatic cancer was not found in this group. Another study looked at the risk of developing cancer in patients with AIP. Of the 108 patients with AIP, 18 malignancies (13.9%) were diagnosed in 15 patients with a motoring median of 3.3 years. The relative risk of malignancy at the time of AIP diagnosis was 4.9. The highest risk of malignancy was in the early phase of diagnosis of AIP. The authors believe that AIP may develop as a paraneoplastic syndrome in cancer patients [63]. However, not all studies confirm the relationship between AIP and malignancies [63–65].

Misdiagnosis of AIP as pancreatic cancer can cause dismal patients' outcome. In some cases, it is extremely difficult to distinguish between focal form of AIP and pancreatic cancer [66].

CA 19–9 is the most beneficial tumor marker for pancreatic cancer with sensitivity of 79% and specificity of 82% [67]. However, elevated levels of CA 19–9 are measurable also in some benign conditions including AIP and obstructive jaundice of various etiology. That discriminates CA 19–9 as a sole marker in differentiating between these two conditions. A combined measurement of serum IgG4 and CA 19-9 seems to be a more promising tool [68,69]. Ideal cut-off parameters need to be established in larger series.

Shih et al. [70], used serum IgG-glycosylation profiles as a diagnostic marker. They found that the patients with pancreatic cancer had significantly higher agalactosylation, lower fucosylation, and sialylation of IgG1, a higher agalactosylation ratio of IgG1 and a higher agalactosylation ratio of IgG2. AIP patients had significantly higher fucosylation of IgG1 and a higher sialylation ratio of IgG subclasses 1, 2 and 4. There was no statistically significant difference of IgG-glycosylation profiles between the diffuse type and focal type of AIP. IgG-glycosylation could be a useful marker in differentiating pancreatic ductal carcinoma from AIP with high accuracy (94.6% sensitivity and 92.9% specificity).

## 3. Conclusions

An autoimmune form of pancreatitis is a rare disease. Its type 1 belongs to the group of so-called IgG4-RD. In the recent years, a number of new findings concerning pathogenetic processes, but also in the field of rational diagnostics, therapy and the classification of the disease, have been introduced. Knowledge about this disease is necessary for clinical practice not only for the correct differential diagnosis but also for the early use of therapy, which is now also recommended for patients with a clinically asymptomatic form of the disease.

There is no doubt that autoimmune pancreatitis is still a challenging diagnosis. Only one quarter of patients exhibit typical sausage-like pancreas in imaging and approximately three quarters of patients have a focal mass. Focal form of AIP is often problematic in differential diagnosis between autoimmune focal pancreatitis and pancreatic cancer. Elevated IgG4 is a typical diagnostic marker for AIP, but 15% of patients with pancreatic cancer have elevated IgG4 as well.

Corticosteroid therapy is generally successful and provides clinical remission approximately in 90% of patients. However, in our experience, the therapy with steroids could be "successful" in the first week of therapy also in patients with pancreatic cancer, when the diagnosis of AIP was incorrect.

Our last comment – the number of patients with diagnosis of AIP is very low. Main epidemiological problem is that the knowledge about this disease among medical doctors is not sufficient. AIP is a rare disease, but many of our diagnoses are incorrect or "nobody thought" of this disease.

Those are the reasons the diagnosis and management of autoimmune pancreatitis is an ongoing challenge.

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## The author contribution

Study Design: n/a

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## Declaration of competing interest

The authors declare that there is no conflict of interest regarding the publication of this article.

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**Příloha 12** - Idiopatický střevní zánět a 1. typ autoimunitní formy pankreatitidy: kazuistika



# Idiopatický střevní zánět a 1. typ autoimunitní formy pankreatitidy: kazuistika

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**Souhrn**
Autoimunitní forma pankreatitidy (AIP) je dělena na 2 subtypy. 1. subtyp je charakterizován vysokou přítomností imunoglobulinu G4 v krevním séru a v tkáni některých orgánů, které mají těsný vztah k tzv. IgG4 asociovaným postižením. Typickým diagnostickým znakem AIP jsou i změny histomorfologické. Tento typ AIP je mnohem častější než 2. typ, se kterým má však společné některé znaky histomorfologické, a především pozitivní odpověď na podání steroidů jako iniciální léčby. Zatímco 1. typ AIP je typicky spojen s postižením různých orgánů jako je biliární trakt, slinné a slzné žlázy, retroperitoneální fibróza, ledviny, prostata a další, u 2. typu AIP je významné spojení AIP pouze s idiopatickým střevním zánětem. Idiopatické střevní záněty jsou naopak jen vzácně u 1. typu AIP. V naší kazuistice uvádíme první zveřejněné pozorování v České republice, kdy AIP 1. typu je provázena idiopatickým střevním zánětem – Crohnovou nemocí.

**Klíčová slova:** autoimunitní forma pankreatitidy – idiopatický střevní zánět – imunoglobulin G4 – imunoglobulin G4 asociovaná onemocnění

# Idiopathic inflammatory bowel disease and the first type of autoimmune form of pancreatitis: case report

**Summary**
The autoimmune form of pancreatitis (AIP) is divided into the following two subtypes. The 1st subtype is characterized by the high presence of immunoglobulin G4 in the blood serum and tissue of some organs which are in the close connection to the so called IgG4 associated disorders. The typical diagnostic signs of AIP are the histomorphological changes. This type of AIP is more frequent than the 2nd type with which has however some common histomorphological signs and mainly the positive response to the administered steroids used in the initial treatment. Whilst the 1st type of AIP is typically connected to the disorders of various organs such are the biliary tract, salivary and lacrimal glands, retroperitoneal fibrosis, reins, prostate gland and the next ones, the 2nd type of AIP is significantly connected to the inflammatory bowel disease only. Inflammatory bowel diseases are rarely present in the 1st type of AIP on the contrary. In our case report we mention the first published observations performed in the Czech Republic when the 1st type of AIP is succeeded by the inflammatory bowel disease – Crohn´s disease.

**Key words:** autoimmune pancreatitis – immunoglobulin G4 – immunoglobulin G4 associated disorders – inflammatory bowel disease

## Úvod

Přestože vztah mezi idiopatickými střevními záněty (inflammatory bowel disease – IBD) a chronickou pankreatitidou je znám již od roku 1956 [1], spojení formy autoimunitní pankreatitidy (AIP) s IBD je stále spíše vzácné. Prvá zmínka v literatuře o steroidně dependentní formě pankreatitidy, byla popsána v roce 1995 Yoshidou, který tuto formu označil jako formu AIP [2]. Významným pří-

nosem v diagnostice AIP u těchto nemocných bylo v roce 2001 potvrzení pozitivity sérového imunoglobulinu G4. Nemoc byla zařazena do skupiny onemocnění, označených jako IgG4 asociované nemoci (IgG4 Related Diseases) [3].

Dle klinických a histologických změn je v současné době na základě mezinárodního diagnostického konsenzu dělena AIP do 2 skupin [4]: 1. subtyp AIP, který je častější než 2. subtyp, je označen jako lymfoplazmatická sklerotizující pankreatitida (LPSP) a 2. subtyp AIP je označen jako idiopatická pankreatitida centrálních vývodů (idiopatická dukto-centrální pankreatitida – IDCP). Subtyp 1. je charakterizován preferenčním výskytem u mužů ve věku kolem 50 let, charakteristickým rysem je pozitivita imunoglobulinu G4 krevního séra, resp. IgG4 pozitivita plazmatických buněk přímo v parenchymu postiženého pankreatu. Tento typ je zvláště často spojen se současným nálezem dalších mimopankreatických IgG4 pozitivních lézí, častá je IgG4 pozitivní sklerozující cholangitida, postižení slzných a slinných žláz (Mikuliczův syndrom), retroperitoneální fibróza, vzácnější jsou IgG4 pozitivní nefropatie, pneumonitida, prostatitida, nebo mastitida [5–7]. V diferenciální diagnostice je mezi subtypem 1. a subtypem 2. zásadním histologickým rozdílem nepřítomnost tzv. granulocytárních epiteliálních lézí a neutrofilního periacinárního infiltrátu u 1. subtypu AIP. Hladina IgG4 u 2. subtypu je až na výjimky normální [8,9]. Jak bylo uvedeno, 1. subtyp AIP je na rozdíl od 2. subtypu spojen s častým nálezem postižení dalších orgánů, které mají pozitivní nález IgG4 v krevním séru. Jednoznačný avšak vzácný je vztah mezi IBD a IgG4 pozitivní autoimunitní pankreatitidou. Jedna z prvých studií, publikovaná již v roce 1999 Barthetem et al nalezla mezi nemocnými s IBD pouze 6 osob s AIP [10]. Podobně i další studie popisují AIP u osob s IBD jen v menším množství případů [11].

Multicentrická mezinárodní studie [12] analyzující retrospektivně soubor 91 osob s IBD a současným nálezem AIP zjistila, že 58 nemocných mělo diagnostikovánu ulcerózní kolitidu (ulcerative colitis – UC) a 33 nemocných Crohnovu chorobu (Crohn's disease – CD). Dále studie prokázala, jak se předpokládalo, že 89 pacientů mělo AIP typu 2 a pouze 2 pacienti měli AIP typu 1. Nepochybně zajímavým nálezem bylo vyšší zastoupení osob s kolektomií a AIP.

V našem sdělení uvádíme kazuistiku nemocného se současným nálezem CD a AIP 1. subtypu.

## Popis případu

46letý muž, pracující jako technik ve strojírenském závodě, byl roku 2012 hospitalizován v jiném zdravotním zařízení s podezřením na akutní apendicitidu. Peroperačně bylo vysloveno podezření na m. Crohn v ileocekální oblasti. Byla provedena ileocekální resekce a histologicky potvrzena diagnóza m. Crohn. Resekční výkon proběhl bez komplikací. Pacient byl dále sledován ve spádové gastroenterologické ambulanci, iniciálně byl léčen steroidy, poté mesalazinem a tato terapie pokračuje doposud. V anamnéze nemocného je údaj o četnějších zánětech horních cest dýchacích a alergie na podání penicilinové řady antibiotik. Pacient je kuřák, kouří do 10 cigaret denně, alkohol pije jen příležitostně, a to pouze víno, destiláty nepije vůbec. V posledním roce je jeho tělesná hmotnost stabilizována na hodnotě okolo 85 kg při výšce 182 cm. Udává, že stolice je většinou formovaná, pravidelná, hnědé barvy, močení probíhá bez potíží.

Do pankreatologické ambulance byl nemocný odeslán na podzim roku 2016 ke konzultaci se symptomatologií břišního diskomfortu až necharakteristických bolestí s lokalizací v mezogastriu, s evidentní manifestací časově vázanou na stravu. V rámci vyšetření bylo provedeno ultrasonografické vyšetření břicha a sonografista nález popsal jako zvětšení pankreatu, bez ložiskových změn a bez dilatace vývodu.

Při fyzikálním vyšetření bylo břicho palpačně bolestivé v oblasti pupku, jinak měkké, dobře prohmatné a bez resistence.

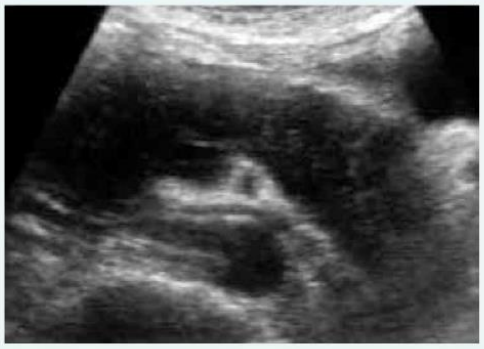
Laboratorní vyšetření: leukocyty 7,8, hematokrit a hemoglobin v normě, trombocyty 188 000. Sedimentace erytrocytů 26/32. Fekální elastáza < 120 µg/g (cut-off 150 µg/g). Bilirubinemie 25,2 µmol/l, ALT 0,88 µkat/l, AST 0,92 µkat/l, GMT 1,05 µkat/l, amylazemie 1,14 µkat/l; glykemie 5,8 mmol/l; gamaglobuliny zvýšeny na 24,4 g/l, IgG4 krevního séra 668 mg/l (norma 135,0 mg/l); cholesterolemie 6,4 mmol/l, triacylglyceroly v séru 0,98 mmol/l, urea 6,3 mmol/l.

Ultrasonografické vyšetření břicha: játra nezvětšena, světlejší barvy – susp. steatóza, ledviny – normální nález, pankreas – zvětšený, hypoechogenní, tvaru „sausage-like", pankreatický vývod není detekovatelný, ložisková léze není patrna, lymfatické uzliny – nezvětšeny. Obraz je charakteristický pro autoimunitní formu pankreatitidy (obr).

Nemocnému byl podán bolus steroidů – prednison 40 mg denně po dobu 4 týdnů, poté po 5 dnech dávka snižována o 5 mg na udržovací dávku 5 mg denně, a to po dobu 3 měsíců.

Při kontrolním vyšetření byl nemocný bez potíží, bilirubinemie se upravila na hodnotu 18,4 µmol/l, hodnoty ALT, AST a GMT se normalizovaly, pokles byl zaznamě-

**Obr. Ultrasonografický obraz autoimunitní formy pankreatitidy 1. subtypu** (slinivka břišní celkově zvětšená, „klobásovitého" tvaru)



nán u glykemie mírný na hodnotu 5,2 mmol/l a u IgG4 v krevním séru významný na hodnotu 212 mg/l.

Nemocný je nyní dispenzarizován ve spádové gastroenterologické ambulanci, subjektivně je nadále bez potíží a je léčen mesalazinem tbl v dávce 1,5 g denně. Koloskopický nález na střevě stabilizován, anastomóza klidná, nález bez progrese. Z hlediska diagnostikované autoimunitní pankreatitidy nedošlo při kontrole před asi 9 měsíci k aktivaci biochemických parametrů, nemění se IgG4 sérová hladina, není přítomna hyperamylazemie nebo hyperlipazemie. Sonograficky je velikost slinivky břišní normalizována.

## Diskuse

Vztah mezi AIP a IBD je stále zvláštností, přestože extraintestinální komplikace IBD jsou udávány v 21–47 % případů [13]. Pankreatické abnormality u osob s IBD jsou obecně relativně časté, ale spektrum je velmi heterogenní, včetně akutní pankreatitidy, chronické pankreatitidy a jak výše uvedeno AIP [14,15]. Změny exokrinní pankreatické funkce u osob s IBD a pankreatitidou popsali již v roce 1988 Angelini et al. U 27 nemocných s UC a CD byl proveden test s ceruleinem a sekretinem [16]. U 11 jedinců z 27 vyšetřených (40,7 %) nalezli snížení sekrece jak bikarbonátů, tak sekrece amylázy, což je jednoznačný průkaz exokrinní pankreatické nedostatečnosti. Izolované snížení výdeje lipázy bylo zjištěno u 18 osob z 27 vyšetřených, což ale ještě není jednoznačným průkazem zevní pankreatické insuficience. Na druhé straně tento nález může být jedním z faktorů vzniku klinicky známé malabsorpce u CD, především při lokalizaci nemoci v tenkém střevě. Heikus et al v roce 1966 použili k hodnocení pankreatické exokrinní funkce orální PABA test. Snížení zevní sekrece nalezli až u 30 % vyšetřených. Když však použili sekretinový test, snížení sekrece bikarbonátů nalezli u 19 % vyšetřených. V každém případě byla u osob s pankreatitidou a IBD exokrinní nedostatečnost u části nemocných identifikována [17].

AIP je dělena dle klinických a histopatologických znaků na 1. subtyp onemocnění, označený jako LPSP – lymphoplasmatic sclerosing pancreatitis a na 2. subtyp, označený jako IDCP – idiopathic duct-centric pancreatitis [18]. Oba typy jsou označeny jako AIP především díky některým společným histopatologickým znakům, ale jako IgG4 asociovaná AIP je uznán pouze AIP 1. subtyp. Pro 2. subtyp je typickým znakem nepřítomnost zvýšené hladiny imunoglobulinu G4 v séru (až na výjimky). V histologickém vyšetření je významným diagnostickým ukazatelem, typickým pouze pro 2. subtyp AIP, průkaz přítomnosti epiteliálních granulocytárních lézí (EGL) a neutrofilní periacinární infiltrace (tab). Další histologické nálezy jako je periduktální lymfoplazmocytární infiltrát, přítomnost IgG4 pozitivních plazmocytů a další se mohou nacházet u obou forem.

Odpověď na podání steroidů je u obou typů AIP a patří mezi diagnostická kritéria. Osoby s AIP 1. subtypu jsou v průměru starší než osoby s AIP 2. subtypu – > 50 let vs < 40 let.

Obecně platí, že AIP 2. subtypu může být spojena s nálezem IBD. Pro 1. subtyp je tento vztah uváděn jako vzácný. Srovnávací studie z roku 2015 [19] hodnotila soubor 138 osob s pankreatitidou a IBD. U 15 osob byla diagnostikována AIP, z toho u 11 osob se jednalo o subtyp IDCP a pouze u 4 jedinců byl potvrzen 1. subtyp. Pro 2. subtyp byla charakteristickým nálezem nízká frekvence přítomnosti obstrukčního ikteru, především díky vzácným změnám průsvitu žlučovodů ve smyslu striktur.

V našem kazuistickém sdělení je zajímavým poznatkem, že se jednalo o mladšího jedince s 1. subtypem AIP a současným nálezem IBD. Standardní terapie steroidy byla u nemocného úspěšná, a to i přes neúplnou normalizaci sérové hladiny IgG4, pokud jde o úpravu dalších laboratorních parametrů, tak ty byly v normě. Subjektivně byl nemocný zcela bez potíží.

Pankreatické manifestace osob s IBD se vyznačují širokým spektrem postižení, autoimunitní pankreatitidu 1. subtypu nevyjímaje.

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**Tab. Diferenciální diagnostika AIP subtyp 1. a subtyp 2. dle histomorfologických znaků**

| | histologický nález | 1. typ (LPSP) | 2. typ (IDCP) |
|---|---|---|---|
| společná kritéria | periduktální lymfoplazmocytární infiltrát | ano | ano |
| | stroma bohaté na zánětlivé buňky | ano | ano |
| | storiformní fibróza | velmi výrazná | vzácná |
| | obliterující flebitida | ano | vzácná |
| | prominující lymfatické folikuly | ano | vzácná |
| | IgG4 plazmatické buňky | zvýšený počet | nezvýšený počet |
| | granulocytární epiteliální léze (GEL) | ne | ano |
| | neutrofilní periacinární infiltrát | ne | velmi četný |

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**Příloha 13** - Ileocaecal Crohn's disease and familial adenomatous polyposis in one patient - a case report



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# Ileocaecal Crohn's disease and familial adenomatous polyposis in one patient – a case report

## Crohnova nemoc ileocekální oblasti a familiární adenomatózní polypóza u jednoho pacienta – kazuistika

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**Summary:** Crohn's disease (CD) and familial adenomatous polyposis (FAP) are two different diseases that both affect the gastrointestinal tract. FAP is an autosomal dominant inherited disease; however, the aetiology of CD is still unknown and is supposed to be multifactorial (genetics, environment, immune state, microbiom). The therapy of these two diseases differs as well. The ultimate solution for FAP is surgery (colectomy or proctocolectomy). On the other hand, CD can be treated either conservatively or surgically. Generally, in cases of bowel resection, the alternative of gastrointestinal tract restoration has to be considered. This decision is more challenging in patients diagnosed with both diseases (CD and FAP). We present the case of a young female with FAP who was diagnosed with active CD in the ileocaecal region. Due to multiple large colon polyps and a stenotic terminal ileum, she was indicated for surgery (colectomy with terminal ileostomy and terminal ileum resection). Subsequently, an ileorectal anastomosis was constructed. In further text, we also discuss other bowel restoration solutions, such as ileal pouch-anal anastomosis and abdominoperineal resection with terminal ileostomy.

**Key words:** familial adenomatous polyposis – Crohn's disease – bowel continuity restoration – colectomy – ileorectal anastomosis – J-pouch – ileal pouch-anal anastomosis

**Souhrn:** Crohnova nemoc (CD – Crohn's disease) a familiární adenomatózní polypóza (FAP – familial adenomatous polyposis) jsou sice dvě rozdílné choroby, obě ale ovlivňují gastrointestinální trakt. FAP je autozomálně dominantní vrozené onemocnění, naproti tomu etiologie CD je stále neznámá, ale předpokládá se multifaktoriální vliv (genetika, vnější prostředí, stav imunitního systému, mikrobiom). Léčba těchto dvou onemocnění se rovněž liší. Definitivním řešením FAP je chirurgická léčba (kolektomie nebo proktokolektomie). Na druhou stranu léčba CD může být jak konzervativní, tak chirurgická. Obecně v případě střevní resekce musí být předem zváženy možnosti obnovy kontinuity gastrointestinálního traktu. Toto rozhodnutí je o to náročnější, pokud je u pacienta zároveň diagnostikována CD i FAP. Prezentujeme případ mladé ženy s FAP, u které byla nově diagnostikována CD s postižením terminálního ilea a známkami aktivity. Vzhledem k přítomnosti mnohočetných velkých polypů a stenóze terminálního ilea byla pacientka indikována k chirurgické léčbě (kolektomii s terminální ileostomií a resekci terminálního ilea). V druhé době byla kontinuita obnovena ileorektální anastomózou. V textu jsou diskutovány i další možnosti obnovení kontinuity trávicího systému u této pacientky (ileopouch-anální anastomóza a abdomino-perineální resekce rekta s terminální ileostomií).

**Klíčová slova:** familiární adenomatózní polypóza – Crohnova choroba – obnova střevní kontinuity – kolektomie – ileorektální anastomóza – J-pouch – ileopouch-anální anastomóza

## Introduction

### Familiar adenomatous polyposis

Familiar adenomatous polyposis (FAP, also adenomatous polyposis coli – APC) is an autosomal dominant inherited disease with incidence varying from 1/7 000 to 1/22 000. The cause of FAP is a mutation of the APC gene localised on the long branch of the 5th chromosome. The APC gene is a tumour suppressor gene responsible for transcription and translation of the APC protein and its mutation can lead to colorectal and other cancer [1].

The classic form of FAP is characterised by a large number (up to thousands) of adenomatous colon polyps. The typical onset of FAP is in early adolescence. If not treated, polyps can become malignant. The colorectal cancer is then diagnosed approximately at the age of 39. There are only case reports of detection of malignant polyps in children with FAP [2].

The attenuated form of FAP (AFAP – attenuated familial adenomatous polyposis) is described only in 8% of families affected by FAP. This variation of FAP is characterised by a smaller number of less malignant polyps. The AFAP is therefore diagnosed much later than classic FAP – at the age of around 55 [3].

### Treatment of FAP

The management of FAP is based on identifying the patients at risk (family history, genetic testing) and introducing their close monitoring. The method of choice for an early polyp detection is a colonoscopy. The removal of any polyp found is necessary to prevent the development of colorectal cancer [4]. Specific pharmacologic treatment of FAP is not yet available. However, several studies consider the cyclooxygenase blockers as a promising treatment of FAP [5,6].

In FAP with advanced dysplastic polyps, endoscopically non-removable lesions or more than 100 polyps, the method of choice is a prophylactic colectomy [7]. This radical procedure minimises the risk of developing colorectal cancer.

Nowadays, there are no specific recommendations for bowel continuity restoration after colonic resections [8]. The decision for performing either colectomy with ileorectal anastomosis or proctocolectomy with ileal pouch-anal anastomosis (IPAA) should be individually based with consideration of the presence of rectal polyps [9]. The proctocolectomy is usually performed in patients with more than 20 rectal polyps, if the polyps are larger than 3 cm or if there are malignant changes [10]. The laparoscopic approach is the method of choice as it ensures lower morbidity and faster postoperative recovery [11].

### Crohn's disease

Crohn's disease (CD) is a chronic inflammatory bowel disease which may affect any part of the gastrointestinal tract. However, in up to 1/3 of cases the disease is localised in the ileocaecal region [12].

The aetiology of CD is still unknown and therefore a causal therapy is not yet available. Concerning the pathogenesis of CD, it is nowadays believed to be multifactorial and genetics probably play an important role in its development. The most frequently mentioned gene mutation is the NOD2/CARD15 that is significantly higher in CD patients than in the healthy population [13,14]. However, it is not the only pathognomonic gene mutation in CD development. Hence, the genetic testing is currently not recommended for routine diagnosis of CD [15].

### Treatment of ileocaecal Crohn's disease

Patients with localised ileocaecal disease can be treated either conservatively or surgically mainly according to the disease activity and the presence of obstructive symptoms due to stenosis.

In mildly or moderately active disease, local or systemic corticosteroids should be considered. In severely active CD, the patients should also be initially treated with systemic corticosteroids. However, for all patients who relapse (who are steroid-refractory or steroid-intolerant) an anti-tumor necrosis factor-alpha based strategy is appropriate.

Surgery is an alternative for patients with disease refractory to conventional medical treatment or in patients with obstructive symptoms but with no significant evidence of active inflammation. The laparoscopically-assisted ileocaecal resection with wide-lumen stapled ileocolic side to side anastomosis is the preferred technique [16,17].

In patients with a concomitant abdominal abscess, management should start with antibiotics, percutaneous or surgical drainage, followed by delayed resection, if necessary [15,18,19].

## Case report

We present the case of a 24-year-old female who was referred to our hospital by a general practitioner for a 4-week lasting abdominal pain, occasionally vomiting and a palpable mass in the right iliac fossa. On examination she was slightly leaning forward when walking, her abdomen was a little distended and the mass in the right iliac fossa was approximately 8 × 4 cm large and painful on deep palpation. The laboratory findings were normal, including the markers of inflammation and the abdominal ultrasound revealed periappendicular infiltration, advanced inflammatory changes in the subcaecal region with a suspicion of an acute appendicitis. She was therefore admitted to our department of surgery.

Concerning her past medical history, she was diagnosed with FAP according to the colonoscopy and genetic results (mutation in APC gene *c.2434-2437delGACA p.Asp812fsX7*) a few years previously. The last colonoscopy (performed 4 months earlier in a different hospital) showed multiple large intestinal polyps, no biopsies were taken and the terminal ileum was not examined. In her family, her grandmother and mother were diagnosed with colorectal cancer and two of her siblings with FAP. She was not using any medication and stated no allergies.

With regards to a possible differential diagnosis (appendicitis, CD) the CT scan was performed and showed inflammatory changes in the ileocaecal region, stenosis of the terminal ileum, a 6 cm long thickening of ileal wall and surrounding lymphadenopathy (Fig. 1a,b). With close cooperation with a gastroenterologist, a conservative approach was indicated. She was treated with antibiotics (metronidazole) and started bowel rest by means of intravenous parenteral nutrition. To confirm the diagnosis of

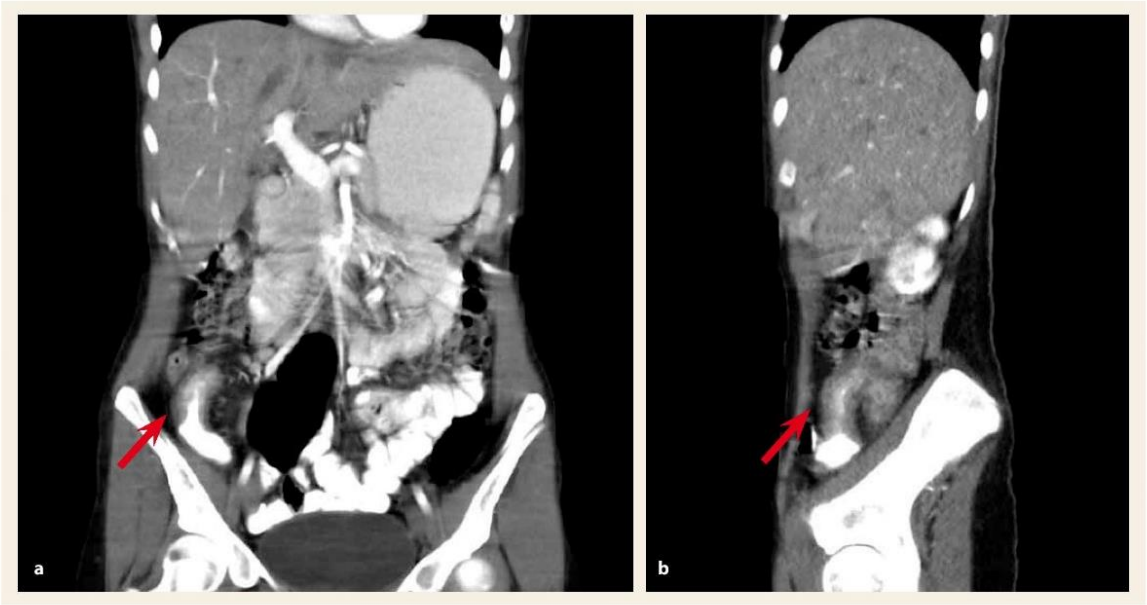


**Fig. 1a,b. Abdominal CT scan. Affected terminal ileum marked with an arrow.**
Obr. 1a,b. CT vyšetření břicha. Postižení terminálního ilea označeno šipkou.

CD a colonoscopy was performed. It revealed stenosis of the ileocaecal valve that enabled only a short intubation of the terminal ileum. There were no signs of macroscopic inflammation either at the ileocaecal valve or the terminal ileum. However, the biopsy from the terminal ileum showed histopathological signs of CD. As the patient repetitively showed obstructive symptoms due to stenosis of the terminal ileum, we decided not to treat her with corticosteroids but indicated her for ileocaecal resection.

Concerning the FAP, the colonoscopy revealed multiple large colonic polyps with low-grade dysplasia adenomas on biopsy. Particularly in the rectum, there were approximately 10 polyps up to 5 mm in size.

Consequently, after a discussion within a multidisciplinary team (surgeons, gastroenterologists and radiologists) it was recommended for the patient to undergo a colectomy with a resection of the terminal ileum and construction of the neoterminal ileostomy at the same time. The procedure was performed laparoscopically with no complications per- or postoperatively and the patient was soon discharged. A definitive histopathologic examination of the resected colon confirmed low-grade adenomas (Fig. 2) and the examination of the terminal ileum showed signs of CD (Fig. 3).

The patient has been regularly seen by a gastroenterologist and treated with azathioprine as a prophylaxis after a surgically induced remission of CD. As far as the bowel restoration is concerned, after 18 months the ileorectal anastomosis was performed without any complication. Regarding the FAP, the remaining rectal polyps were endoscopically removed, and the histology confirmed low-grade adenomas. Nevertheless, the patient has to undergo regular endoscopies of the rectum in order to detect early rectal cancer. The last endoscopy of the rectal stump showed no polyps and the patient is currently doing well without any health problems.

## Discussion

CD and FAP are both diseases that affect the gastrointestinal tract, however the treatment management of the diseases is different. Concerning CD, the treatment can be either conservative or surgical. As CD can affect the whole gastrointestinal tract, any surgery performed is always a bowel saving surgery to prevent short bowel syndrome. On the other hand, the only surgical treatment of FAP is colectomy or proctocolectomy as a prophylaxis of a malignant transformation or a cancer development.

The therapeutic dilemma appears if both diseases occur in one patient as described in our case report. Our patient was indicated for the ileocaecal resection due to CD and obstructive symptoms and at the same time she was indicated for colectomy due to FAP and multiple large polyps. The possibilities of bowel continuity restoration had to be discussed with the patient well in advance.

In the literature, there is a lack of patients diagnosed with CD and FAP and almost no recommendations concerning the most convenient type of bowel continuity procedure in these patients [20–22]. Moreover, these case reports refer to patients who were diagnosed with CD just after the procto-

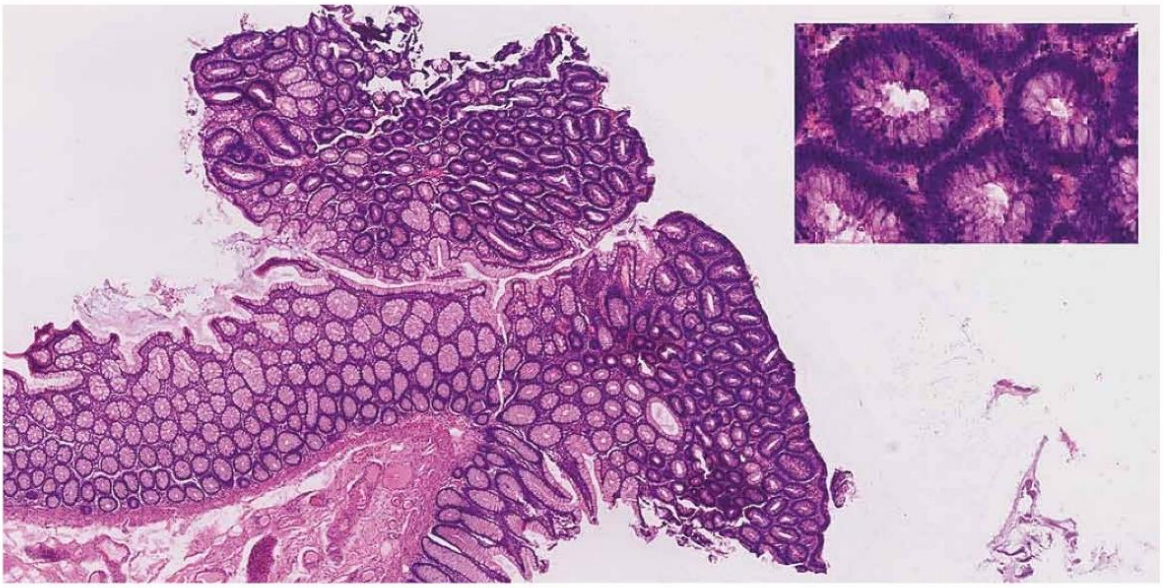

**Fig. 2. Tubular adenoma with low-grade dysplasia, haematoxylin and eosin staining 20×. Inset right corner: features of dysplasia (enlarged, hyperchromatic, basally located nuclei, loss of mucin), haematoxylin and eosin staining 400×.**
Obr. 2. Tubulární adenom s nízkým stupněm dysplazie, barvení hematoxylin-eozinem 20×. Vpravo nahoře: znaky dysplazie (zvětšená, hyperchromatická, bazálně umístěná jádra, ztráta mucinu), barvení hematoxylin-eozinem 400×.

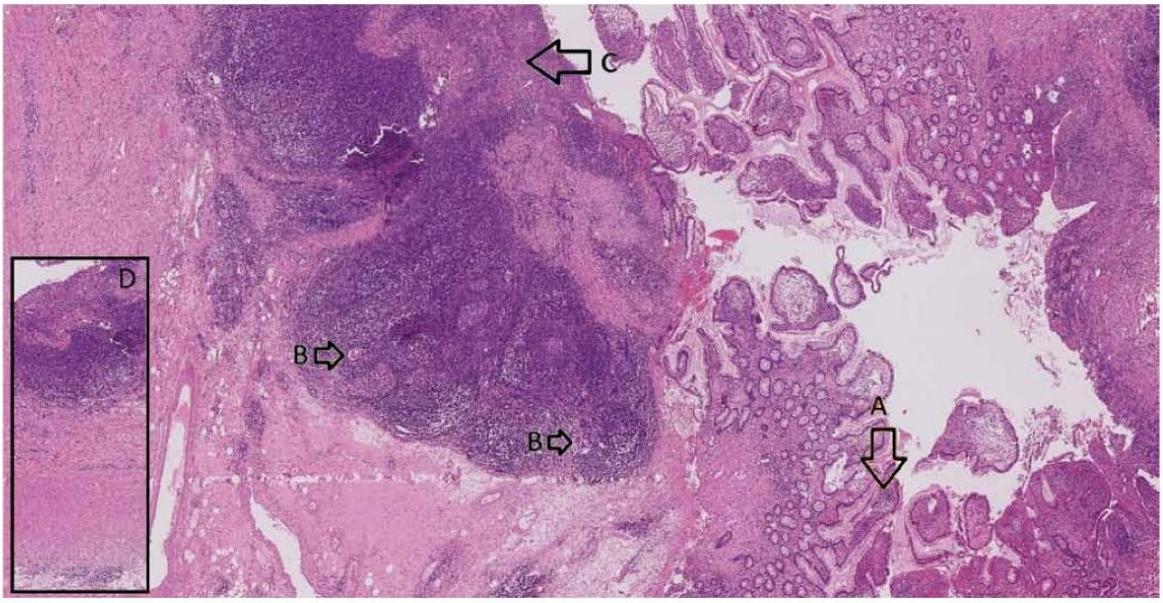


**Fig. 3. Small intestine with Crohn's disease – A. architectural distortion of mucosa, B. giant cells, C. ulceration, D. transmural inflammation.**
Obr. 3. Tenké střevo postižené Crohnovou nemocí – A. distorze architektoniky sliznice, B. mnohojaderné buňky, C. ulcerace, D. transmurální zánět.

colectomy with IPAA due to FAP. In our case the patient with FAP was diagnosed with CD even before any surgery.

