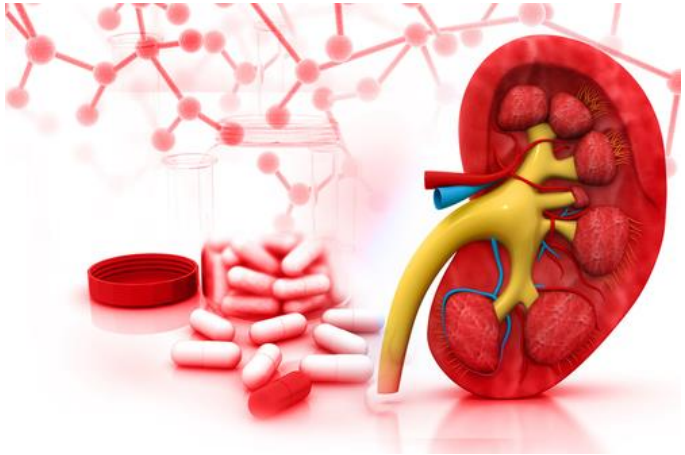
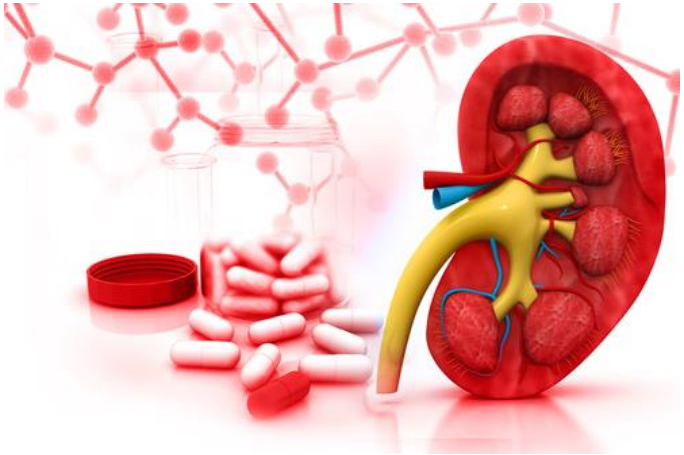


Pharmacotherapy in renal impairment

Jitka Rychlíčková

Summary



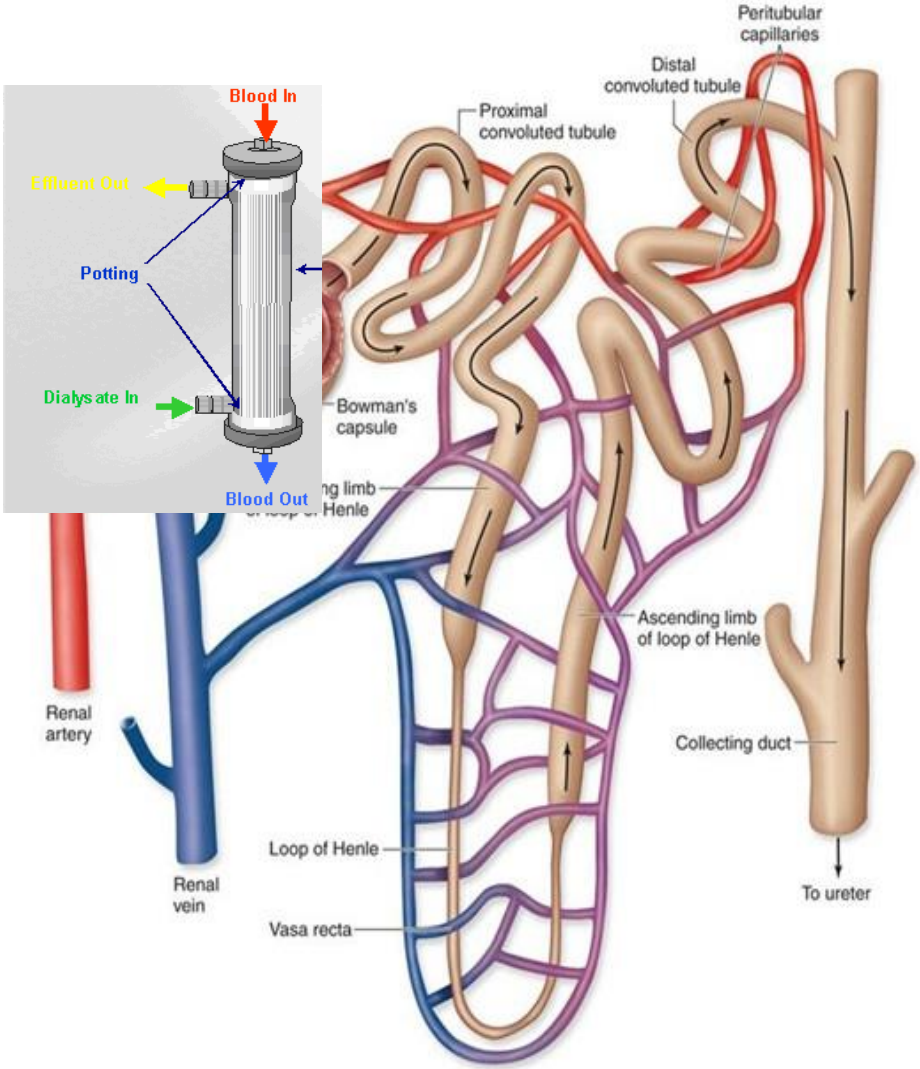
- Renal functions assessment
- Pharmacokinetics
- When to reduce dose and how?

