Clinical pharmacology
GIT

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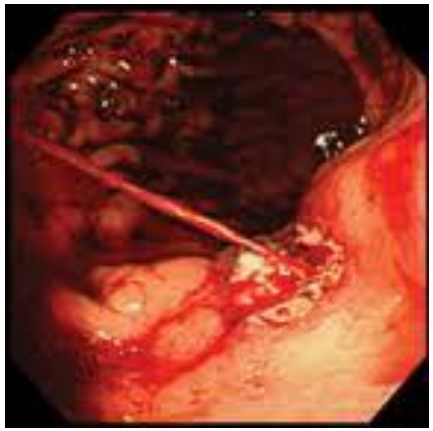
Agenda

- Stress ulceration
- *Clostridium difficile* infection

STRESS ULCERATION

Stress Ulcers Definition

- Gastrointestinal ulcerations of the upper alimentary tract
  - Stomach
  - Duodenum
  - Ileum
  - Jejunum



- Range depends on depth of ulcer
  - Superficial: Asymptomatic
  - Deep: Haemorrhage (Haematemesis /Melena)

What do you think causes ulcers?

A: Stress.

B: Excessive stomach acids.

C: Bacteria.

D: A bad diet and alcohol use.

E: Being overweight.

Epidemiology

- Up through the 1970 stress ulcers were much more common (>30% of ICU patients)
- Today, less than 5% of ICU patients have stress ulcers with macroscopic bleeding

1. ASHP Therapeutic Guidelines on Stress Ulcer Prophylaxis, AJHP 1999;56(4) 347-379
2. Del Valle, J. Chapter 287 - Peptic Ulcer Disease and Related Disorders , Harrison's Principles of Internal Medicine - 17th Ed. (2008).

Epidemiology

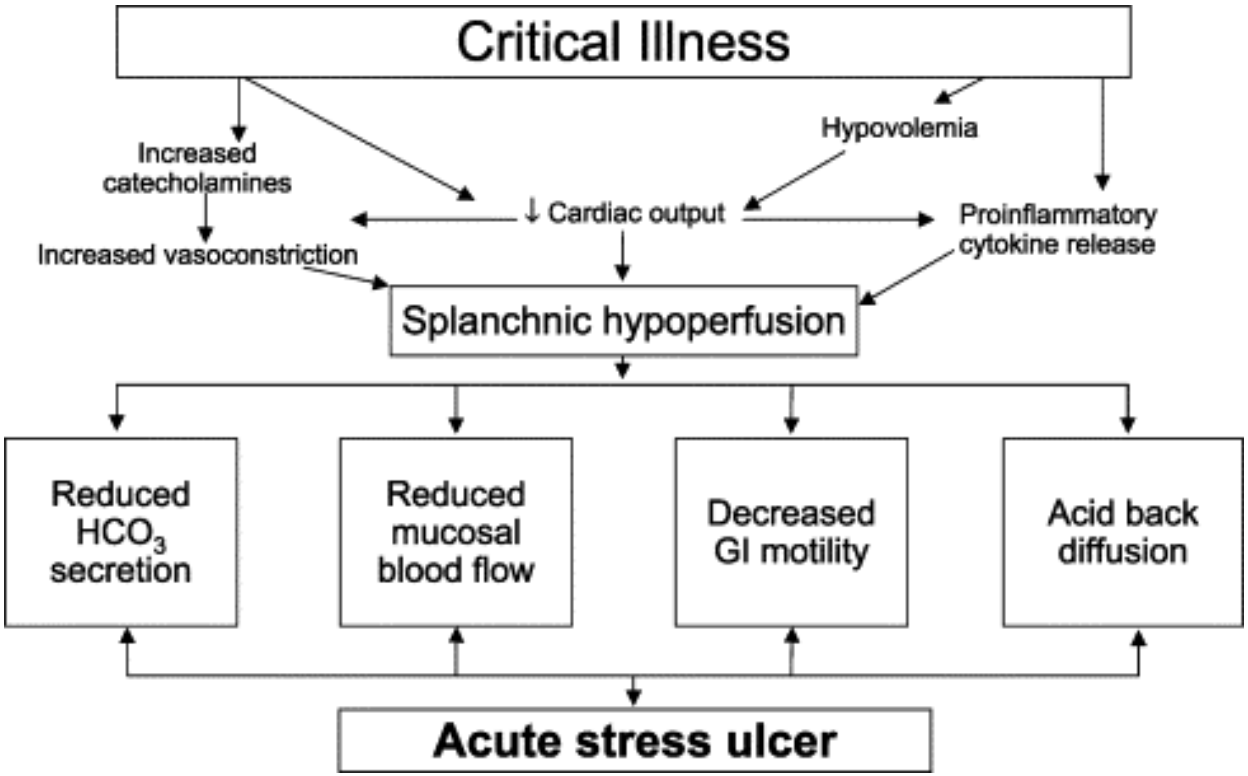
- acute bleeding from mucosal defects in upper GIT in critically ill patient is frequent