A standard procedure to connect the ileum and the anal stump after proctocolectomy is creating an IPAA. At our department we construct a standard J-pouch from the terminal ileum connected to the anal canal. In the last

10 years, we have performed this procedure in 5 patients with FAP and in 45 patients with ulcerative colitis (UC).

When planning a bowel continuity restoration in a patient with FAP and CD after colectomy with ileocaecal resection, the following options have to be considered:

1. Finishing proctectomy and creating IPAA
   - a gold standard after colectomy in patients with FAP or UC;
   - disadvantage: not suitable in CD – construction of J-pouch using ileum as the most common location of CD constitutes a high-risk relapse of CD. Some authors consider CD of terminal ileum as a contraindication for J-pouch construction [23–25].
2. Ileorectal anastomosis
   - suitable for patients with a colonic form of CD;
   - disadvantage: leaving the rest of the rectum represents almost a 100% certainty of developing a rectal cancer in FAP patient in later life.
3. Abdominoperineal resection with terminal ileostomy
   - a definitive and ultimate solution for FAP and CD patients as well;
   - disadvantage: a devastating irreversible procedure in a young patient without proof of malignity.

According to our opinion, in patients with FAP and CD, the most suitable solution for a bowel continuity restoration is to construct an ileorectal anastomosis. However, provided that the rectum is well preserved, the rectal polyps can be treated endoscopically with no signs of malignancy and there are no signs of active CD. The ileorectal anastomosis preserves the patient's anal sphincter and rectum and gives the patient a chance not to have a terminal ileostomy for the rest of the life. Moreover, the rectal stump is easy for endoscopic detection of the polyps.

On the other hand, in the case of severe findings (multiple, large polyps, malignant changes or active CD) in the rectum, the abdominoperineal resection and construction of a terminal ileostomy should be performed.

Concerning the possibilities of a bowel continuity restoration in our patient, a comprehensive discussion with the patient was performed, explaining the pros and cons of all the alternatives. She finally decided to undergo a bowel continuity restoration with ileorectal anastomosis. However, we have to keep in mind that only a total proctocolectomy would minimise the risk of a rectal cancer development in a patient with FAP.

## Conclusion

CD and FAP are two different diseases affecting the gastrointestinal tract and the course of the treatment also varies. In the literature, there are very few cases describing FAP and CD in one patient. In case of need for colectomy due to FAP and ileocaecal resection due to CD at the same time, the decision of possibility bowel continuity restoration might be demanding. In our case report, we present ileorectal anastomosis as a well-balanced solution for bowel continuity restoration. However, the patient needs to undergo a careful endoscopic surveillance in order to detect an early rectal cancer.

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**Příloha 14** - Spinal epidural abscess – a rare complication of Crohn´s disease: case report



# Spinal epidural abscess – a rare complication of Crohn´s disease: case report

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**Summary**
Spinal epidural abscess (SEA) is a rare disease that occurs mainly in immunocompromised patients after spinal surgery or spinal trauma and can lead to a severe neurological deficit or even death if diagnosed too late. However, cases of SEA have also been reported in patients with fistulising Crohn´s disease (CD). We present a case of a young patient with CD and a history of relapsing perianal disease followed by a complication of SEA in the thoracic spine. In close cooperation with the orthopedists and the neurologists, the gastroenterologists have successfully treated the SEA in this patient, allowing her to return back to biological treatment for CD.

**Key words**: biological treatment – Crohn´s disease – perianal fistulas – spinal epidural abscess

## Epidurální absces páteře – raritní komplikace Crohnovy choroby: kazuistika

**Souhrn**
Epidurální absces páteře je raritní onemocnění, které se objevuje především u imunokompromitovaných pacientů po operacích nebo úrazech páteře a pokud je diagnostikováno příliš pozdě, může vést k těžkému neurologickému deficitu nebo dokonce smrti. V literatuře jsou ovšem popsány i případy epidurálního abscesu páteře u pacientů s fistulující formou Crohnovy choroby. Představujeme kazuistiku mladé pacientky s Crohnovou chorobou a recidivujícím perianálním postižením, které bylo komplikováno vznikem epidurálního abscesu v oblasti hrudní páteře. I díky úzké spolupráci s ortopedy a neurology se podařilo gastroenterologům pacientku úspěšně léčit. Následně tak pacientce mohla být navrácena biologická léčba potřebná pro komplikovaný průběh Crohnovy choroby.

**Klíčová slova**: biologická léčba – Crohnova choroba – epidurální absces páteře – perianální píštěl

## Introduction

Spinal epidural abscess (SEA) is a rare disease with incidence of 2–5/10 000 hospitalisations, which is however growing probably due to aging of the population, increases in the numbers of immunocompromised patients and spinal surgeries and improvements in the quality of radiological diagnostics [1,2]. Unfortunately, the mortality of SEA is up to 15 % if diagnosed too late. The location of SEA is mainly the lumbar spine and the etiology is mostly a hematogenous spread from a distant septic focus (such as skin furuncles, dental or tonsillar abscess, pneumonia, renal or psoas abscess) but it can also be direct after a trauma or even iatrogenic [1–3]. Typically, the causative organism cultivated from SEA is *Staphylococcus aureus*. The main presenting symptoms are back pain, fever and a variable degree of neurological deficit [2,3]. SEA is rare in patients with inflammatory bowel disease (IBD), with only a few cases reported – mostly in patients with fistulising Crohn´s disease (CD); however, a case of SEA has also been reported in a patient with ulcerative colitis after proctocolectomy with ileal pouche-anal anastomosis [4].

## Case report

A 24-year-old woman was followed up at our department for CD diagnosed at the age of 14 and located in

the colon and perianal region. She had been treated with adalimumab biologics already for 2 years. This therapy was discontinued in the third trimester of her first gravidity. During the pregnancy she was treated for relapsing perianal abscess with a need of drainage, where the last drainage was performed 14 days before the delivery. Eventually, she delivered a healthy child by a Caesarean section in general anesthesia. The woman´s family had a history of Bechterev disease. Three months after the delivery, she was referred to our department by her general practitioner for lower back pain and fever lasting for 3 weeks.

On examination she was asthenic, slightly hypotensive, tachycardic (with the heart rate of 120 beats per minute), with no apparent neurological deficit, her abdomen was not tender, with only mildly positive tappotement bilaterally. Rectal examination showed scars after healed abscesses but no signs of active disease.

Within the wide differential diagnosis, the following investigations were performed. In terms of laboratory findings, the C-reactive protein (115 mg/l) and border microcytic anaemia were identified; on the other hand, the urinary and stool samples did not show any pathology, and neither did the hemoculters, nor the X-ray and ultrasound of the abdomen, nor the X-ray of the lungs and thoracic and lumbar spine, nor the gynecological examination. Additionally, the neurologist concluded that there were slightly positive upper meningeal symptoms and therefore recommended an acute magnetic resonance imaging (MRI) of the spine to exclude an epidural abscess or other source of infection. The MRI (fig. 1a, fig. 1b, fig. 2) showed epidural abscess formation in the thoracic spine compressing the dural sac but not the spinal cord.

Given the mild neurological deterioration and quite favourable MRI findings, the patient was treated conservatively with antibiotics (oxacillin and cefotaxim) for two weeks, and subsequently with co-trimoxazol and rifampicin for two months. She was allowed to move with a spinal corset. After three months, she was completely asymptomatic, finished the antibiotic treatment and the control MRI of the spine (Fig. 3, 4) showed regression of the abscess. Considering the favorable results, the patient could return back to the biological treatment needed for CD.

## Discussion

SEA is a rare condition that can be fatal if underdiagnosed [1–3]. The most important factor in the therapeutic decision is the level and progression of neurological deterioration that can vary from simple back pain to signs of meningism, motor, sensor or sphincter dysfunction and even paraparesis [5]. The final diagnose is made by MRI. The findings then serve as a basis for therapy, which can be either conservative or surgical. As to the possibility of conservative therapy, it is possible to use antibiotics with a good penetration to the spine in neurologically stabilized patients. In contrast, in patients whose neurological deficit is worsening quickly, it is necessary to perform surgical decompression of the spine, sometimes even an urgent one. The most common procedure performed is a dorsal approach laminectomy [5].

Only a few cases of SEA in patients with CD have been reported, in which the etiology of SEA was mostly wide-

**Fig. 2. MRI – the SEA in thoracic spine**, transversal scan. Department of Radiology, and Nuclear Medicine

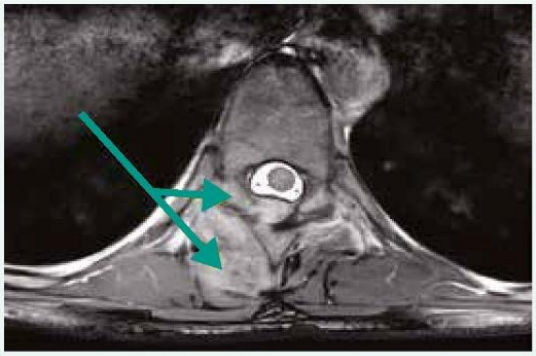


**Fig. 1. MRI – the SEA in thoracic spine**, sagital scan. Department of Radiology, and Nuclear Medicine

**1a.** T1-weighted


**1b.** T2-weighted

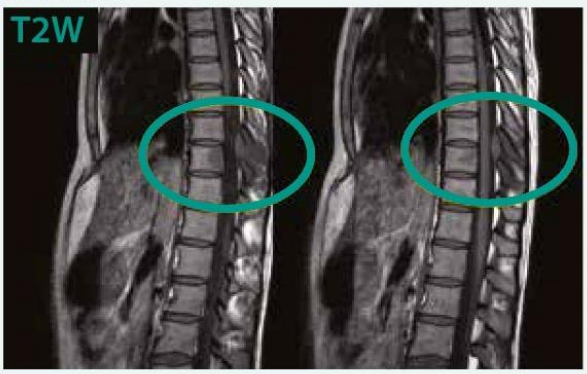


**Fig. 3. Control MRI after 3 months showing regression of SEA**, sagital scan. Department of Radiology, and Nuclear Medicine

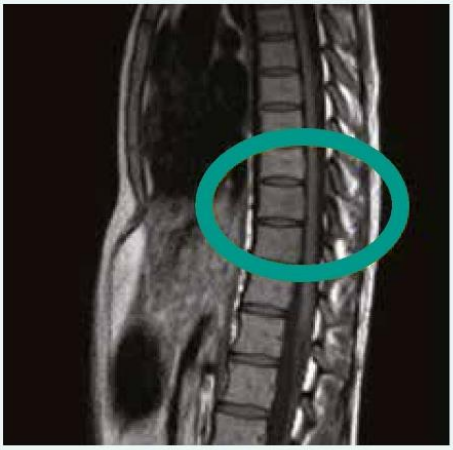
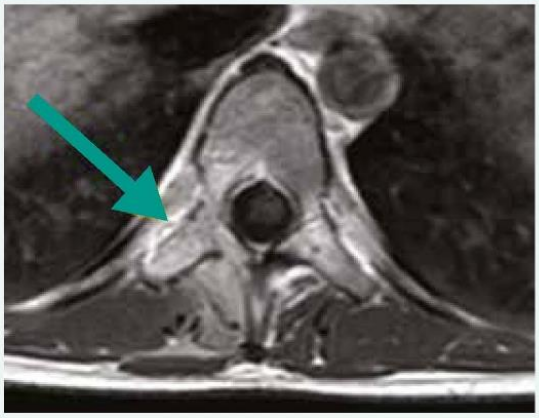


**Fig. 4. Control MRI after 3 months showing regression of SEA**, transversal scan. Department of Radiology, and Nuclear Medicine



spread from the perianal fistulas or abscess [4]. Fistulas can appear in patients with CD in 17–50 % of cases, with a recurrence in 1/3 of patients, moreover the cumulative incidence of developing a fistula in CD patients is approximately 20 % after 1 year and 50 % after 20 years [6–8]. Our patient was treated several times for perianal abscess during her pregnancy; however, when she was admitted for SEA, the perianal region was already healed (according to the MRI findings of the pelvis). The patients with CD and SEA reported in the literature were for their CD mostly treated with steroids or sulfasalazine whereas our patient was receiving with biological treatment, namely adalimumab, which can have an adverse effect of opportunistic infection [9–11]. A majority of patients with CD complicated by SEA had to be treated surgically (laminectomy); nonetheless, our patient was successfully treated conservatively with antibiotics [9,11]. Furthermore, in some surgically treated patients, early recurrence of SEA has been reported. Fortunately, this has not happened in our case and one year later, the patient shows no signs of recurrence of SEA. Moreover, she is able to continue with her biological treatment for CD.

## Conclusion

We present a rare case of SEA of the thoracic spine in a 24-year-old woman as a complication of perianal CD that was successfully treated conservatively with antibiotics.

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**Příloha 15** - Možnosti miniinvazivní chirurgie u pacientů s Crohnovou chorobou a ulcerózní kolitidou



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# Možnosti miniinvazivní chirurgie u pacientů s Crohnovu nemocí a ulcerózní kolitidou

## Possibilities of minimally invasive surgery in patients with Crohn's disease and ulcerative colitis

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**Souhrn:** Crohnova nemoc a ulcerózní kolitida jsou řazeny mezi chronická zánětlivá onemocnění střev, u kterých má i v době možnosti biologické terapie chirurgická léčba stále nezastupitelné místo. V článku jsou stručně shrnuty indikace k operačnímu řešení u pacientů s idiopatickými střevními záněty. Dále se zaměřujeme na možnosti miniinvazivních operačních technik od laparoskopicky asistovaných výkonů po relativně nové miniinvazivní metody. V textu jsou zmíněny naše zkušenosti – výhody či úskalí nově zaváděných operačních technik s odkazem na nejnovější současné studie a literaturu. Rozebrán je také vliv chirurgické léčby na kvalitu života u pacientů s nespecifickými střevními záněty.

**Klíčová slova:** Crohnova nemoc – ulcerózní kolitida – idiopatické střevní záněty – chirurgie – laparoskopie – kvalita života

**Summary:** Crohn's disease and ulcerative colitis are considered as chronic inflammatory bowel diseases where, even with the possibility of biological therapy, surgery still has an irreplaceable role in the treatment. This article briefly summarizes the indications for surgery in patients with inflammatory bowel diseases. Discussed are the possibilities of minimally invasive surgery from laparoscopic-assisted procedures to brand new minimally invasive techniques. The text mentions our experience – the advantages and disadvantages of the new surgical techniques with the references to the latest studies and literature reviews. The article also discusses the influence of surgical treatment on the quality of life of patients with inflammatory bowel disease.

**Key words:** Crohn's disease – ulcerative colitis – inflammatory bowel disease – surgery – laparoscopy – quality of life

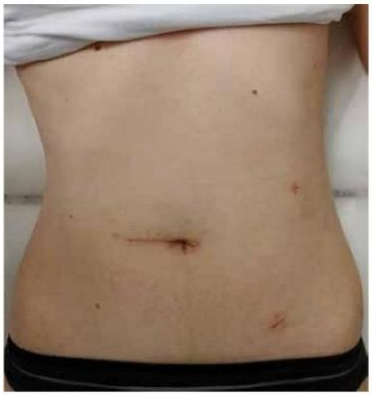
### Úvod

Crohnovu nemoc (CD – Crohn's disease) a ulcerozní kolitidu (UC – ulcerative colitis) řadíme mezi chronická zánětlivá onemocnění střev. Incidence idiopatických střevních zánětů (IBD – inflammatory bowel disease) stále narůstá, a to zvláště ve vyspělých státech světa. Mezi oblasti s nejvyšší incidencí patří Severní Amerika, Austrálie a severozápadní státy Evropy [1–5]. Diagnóza IBD je často stanovena již v mladším věku a zhruba polovina pacientů má stanovenou diagnózu IBD před 30. rokem života [6,7]. Z tohoto důvodu také plyne význam miniinvazivity při chirurgické léčbě a dosažení maximálního kosmetického efektu.

V současnosti však má i při možnostech imunosupresiv a zvláště éry biologické terapie chirurgická léčba IBD stále významnou a nezastupitelnou roli. Zhruba 70–80 % pacientů s CD podstoupí alespoň jedno operační řešení během svého života pro tuto diagnózu [8–10]. U pacientů s UC se toto procento pohybuje v rozmezí 10–20 % [11,12] a některé studie uvádějí až 30% riziko prodělání operace během života pro UC [13–15].

### Indikace k chirurgické léčbě u pacientů s CD

Indikace k operaci u pacientů s CD můžeme rozdělit na akutní a elektivní. Mezi akutní indikace patří perforace, krvácení, akutní těžká kolitida (ATK) a akutní porucha pasáže. Perforace do volné dutiny břišní je velmi vzácnou komplikací CD a je vzhledem k rozvoji peritonitidy indikací k akutní operaci [16,17]. Masivní krvácení u pacientů s CD se objevuje také relativně vzácně, uvádí se v rozmezí 0–6 % [18–20]. Další indikací k akutní operaci je ATK u CD při nereagující konzervativní terapii a horšení klinického stavu pacienta [21,22]. Akutní střevní obstrukce vzniká u CD nejčastěji na podkladě zánětu. Snahou je tyto pacienty léčit primárně konzervativně. Symptomatičtí pacienti, které však nelze zvládnout konzervativní léčbou, jsou indikováni k operační revizi [23].



**Obr. 1. Výsledný kosmetický efekt po laparoskopicky asistované ileocekální resekci.**
Fig. 1. Final cosmetic outcome after laparoscopic-assisted ileocecal resection.

Tito pacienti jsou vystaveni vyššímu riziku vícedobého operačního řešení s primárním založením stomie.

Elektivní operační řešení je indikováno u symptomatických pacientů při nedostatečné odpovědi na konzervativní léčbu či její intoleranci [24]. U pacientů s lokalizovanou CD (např. chronická stenóza či píštěl) připadá v úvahu resekční výkon [25]. V ileocekální oblasti je resekční chirurgický výkon jako metoda první volby u symptomatické stenózy bez předchozí medikamentózní terapie. U stenózy pod 10 cm a bez přítomnosti zánětu stěny je možno provést strikturoplastiku, nejčastěji dle Heineke-Mickulicz [26–28]. U pacientů se zánětlivým pseudotumorem, abscesy či fistulacemi je doporučováno zánětlivý proces zklidnit bowel restem, parenterální výživou, antibiotickou terapií a event. punkcí abscesového ložiska pod ultrazvukem či CT navigovanou kontrolou. Definitivní operační řešení poté plánujeme ve shodě s doporučením ECCO odloženě (ECCO Statement 7B) [29]. Pokud dojde k selhání tohoto postupu, jsme nuceni přistoupit k akutní chirurgické drenáži či resekčnímu výkonu [30–32]. Tyto výkony jsou zatíženy vyšší morbiditou a je doporučeno provádět vícedobé operační výkony. Další indikací k chirurgickému výkonu je malignita v terénu CD nebo podezření na ni. Pacienti s těžkým perianálním postižením, nereagující na konzervativní a chirurgickou léčbu, jsou indikováni k odklonění pasáže založením laparoskopické derivační stomie (ECCO Statement 9M) [23,29].

Jednotlivé chirurgické výkony jsou samozřejmě závislé na lokalizaci CD (oblast ileocekálního přechodu, kolon, perianální fistulující forma CD atd.) a od ní se také odvíjí operační přístup a technika.

## Indikace k chirurgické léčbě u pacientů s UC

Podobně jako u CD je základní dělení operací u pacientů s UC na akutní a plánované.

Nejčastější akutní indikací k operačnímu řešení je ATK při selhání či nedostatečnosti konzervativní terapie [33]. ATK postihuje asi 18 % nemocných s UC [34]. Zhruba u 5 % hospitalizovaných pacientů může ATK progredovat do toxického megakolon [35]. Další indikace, které mohou, ale také nemusí souviset s ATK, jsou masivní krvácení (tvoří asi 10 % urgentních kolektomií) a perforace tračníku u 2 % pacientů s UC, často vznikající na podkladě toxického megakolon [33,36].

Indikace k elektivnímu operačnímu řešení je chronická refrakterní UC při neefektivní konzervativní terapii [37] a vznik dysplazie či kolorektálního karcinomu (CRC – colorectal cancer). Kumulativní riziko vzniku CRC narůstá s délkou onemocnění, a to 2 % po 10 letech, 8 % po 20 letech a 18 % po 30 letech trvání UC [38].

## Miniinvazivní přístupy v chirurgické léčbě CD

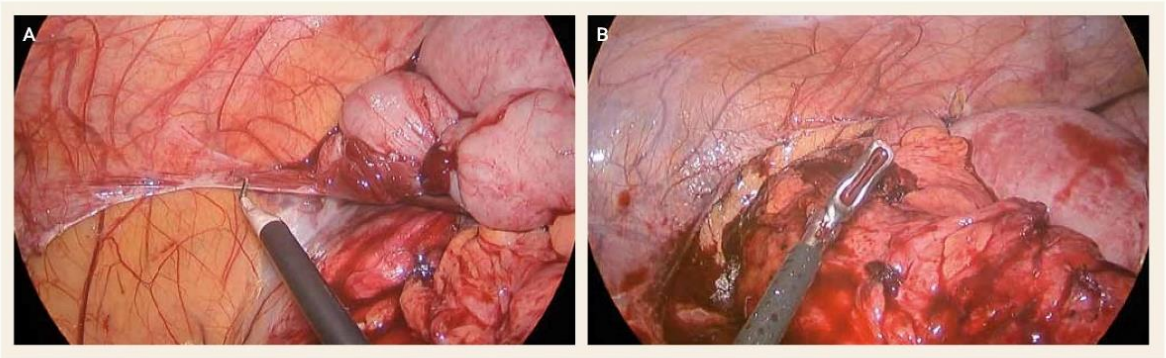
Laparoskopie je dnes již přijímána jako preferovaná metoda u většiny elektivních chirurgických výkonů. Výhody laparoskopie oproti konvenční chirurgii jsou potvrzeny mnoha studiemi. Mezi již obecně uznávané výhody laparoskopie u pacientů s CD patří dřívější obnovení peristaltiky, kratší doba hospitalizace a nižší pooperační morbidita [39–41]. Dále byla prokázána časnější pooperační rekonvalescence [42], lepší kosmetický efekt [43] (obr. 1) a také nižší výskyt vzniku incizionálních hernií [44]. Menší vnímání pooperační bolesti a následně také nižší spotřeba analgetik je popisována u laparoskopické kolorektální chirurgie, nicméně u pacientů s CD nebyl tento přínos ve srovnání s klasickou chirurgií jednoznačně potvrzen [40,42]. Velká výhoda laparoskopie a nově zaváděných miniinvazivních výkonů oproti otevřené chirurgii spočívá také v nižší tendenci tvoření pooperačních srůstů [45]. Následující operace v budoucnu pro pacienta s CD, který vyžaduje reoperaci pro recidivu choroby, je tak lépe technicky proveditelná.

Většina těchto výhod je zatím spíše prokázána u nekomplikované CD a elektivních primárních výkonů. U elektivní primární ileocekální resekce pro nekomplikovanou CD je doporučeno provádět výkon laparoskopicky (ECCO Statement 7F) [29,46,42,47] (obr. 2A a 2B). Laparoskopická technika je také doporučena k založení derivační stomie [48].

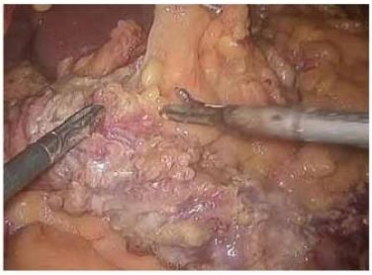
Jednou z mála nevýhod laparoskopického přístupu je delší operační čas výkonu [40,45]. U erudovaných chirurgů v laparoskopické kolorektální chirurgii se ale operační časy v posledních letech srovnávají.

Zatímco u nepenetrující CD jsou jasně prokázány lepší pooperační výsledky u laparoskopického přístupu, u komplexní neboli komplikované CD (absces, fistula, rekurence nemoci) tak přesvědčivé výsledky nejsou. Přesto řada studií dokládá, že laparoskopie i u komplikované CD se jeví jako možná a bezpečná [47,49]. Pacienty s komplexní formou CD je doporučeno operovat ve specializovaných centrech zabývajících se problematikou IBD a výkon provádět zkušeným operatérem [49,50].

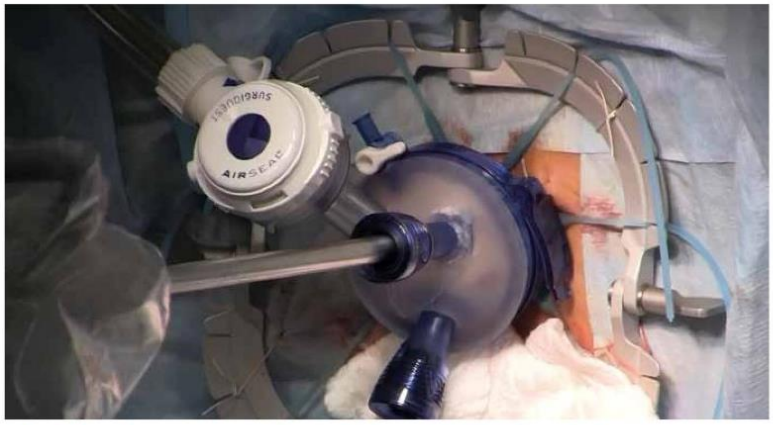
Diskutována je otázka chirurgického přístupu u akutních výkonů. U nejasné příčiny akutního stavu pacientů




**Obr. 2. Laparoskopický pohled na A. uvolňování střevních závěsů v oblasti pravého kolon při ileocekální resekci, B. uvolněný infiltrát v ileocekální oblasti tvořený postiženým úsekem terminálního ilea.**
Fig. 2. Laparoscopic view of A. removal of lateral peritoneal attachments of the right colon during ileocecal resection, B. detached ileocecal infiltrate consisting of the affected part of terminal ileum.



**Obr. 3. Laparoskopický pohled při subtotální kolektomii u IBD.**
Fig. 3. Laparoscopic view during the subtotal colectomy in an IBD patient.




**Obr. 4. Detail na transanálně zavedený port TAMIS při proktektomii.**
Fig. 4. Detail of a transanally inserted TAMIS port during proctectomy.

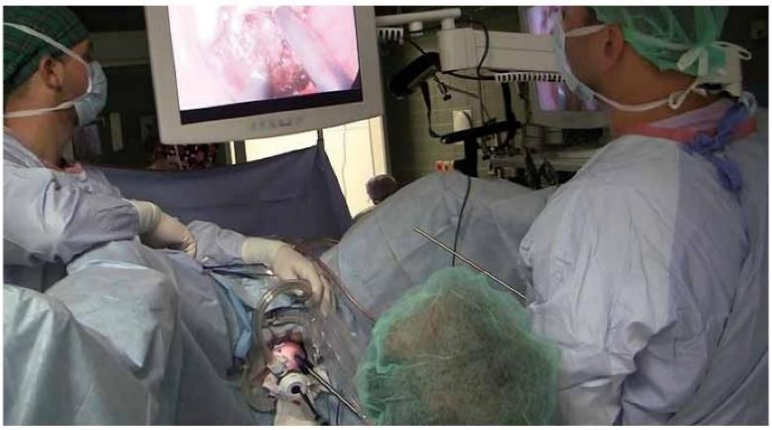
s CD může být laparoskopie indikována k ověření přesné diagnózy, při příznivém lokálním nálezu muže být příčina akutního stavu laparoskopicky vyřešena, a může tak zabránit vzniku zbytečně rozsáhlé laparotomie [51]. Za nevýhodu je považován delší operační čas, který u pacientů v celkově špatném stavu zvyšuje morbiditu [45,52,53]. U pacientů s CD při akutní operaci, zvláště pro peritonitidu a při oběhové nestabilitě a špatném nutričním stavu, by mělo být zváženo vyvedení dočasné terminální či axiální ileostomie [16,54].

Doporučený operační výkon u ATK u CD nereagující na konzervativní terapii je subtotální kolektomie s terminální ileostomií a slepým uzávěrem pahýlu rekta [21,22]. Laparoskopický přístup u ATK (obr. 3) má srovnatelné nebo dle některých studií i mírně lepší pooperační výsledky než chirurgie otevřená [47]. Hlavní výhodou je nižší výskyt srůstů při dalším operačním obnovení kontinuity.

Malignita v terénu CD i podezření na ni jsou indikací k chirurgickému výkonu. U této indikace je však nutné operovat dle onkologických zásad, tedy s konceptem kompletní mezokolické excize [55].

TAMIS (transanal minimally invasive surgery) je relativně nová miniinvazivní technika využívající speciální transanální port (obr. 4). Je to velmi vhodná metoda např. k provedení proktektomie. Operace se skládá jednak z fáze transanální (obr. 5), využívající port pro TAMIS, a jednak z fáze transabdominální (využívající standardních laparoskopických portů, nástrojů a optiky). Výhody této metody jsou v podstatě shodné jako u operací pro UC, které jsou rozebrány níže v textu.

SILS (single incision laparoscopic surgery) je jedna z možností miniinvazivních chirurgických přístupů. Jednou incizí je zaveden speciální laparoskopický port, který má více vstupů, umožňující zavedení více nástrojů do dutiny břišní z jednoho portu, a operaci je tak možné provést z jediné incize. Tuto alternativu provádějí však jen některá pracoviště a metoda není příliš rozšířená. Výhodou je jistě dobrý kosmetický efekt, na druhou stranu je výkon technicky náročný a vyžaduje



**Obr. 5. Pozice operatéra (uprostřed) během transanální fáze při TAMIS proktektomii.**
Fig. 5. Position of the surgeon (in the middle) during the transanal phase of TAMIS proctectomy.

delší čas operačního výkonu [56–58]. Metodou SILS se na pracovištích, kde je tato metoda preferována v rámci miniinvazivních přístupů, mohou provádět laparoskopické resekce na tenkém střevě i na tračníku. V současnosti v ČR není SILS standardem pro kolorektální operační výkony.

Stejně tak robotická chirurgie není zcela jednoznačným přínosem pro miniinvazivní IBD operativu vzhledem k tomu, že resekční výkony nedoplňujeme o lymfadenektomii ani neprovádíme náročné radikální onkologické resekce. Shodně v případě provedení proktektomie neprovádíme obtížnou mezorektální excizi, kde může být robotický přístup určitou výhodou.

## Miniinvazivní přístupy v chirurgické léčbě UC

Uplynulo již více než 30 let, kdy Parks et al [59] publikovali operační postup proktokolektomie s obnovením kontinuity formou ileopouch-anální anastomózy (IPAA). Tento výkon se stal standardem v chirurgické léčbě UC [60]. V současnosti a v době rozvoje kolorektální laparoskopické chirurgie se provádí i laparoskopické či laparoskopicky asistované proktokolektomie s IPAA.

Výhody při užití laparoskopie, jak jsou již zmíněny výše u CD, platí obdobně i u pacientů s UC. U elektivních výkonů mezi ně patří hlavně snížená délka hospitalizace, nižší pooperační morbidita a lepší výsledný kosmetický efekt (ECCO Statement 5A) [61–66].

U klasicky provedené proktokolektomie s IPAA se uvádí až trojnásobné zvýšení rizika sterility [67–69]. Za důvod je považován vznik pooperačních srůstů, které zapříčiní tubární sterilitu [70]. Za jednu z hlavních výhod laparoskopické proktokolektomie s IPAA jsou tak považovány dobré výsledky stran zachování plodnosti u žen s UC. Význam se připisuje hlavně nižší tendenci vzniku pooperačních srůstů po laparoskopickém výkonu [15,70]. Nevýhodou u laparoskopicky prováděného výkonu zůstává delší operační čas [65].

U urgentních operací pro UC je v dnešní době preferována subtotální kolektomie s terminální ileostomií a zaslepením pahýlu rekta [33]. U akutních výkonů u pacientů s UC byly zaznamenány tyto benefity při užití laparoskopické techniky: kratší doba hospitalizace, nižší počet infekčních komplikací ran a intraabdominálních abscesů. Srovnatelná s otevřenou chirurgií byla incidence pooperačního ileu a krvácení [15,71–73]. Pokud je akutní kolektomie prováděna na specializovaném pracovišti zkušeným chirurgem, je dle doporučení ECCO preferován laparoskopický přístup (ECCO statement 5C) [61].

U etapového operačního přístupu má také laparoskopie své výhody, a to zvláště po laparoskopické subtotální kolektomii s terminální ileostomií. Následná rekonstrukční fáze je prováděna snáze, jelikož je operační terén téměř bez srůstů, a je tak i relativně nízké riziko konverze [64,74]. K dokončení proktektomie či resekci rekta je také možné s výhodou použít metodu TAMIS postupem transanálně „down to top" (obr. 4 a 5). Zejména z ní mohou těžit pacienti s rizikovými faktory, jako jsou mužské pohlaví, úzká pánev a obezita. Lze se tak vyhnout rozsáhlé laparotomii, která je nutná při otevřeném výkonu. Laparoskopicky je možné precizněji preparovat a zachovat tak nervové pleteně ovlivňující sexuální funkce nebo omezit vznik adhezí majících následně vliv na plodnost u žen. Studie s početnějším souborem pacientů však zatím nejsou k dispozici. Metodu TAMIS lze užít u pacientů s UC i z onkologické indikace. Pokud jsou pacienti s UC indikováni k proktokolektomii z důvodu dysplazie či CRC, musí být výkon proveden dle onkochirurgických zásad a s dostatečnou radikalitou, tedy s provedením lymfadenektomie a totální mezorektální excizí (ECCO Statement 9A) [61,75].

Provedení subtotální kolektomie s ileostomií u pacientů s UC je možné také pomocí metody SILS [76]. Pooperační výsledky jsou obdobné jako u pacientů s CD zmíněnými výše. V roce 2010 Geisler et al [77] poprvé provedli restorativní proktokolektomie s IPAA technikou SILS s dobrými pooperačními výsledky. K porovnání metody jsou však zatím jen omezená data a chybí studie s dostatečným souborem pacientů.

Do robotické chirurgie byla vkládána relativně velká očekávání, a to zvláště do náročných výkonů jako IPAA u pacientů s UC. Zatím dostupné studie

však ukázaly jen výrazně delší operační čas a cenovou náročnost se stejnou hospitalizační dobou a stejným procentem pooperačních komplikací v porovnání se standardní laparoskopickou chirurgií [15,78]. Velká očekávání tedy tato metoda nesplnila.

## Vliv chirurgické léčby na kvalitu života u pacientů s IBD

Řada studií prokázala sníženou kvalitu života (QoL – quality of life) u pacientů s IBD v porovnání se zdravou populací [79–82]. U pacientů s CD prokázaly některé studie krátkodobé zlepšení QoL po operaci [83,84], nicméně s delším časovým odstupem od operace se QoL vrací u pacienta k původním hodnotám [85,86]. Studie u pacientů s CD porovnávající QoL po laparoskopickém výkonu oproti otevřené chirurgii překvapivě nezaznamenaly signifikantní zlepšení dlouhodobé QoL při užití laparoskopické metody [86,87].

QoL u pacientů s UC po proktokolektomii s IPAA je uváděna jako dostatečná, ačkoli výkon bývá relativně často spojen s pooperačními komplikacemi a také s horším kosmetickým efektem [60,88]. Pooperační QoL u pacientů s UC při užití laparoskopické techniky v porovnání s otevřenou chirurgií se zdá být rovnocenná [89–91]. Nejdůležitějším faktorem majícím vliv na QoL u pacientů s IBD se jeví navození dlouhodobé remise onemocnění [80,82,92].