1.	In renal impairment must be drug doses reduced	**true**	**false**
2.	Highly protein bound drugs are freely filtered	**true**	**false**
3.	There are five stages of chronic kidney disease	**true**	**false**
4.	In AKI the glomerular filtration rate can be calculated	**true**	**false**

Renal functions assessment

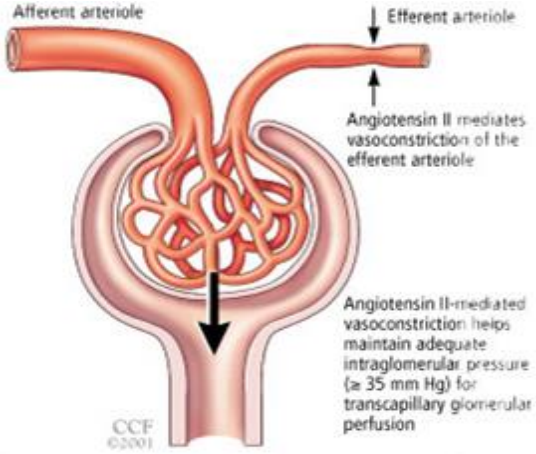
basic processes in kidneys:

- GF
- TS
- TR



Which of them can we measure?
Which of them can we replace?

Renal functions assessment



basic processes in kidneys:

- **GF**
  - intraglomerular pressure
  - pressure gradient vas afferens - vas efferens
  - not filtered:
    - size
    - charge
  - normal rate:

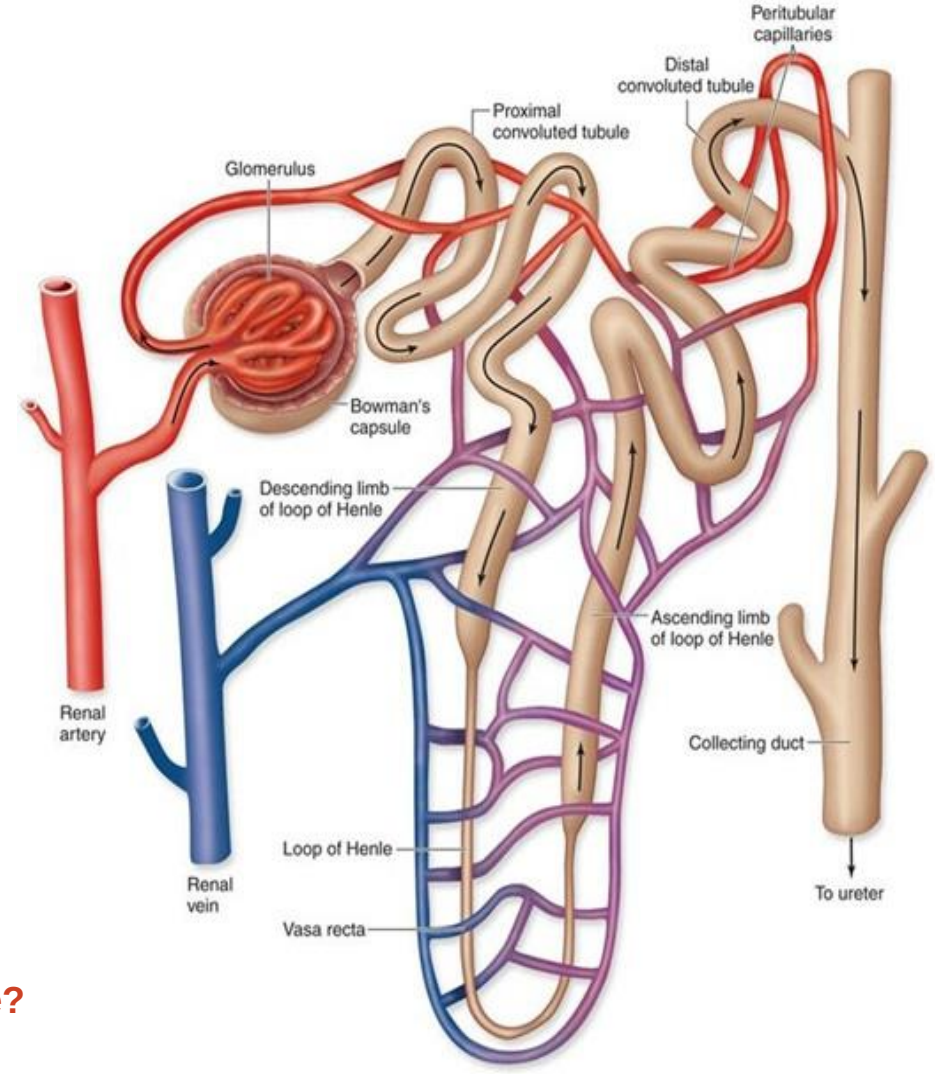
CKD 1	> 1,5	ml/s/1,73 m2	× 60	> 90	ml/min
CKD 2	1,0 - 1,49	ml/s/1,73 m2		60 - 89	ml/min
CKD 3	0,5 - 0,99	ml/s/1,73 m2		30 - 59	ml/min
CKD 4	0,25 - 0,49	ml/s/1,73 m2		15 - 29	ml/min
CKD 5	< 0,25	ml/s/1,73 m2		< 15	ml/min