- 1.5 to 8.5% GI bleeding for all patients in ICU
- 15% -25% ICU patients had no prophylaxis

- 75% of ICU patients - mucosal abnormalities <72hod (multiple burns / head trauma)

Pathophysiology of Stress Ulcers

- Dysbalance of protective and agressive factors
- Multi-factorial:



Pathophysiology of Stress Ulcers

- Etiology is complex
  - Decreased Gastric pH
  - Ischemia
  - Decreased mucous production
- Usually occur within 24-48 hours of trauma/stress
- Gastric pH is a factor and a surrogate marker, not the root cause of stress ulcers

Del Valle, J. Chapter 287 - Peptic Ulcer Disease and Related Disorders , Harrison's Principles of Internal Medicine - 17th Ed. (2008).

Morbidity/Mortality

- Cook and collegues conducted a large (n=2252) multicenter prospective trial evaluating the risk factors of significant bleeding
- Mortality for patients with a significant bleed
  - 48.5% with significant bleeding
  - 9.1% without significant bleeding

Cook DJ, et al. Risk factors for gastrointestinal bleeding in critically ill patients. NEJM 1994;330(6):377-81

Morbidity/Mortality - Continued

- Two independent factors for a clinically significant bleed:
  - Respiratory failure (OR=15.6)
  - Coagulopathy (OR=4.3)
- Incidence of significant bleeds
  - With one or both risk factors 3.7%
  - Without either risk factor 0.1%
- Number need to treat for significant bleeding
  - Without risk factors = 900
  - With risk factors = 30

Cook DJ, et al. Risk factors for gastrointestinal bleeding in critically ill patients. NEJM 1994;330(6):377-81

Who is at risk?

- Intubated patients> 48hrs (Cook. DJ et al '94)
- Patients with coagulopathy

- Other risk factors:
  - SHOCK - any!
  - Sepsis
  - Liver and kidney failure
  - Multiple trauma
  - Burns> 35% will cast body
  - Glucocorticoids

- Intolerance of enteral nutrition

Guidelines

- ASHP Therapeutic Guidelines on Stress Ulcer Prophylaxis

Key Guideline Points – The Big 3

1. Coagulopathy
   - platelet count of <50,000mm^3
   - INR>1.5
   - PTT of >2 times the control
2. Mechanical Ventilation
   - Longer than 24 hours
3. Recent GI ulcers/bleeding
   - Within 12 months of admission

ASHP Therapeutic Guidelines on Stress Ulcer Prophylaxis, AJHP 1999;56(4) 347-379

Key Guideline Points – The Little

- 2 or more of the following:
  1. Sepsis
  2. ICU>1 week
  3. Occult Bleeding within 6 days
  4. High dose corticosteroids
     - 250mg Hydrocortisone
     - 50mg Methylprednisone
- These factors are not consistently found to be contributing factors, but they are significant in some studies

ASHP Therapeutic Guidelines on Stress Ulcer Prophylaxis, AJHP 1999;56(4) 347-379

Guideline Summary

- Big 3
  1. Coagulopathy
  2. Mechanical Ventilation
  3. GI Bleeding within 12 months

- Little 4 (2 or more)
  1. Sepsis
  2. ICU>1 week
  3. Occult Bleeding within 6 days
  4. High dose corticosteroids