## Závěr

U primární ileocekální resekce pro nekomplikovanou stenózu u CD jsou prokázány výhody laparoskopické resekce a je také doporučována. U komplexní CD je laparoskopie možná a ukazuje se i jako bezpečná metoda v rukou zkušeného chirurga na specializovaném pracovišti. Provedení laparoskopické subtotální kolektomie pro ATK u CD či UC v akutním stadiu se jeví také jako možná a bezpečná, pokud je provedena zkušeným laparoskopickým kolorektálním chirurgem. V případě UC byly prokázány i lepší krátkodobé pooperační výsledky a je některými chirurgy preferována. Mezi hlavní výhody laparoskopie a nově zaváděných miniinvazivních výkonů u pacientů s IBD oproti chirurgii otevřené patří zejména dřívější obnovení peristaltiky, kratší doba hospitalizace, nižší pooperační morbidita a lepší kosmetický efekt. Velkou výhodou hlavně u restorativních výkonů u UC nebo u pacientů s CD, u kterých existuje možnost reoperace pro recidivu v budoucnu, je nižší tendence k tvorbě srůstů. Následující operace je tedy o to snadněji proveditelná. U laparoskopické proktokolektomie s IPAA pro UC byla zaznamenána vyšší plodnost u žen ve srovnání s konvenčním přístupem. Benefit laparoskopie v porovnání s otevřenou chirurgií na celkovou pooperační QoL nebyl jednoznačně prokázán.

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**Příloha 16** - Laparoscopic pancreaticoduodenectomy for ampullary adenocarcinoma: a case report and review of literature



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# Laparoscopic pancreaticoduodenectomy for ampullary adenocarcinoma – a case report

## Laparoskopická hemipankreatoduodenektomie u ampulárního adenokarcinomu – kazuistika

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**Summary:** Ampullary adenocarcinoma (AA) is rare disease, accounting for less than 1% of all digestive cancers, although it is the second most common cancer arising from the periampullary region (after pancreatic cancer). Treatment of ampullary neoplasia varies from endoscopic resection, transduodenal surgical ampullectomy to a pancreaticoduodenectomy. At the time of diagnosis, the curative surgical resection rate of AA is higher than that of pancreatic cancer (80% to 20%) and the 5-year survival rate is also significantly longer. Laparoscopic procedures in colorectal surgery became the standard and the benefit of early post-operative outcomes is well proven. In this article, we present a 68-year-old patient with AA treated by laparoscopic pancreaticoduodenectomy (LPD). We consider the pros and cons of LPD and open pancreaticoduodenectomy, discuss possible treatment options of AA (including endoscopy treatment), and present a current review of literature.

**Key words:** adenocarcinoma of the ampulla of Vater – pancreaticoduodenectomy – surgery – periampullary tumors – pancreatic cancer – laparoscopy – endoscopy

**Souhrn:** Ampulární adenokarcinom (AA) je relativně vzácné onemocnění, tvořící méně něž 1 % všech nádorů gastrointestinálního traktu, ačkoli je to druhá nejčastější malignita periampulární oblasti (po karcinomu pankreatu). Mezi možnosti léčby ampulárních neoplazií patří endoskopická resekce, transduodenální chirurgická ampulektomie nebo hemipankreatoduodenektomie. V době diagnózy onemocnění je u AA vyšší pravděpodobnost kurabilní chirurgické resekce než u karcinomu pankreatu (80 vs. 20 %) a rovněž 5leté přežívání je významně delší. Laparoskopické resekční výkony se staly standardem v kolorektální chirurgii s prokázanými výhodami v časném pooperačním průběhu. V tomto článku prezentujeme kazuistiku 68leté pacientky s AA, u které byla provedena laparoskopická hemipankreatoduodenektomie (LPD). Pojednáváme o výhodách a nevýhodách LPD s hepankreatoduodenektomií prováděnou z otevřeného přístupu, rozebrány jsou léčebné možnosti této diagnózy (vč. endoskopické) a přinášíme přehled současné literatury.

**Klíčová slova:** adenokarcinom Vaterské papily – pankreatoduodenektomie – chirurgie – periampulární tumory – karcinom pankreatu – laparoskopie – endoskopie

## Introduction

Ampullary adenocarcinoma (AA) is quite rare, accounting for less than 1% of all digestive cancers [1,2], with a reported incidence of fewer than 1 person per 100 000 [3,4]. However, it is the second most common cancer arising from the periampullary region, comprising 6–20% of periampullary tumours [5,6].

Premalignant lesions of ampulla of Vater are generally treated by endoscopic resection. According to some authors, endoscopic treatment is also feasible in selected patients with early carcinoma limited to mucosa [4,7]. The first endoscopic papillectomy was performed by Suzuki in 1983 [8].

Transduodenal surgical ampullectomy (TSA) is considered if premalignant lesions cannot be endoscopically resected [9,10] and in the early stage of

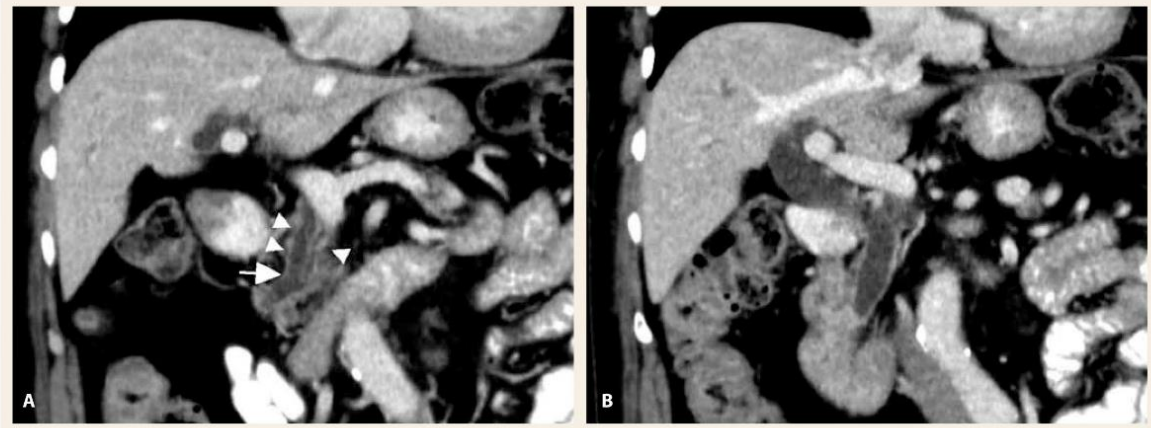


**Fig. 1. A, B. Portal venous phase of contrast-enhanced CT – image A shows the dilatation of pancreatic duct (arrow) and pancreatic head atrophy (arrowheads), image B reveals marked dilatation of extrahepatic bile ducts, so-called double duct sign refers to the presence of obstruction of both ducts, frequently due to tumour invasion. Source: Department of Radiology, Hospital Uherské Hradiště.**

Obr. 1. A, B. Portovenózní fáze kontrastního CT – obrázek A ukazuje dilataci pankreatického duktu (šipka) a atrofii hlavy pankreatu (větší šipky), obrázek B ukazuje výraznou dilataci extrahepatálních žlučových cest, tzv. double duct sign poukazuje na přítomnost obstrukce obou vývodů, často kvůli nádorové invazi. Zdroj: Radiologické oddělení, nemocnice Uherské Hradiště.

cancer in polymorbid patients [11,12]. American surgeon, William Halsted, first performed this procedure in 1898 [11,13].

Nevertheless, in AA pancreaticoduodenectomy (PD) is the preferred therapeutic method. PD can be performed by open surgery, which was first performed by an Italian surgeon, Alessandro Codivilla, in February 1898 (although he never published his surgery) [14]. A German surgeon, Walter Kausch, performed and first published PD for AA in 1909 [14]. Later the PD procedure was improved by an American surgeon, Allen Whipple, in 1935 [15] and is often called Whipple's procedure. With the current increasing role of mini invasive procedures, PD is also possible to carry out laparoscopically. Laparoscopic pancreaticoduodenectomy (LPD) was first described and performed almost 100 years later after an open procedure by Canadian surgeons Gardner and Pomp in 1994 [16]. From that time laparoscopic technology and instruments have been improved, however, LPD remains one of the most advanced and challenging laparoscopic surgeries.

PD is an extensive surgical procedure with high morbidity and mortality even in high volume centres. Surgical post-operative complications as well as non-surgical post-operative complications appear after PD. After laparoscopic colorectal surgery, a lower incidence of respiratory infections is observed compared to open procedures. Improved post-operative outcomes, including lower morbidity, are reasons why minimally invasive surgery is also more expandent in hepatopancreatobiliary surgery.

## Case report

Our patient is a 68-year-old woman. Her case history includes hypertension and cholecystectomy in 2006 (solitary cholecystolithiasis). In 2014, the patient underwent endoscopic retrograde cholangiopancreatography (ERCP) for liver enzyme elevation and suspicion of choledocholithiasis with findings of slight stenosis of papilla (histologically chronic inflammation with fibrosis). There were no gallstones present in the bile duct and papillosphincterotomy was performed.

In 2018, the patient was examined after a weight loss, liver enzyme and bilirubin elevation (alanine aminotransferase 4.9 µkat/L, aspartate transaminase 3.4 µkat/L, alkaline phosphatase 15.0 µkat/L, gamma-glutamyltransferase 21.7 µkat/L, bilirubin 33.1 µmol/L, amylase 0.34 µkat/L, carbohydrate antigen 19-9 6.7 U/ml). Due to a dilation of the biliary tract and ultrasound suspicion of a choledocholithiasis, ERCP was indicated. ERCP revealed a stenosis of ampulla of Vater and there were no lithiasis present in the biliary tract. A biopsy from the papilla and the papillosphincterotomy was performed. The biopsy confirmed adenocarcinoma.

The staging CT scan has added findings of dilation of the bile and pancreatic duct (double duct sign) (Fig. 1 A, B). Due to a double duct sign we suspected invasion of the ducts. The patient was presented at a multidisciplinary committee and was indicated for surgery.

### Surgery procedure

The operation started with a staging laparoscopy. After exclusion of liver metastasis, six ports for the laparoscopy

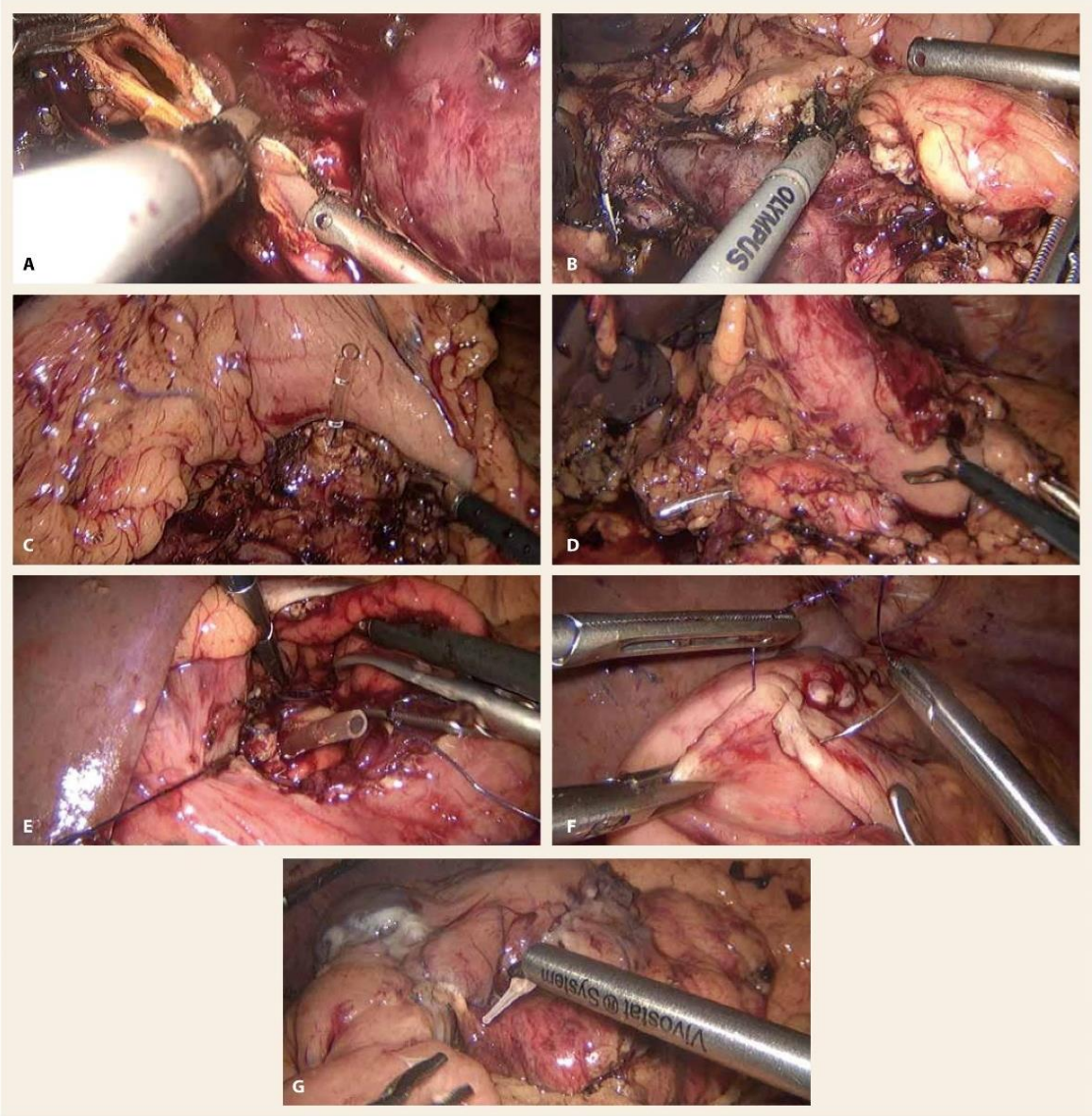


**Fig. 2. A. Interruption of common dilated hepatic duct, B. interruption of pancreas (in the area of neck) with visible superior mesenteric vein and confluence, C, D. posterior gastric wall and remnant of pancreas with inserted stent to the pancreatic duct, E. suturing of pancreatogastro-anastomosis through anterior gastrotomy, at the bottom remnant of pancreas with inserted stent to the pancreatic duct, F. suture of the anterior gastrotomy, G. application of autologous platelet-rich fibrin sealant Vivostat® for anastomosis augmentation.**

Obr. 2. A. Přerušení dilatovaného společného jaterního vývodu, B. Přerušení slinivky v místě krčku s patrnou dolní mezenterickou žílou a konfluens, C, D. zadní stěna žaludku a přerušená slinivka se stentem v pankreatickém vývodu, E. našívání pankreto-gastro-anastomózy přes přední gastrotomii, na spodině patrna slinivka se stentem v pankreatickém vývodu, F. sutura přední gastrotomie, G. aplikace autologního destičkového fibrinem obohaceného lepidla Vivostat® k augmentaci anastomóz.

procedure were placed. First, the lesser sac was opened through the gastrocolic ligament and then the lower edge of the pancreas was released; the superior mesenteric vein (SMV) was found and at its level the pancreas body was liberated from the SMV surface. After this, the pancreas was interrupted by Thunderbeat® (Fig. 2A) and the drain

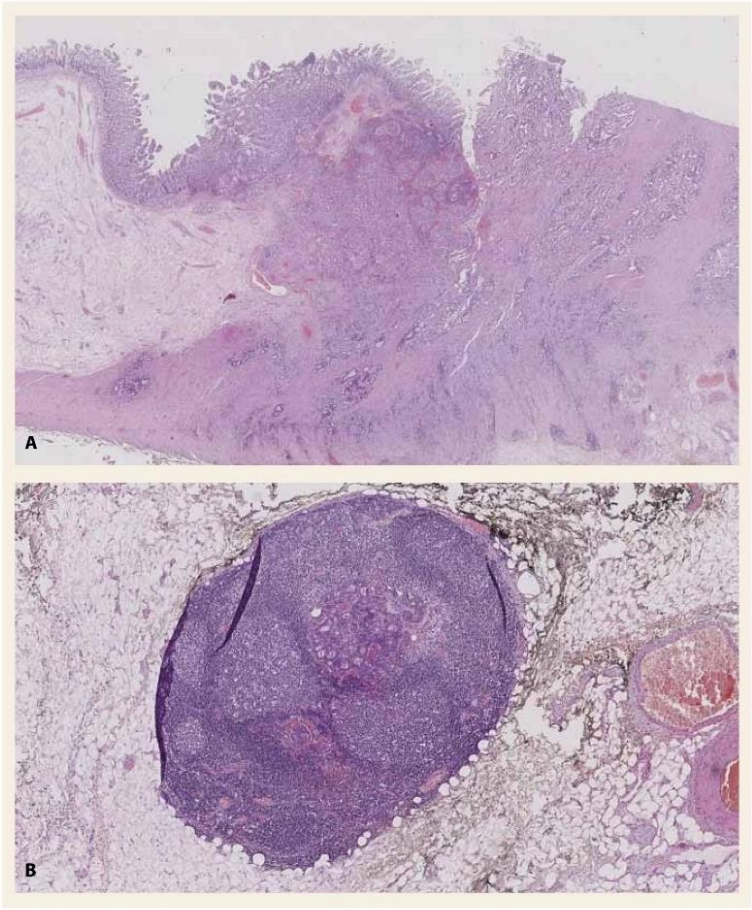


**Fig. 3. A, B. Histological section – ampullary adenocarcinoma. Tumour glands invade the duodenum wall. Haematoxylin-eosin staining 10× (A). Histological section – regional lymph node with metastasis of the adenocarcinoma. Haematoxylin-eosin staining 40× (B).**

Obr. 3. A, B. Histologické vyšetření – ampulární adenokarcinom. Nádorové žlázky invadují stěnu duodena. Barvení hematoxylin-eozinem 10× (A). Histologické vyšetření – regionální lymfatická uzlina s metastázou adenokarcinomu. Barvení hematoxylin-eozinem 40× (B).

was inserted into the dilated pancreatic duct. Near the upper pancreatic edge, the common hepatic artery was located and a lymphadenectomy from her detachment from the celiac trunk to the hepatoduodenal ligament was performed. The gastroduodenal artery was ligated and the common dilated hepatic duct was interrupted (Fig. 2B). The duodenum was cut below the pylorus, released from retroperitoneum, followed by a dissection of the uncinate process from SMV and a radical resection was finished by dissection from superior mesenteric artery.

The reconstruction phase differs from the colorectal laparoscopic procedures as most of the anastomoses are possible to carry out by stapler. In this procedure all anastomoses were done by laparoscopic suture (however, there are some authors, who prefer to perform the reconstruction phase from minilaparotomy). Our department prefers to construct the pancreaticogastric anastomosis (PGA) to the posterior wall of the stomach, as was also done in this laparoscopic procedure. First, the posterior portion of PGA was performed with single stitches between the remnants of the pancreas and posterior gastric wall (Fig. 2C,D), followed by anterior and posterior gastrotomy. The pancreatic body was pulled through the posterior gastrotomy into the stomach. The anterior portion of PGA was finished by single stitches (through the anterior gastrotomy) (Fig. 2E) and finally the anterior gastrotomy was sutured (Fig. 2F). The reconstruction phase was completed by Y-Roux hepaticojejunal anastomosis (HJA) and gastrojejunal anastomosis. The specimen was extracted in a protective bag by a Pfannenstiel incision. Two drains were placed into the abdomen cavity (in proximity to HJA and PGA). PGA and HJA were augmented by autologous platelet-rich fibrin sealant Vivostat® (Fig. 2G).

The patient was discharged 10 days after the surgical procedure without any post-operative complications. Definitive histology (Fig. 3A) established a diagnosis of AA (grade 2) with invasion of duodenal wall and pancreas (T3). Resection margins, evaluated according to a Leeds pathology protocol [17,18], were negative, 2 of 11 removed lymph nodes were positive (N1) (Fig. 3B) and perineural invasion was present. Considering these risk factors we prescribed adjuvant treatment with gemcitabine for 6 months.

## Discussion

Endoscopic papillectomy is globally recognised as the first method of choice in premalignant ampullary lesions [10,19]. The possibility of endoscopic therapy of early adenocarcinoma of the ampulla of Vater bounded to mucosa, without a deeper invasion to submucosa, is stated by some authors [4,7,20]. In cases where the premalignant lesions cannot be resected endoscopically [9,10] or in select patients within the early carcinoma stage (without a lymph node invasion and in polymorbid

patients) [11,12,17], the TSA should be considered. However, PD remains a method of choice in AA.

Due to its anatomical location, AA usually presents early with jaundice or pancreatitis [21] and due to an earlier clinical presentation, resection rates (possibility of resection) for most patients are much higher than for pancreatic cancer. Curative surgery is possible in up to approximately 80% of cases at the time of diagnosis of ampullary cancer compared to pancreatic adenocarcinoma, where the resectability rate is around 20% [2,22,23].

Easier feasibility of laparoscopic resection in the case of ampullary tumours compared to pancreatic cancer can be due to its earlier clinical manifestation and so, at time of diagnosis, the surrounding organs, arteries (superior mesenteric artery, celiac trunk) and veins (portal vein) are not infiltrated by tumour.

In comparison with other periampullary cancers, AA has better surgical outcomes in treatment and long-term survival rate. The 5-year survival rates following resection range from 38% to 67% [24,25]. Choi et al. [26] in 2011 reported a 59.9% overall 5-year survival rate after PD (R0/R1 resection). Sudo et al. [24] even published a 64% overall 5-year survival rate after PD resection for AA. The reason seems to be due to earlier clinical diagnosis and so a higher resectability rate and less aggressive tumour characteristics compared to other periampullary cancers (pancreatic cancer, distal bile duct carcinoma) [2,24,25].

The advantages and benefits of laparoscopy for patients have been well described in other kinds of abdominal surgery (primarily in colorectal and inflammatory bowel disease surgery), such as shortened hospital stay, quicker recovery, lower morbidity, better cosmetic outcome and lower percentage of incisional hernias [27–31].

However, in hepatopancreatobiliary surgery, it still remains a challenge for surgeons and represents one of the most difficult laparoscopic procedures. What also must be considered is that in oncologic curative surgery, the radicality and complete resection of the tumour is the primary goal. Many studies have been comparing the surgical oncologic results and survival rate after laparoscopic and open pancreaticoduodenectomy (OPD). Long-term overall survival after LPD is comparable to and also appears to be true for pancreatic cancer as well [32–35].

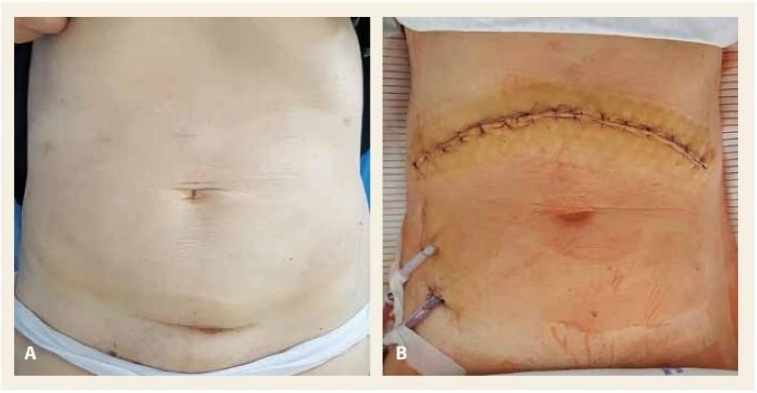


**Fig. 4. A, B. Comparison of cosmetic outcome in laparoscopic (A) and open (B) pancreaticoduodenectomy.**
Obr. 4. A, B. Srovnání výsledného kosmetického efektu po laparoskopické (A) a otevřené (B) pankreatoduodenektomii.

Studies that also compared pathology results did not demonstrate any significant difference and achieved similar negative resection margins and number of lymph node harvest in LPD and OPD (in AA and also pancreatic cancer) [32,34,36–38].

PD is associated with high mortality and morbidity rate even in high volume centres. The post-operative mortality rate is between 3 and 5% [39,40]. The morbidity ranging from 40 up to 60%, primarily due to pancreatic fistula, post-operative bleeding and delayed gastric emptying [11,39,41]. Just Dokmak et al. [39] reported higher morbidity in cases of LPD. Otherwise, the same morbidity rate has been recorded in comparison of LPD with OPD [32,35,37,38,42] and some studies and systematic meta-analysis have even reported a lower occurrence of post-operative complications in LPD [33,43,44].

Adjuvant oncologic therapy should be considered after surgery resection if risk factors occur (positive lymph nodes, positive resection margins, unfavourable grading, perineural, angio or lymphovascular invasion) [17,22,45]. As presented in our case, because of positive lymph nodes and perineural invasion, the adjuvant therapy was indicated.

Typical advantages of laparoscopy were confirmed in LPD, such as less abdomen pain, less blood loss, shorter hospital stay and faster post-operative recovery [32,38,42,43]. Comparison of incisions and cosmetic outcome between LPD and OPD can be seen in figure 4.

On the contrary, the length of the operative time has been described as shorter in OPD in some comparative studies [35,42–44], but it is dependent on the surgeon's learning curve of this highly advanced technical laparoscopic procedure [46].

It has to be said that most studies performed LDP on select patients. Inclusion criteria in cohorts were tumours which had not spread to the

main vessels or smaller tumour size (up to 2–3 cm); excluded were patients with high cardiopulmonary morbidity or relative exclusion criterion for laparoscopy with previous history of major surgery [32,36,37,47].

## Conclusion

We present a 68-year-old woman with adenocarcinoma of ampulla of Vater that successfully underwent LDP. Patients with periampullary adenocarcinoma treated by LPD have a similar long-term survival rate compared to OPD and similar or lower post-operative complications, with shorter length of hospital stay and faster post-operative recovery (and other more positive surgical outcomes). However, future prospective studies are needed because most of the current published studies are retrospective. LPD is performed optimally on select patients (smaller tumour, no vessels infiltration, as mentioned above) due to the procedure's technical difficulties. LPD is an extremely challenging and difficult procedure with a slow learning curve and should be performed by experienced laparoscopic surgeons. Due to this, AA has a higher resectability rate than pancreatic carcinoma, and in the early stage of AA where there is usually no spreading of the tumour to mesenteric vessels and portal vein, it seems to be suitable for a minimally invasive procedure.

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**Příloha 17** - Laparoscopic liver resection for alveolar echinococcosis



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# Laparoscopic liver resection for alveolar echinococcosis

## Laparoskopická resekce jater pro alveolární echinokokózu

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**Summary:** Echinococcosis is a rare parasitic infection in Central Europe. The most commonly affected organ is the liver. There are two types, cystic and alveolar echinococcosis with different types of treatment management. A radical liver resection remains the method of choice in the management of alveolar echinococcosis. We report a case of a 40-year-old woman with an echinococcal alveolar liver lesion successfully treated with a laparoscopic resection of the 5th liver segment. The laparoscopic technique, with all its benefits over open surgery, provides a safe and efficient treatment of selected types of echinococcal cysts located in the liver. It is a mini-invasive surgical approach which enables lower postoperative discomfort, quicker recovery and better cosmetic outcome.

**Key words:** echinococcosis – liver resection – laparoscopy – surgery

**Souhrn:** Echinokokóza je ve střední Evropě vzácně se vyskytující parazitární onemocnění. Nejčastěji postiženým orgánem jsou játra. Existují dva typy této nemoci, cystická a alveolární echinokokóza, které se také liší v terapii. Radikální chirurgická resekce zůstává metodou volby v léčbě alveolární formy. Prezentujeme případ 40leté pacientky s alveolární formou echinokokózy, která podstoupila úspěšnou laparoskopickou resekci 5. segmentu jater. Laparoskopická technika se všemi svými výhodami oproti otevřené chirurgii představuje bezpečnou a efektivní léčbu vybraných typů echinokokových jaterních ložisek. Jedná se o miniinvazivní chirurgický přístup, který snižuje pooperační diskomfort, umožňuje časnou pooperační rekonvalescenci a lepší kosmetický efekt.

**Klíčová slova:** echinokokóza – jaterní resekce – laparoskopie – chirurgie

## Introduction

Human echinococcosis is a rare zoonotic infection caused by parasites of the genus *Echinococcus*. The most frequent clinical forms of the disease are cystic echinococcosis (CE) caused by *Echinococcus granulosus* (EG) and alveolar echinococcosis (AE) caused by *Echinococcus multilocularis* (EM) [1]. The reported incidence rate of echinococcal infections in the Czech Republic between 2008 and 2017 was 0.023 cases per 100 000 person-year [2]. In endemic areas, the annual incidence of AE ranges from 0.03 to 1.2 per 100 000 persons [3].

EM is a small tapeworm (1.2–3.7 mm) that infects mainly foxes as a definitive host, and to a lesser extent dogs, cats, coyotes and wolves [4]. Humans are usually infected by food or water contaminated by carnivores' faeces containing echinococcus eggs [5]. The egg hatches in the small bowel and releases an oncosphere that penetrates the intestinal wall and migrates through the circulatory system into the liver [4]. Primary extra-hepatic locations of EM are rare (1–3%), but EM can spread to other organs by infiltration or metastasis formation [3,6].

In the liver, the oncosphere develops into a larval stage creating multilocular cyst [4]. EM cysts are more poorly limited than EG cysts because there is no sharp separation between the parasitic tissue and the liver parenchyma. The initial phase of infection is always asymptomatic, usually for several years due to slow growth rate. Common symptoms of hepatic cysts are right epigastric pain, nausea, vomiting and jaundice [7].

## Case report

We present a 40-year-old female patient, who was examined for decompensated

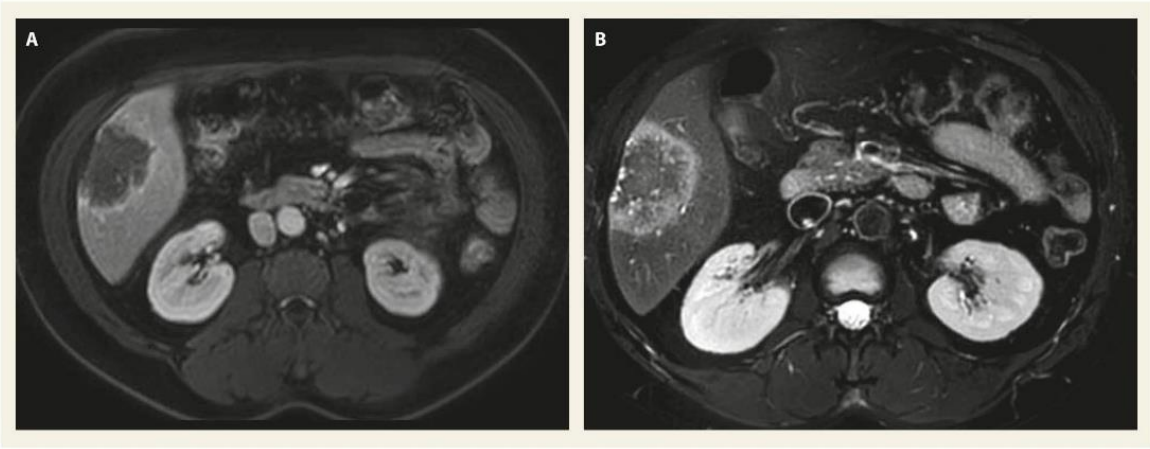


**Fig. 1. Echinococcal liver lesion on MRI – A. T1 weighted image in portal phase of contrast enhancement – axial scan; B. T2 weighted image – axial scan.** In the right liver lobe in the 5th segment there is a post-contrast T1 hypointense hypovascular focal lesion with hyperintense margin of hyperperfusion, the centre of the lesion remains unenhanced (A). On the T2 weighted image the lesion is hypointense, on the margin we can see small hyperintense areas – small cystic formations (B). Source: Department of Radiology, Hospital Kyjov.

Obr. 1. Echinokokové postižení jater na MR – A. T1 vážená sekvence po podání kontrastní látky v portální fázi v axiální rovině; B. T2 vážená sekvence v axiální rovině. V pravém laloku jater v 5. segmentu je postkontrastně v portální fázi T1 hypointenzní hypovaskularizované ložisko s hypervaskularizovaným hyperintenzním lemem (A). Na T2 je léze hypointenzní, po obvodu patrny drobné hyperintenzní okrsky v rámci drobných cystických kolekcí (B). Zdroj: Radiologické oddělení, nemocnice Kyjov.

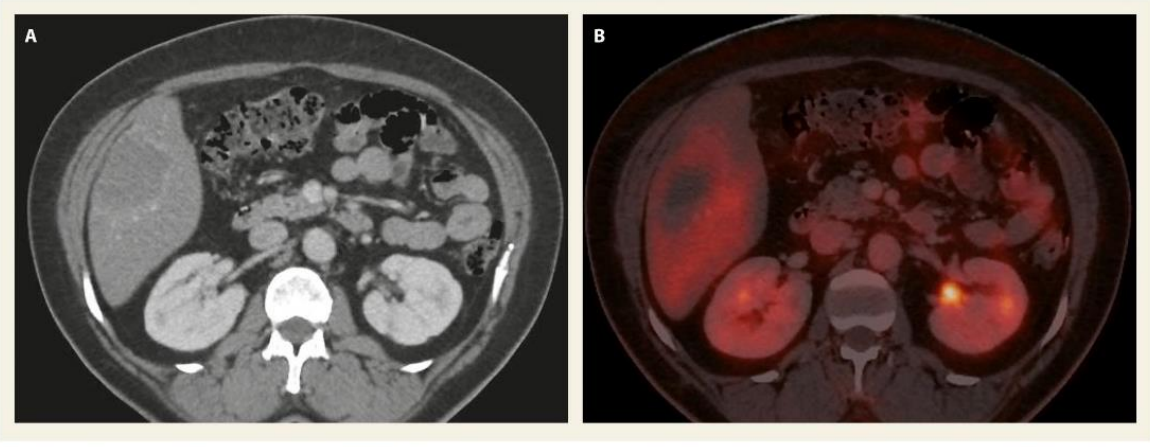


**Fig. 2. Echinococcal liver lesion on PET/CT after 1-year treatment with albendazole – A. contrast enhanced CT – axial scan; B. fusion – axial scan.** After intravenous application of a contrast dye, there is a discrete saturation hem around a hypodense lesion in the 5th liver segment. In the fusion images of the 5th liver segment, there is a metabolically inactive hypodense lesion with a discrete post-contrast hem opacity and a complete disappearance of a fluorodeoxyglucose (FDG) accumulation over the surrounding hepatic parenchyma. Source: Department of imaging methods, T. Bata Regional Hospital, Zlín.