What is needed for the effective glomerular filtration?
What is not filtered under physiological conditions?
Is albumin filtered under physiological conditions?
When to think about dose reduction in general?

Renal functions assessment

basic processes in kidneys:

- GF
- TS
- TR



Which of them can we measure?
Which of them can we replace?
How to estimate/meassure glomerular filtration rate?

Renal functions assessment

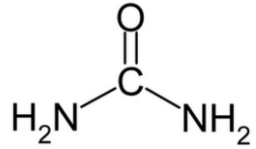
basic processes in kidneys: GF, TS, TR
biochemical parameters:

- urea
- creatinine
- cystatin C

Na	145 mmol/L
K	8,0 mmol/L
Cl	100 mmol/L
urea	40 mmol/L
crea	800 µmol/L

urea

- endogenous substance - protein catabolism
- physiological range 2,5-7,5 mmol/L
- osmotic activity !
- kinetics:
  - freely filtered
  - partial/minor tubular *resorption*



creatinine

- endogenous substance - muscle metabolism
- physiological range 44-100 µmol/L
- no osmotic activity !
- kinetics:
  - freely filtered
  - partial/minor tubular *secretion*

Renal functions assessment

basic processes in kidneys: GF, TS, TR
biochemical parameters:

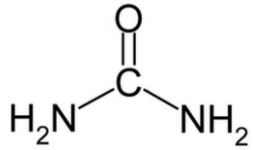
- urea
- creatinine
- cystatin C

Pt. A: male, 30 yo, bricklayer, BH 185 cm, BW 100 kg
Pt. B: woman, 70 yo, retired, BH 165 cm, BW 45 kg

both of them serum creatinine 110 µmol/L

urea

- endogenous substance - protein catabolism
- physiological range 2,5-7,5 mmol/L
- osmotic activity !
- kinetics:
  - freely filtered
  - partial/minor tubular *resorption*



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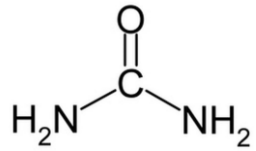

cystatin C

- endogenous substance - cell nucleus (any)
- kinetics:
  - freely filtered
  - intracellular metabolism in tubular cells
- higher sensitivity in mild impairment

creatinine

- endogenous substance - muscle metabolism
- physiological range 44-100 µmol/L
- no osmotic activity !
- kinetics:
  - freely filtered
  - partial/minor tubular *secretion*

Renal functions assessment

basic processes in kidneys: GF, TS, TR
biochemical parameters:

- urea
- creatinine
- cystatin C

estimation:

- CKD vs. AKI
  - Cocroft-Gault
  - MDRD
  - CKD-EPI

$$\text{CrCl (mL/min)} = \frac{140 - \text{age (years)} \times \text{bodyweight (kg)}^{\dagger}}{0.815 \times \text{serum creatinine (micromol/L)}}$$

$$\text{GFR} = 186.3 \times (\text{creatinine in mg/dL})^{-1.154} \times (\text{age in years})^{-0.203} \times (0.742 \text{ if female}) \times (1.21 \text{ if black})$$

measurement:

24 hours collection, total volume, SCr, UCr
scintigraphy

Renal functions assessment

basic processes in kidneys: GF, TS, TR
biochemical parameters:

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- cystatin C

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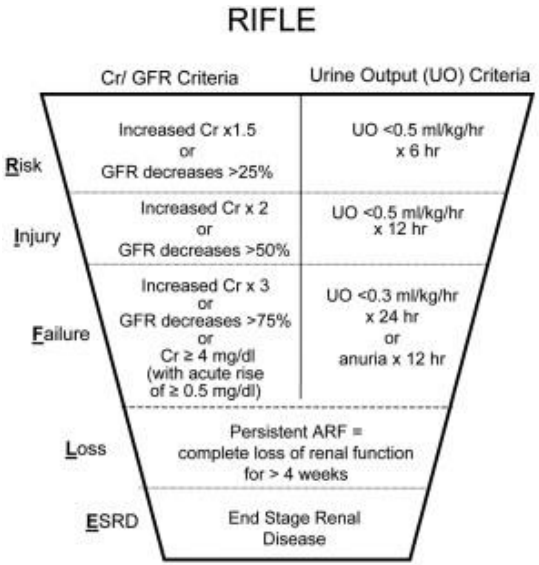

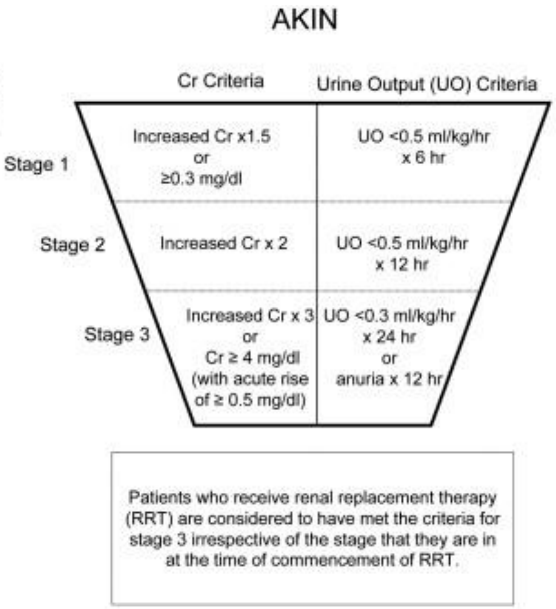

Renal functions assessment

basic processes in kidneys: GF, TS, TR
biochemical parameters:

- urea
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estimation:

- CKD vs. AKI
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  - CKD-EPI

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24 hours collection: total volume, SCr, UCr
scintigraphy

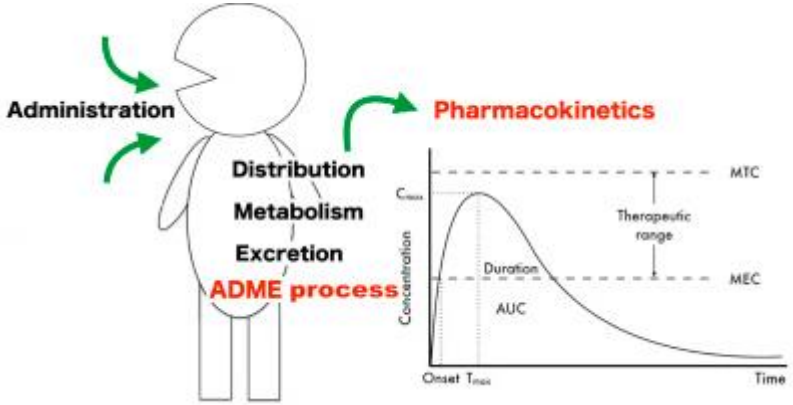
renal function assessment:

- basic processes, biochemical parameters
- not only urea, creatinine → BW, PS, personal history, nutrition
- CG, MDMD, CKD-EPI are not for AKI
- CG, MDRD, CKD-EPI in CKD
- diagnostic criteria for AKI