Prophylaxis and treatment

1) Protecting stomach mucosa – nil buffering

Sucraflate - polysaccharide + Aluminium hydroxide

2) Prostaglandin analogues

Misoprostol – inhibit parietal cells to generate cAMP, thus reduce stomach acid secretion

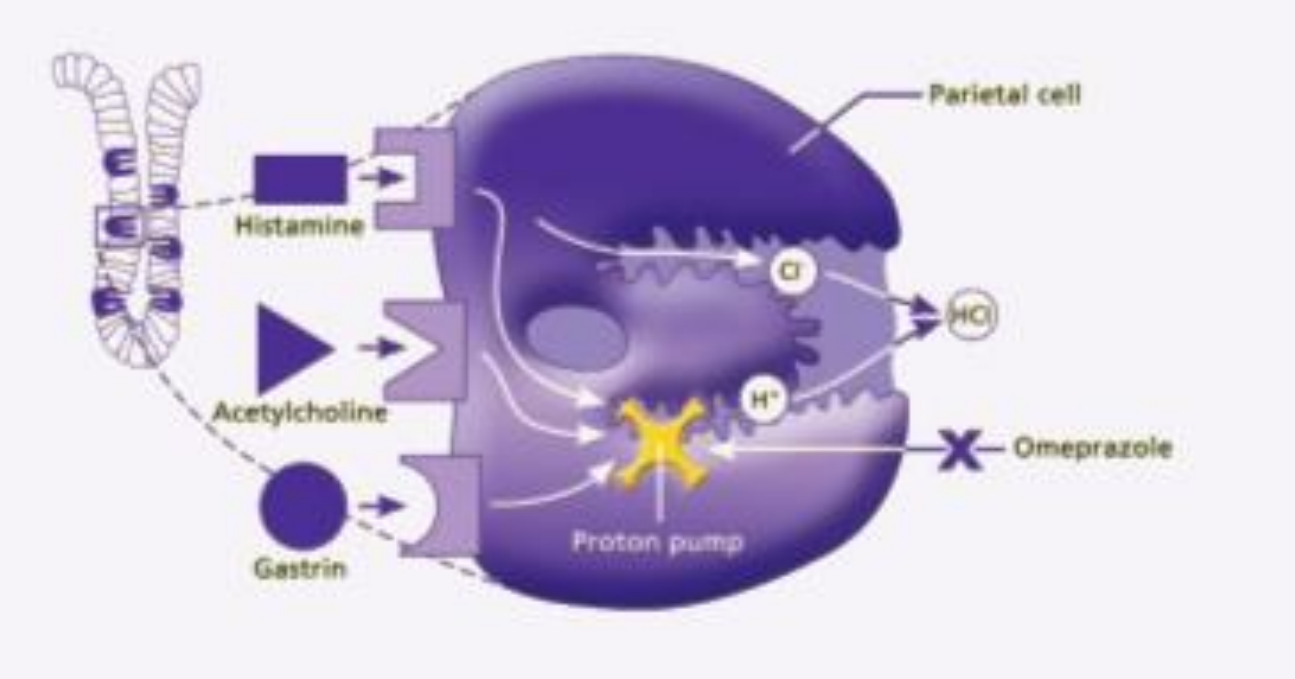
3) Neutralise stomach acid contents

Antacids (Gaviscon) – Bicarbonate neutralises pH

Prophylaxis and treatment

3) Block acid secretion

- Competitive H_2 antagonists (Ranitidine)
- Proton pump inhibitors (Omeprazole)



Agents and Dosing – How much of a good thing?

- IV Agents
  - Pantoprazole 40 mg (Q12-24h)
  - Ranitidine 50mg (Q8h)
- Oral Agents
  - Omeprazole 40mg (Q24h)
    - Powder for suspension is FDA Approved!
  - Ranitidine 150mg (Q12h)
  - Sucralfate 1-2 grams 4 times per day
    - Hey this one has an FDA indication!