Obr. 2. Echinokokové postižení jater na PET/CT po roční terapii albendazolem – A. CT po aplikaci kontrastní látky intravenózně – axiální řez; B. fúze – axiální řez. Po aplikaci kontrastní látky intravenózně je patrný diskrétní lem sycení kolem hypodenzního ložiska v 5. segmentu jater. Na fúzních snímcích v 5. segmentu jater je patrno metabolicky neaktivní hypodenzní ložisko s diskrétní postkontrastní opacifikací lemu a úplným vymizením akumulace fluorodeoxyglukózy (FDG) oproti okolnímu jaternímu parenchymu. Zdroj: Oddělení zobrazovacích metod, Krajská nemocnice T. Bati, Zlín.

hypertension. Concerning her medical history, she had diabetes mellitus type 2 treated by oral antidiabetics and underwent a laparoscopic resection of an ovarian cyst. During the series of tests and examinations, an abdominal ultrasound showed several non-specific lesions of the liver. The magnetic resonance imaging (MRI) of the liver was performed and revealed

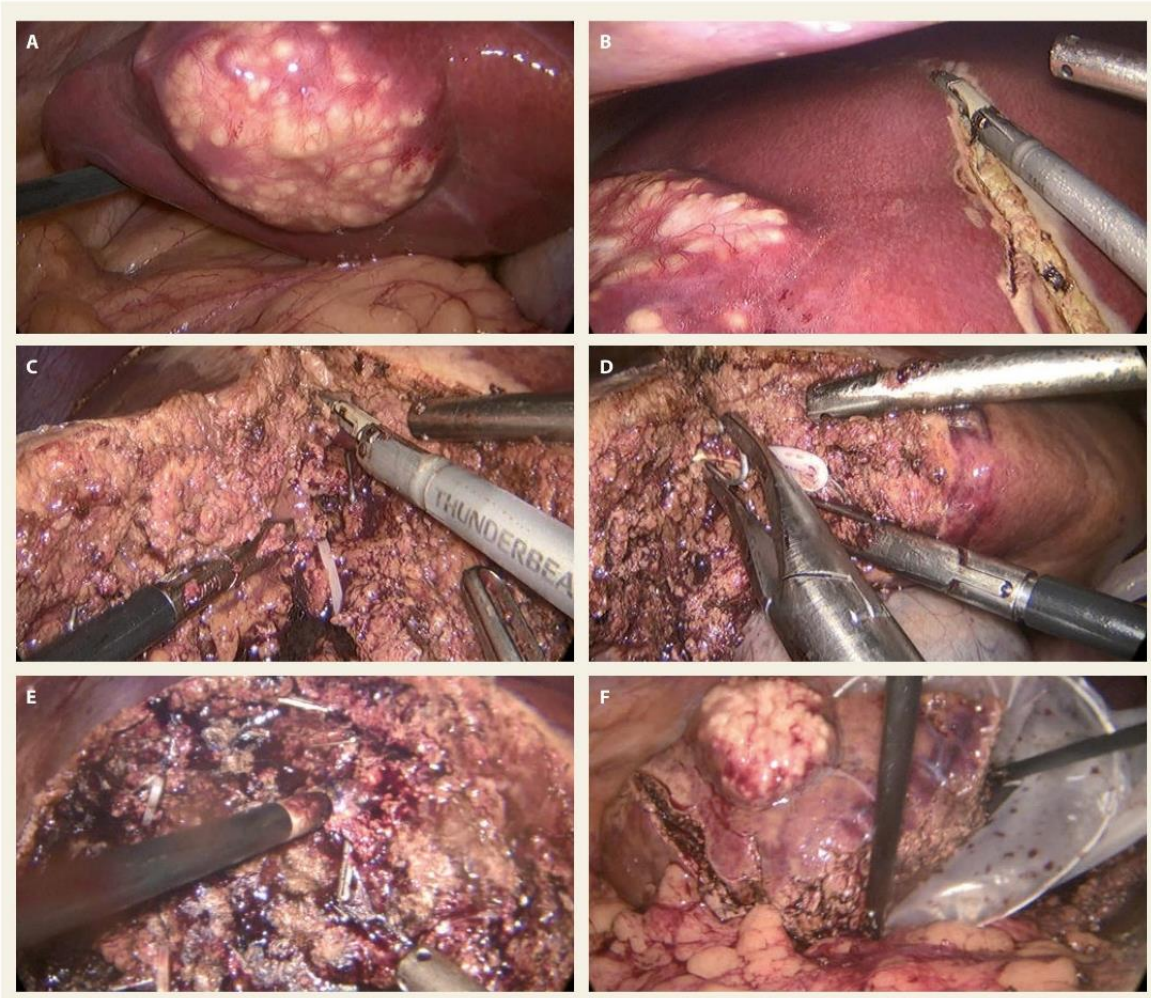


**Fig. 3 A. An echinococcal lesion in liver segment S5 (view of visceral surface of the liver); B. demarcation of the resection line by an electrocoagulation tool (view of diaphragmatic surface of the liver); C. interruption of liver parenchyma by an electrocoagulation tool; D. clipping of the vessel during the interruption of the liver parenchyma tissue; E. the use of argon plasma coagulation in secondary haemostasis of the liver resection surface; F. placing the specimen in a protective bag before extraction.**

Obr. 3 A. Echinokokové ložisko v segmentu S5 (pohled na viscerální plochu jater); B. vytyčení resekční linie elektrokoagulačním nástrojem (pohled na diafragmatickou plochu jater); C. přerušování jaterního parenchymu elektrokoagulačním nástrojem; D. ošetření cév klipováním při přerušování jaterního parenchymu; E. ošetření resekční plochy jater pomocí argon plazma koagulace; F. vložení resekátu do ochranného vaku před jeho následnou extrakcí.

two small hemangiomas in segments 4 and 8 and one lesion 43×65×80 mm in size located in the segment 5 (Fig. 1A,B). In differential diagnosis, metastatic process or echinococcal cyst were considered. The tumour markers were negative. A serology test confirmed echinococcosis (cystic form). The patient had no relevant epidemiological anamnesis apart from a dog in her household. Regarding the echinococcosis therapy, she was treated with albendazole for 1 year at the department of infectious diseases. During the treatment she started to have intermittent abdominal pain in right upper quadrant. Therefore and in order to exclude dissemination to other organs, she had a positron emission tomography – computed tomography (PET/CT) scan that showed neither a progression of the liver lesion nor a dissemination to other organs (Fig. 2A,B). However, the liver lesion had a more alveolar appearance according to the PET/CT. For that reason, her case was presented at a multidisciplinary committee and a surgical resection was indicated.

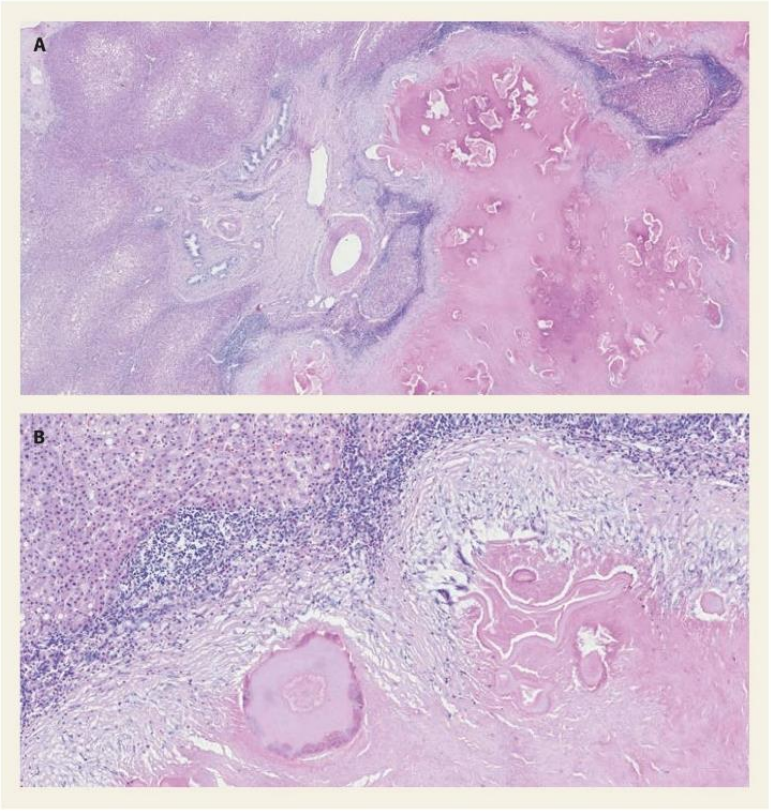


**Fig. 4. Histological section – A. necrosis with acellular membrane material on the right. Hepatic parenchyma with centrolobular steatosis on the left. Haematoxylin-eosin staining 10×; B. necrosis with acellular membrane material at the bottom of the image.** The necrotic tissue is bounded by a giant cellular resorptive reparative reaction with fibrosis and chronic inflammatory infiltrate involving eosinophilic granulocytes at the upper margin. Haematoxylin-eosin staining 50×.
Obr. 4. A. Nekróza s materiálem acelulárních membrán napravo. Parenchym jater s centrolobulární steatózou nalevo. Barvení hematoxylin-eozinem 10×; B. nekróza s materiálem acelulárních membrán ve spodní části obrázku. Nekróza je při horním okraji ohraničena obrovskobuněčnou resorptivně reparativní reakcí s fibrózou a chronickým zánětlivým infiltrátem s účastí eozinofilních granulocytů. Barvení hematoxylin-eozinem 50×.

## Surgery procedure

We have decided to perform a laparoscopic resection due to a favourable lesion location. We started by diagnostic laparoscopy, lesion was 8 cm in diameter located in the segment 5 (Fig. 3A), there was no evidence of peritoneal dissemination. Five trocars were inserted in standard positions. The hepatoduodenal ligament was secured by Pringle's maneuver during the resection. An atraumatic haemostat was used to clamp the hepatoduodenal ligament in order to interrupt a blood flow in the hepatic artery and the portal vein and to control a bleeding from the liver parenchyma during the dissection. A distance between the lesion and the principal plane (Rex-Cantlie line) was too close, therefore a cholecystectomy had to be performed. The liver resection was performed with 2 cm safety margins (Fig. 3B,C,D). An argon plasma coagulation was applied to improve a haemostasis in the liver parenchyma (Fig. 3E). The liver specimen was extracted in a protective bag from suprapubic Pfannenstiel incision (Fig. 3F). An abdominal drain was inserted to control a postoperative bleeding or a bile leak. The blood loss was 700 ml, the operation time 220 minutes.

Postoperatively, the patient could walk and eat 1 day after surgery. There was no bile leakage from the drain. There were no postoperative complications. The patient was discharged 7 days after the surgical procedure. The final histopathology results reported a necrotic liver tissue with an eosinophilic inflammatory reaction (corresponding to parasitic disease) without any evidence of a malignant tumour (Fig. 4A,B). The patient is still on albendazole therapy as a secure postoperative therapy to avoid a recurrence of the disease.

## Discussion

AE is a potentially lethal disease. It is characterised by an initial asymptomatic period of 5–15 years. In the progressive phase, symptoms include abdominal pain, jaundice, anaemia or fever. A later stage is characterised by severe hepatic dysfunctions [8]. Distant metastases to lungs, brain or bones may be seen in the late stage of the disease [6,9]. In our case report, the patient was asymptomatic and diagnosed incidentally during examinations for decompensated hypertension.

The diagnosis of AE is mainly based on a clinical presentation, epidemiological evidence, serology tests and a radiological examination [10]. The MRI or CT scan of the liver are the standard imaging methods. It is also necessary to rule out metastases of the disease to other organs; we performed a whole-body PET/CT scan that ruled out distant metastasis.

Concerning the therapy of echinococcosis, in patients with cystic form, the preoperative therapy with albendazole is recommended, however with no exact treatment duration [3]. This recommendation was initially followed in our patient, too. As she was diagnosed with

a CE according to the MRI scan and serology, she received one-year long therapy with albendazole.

On the other hand, in patients with alveolar form, a radical surgery (a liver resection) is the treatment of choice. However, it is possible only in 35% of patients due to a late diagnosis [11]. As the parasite's growth resembles a malignant tumour, the procedures and techniques (including 2 cm safety resection margin) of oncological surgery are recommended. If a R0 resection is not possible, a palliative surgery is no longer recommended, and the patient should stay on a life-long anti-parasitic drug therapy [8]. A liver transplantation (LT) should be reserved for patients with advanced forms of the disease as a salvage therapy. A pericystectomy (removal of a cyst without a resection of healthy liver tissue) broadly used for CE treatment, is not possible in AE due to a solid nature of the lesion [3,11,12]. There are also percutaneous methods like ultrasound-guided PAIR (puncture, aspiration, injection and respiration) which is sometimes used as an alternative to surgery or if a surgery is contraindicated but only in a cystic form of the disease [13]. Our patient had a superficial lesion in the 5$^{th}$ segment, which was favourable for a laparoscopic, minor liver resection (segmentectomy).

After the first laparoscopic liver resection in 1991, dramatic progress has been made in the field of liver surgery. Nowadays even major liver resections are carried out laparoscopically. When compared to an open liver surgery, a laparoscopic liver resection is more feasible and safer in both benign and malignant liver lesions [14].

There are 20 meta-analyses comparing the results of laparoscopic and open approach. Most studies demonstrate a significantly quicker hospital discharge, an earlier return of bowel activity and lesser requirement of analgesics in patients after laparoscopic liver resections [15].

Postoperative administration of antiparasitic drugs for at least 2 years and a long-term follow-up are mandatory in all cases. The most preferred anti-parasitic drug is albendazole given orally at a dose of 10–15 mg/kg/day. Alternative drugs are mebendazole or amphotericin B as a salvage therapy. A long-term drug treatment is mandatory in all inoperable cases.

According to the current guidelines, a preoperative antiparasitic drug administration is not recommended (except in the case of LT) in AE, however can be considered in special cases (in order to downsize the lesion or to prevent from a parasitic dissemination).

## Conclusion

Hepatic alveolar echinococcosis is a rare but a potentially life-threatening parasitic disease that should be considered in a differential diagnosis of liver lesions. If resectable, a surgical treatment should be a method of choice in patients with AE. Moreover, a laparoscopic approach is considered to be safe and effective as presented in our case report.

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**Příloha 18** - The influence of microscopic inflammation at resection margins on early postoperative endoscopic recurrence after ileocaecal resection for Crohn's disease

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Original Article

# The Influence of Microscopic Inflammation at Resection Margins on Early Postoperative Endoscopic Recurrence After Ileocaecal Resection for Crohn's Disease

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## Abstract

**Background and Aims:** The pathogenesis and risk factors for early postoperative endoscopic recurrence of Crohn's disease [CD] remain unclear. Thus, this study aimed to identify whether histological inflammation at the resection margins after an ileocaecal resection influences endoscopic recurrence.

**Methods:** We have prospectively followed up patients with CD who underwent ileocaecal resection at our hospital between January 2012 and January 2018. The specimens were histologically analysed for inflammation at both of the resection margins [ileal and colonic]. We evaluated whether histological results of the resection margins are correlated with endoscopic recurrence of CD based on colonoscopy 6 months after ileocaecal resection. Second, we assessed the influence of known risk factors and preoperative therapy on endoscopic recurrence of CD.

**Results:** A total of 107 patients were included in our study. Six months after ileocaecal resection, 23 patients [21.5%] had an endoscopic recurrence of CD. The histological signs of CD at the resection margins were associated with a higher endoscopic recurrence [56.5% versus 4.8%, $p < 0.001$]. Disease duration from diagnosis to surgery [$p = 0.006$] and the length of the resected bowel [$p = 0.019$] were significantly longer in patients with endoscopic recurrence. Smoking was also proved to be a risk factor for endoscopic recurrence [$p = 0.028$].

**Conclusions:** Histological inflammation at the resection margins was significantly associated with a higher risk of early postoperative endoscopic recurrence after an ileocaecal resection for CD.

**Key Words:** Crohn's disease; ileocaecal resection; early postoperative endoscopic recurrence

## 1. Introduction

Despite the era of biologics, surgical treatment of Crohn's disease [CD] still plays an important role. Up to 80% of patients need surgery during their lifetime.[1,2] Moreover, early postoperative endoscopic recurrence [EPER] of the disease occurs in approximately 70% of patients within the first year after the surgery.[2,3] As EPER precedes clinical symptoms, its detection is essential in the further management of postoperative CD.[2,4] The exact pathogenesis of EPER is unknown. However, according to the literature, the risk factors include smoking, previous intestinal surgery, absence of prophylactic treatment, penetrating disease at index surgery, perianal location, granulomas in the resection specimen, and myenteric plexitis.[5] Although some recent data have suggested that histopathology results of the resection margins could predict EPER,[1,6,7] such relationship remains to be further established. Recurrence prevention concerning patient selection as well as postoperative treatment and its timing remains a clinical challenge, as no standard recommended algorithm exists.[1,8–10] Hence, this study aimed to identify whether histological inflammation at the resection margins influences EPER in patients with CD after an ileocaecal resection [ICR], and to assess the influence of the aforementioned risk factors and preoperative therapy on EPER.

## 2. Materials and Methods

### 2.1. Patient selection

In this prospective study, we have included patients with CD who underwent ICR between January 2012 and January 2018 at the University Hospital in Brno. ICR was performed by either the open or the laparoscopic approach. The resection extended to macroscopically uninvolved tissue, and a primary anastomosis was constructed. All the surgeries were performed by three surgeons who are experienced in colorectal and IBD surgery. Ileocolonoscopy was performed 6 months after ICR. Patients who underwent other resection procedures, such as a hemicolectomy, multiple ileal resections, and stricturoplasties, or had either a permanent or a diverting loop ileostomy, were excluded. Moreover, patients with any postoperative prophylactic treatment before the postoperative ileocolonoscopy check-up and those with missing data were also excluded.

All patients provided written informed consent and procedures were performed in accordance with the ethical standards according to the Declaration of Helsinki.

### 2.2. Variables analysed

We analysed the general characteristics of the patients, including age, gender, the Montreal classification of CD [including perianal disease], and the disease duration from diagnosis to ICR. In regard to the surgery, we evaluated the type of approach [open or laparoscopic], length of the resected bowel, type of anastomosis [end-to-end or side-to-side], and postoperative complications [according to the Clavien-Dindo classification].[11]

Histopathological analysis of the resected tissue was performed by an experienced IBD pathologist. As there is no histopathology score validated for CD,[12] the pathologist marked the resection margin as positive if the following signs of CD were noted: architectural distortion, inflammation activity [mild: cryptitis in <25% crypts; moderate: cryptitis in >25% of crypts; severe: with ulcerations], granulomas, ulcerations, erosions, fibrosis, neuronal hyperplasia, Paneth cells metaplasia, or signs of chronic inflammation [transmural inflammation with lymphoid aggregates and basal plasmacytosis]. When assessing the resection margins, the pathologist always evaluated both the ileal and the colonic margins and assessed for the aforementioned signs of CD. Specimens with inflammation in the ileal, colonic, or both resection margins were counted as positive.

Regarding EPER, ileocolonoscopy 6 months after the ICR was performed and endoscopic recurrence was evaluated using Rutgeert's score [positive EPER was defined as Ri ≥2]. The use of preoperative medication [≤12 weeks before ICR] as well as smoking and any family history of CD as possible risk factors were also analysed.

### 2.3. Statistical analysis

EPER was the primary endpoint of this study. The difference in the primary endpoint between the two study groups according to the histological inflammation at the resection margins was evaluated using a univariate logistic regression model.

No sample size calculations were performed before the study started. However, the number of patients in both the study arms [90 patients with negative and 17 patients with positive resection margins] as well as the observed difference in the primary endpoint ensured a statistical power of the univariate logistic regression model of >99%.

Standard frequency tables and summary statistics, i.e. means, standard deviation, median, minimum, and maximum, were used to describe the baseline demographic and clinical characteristics. Statistical significance of the differences for categorical variables was assessed using Fisher's exact test. Comparisons of continuous variables were performed using the Mann–Whitney U test. The secondary outcomes were evaluated using univariate and multivariate logistic regression models. A $p$ <0.05 was considered statistically significant for all analyses. All statistical analyses were performed with SPSS Statistics for Windows, version 24.0 [IBM Corp., Armonk, NY, USA].

## 3. Results

A total of 107 patients, who provided written informed consent, were included in this study. Thirty-six patients were excluded because of a different intestinal resection or prophylactic treatment administered before postoperative ileocolonoscopy. The baseline characteristics of the study group are listed in Table 1.

For EPER, ileocolonoscopy was performed 6 months after ICR, and the endoscopic results were evaluated using Rutgeert's score as shown in Table 2. With reference to the primary outcome of the study, histological results showed that inflammation at the resection margins has a significant statistical influence on EPER [56.5% versus 4.8%, $p < 0.001$; Figure 1]. The histological signs of inflammation in the resection margins were as follows: ileal [I]-positive and colonic [C]-negative in 21.7%; I-negative and C-positive in 13.0%; and I-positive and C-positive in 21.7%. In particular, the risk of EPER was 26-fold higher in patients with positive than in those with negative histology (odds ratio [OR] 26.00, 95% confidence interval [CI] 7.09–95.33) [Tables 3 and 4].

A significant difference in the time from diagnosis of the disease to the ICR between patients with endoscopic recurrence (median 8 years [0–14 years]) and those with endoscopic remission (median 3 years [0–18 years]) [$p$ = 0.006] was found. Thus, the longer the disease duration, the higher the risk of EPER [every year, the risk increases by 14%; OR 1.14, 95% CI 1.03–1.26; $p$ = 0.015]. Moreover, a significant difference in terms of smoking, which was identified as a risk factor for endoscopic recurrence, between patients with recurrence and those with remission was found [$p$ = 0.028] [Tables 3 and 4].

**Table 1.** Baseline characteristics of the patients, subdivided in the two groups according to the histological signs of inflammation at the resection margins, expressed as median [minimum-maximum] or frequency [percent].

| Characteristics | | Patients [n = 107] | Negative resection margins [*n* = 90] | Positive resection margins [*n* = 17] |
|---|---|---|---|---|
| Age at diagnosis | [Years] | Median [min–max] | | |
| | | 26 [8–75] | 26 [8–75] | 28 [8–62] |
| Time from diagnosis to ICR | [Years] | Median [min–max] | | |
| | | 3 [0–18] | 3 [0–15] | 7 [0–18] |
| Gender | Male | 48 [44.9%] | 39 [43.3%] | 9 [52.9%] |
| | Female | 59 [55.1%] | 51 [56.7%] | 8 [47.1%] |
| Montreal classification | | | | |
| A [age] | A1 [<16 years] | 13 [12.1%] | 10 [11.1%] | 3 [17.6%] |
| | A2 [17–40 years] | 74 [69.2%] | 64 [71.1%] | 10 [58.8%] |
| | A3 [>40 years] | 20 [18.7%] | 16 [17.8%] | 4 [23.5%] |
| L [location] | L1 [ileum] | 74 [69.2%] | 62 [68.9%] | 12 [70.6%] |
| | L1 + L4 [ileum + upper GI] | 2 [1.9%] | 1 [1.1%] | 1 [5.9%] |
| | L3 [ileum + colon] | 28 [26.2%] | 24 [26.7%] | 4 [23.5%] |
| | L3 + L4 [ileum + colon + upper GI] | 3 [2.8%] | 3 [3.3%] | 0 [0.0%] |
| B [behaviour] | B1 [inflammatory] | 13 [12.1%] | 12 [13.3%] | 1 [5.9%] |
| | B2 [stenosing] | 58 [54.2%] | 46 [51.1%] | 12 [70.6%] |
| | B3 [perforating] | 36 [33.6%] | 32 [35.6%] | 4 [23.5%] |
| Perianal disease | No | 82 [76.6%] | 68 [75.6%] | 14 [82.4%] |
| | Yes | 25 [23.4%] | 22 [24.4%] | 3 [17.6%] |
| Ileocaecal resection | | | | |
| Surgical approach | Open | 66 [61.7%] | 58 [64.4%] | 8 [47.1%] |
| | Laparoscopic | 41 [38.3%] | 32 [35.6%] | 9 [52.9%] |
| Length of resected bowel | [cm] | Median [min–max] | | |
| | | 25 [5–80] | 25 [6–80] | 25 [5–50] |
| Anastomosis | Side to side | 91 [85.0%] | 76 [84.4%] | 15 [88.2%] |
| | End to end | 16 [15.0%] | 14 [15.6%] | 2 [11.8%] |
| Postoperative complications | No | 71 [66.4%] | 61 [67.8%] | 10 [58.8%] |
| | Yes | 36 [33.6%] | 29 [32.2%] | 7 [41.2%] |
| Clavien-Dindo classification of postoperative complications | Grade 1 | 12 [11.2%] | 8 [8.9%] | 4 [23.5%] |
| | Grade 2 | 7 [6.5%] | 4 [4.4%] | 3 [17.6%] |
| | Grade 3a | 2 [1.9%] | 2 [2.2%] | 0 [0.0%] |
| | Grade 3b | 15 [14.0%] | 15 [16.7%] | 0 [0.0%] |
| | Grade 4 | 0 [0.0%] | 0 [0.0%] | 0 [0.0%] |
| | Grade 5 | 0 [0.0%] | 0 [0.0%] | 0 [0.0%] |
| Histological results | | | | |
| Presence of granulomas | Negative | 71 [66.4%] | 64 [71.1%] | 7 [41.2%] |
| | Positive | 36 [33.6%] | 26 [28.9%] | 10 [58.8%] |
| Preoperative therapy | | | | |
| Medication ≤12 weeks before ICR | Antibiotics | 43 [40.2%] | 39 [43.3%] | 4 [23.5%] |
| | 5-ASA | 58 [54.2%] | 49 [54.4%] | 9 [52.9%] |
| | Local GCS | 26 [24.3%] | 21 [23.3%] | 5 [29.4%] |
| | Systemic GCS | 23 [21.5%] | 21 [23.3%] | 2 [11.8%] |
| | AZA | 31 [29.0%] | 26 [28.9%] | 5 [29.4%] |
| | MTX | 0 [0.0%] | 0 [0.0%] | 0 [0.0%] |
| | Biologic treatment | 13 [12.1%] | 13 [14.4%] | 0 [0.0%] |
| Smoking | Non-smoker | 49 [45.8%] | 44 [48.9%] | 5 [29.4%] |
| | Ex-smoker | 26 [24.3%] | 23 [25.6%] | 3 [17.6%] |
| | Smoker | 32 [29.9%] | 23 [25.6%] | 9 [52.9%] |
| Family history of IBD | No | 94 [87.9%] | 80 [88.9%] | 14 [82.4%] |
| | Yes | 13 [12.1%] | 10 [11.1%] | 3 [17.6%] |

ICR, ileocaecal resection; GI, gastrointestinal tract; 5-ASA, 5-aminosalicylates; GCS, glucocorticoids; AZA, azathioprine; MTX, methotrexate; IBD, inflammatory bowel disease.

With respect to disease phenotype, the number of patients who developed EPER was significantly higher in those with stenosing behaviour [73.9%] than in those with perforating behaviour [13%] [$p$ = 0.045]. Perianal involvement was present only in four patients [17.4%] with EPER; however, the results were not significant [$p$ = 0.582] [Tables 3 and 4].

Another significant difference was found in terms of the length of the resected bowel; the longer the resection needed, the more likely EPER should occurr [median 30 cm [5–80 cm] in patients with endoscopic recurrence versus 25 cm [6–70 cm] in patients with endoscopic remission; $p$ = 0.019]. On average, patients with EPER required a 7 cm longer resection. With reference to the surgical

**Table 2.** Assessment of EPER using Rutgeerts score [Ri] 6 months after ICR.

| Endoscopic recurrence | Ri score | *n* | % |
|---|---|---|---|
| Negative | Ri 0 | 39 | 36.4 |
| | Ri 1 | 45 | 42.1 |
| | | **84** | **78.5** |
| Positive | Ri 2 | 14 | 13.1 |
| | Ri 2–3 | 3 | 2.8 |
| | Ri 3 | 4 | 3.7 |
| | Ri 4 | 2 | 1.9 |
| | | **23** | **21.5** |

EPER, early postoperative endoscopic recurrence; ICR, ileocaecal resection.

approach, 66 of 107 [61.7%] procedures were open surgeries and 41 [38.3%] were performed laparoscopically. Of 43 surgeries that were initially started laparoscopically, two had to be converted to open approach [the conversion rate was 4.6%]. Postoperative complications showed no statistical influence on EPER [$p = 0.333$] [Table 3].

Furthermore, out of 107 specimens, 36 specimens were positive for granulomas [33.6%]. In the group with positive resection margins [$n = 17$], 10 specimens [58.8%] had granulomas. Moreover, a significant correlation between the presence of granulomas and EPER was found [60.9% versus 26.2%; $p = 0.003$] [Tables 1 and 3]. Regarding preoperative therapy, the use of antibiotics at <12 weeks before the surgery decreased EPER by up to 66% [OR 0.34, 95% CI 0.11–0.99; $p = 0.048$] [Tables 3 and 4].

According to the multivariate analysis results, positive resection margins have the greatest influence on EPER [OR 26.46, 95% CI 6.42–109.06; $p < 0.001$]. A statistically significant effect of disease duration [OR 1.20, 95% CI 1.02–1.41; $p = 0.031$] and stenosing disease behaviour [OR 0.08, 95% CI 0.01–0.87; $p = 0.038$] was also found [Table 5]. The groups were comparable in the other analysed variables [demographic characteristics, other surgical characteristics, and preoperative therapy, with the exception of use of antibiotics and family history of IBD].

## 4. Discussion

Disease recurrence after surgical resection in CD has been studied since the end of the 20th century.[13] The incidence of postoperative recurrence differs considerably in the literature and ranges from 10% to 90%, depending on the used definition of recurrence [i.e. clinical, endoscopic, radiological, or surgical recurrence], study designs, and postoperative therapy.[2,3,14,15] In our cohort, we have investigated EPER in patients without any postoperative therapy. EPER occurred in 21.5% of patients in our study.

It has been proven that endoscopic recurrence both precedes and predicts clinical relapse.[3,4] Currently, postoperative ileocolonoscopy within the first year following surgery is recommended.[4,5] We performed ileocolonoscopies 6 months after ICR, and the findings were assessed according to Rutgeert's score.

A diagnosis of EPER seems to be crucial for further postoperative management to prevent any flare-up of the disease.[16] According to the current guidelines, the risk factors used as predictors of postoperative recurrence include smoking, previous intestinal surgery, absence of prophylactic treatment, penetrating disease at index surgery, perianal location, granulomas in the resection specimen, and myenteric plexitis.[4] Smoking appears to be the only consistently

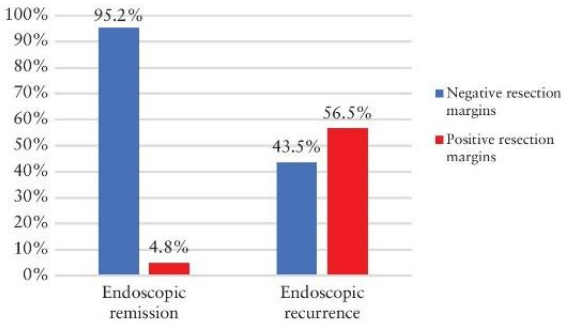


**Figure 1.** Influence of histologically inflamed resection margins on endoscopic recurrence.

reported risk factor that increases the risk of postoperative recurrence by 2.5-fold.[4,16,17] In our study, we have also confirmed that smoking is a risk factor [among non-smoking patients, 52.4% had endoscopic remission and 21.7% had endoscopic recurrence; $p = 0.028$]. Nevertheless, a clear identification of patients at a higher risk of EPER, who would benefit from more aggressive and financially demanding therapy, remains a clinical challenge, as no standard for postoperative treatment exists.[1,8–10]

The primary aim of our study was to identify whether thistological inflammation at the resection margins after ICR could be considered a significant risk factor for EPER. In the literature, data concerning this assumption are inconsistent.[4] The relevant studies, mainly published in the late 1990s, reported no relationship between the microscopic involvement of the resection margins and postoperative recurrence.[18–21] However, the frequently cited study of Fazio *et al.*,[19] who conducted a randomised controlled trial of 152 patients, showed that microscopic CD at the resection margins is correlated with surgical recurrence in the long-term follow-up [up to 96 months]. The types of operation in their study population included not only primary ileocolic resection [49%] but also secondary resection of ileocolic anastomosis [46%], as well as other types. The patients did not receive any postoperative immunoprophylaxis.[19] In our cohort, we have specifically assessed endoscopic recurrence after 6 months only in patients who had primary ICR. Consistent with the study of Fazio *et al.*, our patients did not receive any postoperative therapy before ileocolonoscopy. Furthermore, recent studies have confirmed that histological inflammation at the resection margin is associated with a higher risk of postoperative recurrence.[1,6,7] The retrospective study of Bobanga *et al.*, including 142 patients, investigated the different aspects of postoperative recurrence after ileocaecal resection between adolescents and adults; multivariate analysis showed that positive resection margins are predictive of endoscopic recurrence in the adult group [$p = 0.007$].[1] Concerning the histological assessment of the resection margins, we have always evaluated both the ileal and the colonic margins. On the other hand, previous studies have either assessed only the proximal margin or the margins have not been further specified.[1,6,19] Disease duration as a risk factor is not uniformly accepted.[5,8,9] However, our results imply that the longer the disease duration, the higher the risk of EPER. The longer duration could be explained by the more conservative therapeutic approach at our hospital, which would in turn lead to more complicated cases with a higher EPER incidence.

In relation to the length of the resected bowel, current data are also equivocal. Our results showed that the patients with EPER needed, on average, a 7 cm longer resection, which could

**Table 3.** Influence of the variables on EPER. Results expressed as median [minimum-maximum] or frequency [percent].

| Characteristics | | Normal endoscopy [$n$ = 84] | Endoscopic recurrence [$n$ = 23] | $p$-value |
|---|---|---|---|---|
| Age at diagnosis | [Years] | Median [min – max] | | 0.660 |
| | | 25 [8–75] | 28 [8–62] | |
| Time from diagnosis to ICR | [Years] | Median [min – max] | | **0.006** |
| | | 3 [0–18] | 8 [0–14] | |
| Gender | Male | 39 [46.4%] | 9 [39.1%] | 0.638 |
| | Female | 45 [53.6%] | 14 [60.9%] | |
| Montreal classification | | | | |
| A [age] | A1 [<16 years] | 10 [11.9%] | 3 [13.0%] | 0.817 |
| | A2 [17–40 years] | 59 [70.2%] | 15 [65.2%] | |
| | A3 [>40 years] | 15 [17.9%] | 5 [21.7%] | |
| L [location] | L1 [ileum] | 58 [69.0%] | 16 [69.6%] | 0.649 |
| | L1 + L4 [ileum + upper GI] | 1 [1.2%] | 1 [4.3%] | |
| | L3 [ileum + colon] | 22 [26.2%] | 6 [26.1%] | |
| | L3 + L4 [ileum + colon + upper GI] | 3 [3.6%] | 0 [0.0%] | |
| B [behaviour] | B1 [inflammatory] | 10 [11.9%] | 3 [13.0%] | **0.045** |
| | B2 [stenosing] | 41 [48.8%] | 17 [73,9%] | |
| | B3 [perforating] | 33 [39.3%] | 3 [13.0%] | |
| Perianal disease | No | 63 [75.0%] | 19 [82.6%] | 0.582 |
| | Yes | 21 [25.0%] | 4 [17.4%] | |
| Ileocaecal resection | | | | |
| Surgical approach | Open | 53 [63.1%] | 13 [56.5%] | 0.631 |
| | Laparoscopic | 31 [36.9%] | 10 [43.5%] | |
| Length of resected bowel [cm] | | 25 [6–70] | 30 [5–80] | **0.019** |
| Anastomosis | Side to side | 74 [88.1%] | 17 [73.9%] | 0.106 |
| | End to end | 10 [11.9%] | 6 [26.1%] | |
| Postoperative complications | No | 55 [65,5%] | 16 [69.6%] | 0.807 |
| | Yes | 29 [34.5%] | 7 [30.4%] | |
| Clavien - Dindo classification of postoperative complications [grade] | 1 | 9 [10.7%] | 3 [13.0%] | 0.333 |
| | 2 | 4 [4.8%] | 3 [13.0%] | |
| | 3a | 2 [2.4%] | 0 [0.0%] | |
| | 3b | 14 [16.7%] | 1 [4.3%] | |
| | 4 | 0 [0.0%] | 0 [0.0%] | |
| | 5 | 0 [0.0%] | 0 [0.0%] | |
| Histological results | | | | |
| Inflammation at resection margins | Negative | 80 [95.2%] | 10 [43.5%] | **<0.001** |
| | Positive | 4 [4.8%] | 13 [56.5%] | |
| | Ileal negative, colonic negative | 80 [95.2%] | 10 [43.5%] | |
| | Ileal positive, colonic negative | 3 [3.6%] | 5 [21.7%] | **<0.001** |
| | Ileal negative, colonic positive | 1 [1.2%] | 3 [13.0%] | |
| | Ileal positive, colonic positive | 0 [0.0%] | 5 [21.7%] | |
| Presence of granulomas | Negative | 62 [73.8%] | 9 [39.1%] | **0.003** |
| | Positive | 22 [26.2%] | 14 [60.9%] | |
| Preoperative therapy | | | | |
| Medication ≤12 weeks before ICR | Antibiotics | 38 [45.2%] | 5 [21.7%] | 0.055 |
| | 5-ASA | 45 [53.6%] | 13 [56.5%] | 0.818 |
| | Local GCS | 19 [22.6%] | 7 [30.4%] | 0.425 |
| | Systemic GCS | 20 [23.8%] | 3 [13.0%] | 0.392 |
| | AZA | 23 [27.4%] | 8 [34.8%] | 0.604 |
| | MTX | 0 [0.0%] | 0 [0.0%] | – |
| | Biologic treatment | 11 [13.1%] | 2 [8.7%] | 0.730 |
| Smoking | Non-smoker | 44 [52.4%] | 5 [21.7%] | **0.028** |
| | Ex-smoker | 18 [21.4%] | 8 [34.8%] | |
| | Smoker | 22 [26.2%] | 10 [43.5%] | |
| Family history of IBD | No | 73 [86.9%] | 21 [91.3%] | 0.730 |
| | Yes | 11 [13.1%] | 2 [8.7%] | |

EPER, early postoperative endoscopic recurrence; ICR, ileocaecal resection; GI, gastrointestinal tract; 5-ASA, 5-aminosalicylates; GCS, glucocorticoids; AZA, azathioprine; MTX, methotrexate; IBD, inflammatory bowel disease.

be attributed to disease severity. Nonetheless, several studies reported that the length of the resected bowel does not significantly affect EPER.[1,9,22] Moreover, other variables associated with surgery [surgical approach, type of anastomosis, postoperative complications] did not show any significant effect on EPER. The guidelines state that perforating disease is an independent risk factor [level 2

**Table 4.** Associations between endoscopic recurrence of CD and categorical variables [standard logistic regression models, $n = 107$].

| Characteristics | | *n* | OR [95% CI] | *p*-value |
|---|---|---|---|---|
| Inflammation of resection margins | Negative | 90 | 1.00 [-] | – |
| | Positive | 17 | **26.00 [7.09–95.33]** | **<0.001** |
| Age at diagnosis | Increase of 10 years | 107 | 1.09 [0.78–1.54] | 0.618 |
| Disease duration | Increase of 1 year | 107 | **1.14 [1.03–1.26]** | **0.015** |
| Montreal classification | | | | |
| A [age] | A1 [<16 years] | 13 | 1.00 [-] | – |
| | A2 [17–40 years] | 74 | 0.85 [0.21–3.47] | 0.818 |
| | A3 [>40 years] | 20 | 1.11 [0.22–5.73] | 0.900 |
| B [behaviour] | B1 [inflammatory] | 13 | 1.00 [-] | – |
| | B2 [stenosing] | 58 | 1.38 [0.34–5.65] | 0.653 |
| | B3 [perforating] | 36 | 0.30 [0.05–1.74] | 0.181 |
| Perianal disease | No | 82 | 1.00 [-] | – |
| | Yes | 25 | 0.63 [0.19–2.07] | 0.448 |
| Preoperative therapy | | | | |
| Medication ≤12 weeksbefore ICR | Antibiotics | 43 | **0.34 [0.11–0.99]** | **0.048** |
| | 5-ASA | 58 | 1.13 [0.45–2.85] | 0.801 |
| | Local GCS | 26 | 1.50 [0.54–4.17] | 0.441 |
| | Systemic GCS | 23 | 0.48 [0.13–1.79] | 0.273 |
| | AZA | 31 | 1.41 [0.53–3.78] | 0.489 |
| | Biologic therapy | 13 | 0.63 [0.13–3.08] | 0.570 |

CD, Crohn's disease; ICR, ileocaecal resection; 5-ASA, 5-aminosalicylates; GCS, glucocorticoids; AZA, azathioprine; MTX, methotrexate; OR, odds ratio; CI, confidence interval.