Practical aspects of pharmacokinetics

(L)ADME process

- low/no oral bioavailability
- protein bound
- metabolized/excreted unchanged
- hepatal/renal excretion



vancomycin

PHARMACOKINETICS	
Molecular weight (daltons)	1449.3; (1485.7 as hydrochloride)
% Protein binding	10–50 (19 CKD 5)
% Excreted unchanged in urine	80–90
Volume of distribution (L/kg)	0.47–1.1 (0.88 CKD 5)
Half-life – normal/ ESRF (hrs)	6/120–216

zoledronic acid

PHARMACOKINETICS	
Molecular weight (daltons)	249.1 (325.1 as sodium salt)
% Protein binding	78
% Excreted unchanged in urine	Approx 50
Volume of distribution (L/kg)	28 litres
Half-life – normal/ ESRF (hrs)	>10 years/Increased

metformin

PHARMACOKINETICS	
Molecular weight (daltons)	165.6
% Protein binding	Negligible
% Excreted unchanged in urine	100
Volume of distribution (L/kg)	1–4
Half-life – normal/ ESRF (hrs)	2–6/prolonged

amlodipine

PHARMACOKINETICS	
Molecular weight (daltons)	567.1 (as besilate)
% Protein binding	>95
% Excreted unchanged in urine	<10
Volume of distribution (L/kg)	20
Half-life – normal/ ESRF (hrs)	35–50/50

Practical aspects of pharmacokinetics

Male, 65 yo, BH 180 cm, BW 65 kg,

urea 20 mmol/L, creatitine 210 µmol/L, albumine 35 g/L

fluconazole IV 400 mg/200 ml NS (during 30 min) every 12 hours the **day 4**

personal history: CKD 4 (25 ml/min) (vascular nefropathy)

Molecular weight (daltons)	306.3
% Protein binding	11–12
% Excreted unchanged in urine	80
Volume of distribution (L/kg)	0.65–0.7
Half-life – normal/ ESRF (hrs)	30/98

What is the indication of fluconazole?
Normal dosing of fluconazole?
Would you recommend dose reduction?
Would you recommend to reduce the dosing as early as on the day 1?
Possible adverse effects/toxicity?

When to reduce a dose?

before automatic dose reduction think about:

- absorption/bioavailability
- % excreted renally unchanged
- potential toxicity (consequence of cummulation)
- risk of underdosing

- non-effective tubular concentrations

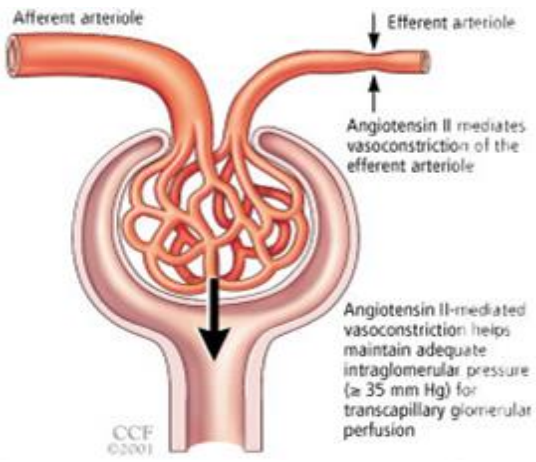
Which drugs are excreted renally unchanged (>60%)?
Reduction of loading dose?
Reduction of dose vs. extension of dosing interval vs. both?

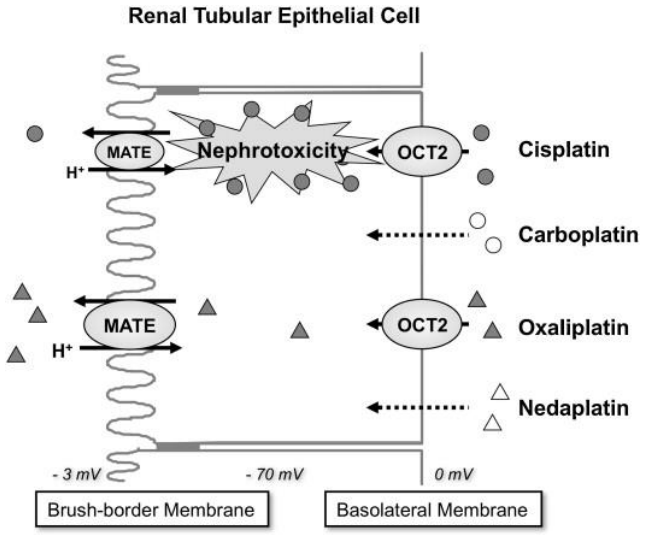
Renal excretion vs. nephrotoxicity

- **mechanisms**:
  - direct toxicity, toxic metabolites
    - cis-Pt (vs. oxaliplatin, carboplatin)
    - ...
  - hemodynamic changes
  - tubular obstruction

tubuloglomerular feedback

prevention: hydration, pH changes, mineral substitution





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