Proton Pump Inhibitors, High-dose, Criteria for Use, VHA Pharmacy Benefits Management Strategic Healthcare Group and the Medical Advisory Panel

Duration of Therapy

- ASHP guidelines note that durations vary widely by study
- Cook's seminal prospective trial defined SUP as 2 or more doses of a H_2RA, PPI, or antacid.
- The pathophysiology suggests that duration of therapy as short as 2-3 days may be sufficient
- Clinical prudence might be to continue therapy as long as risk factors are present

Cook DJ, et al. Risk factors for gastrointestinal bleeding in critically ill patients. NEJM 1994;330(6):377-81

Over-used PPI

- Retrospective, chart review of non-ICU admits[1]
  - 22% received stress ulcer prophylaxis
  - 54% of those were discharged home on it
- Retrospective chart review of nursing home admits[2]
  - 50% did NOT have an appropriate diagnosis for PPI
- Retrospective chart review of *C.diff* positive patients[3]
  - 63% of did NOT have valid indication for PPI
- Retrospective chart review of cirrhotics + SBP[4]
  - 47% did NOT have valid reason for PPI

What are the common S/Es of pharmacological agents?

- Hospital Acquired Pneumonia (HAP)[1]
- C Difficile[2]
- Osteoporosis & Hip Fractures[3,4]

1. Herzig HJ et al, JAMA 2009;301(20):2120-2128
2. Dial, S, Delaney, AC, Barkun AN, et al. JAMA 2005;294(3):2989-2995
3. Yang et al. JAMA 2006:296(24):2947-2953
4. Targownik, LE et al. CMAJ 2008:179(4):319-326

HAP

- Prospective (n=63,878) pharmacoepidemiologic cohort study
  - Excluding ICU Patients
- PPIs associated with a significant 30% increase in HAP
- H2RA association was not significant after multivariate analysis

Table 4. Rates of Hospital-Acquired Pneumonia According to Type of Acid-Suppressive Medication

	Acid-Suppressive Medication	No Acid-Suppressive Medication	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Proton-Pump Inhibitors[a]				
Total admissions, No.	25374	30956	56330	56330
Hospital-acquired pneumonia, No. (%)	1340 (5.3)	610 (2.0)	2.8 (2.5-3.1)	1.3 (1.1-1.4)[b]
Histamine$_2$ Receptor Antagonists[c]				
Total admissions, No.	5686	30956	36642	36642
Hospital-acquired pneumonia, No. (%)	176 (3.1)	610 (2.0)	1.6 (1.3-1.9)	1.2 (0.98-1.4)[b]

Abbreviations: CI, confidence interval; OR, odds ratio.
[a] Patients prescribed histamine$_2$ receptor antagonists were excluded from this analysis.
[b] Adjusted for all variables listed in Table 1, plus admission day of the week, using a multivariable generalized estimating equation (GEE) to take into account dependency of the data due to repeated admissions.
[c] Patients prescribed proton-pump inhibitors were excluded from this analysis.

Shoshana J. Herzig; Michael D. Howell; Long H. Ngo; et al, Acid-Suppressive Medication Use and the Risk for Hospital-Acquired Pneumonia JAMA 2009;301(20):2120-2128

C Difficile

- Case-Control study in the UK showing an increased risk associated with acid suppressive therapy

Table 4. Comparison of Community-Acquired Matched Cases and Controls—Medication Variables

Variable	No. (%) Nonhospitalized Incident Cases	No. (%) Nonhospitalized Age- and Practice-Matched Controls	Crude Rate Ratio (95% CI)	Adjusted Rate Ratio (95% CI)*
No. of patients	1233	12 330		
Medications received in the 90 d prior, %				
Antibiotics	456 (37)	1649 (13)	3.9 (3.4-4.4)	3.1 (2.7-3.6)
Proton pump inhibitors	280 (23)	1038 (8)	3.3 (2.9-3.9)	2.9 (2.4-3.4)
H_2-receptor antagonists	83 (8)	367 (4)	2.4 (1.9-3.1)	2.0 (1.6-2.7)
Nonsteroidal anti-inflammatory drugs	467 (38)	3043 (24)	1.9 (1.8-2.4)	1.3 (1.2-1.5)
Aspirin	245 (20)	2148 (17)	1.2 (1.0-1.4)	1.0 (0.9-1.2)

Abbreviation: CI, confidence interval.
*Adjusted for all variables in Table 2 plus use of medications listed in this table in the past 90 d.