**Table 5.** Multidimensional logistic regression model [$n = 107$] of the relationship between selected variables and recurrence of Crohn's disease.

| Characteristics | | *n* | OR [95% CI] | *p*-value |
|---|---|---|---|---|
| Inflammation at resection margins | Negative | 90 | 1.00 [-] | – |
| | Positive | 17 | **26.46 [6.42–109.06]** | **<0.001** |
| Disease duration | Increase of 1 year | 107 | **1.20 [1.02–1.41]** | **0.031** |
| Montreal classification | | | | |
| A [age] | A1 [<16 years] | 13 | 1.00 [-] | – |
| | A2 [17–40 years] | 74 | 3.24 [0.31–33.52] | 0.323 |
| | A3 [>40 years] | 20 | 5.16 [0.35–76.62] | 0.233 |
| B [behaviour] | B1 [inflammatory] | 13 | 1.00 [-] | – |
| | B2 [stenosing] | 58 | 0.66 [0.12–3.65] | 0.629 |
| | B3 [perforating] | 36 | **0.08 [0.01–0.87]** | **0.038** |
| Perianal disease | No | 82 | 1.00 [-] | – |
| | Yes | 25 | 1.15 [0.23–5.69] | 0.863 |
| Preoperative therapy | | | | |
| Medication ≤12 weeks before ICR | Antibiotics | 43 | 0.45 [0.12–1.71] | 0.242 |
| | 5-ASA | 58 | 1.11 [0.28–4.43] | 0.885 |
| | Local GCS | 26 | 1.43 [0.33–6.25] | 0.635 |
| | Systemic GCS | 23 | 0.68 [0.13–3.54] | 0.652 |
| | AZA | 31 | 1.66 [0.46–5.92] | 0.436 |
| | Biologic therapy | 13 | 1.54 [0.22–10.80] | 0.664 |

ICR, ileocaecal resection; 5-ASA, 5-aminosalicylates; GCS, glucocorticoids; AZA, azathioprine; MTX, methotrexate; OR, odds ratio; CI, confidence interval.

evidence].[5] However, conflicting data with regard to the early recurrence of perforating disease exist based on the meta-analysis by Similils *et al.*[23] Similarly, our data showed that the number of patients who developed EPER was fewer among those with a perforating behaviour of the disease than in those with a stenosing disease [$p = 0.045$].

Perianal disease is also a risk factor according to the guidelines;[5] nevertheless, the cited studies in the guidelines included patients who had different types of surgeries [not only ICR], presumably because of a more extensive type of the disease. Moreover, patient follow-up after surgery for perianal disease is much longer [up to years], which could be attributed to a cumulative frequency of perianal disease.[4] This could explain why our data did not confirm perianal disease as a risk factor for EPER [$p = 0.582$] as our cohort included only EPER assessed 6 months after the ICR.

The current guidelines also reported on histological features, such as presence of granulomas and myenteric plexitis, as risk factors for EPER.[5] In our study, we have confirmed that granulomas in the specimens are significantly correlated with EPER [$p = 0.003$]. Myenteric plexitis has been reported as a risk factor only recently in the guidelines [level 3 evidence].[5,24] During the

initiation of our study in 2012, myenteric plexitis was not widely accepted as a risk factor; thus, this histological sign was not evaluated by our pathologist. We have included this as a limitation of our study.

As previously mentioned, preoperative therapy with antibiotics [e.g. metronidazole] administered <12 weeks before the surgery decreases the risk of EPER. However, in a multidimensional analysis, the results were not statistically significant and have to be further verified. In the literature, only the possible protective effect of the postoperative antibiotic therapy was discussed.[25,26]

According to the multivariate analysis, positive resection margins have the greatest influence on EPER. A statistically significant effect of disease duration and stenosing disease behaviour [as discussed previously] was also found. However, with regard to the small number of patients and presentation of characteristics in our cohort, such a multivariate analysis is quite unstable, which could be seen, for example, in the 95% CI for OR of the resection margins.

Our study has some limitations. The group of patients in our cohort was specifically chosen [patients on prophylactic therapy or who had different types of surgery were excluded], which could in turn decrease the generalisability of the study. Moreover, the patients were followed up 6 months after ICR only, and we have not included myenteric plexitis as a risk factor in this study.

In conclusion, in our prospective study of 107 patients, we have shown that microscopic inflammation at the resection margins after ICR is associated with EPER. Although validation of this finding by larger studies is needed, our results may contribute to the identification of patients with a high risk of EPER, who could benefit from a more aggressive and targeted postoperative therapy. Consensus on a clear and definite recommendation remains to be reached, to identify the best practice for these patients.

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## Conflict of Interest

All authors declare that they have no conflicts of interest.

## Author Contributions

KP: study concept and design, analysis and interpretation of data, writing, literature review; LK: concept and design of the study, review of data and the manuscript, consultant; FM: consultant, concept and design of the study, literature review; ZK: consultant, review of the manuscript; VP: consultant, review of data, concept and design of the study, literature review; JD: consultant, review of the manuscript; VZ: consultant, review of the data and the manuscript; PK: statistical analysis; TP: statistical analysis; PJ: consultant, review of the manuscript; ZP: histological analysis; JV: histological analysis; LM: consultant, literature review. All authors have made scientific contribution to the study design and discussion and have read and approved the final version of the manuscript. Moreover, all authors had full access to all the data in this study and had final responsibility for the decision to submit for publication.

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**Příloha 19** - Endoscopic recurrence after ileocaecal resection for Crohn´s disease relating to microscopic inflammation at resection margins



## ePP305 ENDOSCOPIC RECURRENCE AFTER ILEOCAECAL RESECTION FOR CROHN´S DISEASE RELATING TO MICROSCOPIC INFLAMMATION AT RESECTION MARGINS

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**Aims** An early postoperative endoscopic recurrence of Crohn´s disease after ileocaecal resection remains unclear concerning its pathogenesis and risk factors. In our study, we evaluated the influence of histological inflammation at the resection margins on endoscopic recurrence.

**Methods** Patients with CD who underwent ileocaecal resection have been prospectively followed up in our study. The specimens were histologically analysed for inflammation at both of the resection margins (ileal and colonic). We evaluated whether histological results of the resection margins are correlated with endoscopic recurrence of CD based on colonoscopy 6 months after ileocaecal resection.

**Results** We have included 107 patients in our study. Six months after ileocaecal resection, 23 patients (21.5 %) had an endoscopic recurrence of CD. The histological signs of CD at the resection margins were associated with a higher endoscopic recurrence (56.5 % versus 4.8 %, $p < 0.001$).

**Conclusions** Microscopic inflammation at the resection margins was significantly associated with a higher risk of early postoperative endoscopic recurrence after an ileocaecal resection for CD.

**Saturday, April 25, 2020 11:30 – 12:00**
**Percutaneous Endoscopic Gastrostomy (PEG) and duodenal polyps ePoster Podium 6**

## ePP307 DUODENAL POLYPS – ARE WE SEEING SOMETHING THAT ISN'T THERE?

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**Aims** Duodenal polyps (DP) are found incidentally during diagnostic upper GI endoscopy. The proportion of DPs that are duodenal adenomas and have malignant potential is not clearly known due to their low incidence. We aimed to determine the endoscopic-histological correlation for DPs.

**Methods** Retrospective study at a tertiary London-based hospital Trust. Endoscopy software (Unisoft GI reporting tool) used to identify the last 200 patients to be diagnosed with a duodenal polyp in reverse chronological order from December 2018.

**Results** 200 patients had duodenal polyps diagnosed between February 2016 and December 2018 (median age 70 (IQR 59–77), Female 94 (47%)). The size of the polyp was not described in 88 patients (44%), the median size in the remain 112 patients was 6 mm (IQR 4–10). 13 (6.5%) polyps were > 20 mm.

Polyp morphology was described as sessile in 30 (15%), pedunculated in 11 (5.5%) and not described in 159 (79.5%). Pit pattern was described as hyperplastic in 6 (3%) and adenomatous in 20 (10%).

Biopsies of the polyp were taken in 189 patients (94.5%) and polypectomy was performed in 15 (7.5%). Of those resected, polyps were retrieved in 13 (86.7%). Only 7 of 20 polyps thought to be adenomas at endoscopy were confirmed on histology (35%).

**Conclusions** 3 out of 4 patients diagnosed with DPs do not have a description of the morphology or pit pattern in the report and less than half describe the size. Less than 10% of DPs undergo polypectomy. One third of patients have normal duodenal mucosa on histology.

There is significant variability of practice with regards to management of DPs. Better endoscopic descriptions are required for DPs which may in turn reduce the number of unnecessary histological samples being taken. Automated duodenal polyp characterisation on the endoscopy reporting tool may help in better documentation of DPs.

## ePP308 PERCUTANEUS ENDOSCOPIC GASTROSTOMY (PEG). SUCCESSFUL PLACEMENT AND COMPLICATION RATES. A RETROSPECTIVE STUDY CONDUCTED AT A TETRIARY CENTER

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**Aims** Percutaneous Endoscopic Gastrostomy(PEG)is an endoscopic procedure aiming to create a stoma in order to facilitate the delivering of water and nutrients to the small intestine when oral feeding is impossible or contraindicated. The purpose of this study was to assess the effectiveness and safety of PEG formation in our center.

**Methods** This was a retrospective study on prospectively acquired data regarding the success and safety of PEG procedures in our center between January 2015 and December 2018.The study includes patients hospitalized for various medical conditions or admitted in order to place a PEG to restore intestinal nutrition. Detailed data from PEG placement were retrieved from the hospital´s electronic recording system.The procedure was executed by experienced endoscopic staff(endoscopists and nurses)of our department assisted by specialized medical staff(ICU doctors,nurses,anesthesiologists,and surgeons)on a case to case base.The pull-through technique was used with a PEG diameter of 24Fr.Patients were excluded from this study when the outcome of the PEG endoscopic procedure was unknown after 7 days.

**Results** In total,203 PEGs were placed.145(71.4%)patients were men with median age 61.7 years and 58 were women(28.6%)with median age 65.3 years.The main reasons for PEG placement were:Neurological and neurodegenerative diseases(dementia,multiple sclerosis,stroke,motor neuron disease,etc)in 124/203(61.2%)cases;malignant diseases(neck,larynx,tongue,brain, hematological diseases,etc)in 34/203(16.7%)cases;head injuries (road accidents,falls)in 24/203(11.8%)cases;prolonged hospitalization in Intensive Care Units for various reasons(sepsis,aspiration,cardiac arrest, central nervous system infections,suicidal attempts,postoperative complications,burns,etc)in 21/203(10.3%)cases.The rate of successful PEG placement was 92.1%(187/203).Placement of PEG failed in 16 cases:Inability to locate a suitable insertion spot 12/16(75%)cases,desaturation of the patient during sedation 3/16(18.75%)cases,and due to a tracheo-esophageal fistula one(6.25%)patient.One patient died within 2 days after PEG placement.Serious complications occurred in 4 patients within 7 days after insertion.Aspiration pneumonia 3/203(1.5%)and bleeding 1/203(0.5%)patient.11/203 patients(5.4%)experienced minor complications:trauma infection or leak of the stoma[4(2%)and3/203(1.5%)patients],unintentional PEG removal[3/203(1.5%)]and obstruction[1/203(0.5%)].

**Conclusions** PEG placement has high success and safety rates when performed with careful patient selection and close collaboration of specialised personnel.

**Příloha 20** - The role of the NOD2/CARD15 gene in surgical treatment prediction in patients with Crohn's disease

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SHORT COMMUNICATION

# The role of the NOD2/CARD15 gene in surgical treatment prediction in patients with Crohn's disease

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**Abstract**
**Purpose** Crohn's disease (CD) belongs to chronic disorders with unpredictable disease course. The aim of this study was to identify how genetic testing (NOD2/CARD15) can be used in patients with CD to predict the need for surgical treatment (to define an aggressive type of disease where the patient can profit from early surgery).
**Methods** The patients who were tested genetically had undergone a surgery due to CD at the Department of Surgery University Hospital Brno Bohunice between 2010 and 2016. The control group consisted of patients with CD who had been diagnosed with CD at least 5 years prior to the testing and had not required any surgical intervention. The second control group was healthy subjects.
**Results** In total, there were 117 operated patients for CD, 77 patients with CD that had not undergone surgery for CD and 30 healthy subjects. For patients with at least one genetic mutation, the risk of the necessity of surgical treatment of CD is 1.96 times higher than for patients with no mutation. Patients with two or more mutations were generally operated on at a younger age, in a shorter time after being diagnosed and each patient had a partial resection of the ileum.
**Conclusion** The group of operated patients with CD had a significantly higher distribution of at least one genetic mutation as opposed to the non-operated group. In patients with two or more mutations, the disease course was more aggressive. This group of patients might profit from the conservative top-down or early surgical therapy.

**Keywords** Crohn's disease · Inflammatory bowel disease · Disease course · Genetics · NOD2/CARD15 · Surgery · Intestinal resection · Czech cohort

## Introduction

Crohn's disease (CD) is a chronic bowel inflammatory disease with an increasing incidence, affecting mostly patients at an early age. It is a disease of unknown etiology, unpredictable development, and in addition most patients need to undergo surgical treatment of CD during their life [1].

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A possible relation between CD and a mutation of the NOD2/CARD15 gene was first published by Ogura et al. [2] in 2001. Several independent studies describe three mutations of this gene in the western (Caucasian) population that are related to CD (R702W, G908R, and L1007fs, sometimes also referred as 3020insC). A carrier of a mutant allele (heterozygote) in the NOD2/CARD15 gene is 2–4 times more likely to develop CD and a carrier of two mutant alleles (homozygote or a mixed heterozygote) is 20–40 times more likely to develop CD [3].

According to the ECCO (European Crohn's and Colitis Organisation) guidelines, the general factors of an aggressive disease course and factors increasing the risk of surgical treatment include the following: cigarette smoking, a stricturing or penetrating form of the disease, an early necessity to prescribe corticosteroids in medication, location of the disease in the ileum, or an early age of the patient at the time of diagnosis [4].

Some studies have proved a connection between the NOD2/CARD15 gene mutations and a complicated disease course [5]. The relation between an aggressive form of CD

and a NOD2/CARD15 gene mutation is especially noticeable in cases of patients diagnosed at an early age, dominant ileum location or a stricturing form of the disease [6, 7].

The aim of the analysis was to find a clinical relation between the mutations in the NOD2/CARD15 gene and the CD phenotype, relation to the operative and postoperative course of the disease and try to determine CD patients with a fast-progressing form of the disease who would profit from an early surgical solution.

## Material and methods

Three groups of patients underwent genetic testing. The main group consisted of CD patients who had undergone surgical treatment during 2010–2016 for CD. The first control group was CD patients who had been diagnosed with CD for at least 5 years and had not undergone any surgical treatment for this disease. This group consisted of patients with a less aggressive form of CD, in which we supposed a lower occurrence of NOD2/CARD15 gene mutations. The second control group was healthy individuals without any disease or internal diagnosis. All the patients including the control groups were tested for a genetic mutation in the NOD2/CARD15 gene.

The study was prospective, and the patients were monitored for these basic parameters—age, gender, Montreal classification of CD, medication, cigarette smoking, number of previous CD surgeries, history of CD in the family, and genetic analysis of NOD2/CARD15.

Furthermore, other data related to the operation and postoperative development were recorded—the time interval between being diagnosed with CD and surgery, type of surgical treatment, and the extent of bowel resection, type of anastomosis, operative approach, and postoperative complications.

## Results

The group of patients operated for CD included 117 patients; 53 of them were men (45.3%) and 64 women (54.7%). The most frequent location of the disease was the ileum and the colon (L3) in 55 of the cases (47.0%), closely followed by the ileum (L1) in 51 of the cases (43.6%) and colon (L2) in 11 patients (9.4%). Twenty-one (17.9%) of the patients suffered from an inflammatory type (B1) of the disease, 56 (47.9%) patients had a stricturing type (B2), and 40 (34.2%) patients had a penetrating type (B3). The difference in the number of patients with a stricturing and penetrating type was significantly higher than in the group of patients without surgery. Eighty-three patients (70.9%) underwent surgery for CD for the first time, 27 patients (23.1%) had already undergone one CD-related surgery in the past, 3 patients (2.6%) had undergone 2 surgeries in the past, and 4 patients (3.4%) even 3 CD-related surgeries.

The first control group consisted of 77 CD patients who had not required any surgery for this diagnosis during their life. Female gender prevailed—there were 50 (64.9%) women as opposed to 27 (35.1%) men. CD duration median was 13 years (9–18 years IQR). In this group, the most frequent location was the ileum (L1) in 36 patients (46.8%), followed by the ileum and colon (L3) in 28 patients (36.4%). The least frequent location was the colon (L2) in 13 of the cases (16.9%). The prevailing type of the disease was the inflammatory form (B1), specifically in 68 patients (88.3%).

The second control group of persons without CD or any other internal diagnosis who underwent genetic testing consisted of 30 healthy individuals (16 of whom were men and 14 women).

Out of a total of 117 surgical procedures, the most common one was ileocecal resection ($n = 72$), followed by left hemicolectomy or rectal resection ($n = 21$), then resection of anastomosis in 13 patients and right hemicolectomy in 11 patients. The laparoscopic approach was chosen for 28 patients (24%) and open surgery for 89 patients (64%). Regarding the construction of anastomosis, the most frequent one was side-to-side (STS) anastomosis ($n = 83$) in comparison with end-to-end (ETE) anastomosis ($n = 18$) and 14 patients had terminal ileostomy.

Afterwards, a statistical analysis of the high-risk mutations in the NOD2/CARD15 gene was performed in all three studied groups. The distribution according to the number of mutations is shown in Table 1 and the particular alleles of the gene summarizes Table 2. The associations between a specific number of mutations and individual characteristics of operated CD patients can be seen in Table 3. Operated patients with two or more mutations had their first CD-related surgery performed at a considerably lower age than patients with one or no mutation. In particular, the median age at the time of their first CD-related surgery was 24 years, as opposed to 31 or 32 years, respectively. Another important finding was that patients with two or more mutations had an operation much earlier after being diagnosed than patients with one mutation. Operated CD patients with two or more mutations were therefore generally operated on at an earlier age and needed surgery earlier after being diagnosed. Furthermore, in the group of patients with two or more mutations, each patient had a resection of the ileum (100%) as opposed to patients with one or no mutation, which means that this information presents a high specificity.

The relation between a mutation in the gene and the time interval between diagnosis and the first CD-related surgery has also been measured. Patients with two or more mutations underwent surgery earlier in comparison with the patients with one mutation. The median interval between diagnosis and surgery was only 1 year compared to 5 years.

Another statistically significant correlation was found regarding the form of the disease. Patients with two or more

**Table 1** Number of mutations in NOD2/CARD15 gene

| | No mutations | 1 mutation | ≥ 2 mutations | 1–3 mutations |
|---|---|---|---|---|
| Operated CD patients ($N = 117$) | 52 (44.4%) | 43 (36.8%) | 22 (18.8%) | 65 (55.5%) |
| Non-operated CD patients ($N = 77$) | 47 (61.1%) | 17 (22.1%) | 13 (16.8%) | 30 (38.9%) |
| Controls ($N = 30$) | 29 (96.7%) | 1 (3.3%) | 0 (0.0%) | 1 (3.3%) |
| $P^1$ | *0.028* | *0.039* | 0.849 | *0.028* |
| $P^2$ | *< 0.001* | *< 0.001* | *0.008* | *< 0.001* |
| $P^3$ | *< 0.001* | *0.021* | *0.018* | *< 0.001* |

*P* value of Fisher's exact test compares relative frequencies of genotypes between operated CD patients and non-operated CD patients[1], operated CD patients and controls[2], and non-operated CD patients and controls[3]

mutations were operated on significantly earlier after being diagnosed as opposed to patients with one mutation if the patient had a stricturing or penetrating form of the disease (B2 and B3 were counted together, $P = 0.016$).

No relation between the genetic mutation and a higher number of reoperations for CD (resection of anastomosis in stenosis, etc.) was found and there was not observed any association between the genetic mutation and the extent of intestine resection.

There was significantly higher occurrence of mutations in the operated group than in the group of non-operated CD patients (55% of the operated patients had a mutation in the gene, compared with 39% of the non-operated patients with a mutation in the gene, $P = 0.028$). Patients with a mutation in the gene are 1.96 times more likely to have another CD-related surgery compared to patients without a mutation.

**Table 2** Distribution of NOD2/CARD15 risk alleles (R702W, G908R and 3020insC)

| | R702W | G908R | 3020insC |
|---|---|---|---|
| Operated CD patients ($N = 117$) | | | |
| Homozygous wild-type (−/−) | 96 (82.1%) | 103 (88.0%) | 74 (63.2%) |
| Heterozygous mutation (±) | 21 (17.9%) | 14 (12.0%) | 33 (28.2%) |
| Homozygous mutation (+/+) | 0 (0.0%) | 0 (0.0%) | 10 (8.5%) |
| Non-operated CD patients ($N = 77$) | | | |
| Homozygous wild-type (−/−) | 70 (90.9%) | 68 (88.3%) | 57 (74.0%) |
| Heterozygous mutation (±) | 7 (9.1%) | 7 (9.1%) | 15 (19.5%) |
| Homozygous mutation (+/+) | 0 (0.0%) | 2 (2.6%) | 5 (6.5%) |
| Controls ($N = 30$) | | | |
| Homozygous wild-type (−/−) | 30 (100.0%) | 30 (100.0%) | 29 (96.7%) |
| Heterozygous mutation (+/−) | 0 (0.0%) | 0 (0.0%) | 1 (3.3%) |
| Homozygous mutation (+/+) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| $P^1$ | 0.098 | 0.205 | 0.330 |
| $P^2$ | *0.008* | 0.074 | *< 0.001* |
| $P^3$ | 0.187 | 0.249 | *0.027* |

*P* value of Fisher's exact test compares relative frequencies of genotypes between CD patients with surgery and without surgery[1], CD patients with surgery and controls[2], and CD patients without surgery and controls[3]

## Discussion

In 2005, Annese et al. [5] published a study of a group of 316 CD patients which proved that the carriers of at least one mutant allele in the NOD2/CARD15 gene had a tendency toward a more aggressive disease course. These conclusions correspond to ours, where the number of patients with at least one mutation was significantly higher in the operated group compared to the control non-operated group of CD patients ($P = 0.028$). After a subdivision into individual alleles, the operated group of CD patients was found to have more mutations in the R702W and 3020insC allele compared to a healthy population. In the group of non-operated CD patients compared to the healthy group, only the 3020insC allele had a higher representation. In 2006, Seiderer et al. [8] even described that a mutation in this particular allele (3020insC) significantly increases the risk of intestinal stenosis and resection in CD patients.

Some studies correlate the NOD2/CARD15 gene mutation with a greater risk of an earlier intestinal resection after being diagnosed with CD [7, 9] or a generally greater risk of a CD-related surgery [8]. A greater risk for CD patients with a mutation of the NOD2/CARD15 gene is, according to previous studies, mainly connected to a disease of the ileum, the stricturing and penetrating form and being diagnosed with CD at an early age (unfavorable factors causing a more aggressive disease course) [8, 10].

In our group, patients with two or more mutations (homozygotes or mixed heterozygotes) formed a risk group with a more aggressive disease course. Specifically, patients with two or more mutations were operated on for CD at a significantly lower age and also significantly earlier after being diagnosed. We have also demonstrated the relation of an earlier operation after diagnosis in patients with two or more mutations and a stricturing or penetrating form of the disease. Another fact that makes this group of patients with two or more mutations high-risk is that 100% of them had to undergo a small bowel resection. This corresponds with many studies that have demonstrated the relationship between the ileum (L1) and mutations in the NOD2/CARD15 gene [7, 9, 10].

**Table 3** Associations between mutations in NOD2/CARD15 and characteristics of operated CD patients

| Parameters | | No mutations $N = 52$ | 1 mutation $N = 43$ | ≥2 mutations $N = 22$ | $P^1$ |
|---|---|---|---|---|---|
| Clinical characteristics | | | | | |
| Sex | Male | 24 (46.2%) | 19 (44.2%) | 10 (45.5%) | 0.999 |
| | Female | 28 (53.8%) | 24 (55.8%) | 12 (54.5%) | |
| Age at diagnosis | Years | 26 (22; 37) | 26 (22; 32) | 22 (17; 29) | 0.061 |
| | < 17 years | 2 (3.8%) | 5 (11.6%) | 5 (22.7%) | 0.089 |
| | 17–40 years | 41 (78.8%) | 35 (81.4%) | 15 (68.2%) | |
| | > 40 years | 9 (17.3%) | 3 (7.0%) | 2 (9.1%) | |
| Location of disease | L1—ileum | 27 (51.9%) | 17 (39.5%) | 7 (31.8%) | *0.031* |
| | L2—colon | 8 (15.4%) | 3 (7.0%) | 0 (0.0%) | |
| | L3—ileum + colon[#] | 17 (32.7%)[a] | 23 (53.5%)[ab] | 15 (68.2%)[b] | |
| | Not L4 | 51 (98.1%) | 40 (93.0%) | 20 (90.9%) | 0.286 |
| | L4—upper GIT (concomitant) | 1 (1.9%) | 3 (7.0%) | 2 (9.1%) | |
| Behavior of disease | B1—inflammatory | 12 (23.1%) | 7 (16.3%) | 2 (9.1%) | 0.638 |
| | B2—stricturing | 25 (48.1%) | 20 (46.5%) | 11 (50.0%) | |
| | B3—penetrating | 15 (28.8%) | 16 (37.2%) | 9 (40.9%) | |
| Perianal disease | No | 36 (69.2%) | 28 (65.1%) | 14 (63.6%) | 0.902 |
| | Yes | 16 (30.8%) | 15 (34.9%) | 8 (36.4%) | |
| Surgical characteristics | | | | | |
| Age at first surgery | Years | 32 (25; 42)[a] | 31 (27; 37)[a] | 24 (20; 34) | *0.005* |
| Time from diagnosis to first surgery | Years | 3 (1; 8)[ab] | 5 (2; 9)[a] | 1 (1; 7)[b] | *0.024* |
| Surgical procedure | IC resection | 32 (61.5%) | 25 (58.1%) | 15 (68.2%) | 0.093 |
| | Right-sided hemicolectomy | 4 (7.7%) | 4 (9.3%) | 3 (13.6%) | |
| | Resection of anastomosis | 3 (5.8%) | 6 (14.0%) | 4 (18.2%) | |
| | Resection of left colon or rectum | 13 (25.0%) | 8 (18.6%) | 0 (0.0%) | |
| Ileum resection | No | 13 (25.0%) | 10 (23.3%) | 0 (0.0%) | *0.016* |
| | Yes | 39 (75.0%)[a] | 33 (76.7%)[a] | 22 (100.0%) | |
| | (cm; if yes) | 25 (15; 30) | 25 (20; 30) | 25 (15; 30) | 0.977 |
| Anastomosis | STS | 34 (66.7%) | 31 (73.8%) | 18 (81.8%) | 0.602 |
| | ETE | 8 (15.7%) | 7 (16.7%) | 3 (13.6%) | |
| | Terminal ileostomy | 9 (17.6%) | 4 (9.5%) | 1 (4.5%) | |
| Surgical approach | Open | 40 (76.9%) | 30 (69.8%) | 19 (86.4%) | 0.379 |
| | Laparoscopic | 12 (23.1%) | 13 (30.2%) | 3 (13.6%) | |
| Complications | No | 34 (65.4%) | 30 (69.8%) | 13 (59.1%) | 0.667 |
| | Yes | 18 (34.6%) | 13 (30.2%) | 9 (40.9%) | |

Continuous variables are described by median (IQR); categorical variables are characterized by absolute and relative frequencies. [a, b] Same letters denote groups of patients which do not significantly differ (post hoc analysis with Bonferroni correction applied)

[1] $P$ value of Fisher's exact test for categorical variables or $P$ value of Kruskal-Wallis test for continuous variables

[#] Significant difference between groups of patients (post hoc analysis with Bonferroni correction applied)

The work of Jürgens et al. [11] from 2010 also points to patients with a homozygous mutation of the 3020insC allele as being at a high risk for stenosis and intestinal resection. Another important work by Adler et al. [7] from 2011 also finds out that patients with two mutations are at a higher risk of an aggressive and complicated course of CD.

In 2009, Maconi et al. [12] did not show any correlation between the mutation in the gene and higher frequency of reoperations (stenosis in anastomosis, involvement of another part of the intestine, etc.). In our analysis, we also did not detect any relation between a mutation in the gene and more frequent reoperation in CD patients.

## Conclusion

An essential finding was that patients with two or more mutations were generally operated on at a younger age and also earlier after being diagnosed with CD. Moreover, each patient with two or more mutations had a resection of a part of the

ileum. This group of patients could therefore be considered as a group with a more aggressive type of CD and a higher probability of a resection of the small intestine, and would benefit from conservative top-down therapy or early surgical treatment.

In the operated group, there was at least one mutation in the gene found significantly more often than in the non-operated group. Patients with a mutation in the NOD2/CARD15 gene are at a 1.96 times greater risk of CD-related surgery than patients without a mutation.

## Compliance with ethical standards

**Ethical standard statement** All procedures which followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008.

**Informed consent** Informed consent was obtained from all patients for being included in the study.

**Conflict of interest** The authors declare that they have no conflict of interest.

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**Příloha 21** - Increased risk of anastomotic leak in Crohn's disease patients unable to complete preoperative mechanical bowel preparation



discontinuation (57 vs. 22%), although this association did not reach statistical significance ($p = 0.08$).
**Conclusion:** The risk of needing reintroduction of anti-TNF therapy after mucosal healing in IBD is around 50% in 5 years, being superior in CD patients. Reintroduction success rate is 76%. In CD, this risk is higher when the reason for starting anti-TNF was corticodependence, and much lower when stricturing/fibrotic pattern predominates. For UC patients, anti-TNF drugs should not be stopped if IM therapy cannot be held.

## P557

## Increased risk of anastomotic leak in Crohn's disease patients unable to complete preoperative mechanical bowel preparation

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**Background:** To assess the risk of postoperative anastomotic leak in Crohn's disease patients unable to complete the preoperative mechanical bowel preparation (MBP): a prospective observational study from two referral centres in Germany and the Czech Republic.
**Methods:** Preoperative MBP was used routinely in all Crohn's disease patients undergoing elective ileocolic or colorectal resections completed by the formation of an anastomosis since 6/2016. The MBP consisted of 2 L Polyethyleneglycol (PEG) solution combined with two doses of oral antibiotics Metronidazole and Paromomycin. The MBP was defined as incomplete when patients were not able to drink the whole amount of PEG solution due to side effects or complications. The primary endpoint was occurrence of anastomotic leak. The secondary endpoint was the incidence of postoperative intraabdominal septic complications (IASC) which were defined as an anastomotic leak, intraabdominal abscess or fistula and peritonitis.
**Results:** Between 6/2016 and 11/2019, 96 Crohn's disease patients underwent elective ileocolic or colorectal resections after receiving preoperative MBP and oral antibiotics. Twenty-four (25%) developed complications of MBP, mostly vomiting; 17 patients (18%) were not able to complete MBP. The presence of extraintestinal disease manifestations (Hazard Ratio 4.8, $p = 0.029$), preoperative weight loss (HR 5.7, $p = 0.019$) and female sex (HR 13.3, $p = 0.005$) were associated with an increased probability not to be able to complete MBP. Postoperative anastomotic leak occurred in 2 patients (2%). The risk of anastomotic leak was significantly higher in patients unable to complete MBP (12%) as compared with patients with complete MBP (0%, $p = 0.03$). Postoperative IASC occurred in 7 patients (7%). Patient unable to complete preoperative MBP were at higher risk to develop IASC; however, the difference was not statistically significant (18% vs. 5%, $p = 0.10$)
**Conclusion:** The anastomotic leak rate is very low when preoperative mechanical bowel preparation and oral antibiotics have been used. However, patients not able to complete MBP might be at an increased risk.

## P558

## Validation of the 'IBD Disk' in clinical practice

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**Background:** The inflammatory bowel disease (IBD) Disk is a tool that has been developed from the IBD Disability Index in order to objectively measure the degree of disability in patients suffering from IBD. It provides a visual representation of disability state, thereby increasing the ease of application in a clinical setting. Currently, it has not yet been validated in any population. Our primary aim was to hence validate the IBD Disk in a clinical setting.
**Methods:** 40 patients were recruited from an outpatient setting in a tertiary centre in Australia. All patients completed four surveys, the IBD Disk, the IBD Disability Index (IBD-DI), the Hospital Anxiety and Depression Score (HADS) and the Shortened IBD Questionnaire (SIBDQ). Nineteen of these patients then elaborated on their answers in a semi-structured narrative interview based on the IBD Disk. After a consultation with a gastroenterologist, the treating doctors were also asked to fill out an IBD Disk based on their own perceptions of the participant's degree of disability. The IBD Disk was assessed for its internal consistency, construct validity and factor structure. The qualitative data were analysed and coded using NVIVO and then associated to IBD Disk scores.
**Results:** Of the patients recruited 48% were female, 30% had ulcerative colitis and 52% were in clinical remission. Average IBD Disk score was 40.75. Our results suggest the IBD Disk is an internally consistent tool for clinical use when assessing disability (Cronbach's A = 0.888). This is supported by statistically significant differences in IBD Disk scores between patients in clinical remission and patients with active disease ($p = 0.002$). There is also a good correlation between the Patient-Reported IBD Disk scores and the IBD-DI scores ($r = 0.864$), Doctor Perceived IBD Disk scores ($r = 0.794$) and the HADS Depression score ($r = 0.759$). IBD Disk scores also negatively correlated with the Shortened IBD Questionnaire ($r = -0.864$). Qualitative data also correlate well thematically with IBD Disk scores. These results suggest an appropriate system for grading disability status via the IBD Disk is: 0–24 = no disability; 25–49 = mild disability; 50–74 = moderate disability; and, 75–100 = severe disability.
**Conclusion:** This study supports the use of the IBD Disk as a reliable and valid self-reporting tool in clinical situations. There is strong internal consistency, construct validity, factor structure and qualitative thematic association. However, more data are needed to further validate the IBD Disk. Most significantly though, the IBD Disk is likely to become a valuable tool for the practical assessment of disability in patients with IBD in the near future.

## P559

## Effect of vedolizumab and ustekinumab on articular manifestations in patients with inflammatory bowel disease refractory or intolerant to anti-TNF therapy: An observational prospective study

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**Příloha 22** - Quality of life after bowel resection for Crohn's disease - first results

Original article

# Quality of life after bowel resection for Crohn´s disease – first results

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**Summary**
*Introduction:* Crohn´s disease (CD) highly affects a patient´s quality of life. The aim of the study was to find out the impact of surgery on the quality of life (QoL) in CD patients and factors affecting their postoperative QoL.
*Methods:* 90 patients with CD who underwent surgery (bowel resection) filled out an EORTC QLQ-CR29 questionnaire preoperatively and again after the surgical procedure.
*Results:* 77% of the patients experienced a positive change ($p<0.001$), 22% negative and 11% no change.
*Conclusion:* In this cohort, we proved that surgical treatment improves the overall QoL in patients with CD. To determine factors which affect postoperative QoL, more patients need to be enrolled in future studies.
***Key words:*** Crohn´s disease – quality of life – surgery – bowel resection – Czech cohort

**Souhrn:**
**Kvalita života u pacientů s Crohnovou chorobou po střevní resekci – první výsledky**
**L. Kunovský, Z. Kala, L. Mitáš, J. Dolina, V. Čan, L. Kučerová, V. Jadczaková, I. Penka**

Úvod: Crohnova choroba značně ovlivňuje kvalitu života u pacientů trpících touto chorobou. Cílem naší studie bylo zjistit, jaký vliv má chirurgické řešení na kvalitu života u pacientů s Crohnovou chorobou a určit faktory, které pooperační kvalitu života ovlivňují.
*Metody:* 90 pacientů s Crohnovou chorobou, kteří na našem pracovišti podstoupili resekci střeva, vyplnili v předoperačním a pooperačním období dotazník kvality života EORTC QLQ-CR29.
*Výsledky:* U 77 % pacientů bylo zjištěno zlepšení kvality života ($p<0.001$), u 22 % pacientů zhoršení a u 11 % pacientů nebyla zjištěna změna.
*Závěr:* V našem souboru operovaných pacientů s Crohnovou chorobou jsme prokázali, že chirurgická léčba zvyšuje jejich celkovou kvalitu života. K určení faktorů, které ovlivňují pooperační kvalitu života, je zapotřebí soubor s větším počtem pacientů.
***Klíčová slova:*** Crohnova choroba – kvalita života – chirurgie – resekce střeva – česká kohorta

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## INTRODUCTION

Being a chronic disorder, Crohn´s disease (CD) highly affects the quality of life (QoL) of patients suffering from this disease and is characterized by periods of remission and disease relapses.

Some of the symptoms that may alter QoL include abdominal pain, frequent stool, bowel obstruction, weight loss, malnutrition and extraintestinal manifestations.

Population-based studies showed that patients with inflammatory bowel disease (IBD) have significant impairment of QoL compared to the general healthy population [1,2]. Studies proved that QoL in IBD individuals responds to disease activity and it seems that remission has the strongest impact that contributes to the improvement of their QoL [2–4].

Manifestation of CD occurs most often at a younger age [5–7]. The incidence shows a current increase [8–11], the highest number of patients being in North America, Australia and Western Europe [8–13].

Despite all the possibilities of conservative therapy, approximately 80% of patients with CD have to undergo a surgical procedure during their lives [14–18]. The aim of the study was to compare the QoL before and after surgical treatment of CD in a Czech cohort.

## METHODS

During the years 2010–2014, patients with CD consecutively filled out a questionnaire preoperatively and again after a surgical procedure (bowel resection) related to CD.

The patients with perianal CD that were indicated for surgery due to perianal disease were excluded from the study (abscess, fistula, etc.). Patients that were indicated for intestinal resection filled out the questionnaire in the 6 week period prior to the operation. The same questionnaire was filled out 2 months after the surgical procedure. The period of 2 months after the operation was set as a sufficient time for healing and reconvalescence, and conversely a short time for CD recurrent activity after surgery.

### Questionnaire

A routinely used questionnaire for assessing QoL in IBD patients is IBDQ-32 [19]. For a better evaluation of QoL related to surgery, we decided to use QLQ-CR 29, a module for colorectal disorders, which can better reflect the postoperative outcome.

The European Organisation for Research and Treatment of Cancer (EORTC) has a working group on QoL and has created a combined system for QoL assessment using a generic core (EORTC QLQ-C30) [20] and a supplementary module for a specific disease. QoL was evaluated using validated questionnaire module QLQ-CR 29 developed by EORTC [21,22]. Purely oncologically focused questions were excluded and the questionnaire was modified and validated in cooperation with a statistician. The content validity of the questionnaire was discussed with gastroenterologists who specialize in CD at the University Hospital Brno and a psychometrician.

The questionnaire included questions about abdominal pain and discomfort, urinary and sexual functions, stool, quality of defecation, physical functioning and body image. Questions about stool were focused on frequency, admixture of blood or mucus in the stool. In the quality of defecation, parameters such as flatulence, faecal incontinence and perianal skin discomfort were measured.

Patients rated all items of the EORTC QLQ-CR29 questionnaire on a 7-point scale which was linearly transformed to give a score ranging from 0 to 100 according to the formula suggested by developers. In doing so, a high score indicated a high ("worse") level of symptomology (or problems), and thus a lower level of quality of life, and vice versa. The score for overall QoL was calculated as a summated scale by averaging items compromising it.

### Statistics

A total of 90 patients was subjected to the analysis. Due to the ordinal nature of the data and non-Gaussian distributions, the level and variation of quality of life components was presented as median and interquartile range and nonparametric analysis was used to examine the effects in the sample. Specifically, Wilcoxon signed-rank test was performed to assess the difference between preoperative and postoperative components of the quality of life. The Mann-Whitney U test or Kruskal-Wallis one-way ANOVA for k samples was used to assess the association between the overall QoL and selected demographic and clinical characteristics. To treat the effect of multiple comparisons, the Bonferroni correction or multivariate canonical analysis was applied. In doing so, if not specified otherwise, the $p < 0.05$ was considered statistically significant for all analyses.

## RESULTS

We recruited 90 patients with CD who underwent intestinal resection. Basic characteristics of the patients can be seen in Tab. 1. In our group, we had 51 females and 39 males, the mean age at the time of the surgical procedure was 33.5±10.7 years. 49 patients (54.4%) were smokers and 33 patients (36.7%) had at least one previous abdominal surgical procedure.

In 25 cases, the laparoscopic approach (27.8%) was chosen, in 65 cases the surgery was done by open approach (72.2%). The spectrum of all surgical procedures is mentioned in Tab. 2. The most frequent procedure was ileocecal resection in 61 patients (67.8%). The 30-day postoperative complications were also recorded. The most frequent complications were surgical site infections or wound hematoma in 17 patients (18.9%). Severe complications such as anastomotic leakage were reported in 3 patients (3.3%), bowel obstruction in 3 patients (3.3%), intraabdominal abscess in 5 patients (5.6%) and postoperative bleeding in 2 patients

**Tab. 1: Basic characteristics of patients**

| Variable | Number of cases n=90 (%) |
|---|---|
| **Age at surgery** | |
| <17 | 0 (0%) |
| 17–40 | 65 (72%) |
| >40 | 25 (28%) |
| **Sex** | |
| Male | 39 (43%) |
| Female | 51 (57%) |
| **Cigarette smoking** | |
| Yes | 49 (54%) |
| No | 41 (46%) |
| **Preoperative medication** | |
| No medication | 10 (11%) |
| Biological treatment | 12 (13%) |
| 1–3 types of medication* | 68 (76%) |
| 5-aminosalycilates** | 52 |
| steroids** | 37 |
| immune suppressors** | 26 |
| **Location of disease** | |
| L1 | 53 (59%) |
| L2 | 8 (9%) |
| L3 | 29 (32%) |

** 5-aminosalycilates, steroids, immune suppressors or combination*
*** counted independently*

**Tab. 2: Summary of surgical procedures**

| Type of surgical procedure | Number of cases (n=90) |
|---|---|
| Ileocecal resection | 61 |
| Right side hemicolectomy | 8 |
| Resection of anastomosis | 11 |
| Subtotal colectomy | 4 |
| Left side hemicolectomy | 4 |
| Proctectomy | 2 |

**Tab. 3: Summary of complications within 30 days**

| Type of complication | Number of cases (n=90) |
|---|---|
| Wound infections or hematoma | 17 |
| Ileus/bowel obstruction/ paralysis | 3 |
| Intraabdominal abscess | 5 |
| Anastomotic leakage | 3 |
| Postoperative bleeding | 2 |
| Uroinfection | 3 |
| Bronchopneumonia | 2 |
| Pneumothorax | 1 |
| Fever of unknown origin | 2 |
| other | 3 |

(2.2%). Other complications can be seen in Tab. 3. The assessment of the surgical approach and complications as postoperative QoL predictors are listed in Tab. 4.

At the time of surgery, most of the patients were on 5-aminosalicylates, steroids, immune suppressors or any combination of these medications. 12 patients were treated by biological therapy and 10 were not using any pharmacotherapy for CD. The location of the disease was classified by the Montreal classification [23] (L1 in 53 patients, L2 in 8 and L3 in 29). The evaluation of pharmacotherapy and location of the disease as postoperative QoL predictors are mentioned in Tab. 5. In our first results, we proved that the short-term QoL measured 2 months after surgery improved. The postoperative overall QoL improved statistically significant-

**Tab. 4: Analysis of factors affecting overall postoperative QoL**

| Variable | Group 1 (n) | Median (IQR) | Group 2 (n) | Median (IQR) | p-value* | p-value** |
|---|---|---|---|---|---|---|
| Age | <40 (65) | 17.1 (10.9–27.2) | >40 (25) | 18.4 (12.4–24.9) | 0.934 | |
| Sex | Female (51) | 21.5 (13.9–33.8) | Male (39) | 14.8 (8.3–21.0) | 0.001 | 0.00027 |
| Smoking | Yes (49) | 19.4 (10.9–27.2) | No (41) | 16.2 (12.04–26.6) | 0.783 | |
| Complications | Yes (32) | 21.1 (12.7–32.1) | No (58) | 16.0 (10.9–25) | 0.129 | |
| Former operations | None (57) | 16.9 (10.6–25) | at least 1 (33) | 18.3 (13.2–29.9) | 0.373 | |
| Surgical approach | Laparoscopic (25) | 21.5 (12.0–26.7) | Open (65) | 16.9 (11.3–27.2) | 0.505 | |

*Mann-Whitney U test (significant p-value <0.05)
** Canonical analysis (significant p-value <0.05)
IQR: Inter-quartile-range; QoL: Quality of life

**Tab. 5: Analysis of factors affecting overall postoperative QoL**

| Variable | n | Median (IQR) | p-value* |
|---|---|---|---|
| **Pharmacotherapy** | 90 | | 0.171 |
| No medication | 10 | 14.6 (8.6–27.2) | |
| 1–3 types of medication** | 68 | 16.9 (11.3–25.8) | |
| Biological treatment | 12 | 24.3 (17.3–32.5) | |
| **Location of disease** | 90 | | 0.674 |
| L1 | 53 | 19.2 (10.2–26.9) | |
| L2 | 8 | 21.2 (13.0–36.8) | |
| L3 | 29 | 16.9 (12.7–24.8) | |
| **Surgical procedure** | 90 | | 0.336 |
| IC resection*** | 69 | 16.9 (11.3–26.6) | |
| Resection of anastomosis | 11 | 17.1 (12.0–29.2) | |
| Resection of left colon or rectum | 10 | 24.3 (15.3–42.6) | |

*Kruskal-Wallis one-way ANOVA for *k* samples (significant p-value <0.017, Bonferroni p-value threshold)
** 5-aminosalycilates, steroids, immune suppressors or combination
*** Right side hemicolectomy was evaluated together with IC resection

**Tab. 6: Preoperative and postoperative changes of QoL in patients after bowel resection for Crohn´s disease**

| | | Preoperative | | Postoperative | | Change of QoL in patients n (%) | | | p-value* |
|---|---|---|---|---|---|---|---|---|---|
| Variable | n | Median | IQR | Median | IQR | + | - | No change | |
| Abdomen pain and discomfort | 90 | 33.3 | 16.6–50 | 8.3 | 0–16.7 | 75 (83%) | 6 (7%) | 9 (10%) | <0.001 |
| Questions about stool | 90 | 27.8 | 11.1–44.4 | 16.7 | 15.3–33.3 | 51 (57%) | 25 (28%) | 14 (15%) | <0.003 |
| Urinary functions | 90 | 0 | 0–6.9 | 0 | 0–5.6 | 17 (19%) | 13 (14%) | 60 (67%) | <0.144 |
| Physical functioning and body image | 90 | 38.9 | 22.2–77.8 | 27.8 | 11.1–50.0 | 53 (59%) | 27 (30%) | 10 (11%) | <0.001 |
| Sexual functions | 85 | 41.7 | 16.7–66.7 | 25 | 8.3–43.8 | 47 (55%) | 10 (12%) | 28 (33%) | <0.001 |
| Quality of defecation | 68 | 29.2 | 9.4–45.8 | 16.7 | 4.2–33.3 | 43 (63%) | 9 (13%) | 16 (24%) | <0.001 |
| overall QoL | 90 | 30.4 | 18.8–44.5 | 17.7 | 11.3–26.9 | 69 (77%) | 20 (22%) | 1 (11%) | <0.001 |

*Wilcoxon signed-rank test (significant p-value <0.008, Bonferroni p-value threshold)
IQR: Inter-quartile-range; QoL: Quality of life

ly (77% patients experienced a positive change, 22% negative and 11% no change), further improvement of QoL comprised a reduction of abdominal pain and discomfort, reduced frequency of stool, etc. Except for urinary functions, where there was no impact of surgery on QoL, all variables were evaluated with a significant postoperative improvement of QoL. All data are summarized in Tab. 6.

## DISCUSSION

Even though there is a possibility of biological treatment, the majority of patients with CD still has to undergo a surgical procedure during their lifetime. In our group of patients, we proved that surgical treatment improves the QoL in the short-term period after surgery. Except for urinary functions, the QoL was assessed as significantly better postoperatively in all the observed parameters. In 2003, Delaney et al. [24], also published evidence of improvement of QoL measured 30 days after surgery for CD. However, the duration of this level of quality of life is still uncertain, as the clinical recurrence after surgery is about 55–65% in 5 years [14,17,25].

In our analysis, male gender was evaluated as a statistically significant factor of postoperative improvement of QoL (p=0.00027). Tabibian et al. [26] published an article in 2015 about predictors of impaired QoL in patients with inflammatory bowel disease. In his work, female gender was described as a statistically significant predictor of lower QoL among CD patients. Casellas et al. [4] obtained similar results where bowel symptoms were perceived as worse by women patients suffering from CD, although in other domains gender was not crucial for QoL.

Some variables from our analysis indicated predictive value of postoperative QoL, but they did not reach statistically significant values (e.g. complications, pharmacotherapy). Complications within 30 days after surgery are associated with impaired QoL as published by Delaney et al. [24]. In our study, patients with postoperative complications also had reduced QoL, but the results were not statistically significant (p=0.129). Concerning the impact of pharmacotherapy on postoperative QoL, it was most enhanced in patients without medication. Patients on biological treatment had the lowest QoL. However, the factor of pharmacotherapy was not at a statistically significant level (p=0.171).

Other factors in the analysis were not statistically significant or could be misleading due to the total number of patients (e.g. surgery approach, surgical procedure). In previous studies, when laparoscopic approach was compared to open surgery, it was associated with a shortened hospital stay and better effects on body image and cosmetic results, although the overall improvement in QoL was not observed [27]. In our analysis, the laparoscopic approach also did not enhance overall postoperative QoL (p=0.505).

In this article, we publish our first results of the study analysing QoL after bowel resection in patients with CD. For more significant results of factors affecting postoperative QoL, more patients should be enrolled. A control group of a healthy cohort could also be established to reveal the differences in QoL (as presented in table 6) between a healthy cohort and patients with CD after surgery. Another control group of patients with CD who do not need surgery yet could be used for comparison as well.

## CONCLUSION

In this cohort, we proved that surgical treatment (bowel resection) improves the overall QoL in patients with CD. However, to determine factors which affect postoperative QoL, more patients need to be enrolled in future studies.

**Abbreviations:**
CD - Crohn´s disease
QoL - quality of life

IBD - inflammatory bowel disease
IBDQ-32 - Inflammatory bowel disease questionnaire-32
EORTC - The European Organisation for Research and Treatment of Cancer
QLQ-CR 29 - Quality of life questionnaire-colorectal 29

*Conflict of Interests*
*The authors declare that they have not conflict of interest in connection with the emergence of and that the article was not published in any other journal.*

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**Příloha 23** - Impact of surgery on quality of life in Crohn´s disease patients: final results of Czech cohort



# Impact of surgery on quality of life in Crohn´s disease patients: final results of Czech cohort

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**Summary**
**Introduction**: Crohn's disease (CD) belongs to chronic diseases that highly affect the patient´s quality of life (QoL). The effect of the disease and impairment of QoL in CD patients is already known. The aim was to assess how surgical treatment influences the patients' QoL and determine factors that can affect postoperative QoL. **Methods and patients**: We compared the QoL before and after surgery in patients who had undergone a bowel resection at our department due to CD between 2010–2016. The patients filled in a standardized QLQ-CR29 questionnaire to assess QoL in the preoperative period and the postoperative period after a 2-month interval. The control groups were CD patients who had not undergone surgical treatment (bowel resection) and a healthy cohort. In the QoL evaluation, 132 patients with CD who had undergone surgery (bowel resection), 83 patients with CD without an operation and 104 healthy subjects were enrolled. **Results**: 104 of the operated patients experienced a postoperative improvement of the overall QoL (78.8 %), 2 patients did not register any changes in QoL (1.5 %) and 26 patients (19.7 %) experienced a worsening of their postoperative QoL. The results were statistically significant ($p < 0.001$). **Conclusion**: We detected a significant improvement of the overall QoL after surgical resection in CD patients (measured 2 months after surgery). Gender was identified as the only statistically relevant factor with influence on postoperative QoL.

**Key words**: bowel resection – Crohn´s disease – Czech cohort – inflammatory bowel disease – quality of life – surgical treatment

## Vliv chirurgické léčby na kvalitu života u pacientů s Crohnovou chorobou: finální výsledky české kohorty

**Souhrn**
**Úvod:** Crohnova nemoc (Crohn´s disease – CD) patří mezi chronické onemocnění, které značně ovlivňuje kvalitu života (quality of life – QoL) u těchto pacientů. Cílem studie bylo stanovit, jaký vliv má chirurgická léčba na kvalitu života (quality of life – QoL) u pacientů s CD a určit faktory, které ovlivňují pooperační QoL. **Metody a pacienti**: Porovnávána byla QoL před operací a v pooperačním období u pacientů, kteří podstoupili na Chirurgické klinice střevní resekci z indikace CD v letech 2010–2016. Pacienti vyplnili standardizovaný dotazník k měření QoL QLQ-CR29 v předoperačním období a po operaci s odstupem 2 měsíců. Kontrolní skupiny představovali pacienti s CD, kteří nepodstoupili chirurgickou léčbu (resekci střeva) a zcela zdravá kohorta osob. Do studie bylo celkem zahrnuto 132 operovaných pacientů pro CD (resekce střeva), 83 pacientů s CD bez operace a 104 zdravých jedinců. **Výsledky**: Pooperační zlepšení QoL bylo zjištěno celkem u 104 operovaných pacientů (78,8 %), u 2 pacientů nebyla zaznamenána žádná změna v QoL (1,5 %) a u 26 pacientů (19,7 %) bylo zjištěno zhoršení pooperační QoL. Výsledky byly statisticky signifikantně významné ($p < 0,001$). **Závěr**: Prokázali jsme signifikantní zlepšení celkové QoL po střevní resekci u pacientů s CD v měřeném intervalu 2 měsíce od operace. Pohlaví bylo vyhodnoceno jako jediný statisticky významný faktor ovlivňující pooperační QoL

**Klíčová slova**: Crohnova choroba – česká kohorta – chirurgická léčba – idiopatické střevní záněty – kvalita života – resekce střeva

## Introduction

Crohn´s disease (CD) is a chronic, relapsing inflammatory disease of gastrointestinal tract which highly affects the quality of life (QoL). Health-related QoL is impaired in inflammatory bowel disease (IBD) patients, mostly due to chronicity, unpredictable disease course, young age onset, etc [1–4]. IBD patients may suffer from stressors such as abdominal discomfort, rectal bleeding, diarrhea, fecal urgency, weight loss, extraintestinal manifestations and a need for long-term medical therapy [2]. Therefore there has been a poorer QoL in IBD patients assessed compared with a healthy population [1,2,5–9].

Previous studies showed that the disease activity and remission of the disease have the strongest impact on QoL in IBD patients [10–12]. Even with modern biological therapy possibilities, most CD patients have to undergo surgery during their lives (about 80 % of CD patients) [13–18]. The main aim of this study was to find out the impact of surgical therapy in CD patients. We follow up on our previous article published in 2016 with the first results of QoL and bring the final data [19].

## Methods

Our main studied group were patients who underwent bowel resection for CD. Patients who were operated for perianal disease (abscess, fistula) were not included in the study. We studied patients who underwent surgery for CD at the Department of Surgery University hospital in Brno Bohunice between 2010–2016. The patients filled in a standardized QoL QLQ-CR29 questionnaire (Quality of life questionnaire-colorectal 29) prior to the surgery as well as after the surgery [20,21]. The questionnaire was filled in by patients indicated for bowel resection six weeks prior to their surgery and two months after the surgery. The two-month interval was selected as a sufficiently long period for convalescence, while short enough to avoid a relapse of the disease in anastomosis.

The first control group consisted of CD patients who did not undergo surgery for this diagnosis and had been diagnosed with CD for at least 5 years. This group represented patients with a less aggressive form of the disease who did not require surgery. We supposed a better QoL in these patients compared to the main group.

The second control group was a healthy cohort. The individuals included in this group were healthy subjects without any disease or internal diagnosis who had not undergone any abdominal surgery. We naturally supposed the best QoL in this group. Both control groups filled in the QoL questionnaire only once. The study was approved by the Ethical committee of the University hospital Brno and all patients signed an informed consent.

Apart from our main aim, which was to find out how surgical treatment influences patients with CD, we tried to determine the factors affecting postoperative QoL in CD patients. The basic parameters included age, gender, basic data according to the Montreal classification, duration of the disease, medication, comorbidity and smoking. Furthermore, we also monitored peroperative and postoperative data (type of surgery, operative approach and postoperative complications).

### Questionnaire and statistics

The standardized QoL QLQ-CR29 questionnaire is divided into several parts [20,21]. It included questions focused on abdominal pain and discomfort, questions concerning sexual and urinary functions, questions regarding physical functioning and body image and questions related to stool and quality of defecation. The section focused on stool included questions concerning the frequency of defecation and the frequency of blood or mucus in stool. The quality of defecation was assessed based on the type of flatulence, fecal incontinence and perianal discomfort.

A total of 215 CD patients and 104 healthy controls were included in the analysis. 132 CD patients underwent operation for CD, 83 CD patients did not have a CD-related operation. Standard descriptive statistics were applied in the analysis: absolute and relative frequencies for categorical variables and median with interquartile range (IQR) for continuous variables. The level and variation of QoL components was presented as mean and standard deviation, the Wilcoxon signed-rank test was performed to assess the difference between preoperative and postoperative components of the QoL. The Mann-Whitney U test or Kruskal-Wallis one-way ANOVA for k samples was used to assess the association between the overall QoL and selected clinical characteristics as well as to compare the QoL between CD patients and healthy controls. To treat the effect of multiple comparisons, the Bonferroni correction was applied. If not specified otherwise, the $p < 0.05$ was considered statistically significant for all analyses. Statistical analyses were performed in SPSS Statistics for Windows, version 24.0 (IBM Corp., Armonk, NY, USA).

### Patients

The group which underwent bowel resection for CD consisted of 132 patients out of which 59 were men (44.7 %) and 73 women (55.3 %). The median age of patients at the time of surgery was 33 years of age (IQR 25–39 years). The prevailing location of the disease was the ileum (L1) in 71 of the cases (53.8 %) and a simultaneous disease involvement of the ileum and colon (L3) in 52 of the cases (39.4 %). The structuring form of the disease (B2) was the most common, in 55.3 % of the patients. The perianal disease was present in 35 patients (26.5 %). As for preoperative medication, only 7.6 % of patients had biological treatment, 12.9 % were not using any pharmacotherapy, 27.3 % of the patients had monotherapy and 52.3 % were on a combination of 2–3 types of medication (Table 1).

The group of CD patients who did not require surgical treatment consisted of 83 patients, 28 men (33.7 %) and 55 women (66.3 %). The median duration of CD was 13 years (9–17 years IQR). In the non-operated group,

the prevailing location of the disease was, as in the main group, the ileum (L1), unlike the form of the disease, where the inflammatory type (B1) was the most common one; 16.9 % of the patients had biological treatment, while most of the patients, 43.4 % in particular, only used monotherapy in their CD treatment.

The healthy cohort, i. e. subjects without any disease, consisted of 104 subjects out of which 40.4 % were men

**Table 1. Basic characteristics of operated CD patients, non-operated CD patients and controls**
Continuous variables are described by median (IQR); categorical variables are characterized by absolute and relative frequencies (column %).

| parameters | | operated CD patients N = 132 | non-operated CD patients N = 83 | controls N = 104 | P[1] |
|---|---|---|---|---|---|
| sex | male | 59 (44.7 %) | 28 (33.7 %) | 42 (40.4 %) | 0.276 |
| | female | 73 (55.3 %) | 55 (66.3 %) | 62 (59.6 %) | |
| age at diagnosis | years (median) | 26 (20; 33) | 24 (20; 30) | – | 0.177 |
| | < 17 years | 15 (11.4 %) | 4 (4.8 %) | – | 0.065 |
| | 17–40 years | 103 (78.0 %) | 75 (90.4 %) | – | |
| | > 40 years | 14 (10.6 %) | 4 (4.8 %) | – | |
| age at surgery | years (median) | 33 (25; 39) | – | – | – |
| | < 17 years | 0 (0.0 %) | – | – | |
| | 17–40 years | 103 (78.0 %) | – | – | |
| | > 40 years | 29 (22.0 %) | – | – | |
| cigarette smoking | smoker | 45 (34.1 %) | 25 (30.1 %) | 22 (21.2 %) | **0.002** |
| | ex-smoker | 31 (23.5 %) | 16 (19.3 %) | 11 (10.6 %) | |
| | non-smoker | 56 (42.4 %) | 42 (50.6 %) | 71 (68.3 %) | |
| location of disease | L1 – ileum | 71 (53.8 %) | 40 (48.2 %) | – | 0.125 |
| | L2 – colon | 9 (6.8 %) | 13 (15.7 %) | – | |
| | L3 – ileum + colon | 52 (39.4 %) | 30 (36.1 %) | – | |
| | L4 – upper gastrointestinal tract (concomitant) | 6 (4.5 %) | 7 (8.4 %) | – | 0.255 |
| behaviour of disease | B1 – inflammatory | 19 (14.4 %) | 74 (89.2 %) | – | **< 0.001** |
| | B2 – stricturing | 73 (55.3 %) | 5 (6.0 %) | – | |
| | B3 – penetrating | 40 (30.3 %) | 4 (4.8 %) | – | |
| perianal disease | | 35 (26.5 %) | 8 (9.6 %) | – | **0.003** |
| preoperative medication | no medication | 17 (12.9 %) | 3 (3.6 %) | – | **0.001** |
| | biological treatment | 10 (7.6 %) | 14 (16.9 %) | – | |
| | 1 type of medication[2] | 36 (27.3 %) | 36 (43.4 %) | – | |
| | 2–3 types of medication[2] | 69 (52.3 %) | 30 (36.1 %) | – | |
| | 5–aminosalycites[3] | 86 (65.2 %) | 55 (66.3 %) | – | 0.884 |
| | immune suppressors[3] | 47 (35.6 %) | 33 (39.8 %) | – | 0.564 |
| | steroids[3] | 58 (43.9 %) | 19 (22.9 %) | – | **0.002** |
| duration of disease (years) | | 9 (5; 14) | 13 (9; 17) | – | **< 0.001** |
| time from diagnosis to surgery (years) | | 5 (2; 11) | – | – | – |

[1] P-value of Fisher's exact test for categorical variables or P-value of Mann-Whitney U test for continuous variables (significant P-value < 0.05)
[2] 5-aminosalycites, immune suppressors, steroids
[3] counted independently

and 59.6 % women. The median age of patients was 31 years of age (IQR 29–32 years).

The basic characteristics of all the groups (operated CD patients, non-operated CD patients and the healthy cohort) are included in Table 1.

Among the most commonly performed surgeries in this study was the ileocecal resection, performed in 88 of the cases. The right hemicolectomy was performed 14 times. Both the resection of stenotic anastomosis and the left hemicolectomy were performed 15 times each. The surgery was performed laparoscopically in 35 of the cases, open surgery was performed 97 times.

Side-to-side anastomosis (n = 97) prevailed over end-to-end anastomosis (n = 24). Terminal ileostomy with subtotal colectomy was performed in 11 patients.

## Results

When comparing preoperative and postoperative QoL in the operated group, we registered an improvement of the overall QoL. Postoperative improvement of QoL was detected in 104 of the operated patients (78.8 %), 2 patients

**Figure. Distribution of overall QoL score**

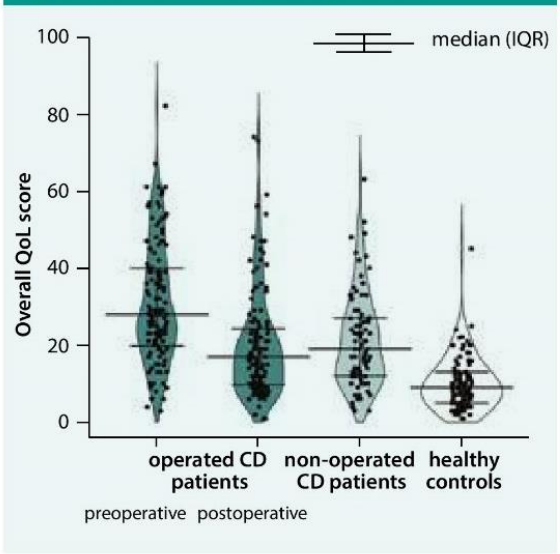


**Table 2. Preoperative and postoperative QoL in operated CD patients**

| QoL scales (N = 132) | preoperative QoL mean (± SD) | postoperative QoL mean (± SD) | P[1] | + N (row %) | no change N (row %) | – N (row %) |
|---|---|---|---|---|---|---|
| abdomen pain and discomfort | 37.9 (± 24.0) | 14.4 (± 17.0) | **< 0.001** | 107 (81.1 %) | 16 (12.1 %) | 9 (6.8 %) |
| questions about stool | 24.3 (± 23.2) | 15.7 (± 16.6) | **< 0.001** | 75 (56.8 %) | 21 (15.9 %) | 36 (27.3 %) |
| urinary functions | 6.0 (± 12.6) | 4.5 (± 9.3) | 0.152 | 24 (18.2 %) | 88 (66.7 %) | 20 (15.2 %) |
| physical functioning and body image | 48.7 (± 28.7) | 36.3 (± 25.9) | **< 0.001** | 75 (56.8 %) | 16 (12.1 %) | 41 (31.1 %) |
| sexual functions | 41.2 (± 26.1) | 27.7 (± 20.5) | **< 0.001** | 69 (52.7 %) | 46 (35.1 %) | 16 (12.2 %) |
| quality of defecation | 31.5 (± 22.3) | 20.9 (± 20.8) | **< 0.001** | 88 (66.7 %) | 26 (19.7 %) | 18 (13.6 %) |
| overall QoL | 30.7 (± 15.5) | 19.9 (± 13.8) | **< 0.001** | 104 (78.8 %) | 2 (1.5 %) | 26 (19.7 %) |

[1] P-value of Wilcoxon signed-rank test (Bonferroni correction; significant P-value < 0.007)

**Table 3. Comparison of QoL of patients before and after surgery for CD with QoL of non-operated CD patients and healthy controls**

| QoL scales | operated CD patients (N = 132) | | non-operated CD patients (N = 83) | controls (N = 104) |
|---|---|---|---|---|
| | preoperative mean (± SD) | postoperative mean (± SD) | mean (± SD) | mean (± SD) |
| abdomen pain and discomfort | 37.9 (± 24.0)[ab] | 14.4 (± 17.0)[b] | 17.9 (± 14.3)[b] | 7.0 (± 8.4) |
| questions about stool | 24.3 (± 23.2)[ab] | 15.7 (± 16.6)[ab] | 9.3 (± 11.5)[b] | 2.4 (± 4.8) |
| urinary functions | 6.0 (± 12.6) | 4.5 (± 9.3)[a] | 7.9 (± 10.4)[b] | 3.5 (± 6.4) |
| physical functioning and body image | 48.7 (± 28.7)[b] | 36.3 (± 25.9)[b] | 39.9 (± 23.0)[b] | 24.1 (± 17.9) |
| sexual functions | 41.2 (± 26.1)[b] | 27.7 (± 20.5)[b] | 31.4 (± 24.5)[b] | 17.8 (± 13.7) |
| quality of defecation | 31.5 (± 22.3)[ab] | 20.9 (± 20.8)[b] | 21.8 (± 18.1)[b] | 7.0 (± 9.0) |
| overall QoL | 30.7 (± 15.5)[ab] | 19.9 (± 13.8)[b] | 21.3 (± 12.3)[b] | 10.0 (± 6.6) |

[a] significant difference from the group 'non-operated CD patients',
[b] significant difference from the group 'controls' (P-value of Mann-Whitney U test with Bonferroni correction; significant P-value < 0.001).

**Table 4. Analysis of factors affecting overall postoperative QoL**

| factors (N = 132) | | overall postoperative QoL | | P[1] |
|---|---|---|---|---|
| | | N | mean (± SD) | |
| sex | male | 59 | 15.5 (± 10.1) | < 0.001 |
| | female | 73 | 23.5 (± 15.4) | |
| age at diagnosis | ≤ 40 | 118 | 20.3 (± 14.2) | 0.369 |
| | > 40 | 14 | 16.9 (± 10.8) | |
| age at surgery | ≤ 40 | 103 | 20.2 (± 13.6) | 0.408 |
| | > 40 | 29 | 19.0 (± 14.8) | |
| cigarette smoking | Smoker | 45 | 21.7 (± 16.5) | 0.280 |
| | Ex-smoker | 31 | 20.8 (± 11.3) | |
| | Non-smoker | 56 | 18.0 (± 12.8) | |
| location of disease | L1 – ileum | 71 | 21.0 (± 14.0) | 0.180 |
| | L2 – colon | 9 | 23.6 (± 14.0) | |
| | L3 – ileum + colon | 52 | 17.9 (± 13.6) | |
| | not L4 | 126 | 19.5 (± 13.2) | 0.344 |
| | L4 – upper GIT (concomitant) | 6 | 28.8 (± 24.0) | |
| behaviour of disease | B1 – inflammatory | 19 | 22.9 (± 14.0) | 0.339 |
| | B2 – stricturing | 73 | 18.6 (± 13.0) | |
| | B3 – penetrating | 40 | 20.8 (± 15.2) | |
| perianal disease | no | 97 | 20.2 (± 12.7) | 0.071 |
| | yes | 35 | 19.0 (± 16.8) | |
| surgical procedure | IC resection | 88 | 19.8 (± 13.4) | 0.720 |
| | right side hemicolectomy | 14 | 17.6 (± 13.0) | |
| | resection of anastomosis | 15 | 17.9 (± 10.8) | |
| | resection of left colon or rectum | 15 | 24.7 (± 19.3) | |
| anastomosis | S-t-S* | 97 | 19.2 (± 13.2) | 0.479 |
| | E-t-E** | 24 | 20.8 (± 13.6) | |
| | terminal ileostomy | 11 | 24.6 (± 19.7) | |
| surgical approach | open | 97 | 19.0 (± 13.0) | 0.194 |
| | laparoscopic | 35 | 22.5 (± 15.8) | |
| complications | no | 88 | 18.9 (± 12.8) | 0.344 |
| | yes | 44 | 22.0 (± 15.6) | |
| time from diagnosis to surgery (years) | < 5 years | 61 | 20.7 (± 13.3) | 0.651 |
| | 5–9 years | 31 | 17.4 (± 11.3) | |
| | ≥ 10 years | 40 | 20.6 (± 16.3) | |
| former operations | 0 | 75 | 20.7 (± 15.3) | 0.934 |
| | 1 | 31 | 19.3 (± 12.2) | |
| | ≥ 2 | 26 | 18.5 (± 11.3) | |
| comorbidities | no | 91 | 20.1 (± 14.5) | 0.772 |
| | at least one | 41 | 19.4 (± 12.5) | |
| preoperative medication | no medication | 17 | 19.6 (± 13.9) | 0.897 |
| | biological treatment | 10 | 21.3 (± 11.6) | |
| | 1 type of medication[2] | 36 | 20.1 (± 14.3) | |
| | 2–3 types of medication[2] | 69 | 19.7 (± 14.2) | |

[1] P-value of Mann-Whitney U test or Kruskal-Wallis test (significant P-value < 0.05);
[2] 5-aminosalycites, immune suppressors, steroids.
*S-t-S – side-to-side
**E-t-E – end-to-end

did not register any changes in their QoL (1.5 %) and the QoL decreased in 26 patients (19.7 %). A statistically relevant improvement of postoperative QoL was found in most of the observed factors – abdominal pain and discomfort, stool (frequency and content), physical condition and body image, sexual functions and quality of defecation. The only factor for which no statistically relevant difference was found were urinary functions. The comparison of preoperative and postoperative QoL is shown in Table 2.