Dial, S, Delaney, AC, Barkun AN, et al. Use of gastric Acid-Suppressive Agents and the Risk of Community-Acquired Clostridium Difficile-Associated Disease. JAMA 2005;294(3):2989-2995

Osteoporosis & Hip Fractures

- Significant increase in the risk of hip fracture in high dose PPI (>1.75 average dose)
  - Yang et al. JAMA 2006:296(24):2947-2953
- Significant increase in risk of hip fractures with use of PPI over 5 years
  - Case (n=15,792)-Control(n=47,289) study
  - Targownik, LE et. al CMAJ 2008:179(4):319-326
- One year mortality in men with a hip fracture may be as low as 50%
  - Diamond, TH, et al. *The Medical Journal of Australia1997; 167: 412-415*

Applications for Pharmacy

- ***Document*** the indication for ongoing therapy
  - Big 3
  - Little 4
- ***Discontinue*** therapy if not indicated
  - Reduce the risk to patients
  - Reduce costs
- ***Discuss*** the indications with the patient/provider
  - Appropriate indications and duration of therapy

Summary

- Give Stress Ulcer Prophylaxis therapy when indicated
  - Stress Ulcer have a high mortality (nearly ½)
  - Big 3, Little 4
- Discontinue Stress Ulcer Prophylaxis when no longer indicated
  - Stress Ulcer Prophylaxis has risks (HAP, C diff, Osteoporosis), in and outside the facility
- Document, Discontinue, Discuss

COMPARISON OF PPI AND H_2- ANTIHISTAMINES EFFECTIVNESS

Meta-analysis: Critical Care Medicine 2013

- Aim:

Determine *efficacy* and *safety* of proton pump inhibitors verses H_2 receptor antagonists for the prevention of upper GI bleeding in ICU

- Methodology:

Search strategy –
MEDLINE (1948-March 2012)
EMBASE (1980-March 2012)
ACPJC (1991-March 2012)
Cochrane (central) database
CINHAL.

Two researchers independently extracted data

Criteria

- Type of study:

- Randomised Control Trials (RCTs)

- Population:

- ICU Adults (Medical and Surgical included)

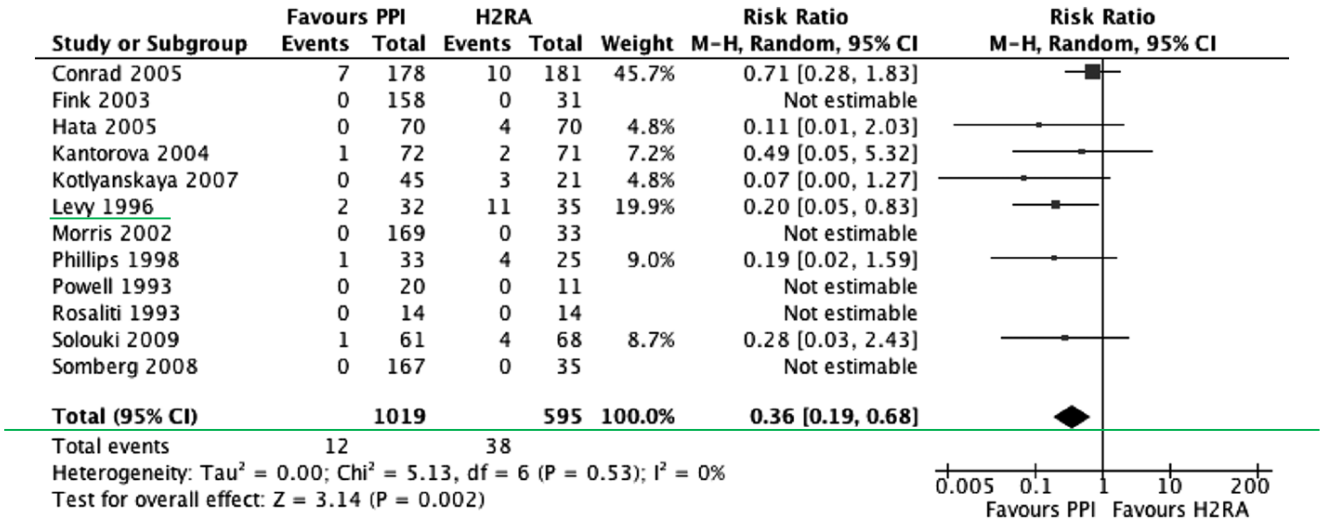
- Intervention:

- Control=H_2antihistamines=PPIs
    - para-enteral/enteral
    - irrespective of the dose, frequency and duration

Results – Primary Outcomes

Primary objectives:

1) Clinically important bleeding (12 Trials n=1614)



Study or Subgroup	Favours PPI Events	Total	H2RA Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Conrad 2005	7	178	10	181	45.7%	0.71 [0.28, 1.83]
Fink 2003	0	158	0	31		Not estimable
Hata 2005	0	70	4	70	4.8%	0.11 [0.01, 2.03]
Kantorova 2004	1	72	2	71	7.2%	0.49 [0.05, 5.32]
Kotlyanskaya 2007	0	45	3	21	4.8%	0.07 [0.00, 1.27]
Levy 1996	2	32	11	35	19.9%	0.20 [0.05, 0.83]
Morris 2002	0	169	0	33		Not estimable
Phillips 1998	1	33	4	25	9.0%	0.19 [0.02, 1.59]
Powell 1993	0	20	0	11		Not estimable
Rosaliti 1993	0	14	0	14		Not estimable
Solouki 2009	1	61	4	68	8.7%	0.28 [0.03, 2.43]
Somberg 2008	0	167	0	35		Not estimable
Total (95% CI)		**1019**		**595**	**100.0%**	**0.36 [0.19, 0.68]**
Total events	12		38			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 5.13$, df = 6 (P = 0.53); $I^2 = 0\%$

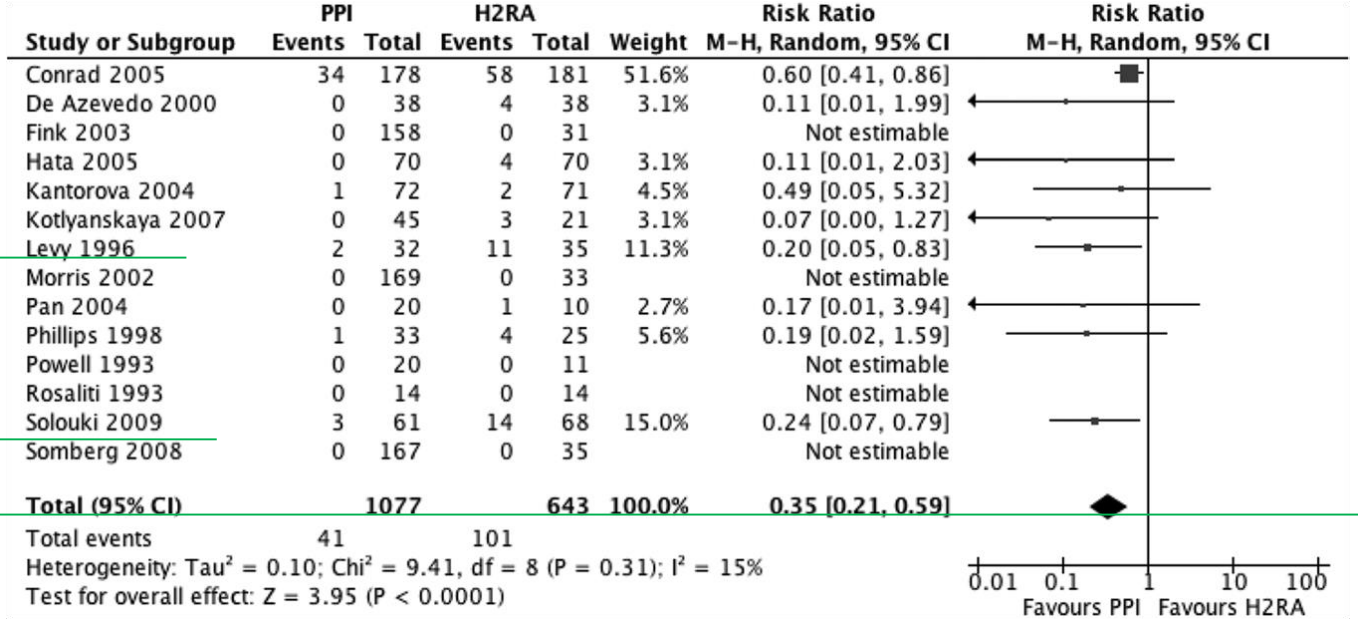
Test for overall effect: Z = 3.14 (P = 0.002)