Furthermore, the overall QoL of all 3 groups (operated CD patients, non-operated CD patients and the healthy cohort) was compared. The lowest value of QoL was recorded in CD patients before surgery. In the postoperative period, the operated CD patients had a QoL comparable to the CD patients without the need of surgery, who supposedly had a less aggressive form of CD. The healthy group clearly had the best QoL. The results were statistically significant. The comparison of the QoL of all three groups can be seen in Table 3.

A graphical representation and distribution of QoL of all three observed groups is shown in Fig.

A careful analysis of the individual factors affecting postoperative QoL was subsequently performed. All the factors included in the analysis are listed in Table 4. The only statistically significant factor affecting overall QoL was gender. A comparison of the individual components according to gender as a factor affecting postoperative QoL can be seen in Table 5. A statistically significant difference was found in the comparison of individual components, namely abdominal pain and discomfort, physical condition and body image and sexual functions.

## Discussion

Despite recently introduced new modalities of conservative treatment, including biological treatment; the results show that this has not led to a significant decrease in the number of surgical performances in CD patients and surgical treatment still plays an important and crucial role in CD therapy [22–24].

Our group of CD patients who had undergone surgery manifested a statistically significant improvement of QoL in the period of two months after the surgery. Except urinary functions, QoL improved in all the monitored factors. In 2003, Delaney et al [25] published their study of a group of 142 operated CD patients focused on postoperative QoL 30 days after surgery. They came to a similar conclusion that a surgically induced remission improved CD patients' QoL measured shortly after surgery. Other studies and review articles also showed postoperative QoL improvement [26–28]. Nevertheless, the duration and level of this QoL remains uncertain in the long term, as clinical postoperative recurrence of the disease is 55–65 % within 5 years [13,14,16,29].

When comparing all 3 studied groups (operated CD patients, non-operated CD patients and a healthy cohort), the healthy cohort had, as we originally expected, the highest QoL, as well as the best values in each particular scale (abdominal pain and discomfort, questions related to stool, urinary functions, physical condition, body image, sexual functions and quality of defecation).

The second control group consisted of CD patients who had not undergone surgical treatment during their life. We presupposed a less complicated and less aggressive progression of the disease in this group than in the operated one. When comparing this group and the group of CD patients in the preoperative period, the non-operated group had significantly higher overall QoL. A subsequent comparison of QoL of the CD patients in their postoperative period showed comparable results to the non-operated group.

In our group of operated patients, 19.7 % (n = 26) experienced a negative change in their overall QoL. This group of patients reported a decrease in all the assessed scales (except urinary functions), most of all regarding stool, physical condition and body image. We tried to focus on this group and determine the possible factors or cause of the negative perception of their postoperative state. Unfortunately, not even an extensive analysis of the individual factors showed any statistically significant results. Only the penetrating and inflammatory form of the disease along with an interval of 5–9 years between being diagnosed with CD and surgical treatment suggested a possible prediction of

**Tab. 5. Comparison of postoperative QoL between men and women**

| postoperative QoL scales | men (N = 59) mean (± SD) | women (N = 73) mean (± SD) | P |
|---|---|---|---|
| abdomen pain and discomfort | 10.3 (± 10.6) | 17.7 (± 20.3) | **< 0.001** |
| questions about stool | 13.6 (± 12.0) | 17.5 (± 19.5) | 0.118 |
| urinary functions | 3.3 (± 6.6) | 5.4 (± 10.9) | 0.067 |
| physical functioning and body image | 29.5 (± 21.9) | 41.8 (± 27.7) | **< 0.001** |
| sexual functions | 20.2 (± 17.5) | 33.8 (± 20.8) | **< 0.001** |
| quality of defecation | 15.8 (± 15.1) | 25.0 (± 23.8) | 0.113 |
| overall QoL | 15.5 (± 10.1) | 23.5 (± 15.4) | **< 0.001** |

P-value of Mann-Whitney U test (Bonferroni correction; significant P-value < 0.007)

negative postoperative QoL, however, it did not reach statistical relevance.

In our analysis of the individual factors affecting postoperative QoL, we found only one statistically significant factor which was gender. Male gender was found to be a predictor of an improvement of QoL after surgery. Tabibian et al [30] obtained similar results in their study. Their cohort consisted of 136 patients with IBD who completed a standardized QoL questionnaire, out of which 78 were CD patients. Tabibian, apart from a stronger perception of stress and more frequent relapse of CD, determined female gender as a general risk factor for lower QoL in CD patients. His results reached statistical significance.

Similarly, Stjernman et al [31] in their study of a large group of 447 CD patients demonstrated that female gender is one of the factors related to lower QoL in CD patients. As reasons for decreased QoL in women, they stated problems and dissatisfaction with body image and concerns related to an influence of the disease on their sexual life. In our subanalysis of the group of female patients (Table 5), we reached identical results, which were also statistically significant.

In 2000, Casellas et al [11] in their study determined gender as the only statistically significant factor among the basic characteristics of CD patients. Although a difference was recorded in the area of bowel symptoms and abdominal discomfort, other areas (emotional, physical and sexual) showed no difference between genders.

Furthermore, the same results were obtained in recently published studies. Magalhaes et al [32] in 2014 in his group of 150 IBD patients (92 CD patients) noted a significant decrease in QoL related to female gender. Female gender also seems to be an important factor for lower QoL in ulcerative colitis. In a Chinese cohort with 224 ulcerative colitis patients, the female patients had a decreased QoL score than male patients [33].

Some results of our analysis suggested possible predictive values of postoperative QoL, but did not reach statistical significance. For instance, cigarette smokers ($p = 0{,}280$) or patients with a location of the disease in the colon L2 ($p = 0{,}180$) inclined towards a lowered QoL, the results were, however, not statistically significant. Furthermore, another frequently mentioned factor of a decrease in the postoperative QoL is an occurrence of postoperative complications. Delaney et al [25] described a connection between worsened postoperative QoL and a higher occurrence of postoperative complications recorded in a 30-day interval after surgery. According to our results, a higher occurrence of postoperative complications was also related to a lower QoL, however, the difference was not statistically significant.

The advantages of the laparoscopic technique as opposed to open surgery are widely recognized today. They include a shorter length of hospitalization, an earlier resumption of peristalsis, lower postoperative morbidity, a lower tendency of postoperative adhesion or incisional hernia and a better cosmetic effect [34]. A positive influence of laparoscopy in comparison to open surgery on postoperative QoL of CD patients, however, was surprisingly not demonstrated [19,35,36]. These studies correlate with our results. When comparing approach of surgical treatment, no statistically significant difference in postoperative QoL was found.

## Conclusion

In our cohort, the CD patients had significantly improved QoL in the postoperative period. After that, the QoL was comparable to the group of patients with CD who did not need to undergo a surgery for CD. The best QoL was perceived by the healthy cohort. The only significant factor affecting overall QoL was gender (male gender was evaluated as a predictor of postoperative QoL improvement).

### Ethical standard statement

*All procedures which followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008.*

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# **Příloha 24** - Intraoperative use of confocal laser microscope (CLM) in pancreas surgery



profile was assessed using a 30-plex inflammatory cytokine panel. p<0.01 was considered significant.

**Results:** Regarding clinical variables smoking was most strongly associated with a negative impact on quality of life in 15 individual domains as diverse as physical functioning (p<0.001), nausea/appetite loss (p<0.001), pain (p<0.001) and body image (p<0.001).

Diabetes mellitus had no impact on quality of life. Poor nutritional status negatively impacted on global quality of life (p<0.001).

Inflammatory mediators associated with altered quality of life including Eotaxin-3, IL-16, IL-6, IL-7, IL-8, IP-10, MCP-1, MDC, MIP-1α, MIP-1β and VEGF. Only IL-6 had an impact on pain related quality of life domains including overall pain (p<0.001), pancreatic pain (p<0.001) and night pain (p<0.001).

There was no link between smoking and increased levels of these inflammatory mediators.

**Conclusion:** A pro-inflammatory profile in the serum of patients with chronic pancreatitis is associated with a poorer quality of life and appears independent of key clinical variables.

Further work is needed to define the source of these mediators and their relationship to the pathological processes in chronic pancreatitis.

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**Abstract ID: 1929.**

**Inflammation and ageing in chronic pancreatitis: A single centre preliminary prospective cohort study**

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**Introduction:** Accelerated biological ageing is a recognised feature of many chronic diseases and is often associated with a low grade inflammatory state. Whether accelerated ageing exists as a phenomenon in chronic pancreatitis and the characteristics of this have not been clearly defined.

**Aims:** To determine if chronic pancreatitis is associated with an ageing phenotype and, if so, the phenotypic characteristics of this.

**Patients & methods:** 76 patients with chronic pancreatitis and 26 healthy controls were recruited to this study. Their comorbidity, medication use, smoking status and physical characteristics were recorded.

Blood was taken for routine clinical analysis as well as serum, plasma and leukocyte DNA for laboratory investigation. The serum cytokine profile was determined using a 30-plex panel. p<0.05 was considered significant.

**Results:** There was no difference in age between the groups (53vs.57 years p=0.552) although there were more males in the chronic pancreatitis group (68%vs.31% p=0.001). More patients in the pancreatitis group were smokers (55%vs.15%; p<0.0001) and were diabetic (53%vs.19%; p<0.0001).

In regard to physiological function patients in the chronic pancreatitis group were more likely to have respiratory comorbidity (41%vs.12%; p=0.005) and had a higher modified frailty index score (1.4vs.0.4 p<0.0001).

There was evidence of a chronic inflammatory state in chronic pancreatitis with a higher baseline CRP (10.1vs.5.9 p<0.05) and higher concentrations of the pro-inflammatory cytokines Eotaxin and IL-8.

**Conclusion:** Preliminary evidence would suggest chronic pancreatitis is related to an ageing phenotype. This warrants further characterisation and could probably be improved by focused targeting of patient's comorbidity and risk taking behaviours e.g. smoking.

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**Abstract ID: 1934.**

**Microbiopsies from pancreatic cysts - a novel approach to obtain a preoperative diagnosis**

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**Introduction:** Pancreatic ductal adenocarcinoma may develop from cystic lesions such as intraductal papillary mucinous neoplasms (IPMN). Controversy in regards to resection arises when cystic lesions without apparent malignancy are discovered by imaging. However, IPMN have a characteristic histomorphology and harbor mutations in genes regulating cell growth and DNA repair. Integrating molecular pathology with the existing clinical algorithm may prevent unnecessary surgery.

**Aims:** To test if 1) it is possible to obtain a microbiopsy from a pancreatic cyst, 2) to make sure the microbiopsy offers sufficient tissue for histology, immunohistochemistry (IHC) and Next Generation Sequencing (NGS).

**Patients & methods:** Five patients with pancreatic cystic lesions referred for endoscopic ultrasound and fine needle aspiration. Microbiopsies of the cystic lesions were performed, using the Moray microbiopsy forceps. The biopsies were processed for histology, and IHC staining for MUC1, MUC2, MUC6, MUC5AC, and CDX2. The biopsies were classified according to the WHO classification. Subsequent examination by NGS, using the Ion AmpliSeq Cancer Hotspot Panel v2 (Life Technologies), was performed.

**Results:** All patients had one or more adequate biopsies for histology, IHC, and NGS-analysis. All cases were classified as IPMN of pancreatobiliary subtype with low grade dysplasia. GNAS and concomitant KRAS mutations, specific of IPMN, were identified in two out of five cases, and one patient had GNAS and BRAF mutation.

**Conclusion:** The microbiopsy offered adequate tissue for histology, IHC, and NGS-analysis, and contributed with additional diagnostic information with regards to subtype of IPMN, inclusive mutational profiling.

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**Abstract ID: 1935.**

**Intraoperative use of confocal laser microscope (CLM) in pancreas surgery**

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**Introduction:** CLM is a method allowing microscopic imaging of the examined tissue in real time, and de facto implementation of non-invasive in vivo biopsy. Use in clinical practice is a relatively new thing.

**Aims:** We introduced CLM in pacreas surgery in year 2015. Our aim was to confirm theory, that it could be new method, which can help us with intraoperative resolution between healthy and diseased tissue of pancreas and bile duct.

**Patients & methods:** In years 2015 and 2016 intraoperative CLM examination was performed in all patient who underwent hemipacreatoduodenectomy. Gained results were evaluated by surgeon during the operation, then record and compared with cryobiopsy and final biopsy

**Results:** We can now reliably distinguish structures of healthy bile duct, acini and adipocytes of healthy pancreas, multiplied blood vessels and lymphatics of patologically changed tissue.

**Conclusion:** CLM is a developing method for diagnosis of various gastroinetstinal disorders. Demonstrably increases the yield of conventional endoscopy. Our initial experiences suggests that CLM could be beneficial also in the intraoperative use in pancreas surgery.

**Příloha 25** - Konfokální laserová mikroskopie v diagnostice onkologických onemocnění gastrointestinálního traktu



# Konfokální laserová mikroskopie v diagnostice onkologických onemocnění gastrointestinálního traktu

## Confocal Laser Endomicroscopy in the Diagnostics of Malignancy of the Gastrointestinal Tract

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**Souhrn**

Při konfokální laserové mikroskopii (confocal laser endomicroscopy – CLE) se užívá druh optického mikroskopu, který využívá jako zdroj světla laserový paprsek a zpracovává získaný obraz pomocí procesorové jednotky. Princip přístroje je znám již od roku 1957, nicméně až technický rozvoj v poslední době umožnil jeho reálné využití v klinické praxi. V rámci diferenciální diagnostiky je tak CLE relativně novou modalitou umožňující mikroskopické zobrazení vyšetřované tkáně v reálném čase, a tím *de facto* provádění neinvazivní *in vivo* biopsie. První zkušenosti s CLE byly získány především na poli endoskopickém, a to především v oblasti patologie jícnu, žaludku, žlučových cest, pankreatu a tlustého střeva. V posledních letech se taktéž rozvíjí neendoskopické peroperační použití, kde nejvíce zkušeností bylo prozatím získáno v oblasti neurochirurgie, chirurgie mammární a chirurgie prostaty. V rámci četných prospektivních randomizovaných studií byl potvrzen přínos CLE při sledování premalignit, v diferenciální diagnostice nádorových či zánětlivých onemocnění, ve zrychlení diagnostiky a ve snížení počtu endoskopických vyšetření. Použití CLE je navíc zatíženo pouze minimálním množstvím potenciálních nežádoucích účinků. Rizikem je možná alergie na fluorescein, který je během vyšetření užíván k barvení tkání. Prodloužení endoskopického vyšetření či operace je v rukou zaškoleného personálu minimální. Limitujícími faktory CLE jsou prozatím nedostatečné klinické zkušenosti, cena přístroje a používaných sond, subjektivní složka při hodnocení mikroskopického obrazu endoskopistou či chirurgem. Cílem této přehledové práce je shrnutí dosud publikovaných studií o užití CLE v diagnostice onkologických onemocnění gastrointestinálního traktu.

**Klíčová slova**

konfokální mikroskopie – gastrointestinální trakt – nádory

Autoři deklarují, že v souvislosti s předmětem studie nemají žádné komerční zájmy.

The authors declare they have no potential conflicts of interest concerning drugs, products, or services used in the study.

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**Summary**

In confocal laser endomicroscopy (CLE), a type of optical microscope that uses a laser beam as its light source and processes the acquired image by processor unit is used. Although the principle behind the device has been known since 1957, its use in clinical practice has only recently been enabled by technical developments, and it is therefore a relatively new modality in differential diagnosis. CLE enables real-time microscopic imaging of the tissue under investigation and in fact non-invasive *in vivo* biopsy. First experiences with CLE have primarily been obtained in the field of endoscopy, in particular in the pathology of the esophagus, stomach, bile duct, pancreas, and colon. Further to its use in endoscopy, CLE was recently developed for perioperative use, with the most experience gained in neurological, breast, and prostate surgery. Numerous prospective randomized trials have confirmed the benefits of CLE in tumor screening, differential diagnosis of tumors or inflammatory diseases, earlier diagnostics of diseases, and reducing the number of required endoscopic examinations. In addition, CLE is associated with minimal side effects. A known possible side effect is allergy to the fluorescein used to stain tissues during the examination. Extending of endoscopic examination or surgery is minimal in the hands of trained personnel. Current limiting factors of CLE include insufficient clinical experience, the price of the CLE device and probes, and the subjectivity inherent in the evaluation of microscopic images by the endoscopist or surgeon. This article summarizes published studies of CLE in the diagnostics of oncological diseases of the gastrointestinal tract.

**Key words**

confocal microscopy – gastrointestinal tract – neoplasms

## Úvod

Idea konfokální laserové mikroskopie (confocal laser endomicroscopy – CLE) je známa již téměř 60 let. V roce 1957 byla patentována americkým matematikem Marvinem L. Minskym, který ale plně funkční mikroskop v době podání patentu nebyl schopen sestrojit pro absenci dostatečně silného zdroje světla [1]. Rovněž čeští vědci se podíleli na jejím rozvoji. Petráň a Hadravský z Lékařské fakulty UK v Plzni patentovali konfokální mikroskop (Tandem Scanning Confocal Microscope), se kterým byly historicky poprvé získány kvalitní optické řezy silným preparátem – mozkovou tkání [2,3]. Přes tyto dílčí úspěchy nebyla CLE příliš využívána, především pro složitost zpracování získaného obrazu. K jejímu rozvoji došlo v 80. letech minulého století s pokrokem výpočetní techniky. Využití v klinické praxi je reálně možné od roku 2004, kdy byl firmou Pentax vyvinut endoskop s konfokálním laserovým mikroskopem. Širší zavedení do praxe poté umožnila konstrukce CLE sond firmy Manua Kea technologies.

## Princip fungování CLE

Konfokální laserový mikroskop je druh optického mikroskopu, který jako zdroj světla užívá monochromatický nízkoenergetický laserový paprsek. Ten je směřován soustavou clon, zrcadel a objektivem na vyšetřovanou tkáň. Po ní je posouván bod po bodu pomocí rastrovacího zařízení. Odražené paprsky jsou pak dichromatickým zrcadlem směřovány na bodovou clonu, která odfiltruje světlo odražené z jiných vrstev sledovaného preparátu. Snímaný obraz tak pochází pouze z jedné roviny vyšetřované tkáně a všechny body výsledného obrazu jsou tedy konfokální – mají společné ohnisko. Definitivní obraz je složen pomocí procesorové jednotky. K adekvátnímu zobrazení tkání je nutné užití barviva, které zvyšuje fluorescenční schopnost lidské tkáně [4,5].

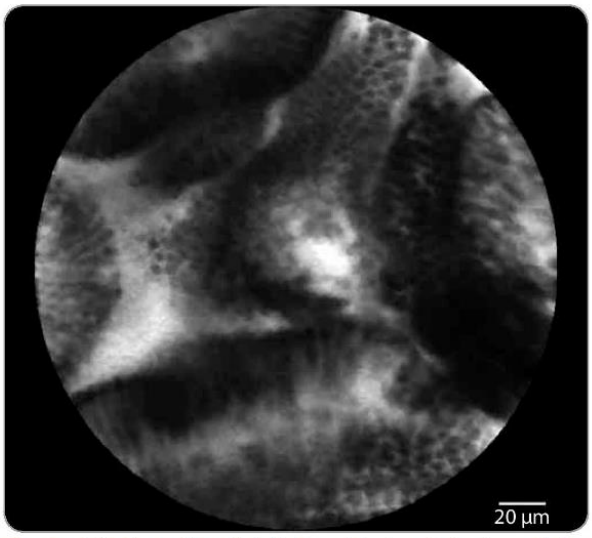
## Přístroje k provádění CLE

V praxi jsou nyní používány dva typy přístrojů umožňující CLE – endoskop firmy Pentax (endoscope based CLE – eCLE) a přístroj Cellvizio firmy Manua Kea technologies s CLE sondami (probe based CLE – pCLE) [6,7].

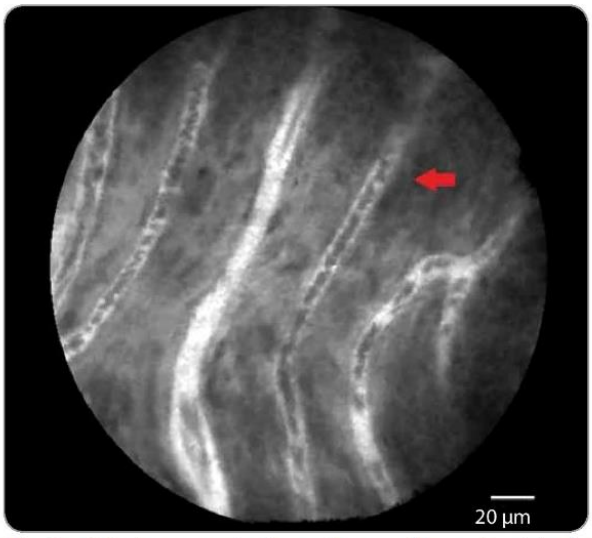
eCLE užívá mikroskop zabudovaný v běžném endoskopu průměru 12,8 mm, jehož koncová část je vzhledem k vestavěnému CLE rigidní a je prodloužena o 5 cm. Tento typ CLE lze užít k vyšetření horních i dolních partií gastrointestinálního traktu. Vzhledem k velikosti je nevhodný pro vyšetřování pankreatobiliárních struktur. Výhodou je možnost opakovaného užití.

pCLE využívá ke snímání mikroskopického obrazu sondy velikostně kompatibilní s pracovním kanálem běžných endoskopů. K dispozici je několik typů sond, pomocí kterých lze vyšetřovat trávicí trakt, dýchací cesty či urotrakt. Průměr a délka sond se liší v závislosti na způsobu užití. Nevýhodou sond je jejich životnost limitovaná počtem použití – 10× (AQ-Flex, Cholangioflex) a 20× (Colo/GastroFlex). Ač se v praxi nadále užívají oba typy CLE, komerčně dostupným nyní zůstal pouze přístroj Cellvizio (obr. 1). Další část článku bude tedy pojednávat o klinických zkušenostech s pCLE.


**Obr. 1. Přístroj Cellvizio.**




Obr. 2. pCLE obraz – intraduktální papilární mucinózní neoplazie.




Obr. 3. pCLE obraz – serózní cystadenom, síť povrchových cév (červená šipka).

## Praktické užití

Provádění pCLE je uživatelsky nenáročné. Spuštění a kalibrace přístroje trvá přibližně 3 min a je plně intuitivní. Průběh mikroskopického vyšetření poté závisí na zkušenostech endoskopisty či chirurga, který jej provádí. Při dostatečném zaškolení a standardizaci vyšetřovacího procesu prodlužuje výkon přibližně o 5–10 min. Před prováděním mikroskopie je nutné pacientovi aplikovat barvivo zvyšující fluorescenční schopnosti tkání. Nejčastěji užívaným a výrobcem doporučeným barvivem je fluorescein (Fluorescite® inj. sol 100 mg/ml) podávaný intravenózně v dávce 2,5–5 ml. Jeho výhodou je, že není toxický, rychle se distribuuje do tkání a dobře zobrazuje cévní struktury. Jiná speciální příprava pacienta není nutná. Samotné pCLE vyšetření je neinvazivní a nezvyšuje tak riziko již prováděné endoskopie či operace. Potenciálním rizikem je možná alergie na fluorescein. Většina zaznamenaných reakcí po intravenózním podání jsou však reakce méně závažného typu a zahrnují nauzeu, přechodnou hypotenzi, erytém v místě žilního vstupu či vyrážku. Bylo zaznamenáno i několik vzácných případů závažných reakcí ve smyslu anafylaxe, infarktu myokardu či šoku. Studie zaměřená na bezpečnost intravenózního užití fluoresceinu prováděná na 2 272 pacientech potvrdila výskyt středně závažné reakce u 1,4 % pacientů a nezaznamenala žádný případ závažné reakce [8]. Vedlejším efektem podání fluresceinu je žluté zbarvení sliznic a kůže, které odezní do 12 hod po aplikaci, a výrazně žluté zbarvení moči odeznívá do cca 36 hod [9].

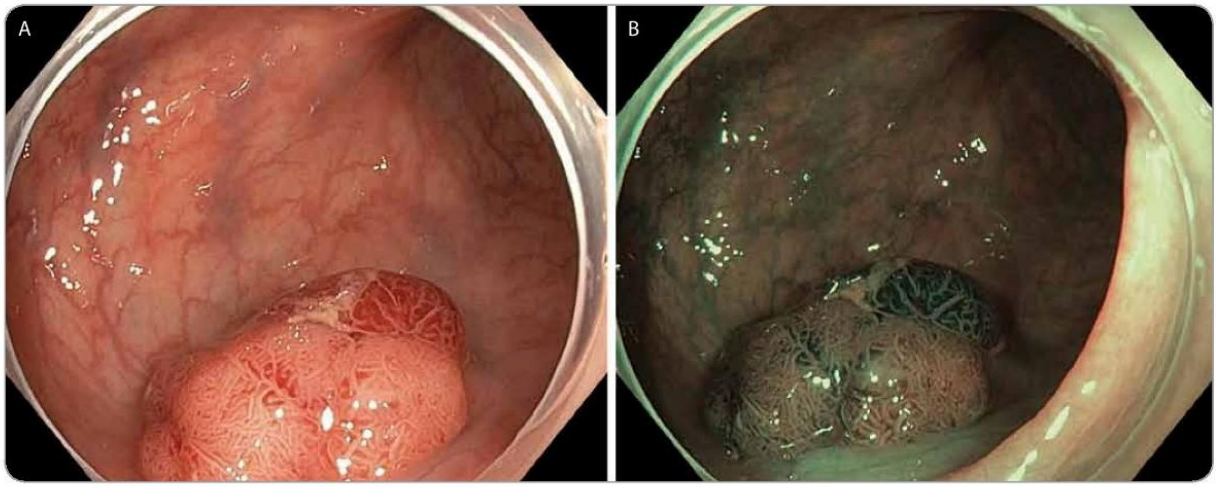
Vlastní mikroskopické vyšetření je prováděno přiložením sondy na povrch vyšetřované tkáně. Dle typu sondy je snímán obraz průměru 240–325 µm s rozlišením 1–3,5 µm. Přehrávání obrazu probíhá okamžitě na připojeném monitoru. Zaznamenávat je možno celé vyšetření či pouze jeho požadované části, a to buď ve formě videa, či fotografií. Ty lze přímo vytisknout na připojené tiskárně či ukládat v digitální formě v běžně užívaných PAC systémech (picture archiving and communicating system – PACS), s kterými je přístroj plně kompatibilní.

Hodnocení získaného mikroskopického obrazu vyžaduje od vyšetřujícího lékaře nabytí postupných zkušeností s tímto zobrazením tkání a taktéž se standardními histologickými obrazy [10]. Možné je rovněž porovnání získaného mikroskopického obrazu s již vytvořenou databází jednotlivých patologií dostupnou jak v přístroji, tak on-line na www.cellvizio.net. Vzhledem k možnosti archivace v PACS lze výsledky hodnotit taktéž zpětně či lékařem jiné odbornosti – např. histopatologem.

## Endoskopické zkušenosti s pCLE

### Barretův jícen

Standardem při gastroskopickém vyšetření je používání endoskopu s kvalitním obrazem (high resolution endoscopy) a zobrazením pomocí bílého světla (white light endoscopy – WLE). Dále je využívána virtuální chromoendoskopie (VCE), např. NBI (narrow band imaging) od firmy Olympus či FICE (Fuji inteligent color enhancement) od firmy Fujifilm [11]. Při chromoendoskopii je obraz modifikován pomocí optického filtru nebo digitálního postprocessingu, s cílem objevení nativně neviditelných lézí či rozlišení benigní léze od neoplastické [12]. Při vyšetření Barretova jícnu je odebírána systematicky biopsie z postižené oblasti jícnu, a to vždy po 2 cm ze čtyř kvadrantů a cíleně z každé suspektní makroskopické abnormality [13,14]. Nevýhodou při odběru četných biopsií bývá krvácení, které ztěžuje přesný odběr dalších vzorků. Limitujícím faktorem pro stanovení diagnózy malignity je také nízký diagnostický výnos z celkového počtu odebraných biopsií, který se pohybuje kolem 6 % [15]. Multicentrická studie DONT BIOPCE z roku 2011 prokázala na souboru 101 pacientů, že rozpoznání intestinální metaplazie při kombinovaném vyšetření WLE a pCLE dosahuje senzitivity až 68 vs. 34 % při samotné WLE. Při




**Obr. 4. Tubulovilozní adenom LGD v kolon sigmoideum, NICE typ 2.**
A – bílé světlo, B – NBI

použití WLE, pCLE a NBI je pak senzitivita až 76 % [16].

### Pankreatické cysty

Za nejpřínosnější diagnostickou modalitu při diferenciální diagnostice cystických lézí pankreatu je v současné době považována endoskopická ultrasonografie (EUS) v kombinaci s tenkojehlovou biopsií (fine needle aspiration biopsy – FNAB) [17]. Přesnost samostatné EUS v diferenciální diagnostice mucinózních (maligních či potenciálně maligních) a non-mucinózních cyst pankreatu je přibližně 50 %, v kombinaci s FNAB pak až 80 % [18]. Vzhledem k rozměrům sondy AQ-Flex je možno její užití přes bioptickou jehlu velikosti 19 G (gauge). V literatuře je toto vyšetření označováno jako needle confocal laser endomicroscopy (nCLE). Prospektivními studiemi Contact, Inspect a Detect byla stanovena charakteristická kritéria pCLE obrazu některých cystických lézí pankreatu. Studie INSPECT z roku 2012 (65 pacientů) popsala typický obraz vilózních epiteliálních struktur charakteristický pro intraduktální papilární mucinózní neoplazii (IPMN) (obr. 2), vyšetření prokázalo vysokou specificitu – 100 %, limitem však byla nižší senzitivita – 59 % [19]. Studie CONTACT z roku 2014 na 31 pacientech stanovila charakteristický obraz serózního cystadenomu se zobrazenou povrchovou sítí vlásečnic, nevyskytující se u ostatních cystických lézí (obr. 3). Senzitivita vyšetření dosáhla 69 %, specificita pak byla 100 % [20]. Ve studii DETECT z roku 2015 (30 pacientů) bylo prováděno vyšetření cystických lézí pankreatu pomocí nCLE a EUS navigované cystoskopie – senzitivita při rozlišení maligních cyst byla u EUS – cystoskopie 90 %, u nCLE 80 %, kombinované vyšetření pak poskytovalo 100% senzitivitu [21].

### Stenózy žlučových cest

Pacienti s podezřením na maligní stenózu žlučových cest jsou standardně došetřováni pomocí endoskopické retrográdní cholangiopankreatikografie (ERCP) s odběrem cytologie (brushing) a biopsie z oblasti stenózy. Senzitivita cytologického vyšetření je nízká a pohybuje se v rozmezí 18–60 % [22,23]. V případě diagnostické nejistoty jsou třeba opakované ERCP s rebiopsií. Pokud tyto nejsou úspěšné a podezření na maligní stenózu na podkladě klinických a paraklinických vyšetření trvá, pacienti jsou indikováni k resekčnímu výkonu. U pacientů operovaných pro podezření na maligní stenózu je až v 15 % malignita definitivní histologií vyloučena [24]. V prvním případě jsou tedy pacienti zatíženi opakovaným invazivním endoskopickým vyšetřením a rizikem prodlení s možností generalizace nádorového onemocnění, ve druhém naopak riziky spojenými s často rozsáhlým operačním výkonem. Prospektivní multicentrická studie FOCUS z roku 2015 hodnotila, zda se změní senzitivita, specificita či přesnost v případě kombinace ERCP s biopsií a pCLE. Hodnoceno bylo 112 pacientů v šesti centrech. Porovnávány byly výsledky ERCP, ERCP + pCLE, ERCP + biopsie + pCLE. Senzitivita samostatné biopsie byla pouze 56 %, specificita 100 % a přesnost 72 %. V případě stanovení diagnózy na podkladě obrazu ERCP a pCLE byla pak senzitivita 89 %, specificita 71 % a přesnost 82 %. Použití pCLE tedy přispívá ke zpřesnění diferenciální diagnostiky biliárních stenóz, zvyšuje pravděpodobnost rozpoznání malignity [25].

### Kolorektální karcinom, prekancerózy kolorekta

Standardním ošetřením prekanceróz a časných karcinomů oblasti kolorekta je endoskopická mukózní resekce (EMR), při které se drobnější léze do průměru 20 mm odstraňují *en bloc*, větší jsou resekovány po částech (piecemeal, tedy metodou označovanou EPMR). Léze podezřelé z povrchové submukózní invaze je možné odstranit endoskopickou submukózní disekcí (ESD) [26]. Předpokladem úspěšné EMR či ESD je predikce hloubky nádorové invaze. K tomuto účelu je využívána NICE (NBI International Colorectal Endoscopic) klasifikace [27]. Ta na základě NBI hodnotí barvu, strukturu cév a povrch neoplazie (obr. 4A, B). Následně je dle typu NICE klasifikace možné předurčit histologii dané léze [28].

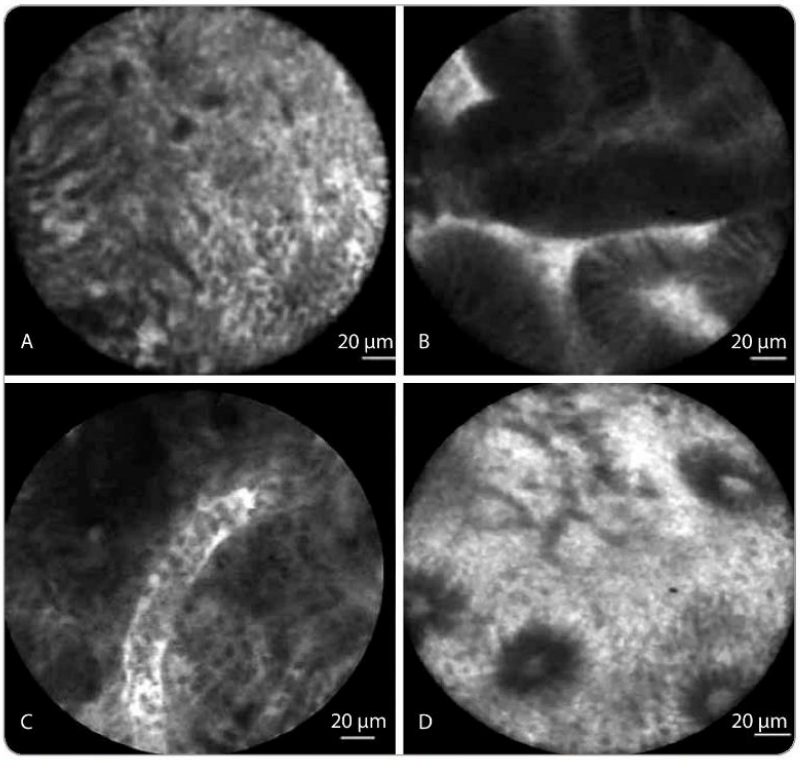
Ačkoli cílem EMR je úplné odstranění patologické léze, reziduální nádorová tkáň se nachází až u 23 % pacientů [29]. Prospektivní studie z roku 2012 se zaměřila na využití pCLE při sledování reziduálního tumoru po endoskopické mukózní resekci. Do studie bylo zařazeno 92 pacientů, kteří podstoupili kontrolní kolonoskopické vyšetření po provedené EMR. Bylo vyšetřeno 129 jizev po EMR, přičemž reziduální neoplazie byla potvrzena ve 29 případech (22 %). Senzitivita pCLE v kombinaci s HRE-VCE (high resolution endoscopy with virtual chromoendoscopy) byla 100 vs. 72 % u samostatného HRE-VCE [30].