Significantly lower RR with PPIs vs H_2RA:

(RR 0.36 95% CI 0.19-0.68 p=0.002)

Results – Primary outcomes

2) Overt Bleeding (14 Trials n= 1720)



Study or Subgroup	PPI Events	PPI Total	H2RA Events	H2RA Total	Weight	Risk Ratio M-H, Random, 95% CI
Conrad 2005	34	178	58	181	51.6%	0.60 [0.41, 0.86]
De Azevedo 2000	0	38	4	38	3.1%	0.11 [0.01, 1.99]
Fink 2003	0	158	0	31		Not estimable
Hata 2005	0	70	4	70	3.1%	0.11 [0.01, 2.03]
Kantorova 2004	1	72	2	71	4.5%	0.49 [0.05, 5.32]
Kotlyanskaya 2007	0	45	3	21	3.1%	0.07 [0.00, 1.27]
Levy 1996	2	32	11	35	11.3%	0.20 [0.05, 0.83]
Morris 2002	0	169	0	33		Not estimable
Pan 2004	0	20	1	10	2.7%	0.17 [0.01, 3.94]
Phillips 1998	1	33	4	25	5.6%	0.19 [0.02, 1.59]
Powell 1993	0	20	0	11		Not estimable
Rosaliti 1993	0	14	0	14		Not estimable
Solouki 2009	3	61	14	68	15.0%	0.24 [0.07, 0.79]
Somberg 2008	0	167	0	35		Not estimable
Total (95% CI)		**1077**		**643**	**100.0%**	**0.35 [0.21, 0.59]**
Total events	41		101			

Heterogeneity: $Tau^2 = 0.10$; $Chi^2 = 9.41$, df = 8 (P = 0.31); $I^2 = 15\%$

Test for overall effect: Z = 3.95 (P < 0.0001)

Significantly lower RR with PPIs vs H_2RA:
(RR 0.35; 95%CI 0.21-0.59 p<0.0001)

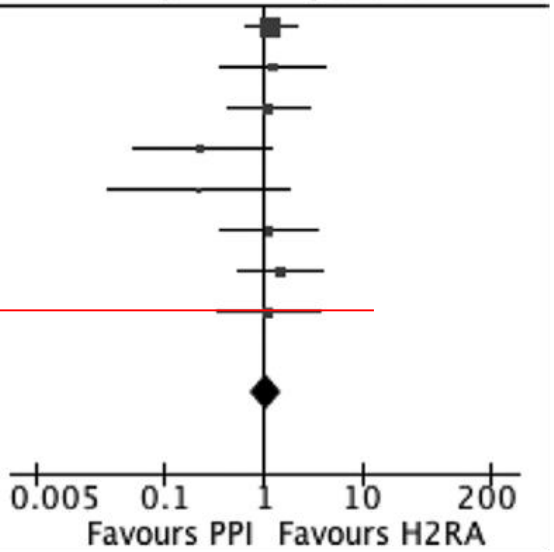
Results – Secondary outcomes

- 1) Nosocomial Pneumonia (8 Trials, n= 1100)