## Chirurgické zkušenosti s pCLE

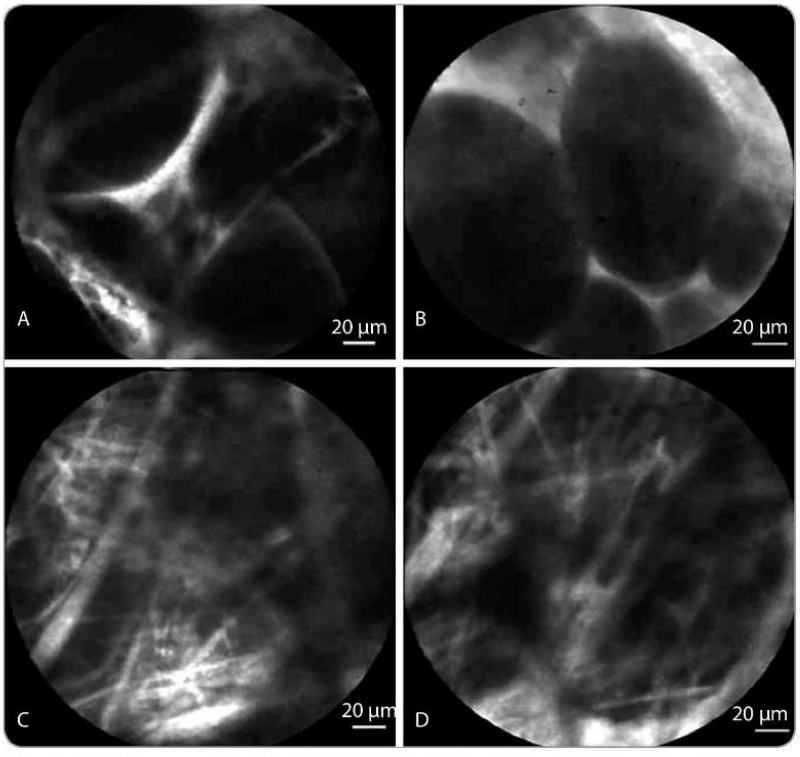
Neendoskopické peroperační vyšetření tkání pomocí endoskopu Pentax bylo z technického hlediska velmi obtížné až nereálné. Konstrukce sond mikroskopu Cellvizio však nově umožňuje jejich vcelku komfortní užití i bez endoskopu během operace. Je tak možno vyšetřit tkáně nedostupné endoskopem. Při nasycení tkání podaným fluoresceinem či topickém obarvení indocyaninovou zelení je taktéž možno provést *ex vivo* vyšetření na resekátu [31]. Chirurgové si teoreticky možný přínos pCLE v posledních letech uvědomili a hledají cestu k jeho využití. Nejvíce zkušeností je prozatím v oblasti mammární chirurgie [32,33], neurochirurgie [34,35] a chirurgie prostaty [36]. První zkušenosti jsou získávány i na českých pracovištích. Na chirurgickém pracovišti FN Brno je pCLE využívána v pankreatobiliární chirurgii. Již byly prezentovány retrospektivně hodnocené výsledky z pCLE vyšetření pacientů, kteří podstoupili resekční výkon na slinivce břišní pro tumor a byl stanoven charakteristický obraz patologicky změněné a zdravé tkáně pankreatu a žlučovodu (obr. 5, 6) [37].

## Závěr

Získání mikroskopického obrazu vyšetřované tkáně v reálném čase neinvazivním způsobem je cesta, která nabízí potenciální zrychlení diagnostiky prekanceróz či maligních onemocnění gastrointestinálního traktu, snížení počtu prováděných endoskopií a biopsií, menší psychickou i fyzickou zátěž




**Obr. 5. pCLE obrazy – zdravý choledochus (A, B), patologicky změněný choledochus (C, D).**




**Obr. 6. pCLE obrazy – zdravý pankreas (A, B), patologicky změněný pankreas (C, D).**

pacientů. Četné studie potvrdily přínos pCLE v oblasti endoskopické, a to především v kombinaci s již běžně užívanými vyšetřovacími modalitami. Slibným se zdá též využití peroperační neendoskopické. Taktéž naše zkušenosti s tímto přístrojem v oblasti pankreatobiliární chirurgie potvrzují, že jeho užitím lze získat validní informace o mikroskopické struktuře tkání. V podstatě okamžité rozlišení zdravé či patologické tkáně může doplnit běžně peroperačně odebíranou kryobiopsii a být tak dalším z vodítek pro indikaci či odmítnutí radikální chirurgické léčby.

Limitujícími faktory pCLE jsou nedostatečné rozšíření v klinické praxi, cena přístroje a používaných sond, subjektivní složka při hodnocení mikroskopického obrazu endoskopistou či chirurgem. I přes tyto faktory celkový počet užívaných přístrojů i prováděných pCLE vyšetření postupně narůstá, zdá se tedy, že přínos pCLE převažuje nad těmito dílčími nevýhodami. Příslibem k jeho dalšímu rozšíření jsou navíc nové směry užití pCLE a nové možnosti zpracování získaných mikroskopických obrazů pomocí výpočetní techniky.

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**Příloha 26** - Confocal laser endomicroscopy in the diagnostics of esophageal diseases: a pilot study



# Confocal laser endomicroscopy in the diagnostics of esophageal diseases: a pilot study

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**Background:** Probe-based confocal laser endomicroscopy (pCLE) is a novel diagnostic technique for endoscopy which enables a microscopic view at a cellular resolution in real-time. Endoscopic detection of early neoplasia in the distal esophagus is difficult and often these lesions can be missed. The aim of the pilot study was to obtain characteristic pCLE figures in esophageal diseases for following studies, and to evaluate the possible future role of pCLE in the diagnostics of dysplastic Barrett's esophagus (BE) or early esophageal adenocarcinoma (EAC). **Methods:** A review of the current literature was performed and previously published pCLE images and classifications of esophageal diseases were searched and studied first. In phase two of the pilot study patients with esophageal diseases such as reflux esophagitis, BE and EAC were enrolled and scheduled for upper endoscopy with pCLE. A healthy cohort was also included. **Results:** From January 2019 to July 2019, a total of 14 patients were enrolled in this prospective pilot study: 3 patients with reflux esophagitis, 4 with BE, 3 with EAC and 4 persons were included in the healthy cohort. The endoscopy with pCLE was performed and characteristic pCLE figures were obtained. The correct diagnoses based on real-time pCLE were evaluated by an endoscopist in 11 of the 14 cases (78.6 %). **Conclusion:** It was possible to obtain typical pCLE images of esophageal diseases during a standard cap-assisted endoscopic procedure. pCLE seems to be a feasible new technique in BE surveillance and early neoplastic lesion detection. However, more studies and data on larger number of patients are needed.

**Key words:** Barrett's esophagus, confocal laser endomicroscopy, esophageal cancer, esophagitis.

## Konfokální laserová endomikroskopie v diagnostice onemocnění jícnu: pilotní studie

**Úvod:** Konfokální laserová endomikroskopie využívající sondy (probe-based confocal laser endomicroscopy – pCLE) je nová diagnostická metoda určená pro endoskopii, která umožňuje mikroskopické vyšetření na buněčné úrovni v reálném čase. Endoskopická diagnostika časných neoplastických lézí distálního jícnu není snadná a často tyto léze mohou být přehlédnuty. Cílem pilotní studie bylo získat charakteristické pCLE obrazy u onemocnění jícnu pro další studie a vyhodnotit možnou roli pCLE v diagnostice dysplastického Barrettova jícnu (Barrett´s esophagus – BE) a časného adenokarcinomu jícnu (esophageal adenocarcinoma – EAC). **Metody:** Nejprve byl vyhledán přehled současné literatury s následným nastudováním předchozích publikací obsahující pCLE obrazy a jejich klasifikací u onemocnění jícnu. V druhé fázi byli do této pilotní studie zařazeni pacienti

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s onemocněním jícnu, kteří podstoupili horní endoskopické vyšetření s pCLE. Zařazena byla i zdravá kohorta osob. **Výsledky:** Od ledna roku 2019 do července roku 2019 bylo vyšetřeno celkem 14 pacientů v rámci této prospektivní pilotní studie: 3 pacienti s refluxní ezofagitidou, 4 s BE, 3 s EAC a 4 zdravé osoby. Byla provedena endoskopie s pCLE a získány charakteristické pCLE obrazy. Správná diagnóza byla endoskopistou stanovena pomocí pCLE (real-time) celkem u 11 ze 14 vyšetřených pacientů (78,6 %). **Závěr:** Bylo možné získat typické pCLE obrazy u onemocnění jícnu během standardní endoskopie s využitím capu. pCLE se zdá být novou slibnou metodou k surveillance BE a detekci časných neoplastických lézí. Na druhou stranu je zapotřebí více dalších studií a dat na větším souboru pacientů.

**Klíčová slova:** Barrettův jícen, ezofagitida, konfokální laserová endomikroskopie, nádory jícnu.

## Introduction

Probe-based confocal laser endomicroscopy (pCLE) is a new diagnostic technique for endoscopic use. pCLE provides a microscopic view at a cellular resolution in real-time. Barrett's esophagus (BE) is considered as a premalignant condition for esophageal adenocarcinoma (EAC). Although the risk of cancer progression from nondysplastic BE is quite low (0.12–0.5 % per year) (1, 2), patients with BE are managed with endoscopic surveillance. According to the European society for gastrointestinal endoscopy (ESGE) guidelines, the patient should undergo high-definition white-light endoscopy (HD-WLE) with targeted biopsies from every visible lesion and random four-quadrant biopsies every 2 cm (3).

Unfortunately, endoscopic detection of early neoplasia is difficult and these lesions can often be missed (4). Moreover, EAC risk is significantly higher in dysplastic BE and the risk increases from 6 % up to 13 % annually (4–6).

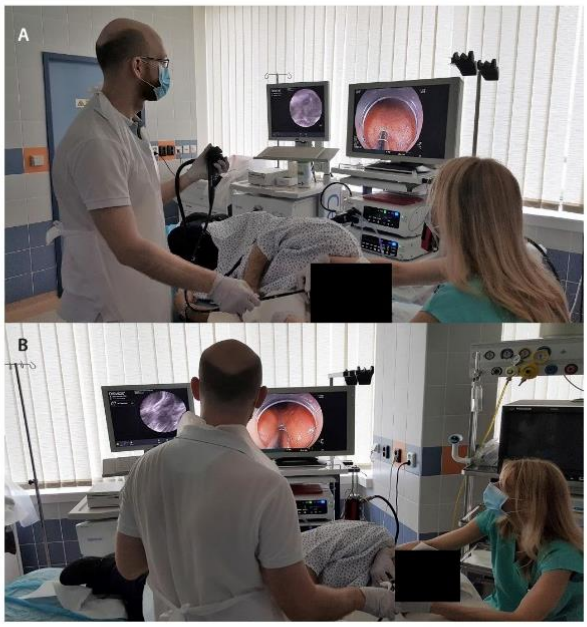
pCLE as a novel endoscopic technique enables real-time microscopic imaging of the mucosal tissue, and may play an important role in future diagnostics of dysplastic BE or early EAC.

## Methods

A review of the current literature about pCLE in esophageal diseases was carried out first. Then the pCLE images from previously published articles, classifications and criteria for pCLE were studied (Miami classification for BE published by Wallace, with the addition of the description for low-grade dysplasia (LGD) by di Pietro and for high-grade dysplasia (HGD) by Gaddam (7–9).

From January 2019 to July 2019, a total of 14 patients were enrolled into this prospective pilot study. The study protocol was approved by the ethical committee of University Hospital Brno and all patients signed the informed consent. The healthy cohort consisted of volunteers from the medical students. Midazolam was used for sedation. A half dose of Fluorescite® (2.5 ml) with 8 ml of saline solution as a contrast agent was used. The cap was placed at the end of the endoscope before the examination. During the endoscopic procedure we used the GastroFlexTM UHD confocal probes connected to a Cellvisio® system (fig. 1a, 1 b). The patients underwent a standard upper endoscopy, the esophagus and gastroesophageal junction were also carefully examined using high definition Fujifilm® endoscopes with white light endoscopy, blue light imaging (BLI), linked color imaging (LCI) and then by pCLE (fig. 2a, 2 b). Biopsies were taken from every area investigated by pCLE, and pCLE videos were later

**Fig. 1a, 1b.** *Position of the endoscopic tower Fujifilm® and the Cellvisio endoscopy system® including the laser scanning unit and display (Mauna Kea Technologies, Paris, France) during the endoscopic procedure*




**Tab. 1.** *Baseline characteristics of patients (n = 14)*

| Variable | Total (n = 14) | Healthy cohort (n = 4) | Reflux esophagitis (n = 3) | Barrett´s esophagus (n = 4) | Esophageal adenocarcinoma (n = 3) |
|---|---|---|---|---|---|
| Male/female | M: 10/F: 4 | M: 3/F: 1 | M: 2/F: 1 | M: 2/F: 2 | M: 2/F: 1 |
| Age (average) | 45.8 | 25.3 | 39.0 | 54.3 | 70.5 |
| BMI (average) | 26.2 | 24.8 | 27.9 | 25.9 | 26.8 |
| Smoking | Y: 3/E: 3/N: 8 | Y: 0/E: 0/N: 4 | Y: 2/E: 0/N: 1 | Y: 1/E: 1/N: 2 | Y: 0/E: 2/N: 1 |
| PPI users | Y: 7/N: 7 | Y: 0/N: 4 | Y: 2/N: 1 | Y: 4/N: 0 | Y: 1/N: 2 |
| Hiatal hernia | Y: 4/N: 10 | Y: 0/N: 4 | Y: 2/N: 1 | Y: 1/N: 3 | Y: 1/N: 2 |

*Y – yes, N – no, M – male, F – female, BMI – body mass index, PPI – proton pump inhibitor, E – ex-smoker*

correlated with the histopathologic findings (by a histopathologist and an endoscopist independently, and in phase two by a histopathologist and an endoscopist together). The aim of the pilot study was to obtain basic microscopic images of a healthy esophagus, esophagitis, BE and EAC.

## Results

A total of 14 patients were enrolled in the study and underwent an upper endoscopy with pCLE, of which 10 patients were male and 4 were female. The average age was 45.8 years and the mean BMI was 26. 2. The following diagnoses were endoscopically identified and later confirmed by histopathology results: 3 patients with reflux esophagitis, 4 with BE (3 patients with intestinal metaplasia (IM), 1 patient with LGD), 3 patients with EAC and 4 persons were included in the healthy cohort. Half of the patients were current users of proton pump inhibitors, 3 patients were smokers, 3 patients were ex-smokers, and in 4 patients hiatal hernia was present among the endoscopic findings. The baseline characteristics of the patients can be seen in table 1.

The upper endoscopy examination was followed by pCLE. No adverse effects were observed after the application of the contrast agent. Videos were recorded during all of the pCLE procedures. Every video record was evaluated during the endoscopy, and then re-evaluated with a final histopathology result according to each diagnosis of reflux esophagitis, BE (IM, LGD), EAC, and also in the healthy cohort.

In a healthy esophagus we observed these pCLE images: normal squamous epithelium which appears as typical scale-like cells (fig. 3a), without the presence of inflammatory cells, sporadically intrapapillary capillary loops were also observed (fig. 3 b).

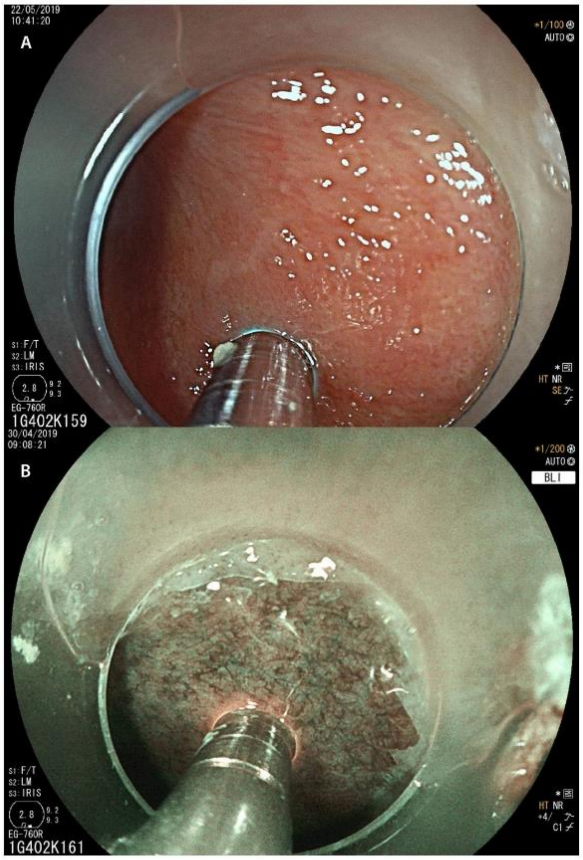
In patients with reflux esophagitis we saw columnar cells, hyperemia and inflammatory cells in the area of the gastroesophageal junction (fig. 4a), and in the squamous epithelium, stromal papillae with hyperemia in the distal esophagus (fig. 4 b).

The characteristic pCLE figures which we saw (and recorded) during the procedure in nondysplastic BE were: columnar cells and uniform villiform architecture and with dark goblet cells (fig. 5a, 5 b). In the patient with both BE and LGD we observed: dark non-round glands, lack of goblet cells, a sharp cutoff of darkness and variable cell size (fig. 6a, 6 b). No patient with HGD participated in our pilot study. In patients with EAC the following signs were seen: disorganization or a loss of structure, dark columnar cells with severe nuclear atypia and dilated irregular vessels (fig. 7a, 7 b).

The comparison of the pCLE images and the final histopathology figures from the biopsies taken can be seen in Fig. 3c–7c.

The correlations between the pCLE images captured by endoscopists and the definitive histopathology results are summarized in table 2. The correct diagnoses based on real-time pCLE were evaluated by an endoscopist in 11 of the 14 cases (78.6 %). The average time of pCLE examination needed to obtain a diagnosis based on pCLE images was 8 minutes.

**Fig. 2.** *Endoscopic view in high-definition white-light endoscopy (HD-WLE) (a) and blue light imaging (BLI) (b) of nondysplastic Barrett´s esophagus investigated with the confocal probe Cellvisio®*




**Tab. 2.** *Correlation between pCLE images and definitive histopathology samples*

| Variable | Total | Healthy cohort (n = 4) | Reflux esophagitis (n = 3) | Barrett´s esophagus (n = 4) | Esophageal adenocarcinoma (n = 3) |
|---|---|---|---|---|---|
| **Histology** | 14 | Esophageal squamous epithelium: 4 | Reflux esophagitis (grade 1): 2, (grade 2): 1 | IM:3, LGD:1 | Esophageal adenocarcinoma: 3 |
| **Correct pCLE established diagnoses/definitive histopathology diagnoses** | 11/14 | 4/4 | 2/3 | 3/4 | 2/3 |
| **Average time of pCLE procedure needed to establish diagnoses based on pCLE images (minutes)** | 8.0 | 6.0 | 7.5 | 9.6 | 9.0 |

*pCLE – probe-based confocal laser endomicroscopy, IM – intestinal metaplasia, LGD – low grade dysplasia*

## Discussion

pCLE is a novel diagnostic method used in gastrointestinal endoscopy (BE, gastric diseases, pancreatic cysts, bile duct structures and inflammatory bowel disease or colorectal lesions in the colon), as well as in the pulmonary and urinary systems, and even during surgical procedures (10, 11).

Promising data and results were gained especially for BE. One of the first prospective multicenter studies was published by Wallace et al in 2010 (7). 40 sites of BE tissue were investigated by pCLE (followed by matching biopsies) and evaluated by 11 experts in BE, with results which suggest that pCLE has a very high accuracy for the diagnoses of neoplasia in BE.

One year later Sharma et al (12) in 2011 published another prospective multicenter study on a larger cohort of patients and with a different study design. The pCLE were examined in 101 patients with BE and the combination of HD-WLE with pCLE significantly improved the ability to detect neoplasia in BE in comparison to just HD-WLE alone.

In 2011 Gaddam et al (8) set the pCLE criteria for dysplastic BE (HGD/cancer). The study resulted in the formulation of a total of six pCLE criteria which predicted dysplasia with a good degree of accuracy. These criteria were as follows: saw-toothed epithelial surface, not easily identifiable goblet cells, non-equidistant glands, unequal size and shape of glands, enlarged cells, and irregular and non-equidistant cells. However, this work did not evaluate the ability of these criteria to diagnose LGD.

Diagnostic criteria from di Pietro et al (9) in 2019 have recently been published. The best cutoff for LGD diagnosis was the positivity of any 3 of the 6 following criteria: dark non-round glands, irregular gland shape, lack of goblet cells, sharp cutoff of darkness, variable cell size, and cellular stratification.

The characteristic pCLE figures we obtained were in accordance with previously published articles and classifications (in diagnosis with BE, EAC and healthy esophagus). We found just one study from Canto et al (13) in which patients with esophagitis were also investigated using pCLE. However, the aim of that study was focused on neoplastic lesion detection and there is a lack of information about pCLE images of esophagitis. In our pCLE figures we recorded columnar cells with hyperemia and inflammatory cells (in the area of the gastroesophageal junction) and squamous epithelium in the distal esophagus with stromal papillae and their hyperemia.

Early detection of dysplastic BE lesions and their treatment is a goal for the prevention of EAC progression. However, the identification and detection of these lesions can be challenging for endoscopists. In 2017, Schölvinck et al (4) published a comparative study where the detection rates of neoplastic visible lesions (HGD or early EAC) were 60 % in community centers and 87 % in expert centers. This supports the value of expert centers for visible lesion detection. The detection and more accurate specification of the lesion can be even higher in combination with pCLE.

**Fig. 3.** *pCLE view of a normal distal esophagus: a, b – normal squamous epithelium of the esophagus (typical scale-like cells), no edema or inflammatory cells; c – histopathology examination: normal squamous epithelium, haematoxylin-eosin staining 40×*

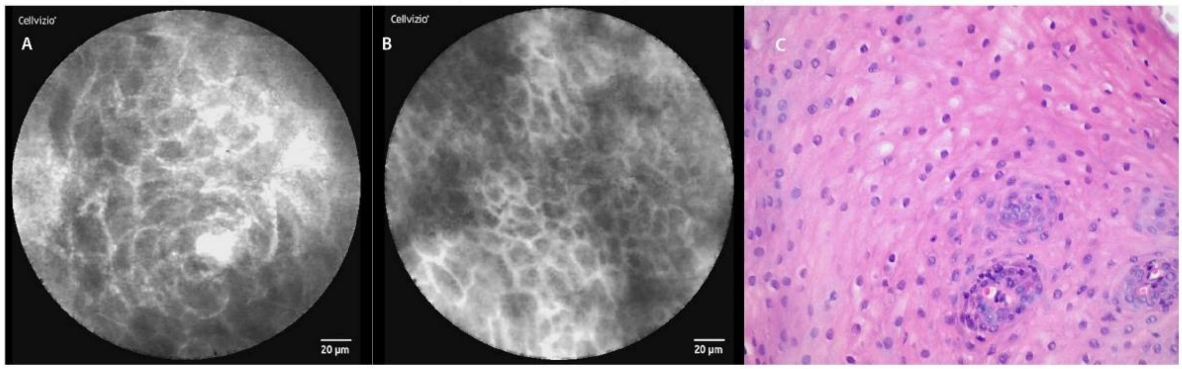



**Fig. 4.** *pCLE view of esophagitis: a – columnar cells, hyperemia and inflammatory cells (area of gastroesophageal junction), b – squamous epithelium, stromal papillae with hyperemia; c – histopathology examination: mixed acute and chronic inflammatory cells in the epithelium, basal cell hyperplasia, elongation and hyperemia of the lamina propria papillae, haematoxylin-eosin staining 40×*

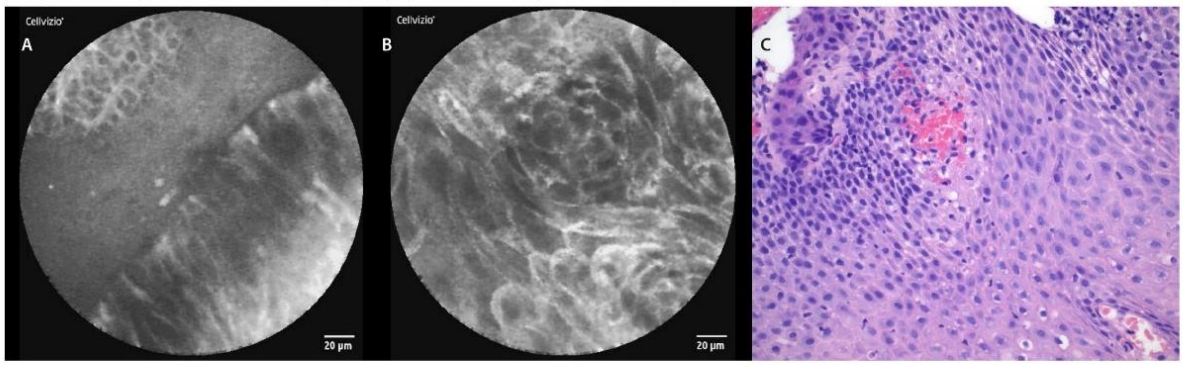


**Fig. 5.** *pCLE view of BE with intestinal metaplasia (nondysplastic): a – columnar cells with dark "goblet" cells, no nuclear atypia, b – columnar cells without nuclear atypia; c – histopathology examination: columnar epithelium of intestinal type with goblet cells, haematoxylin-eosin staining 40×*

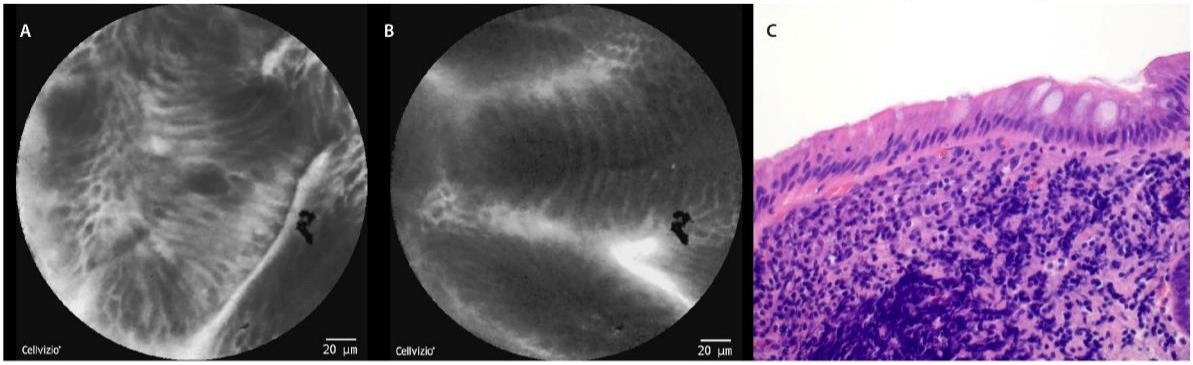
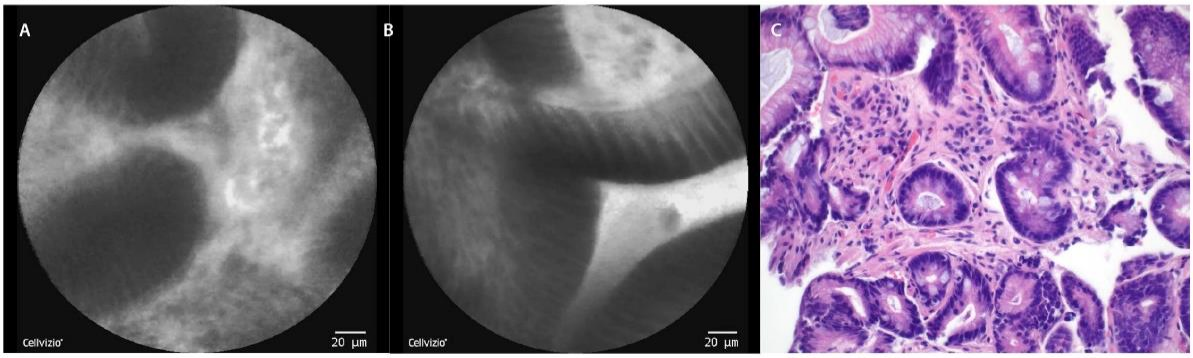



**Fig. 6.** *pCLE view of BE with low grade dysplasia: a - non-round shaped glands with dark columnar cells, b - variable degree of darkness with sharp cutoff of the columnar epithelium; c – histopathology examination: glands with columnar epithelium with lack of goblet cells and nuclear enlargement, haematoxylin-eosin staining 40×*




Alongside the possible higher rate of detection of dysplastic BE by pCLE, there are other advantages discussed. The strategy of the Seattle protocol may miss 10-50 % of esophageal neoplasms and the increased risk of bleeding from multiple biopsies is also under debate (14, 15). The use of pCLE during endoscopy may increase the detection and targeting of neoplastic lesions and could decrease the number of biopsies (resulting in a lower risk of bleeding) (12, 13, 16).

The incidence of EAC is increasing and due to late carcinoma detection the 5-year survival rate is low (less than 20 %) (17, 18). As well as BE as a complication of gastroesophageal reflux disease, there are other well known risk factors for EAC such as male gender, smoking and obesity (19–21).

Most of the data also considers the location in the distal esophagus on the right side of the wall as risk factor for EAC development. According to this data neoplastic lesions are mainly located between the 12 and 3 o'clock position (22) or by other authors between the 2 and 5 o'clock (23). This part of the distal esophagus should be possibly investigated more carefully if pCLE were to be used.

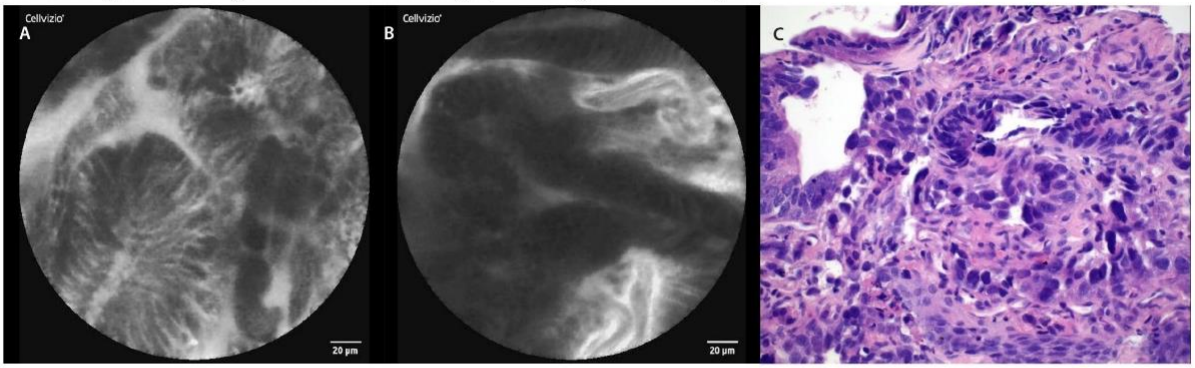
The length of BE segment is also assessed as a risk factor for EAC progression. The risk of progression increased from 19 % to 28 % for every 1 cm increase in the length of the BE (19, 24, 25). Richardson et al (26) in 2018 in his work showed that multiple real-time pCLE can evaluate the entire segment of the BE.

Radiofrequency ablation is an endoscopic ablation technique, and based on the results of several recent studies it is widely used in the eradication of dysplastic BE (without any visible lesion). If visible lesions are apparent, a combination of endoscopic resection and ablation techniques should be performed (3, 6, 27–30). A future benefit of pCLE could be the accurate distinguishing between nondysplastic and dysplastic BE and therefore, better therapy management (16).

The risk of lymph node metastases in cases of intramucosal adenocarcinoma (T1a) is low, around 1–2 % (20, 31). Therefore endoscopic methods of resection such as endoscopic mucosal resection (the preferred method in case of early EAC) or endoscopic submucosal dissection (in selected cases only) are considered as sufficiently definitive treatment (32). An esophagectomy is mostly seen as a second option due a similar success rate but higher morbidity in treatment. If EAC invades the submucosa (T1b) the risk of lymph node metastases increases to 22 % (some data even shows 46 %) and for that reason endoscopic resection is not feasible (31, 33, 34). In cases of EAC (T1b sm1) with favorable grading (well differentiated) and without lymphatic or blood vessel tumor invasion, an endoscopic resection can be considered in patients of a borderline fitness for surgery (3, 30).

One possible role of pCLE can be in the accurate definition of the lesions of BE (LGD, HGD or EAC), leading to the best choice of treatment. Dolak et al (2) in 2015 published a study where patients with BE referred

**Fig. 7.** *pCLE view of esophageal adenocarcinoma: a – disorganized structure, dark columnar cells with severe nuclear atypia (anisokaryosis), b – disorganized structure of the gland with dark columnar cell and dilated irregular vessels; c – histopathology examination: neoplastic glands show highly irregular architectural glandular arrangement and sever nuclear atypia, haematoxylin-eosin staining 40×*




for endoscopic resection were examined by pCLE before the resection. The study revealed additional neoplastic tissue when compared with the prior HD-WLE and narrow band imaging (NBI).

Promising data is also available from two meta-analyses published in 2016 a 2018, both published by Xiong from China. In 2016 his meta-analysis confirmed that pCLE can be applied to BE surveillance and can lead to the early diagnosis of EAC (35). His recently published analysis from 2018 highlighted significantly increased esophageal neoplasia detection when compared to NBI alone (36).

Performing pCLE in the distal esophagus can sometimes be difficult. However, using a cap at the end of the endoscope can help and improve the stabilization of the probe and the final pCLE image (14). Adverse effects or allergic reactions to the contrast agent Fluorescite® have been studied in 2 272 patients (from 16 international centers in total) who underwent pCLE in the gastrointestinal tract. No serious adverse events were reported. Mild adverse events occurred in just 1.4 % of individuals, including nausea/vomiting, transient hypotension without shock, injection site erythema, diffuse rash, and mild epigastric pain (37). In our group we did not record any side effects after the application of the contrast agent. Another relative disadvantage can be the higher purchase price and operational costs. On the other hand, using pCLE during an endoscopy can lead to a decrease in endoscopic procedures and the amount of biopsies taken, potentially reducing the costs (13, 26).

As well as pCLE there are other experimental methods currently in development. De Groof et al (38) published a method of computer-aided detection of early BE neoplasia in 2018. This method also enables real-time detection and locates BE neoplasia on endoscopic images with high accuracy. However, more experience, data and further development of the algorithm for the video evaluation performed in this new technique are needed.

A possible limitation of our study is the low number of patients investigated. However, the aim of this pilot study has been to gain experience with pCLE in esophageal diseases and obtain characteristic pCLE figures for future studies.

## Conclusion

Endoscopic detection of neoplasia in BE (especially in long segments) is challenging and advisable in managing surveillance in expert centers for BE.

We studied and established basic pCLE figures for esophageal diseases during a standard cap-assisted endoscopic procedure. It seems to be a possible new technique in BE surveillance and early neoplastic lesion detection. However, more studies and data on larger numbers of patients are needed.

## Ethical standard statement

All procedures which followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008.

## Informed consent

Informed consent was obtained from all patients for being included in the study.

## Conflict of interest

The authors declare that they have no conflict of interest.

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