Study or Subgroup	PPI Events	PPI Total	H2RA Events	H2RA Total	Weight	Risk Ratio M-H, Random, 95% CI
Conrad 2005	20	178	17	181	35.6%	1.20 [0.65, 2.21]
De Azevedo 2000	5	38	4	38	8.7%	1.25 [0.36, 4.30]
Kantorova 2004	8	72	7	71	14.5%	1.13 [0.43, 2.94]
Kotlyanskaya 2007	2	45	4	21	5.1%	0.23 [0.05, 1.17]
Levy 1996	1	32	5	35	3.0%	0.22 [0.03, 1.77]
Phillips 1998	6	33	4	25	10.0%	1.14 [0.36, 3.60]
Solouki 2009	8	61	6	68	13.3%	1.49 [0.55, 4.04]
Somberg 2008	16	167	3	35	9.6%	1.12 [0.34, 3.63]
Total (95% CI)		**626**		**474**	**100.0%**	**1.06 [0.73, 1.52]**
Total events	66		50			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 6.28$, df = 7 (P = 0.51); $I^2 = 0\%$

Test for overall effect: Z = 0.30 (P = 0.76)



No significant difference: RR 1.06 95% CI (0.73-1.52)
p=0.76

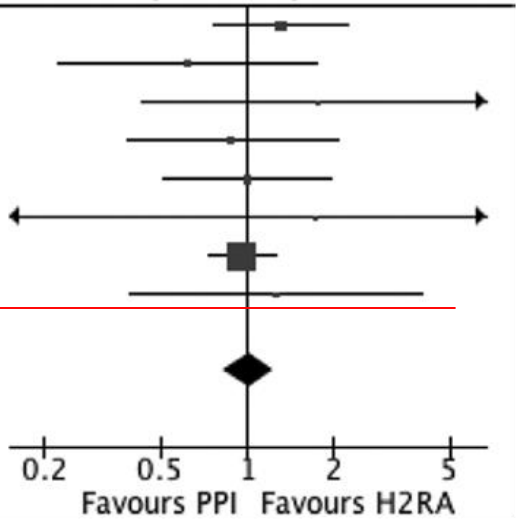
Results – Secondary outcomes

2) Mortality (8 Trials n= 1196)

Study or Subgroup	PPI Events	PPI Total	H2RA Events	H2RA Total	Weight	Risk Ratio M-H, Random, 95% CI
Conrad 2005	27	178	21	181	14.7%	1.31 [0.77, 2.22]
De Azevedo 2000	5	38	8	38	4.0%	0.63 [0.22, 1.74]
Fink 2003	18	158	2	31	2.1%	1.77 [0.43, 7.23]
Kantorova 2004	9	72	10	71	5.9%	0.89 [0.38, 2.05]
Levy 1996	11	32	12	35	9.5%	1.00 [0.52, 1.95]
Powell 1993	1	20	0	11	0.4%	1.71 [0.08, 38.86]
Solouki 2009	38	61	44	68	60.3%	0.96 [0.74, 1.25]
Somberg 2008	18	167	3	35	3.1%	1.26 [0.39, 4.04]
Total (95% CI)		**726**		**470**	**100.0%**	**1.01 [0.83, 1.24]**
Total events	127		100			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 2.94$, df = 7 (P = 0.89); $I^2 = 0\%$

Test for overall effect: Z = 0.12 (P = 0.91)



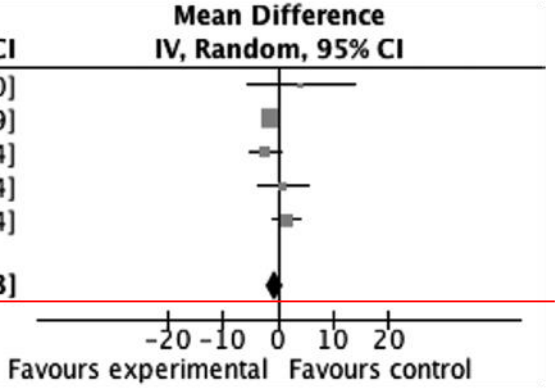
No significant difference: RR 1.01 95% CI (0.83-1.24)
p=0.91

Results – Secondary outcomes

3) ICU Length of stay (5 Trials n=555)

Study or Subgroup	PPI Mean	PPI SD	PPI Total	H2RA Mean	H2RA SD	H2RA Total	Weight	Mean Difference IV, Random, 95% CI
De Azevedo 2000	12.3	28.8	38	8.2	8	38	2.9%	4.10 [-5.40, 13.60]
Hata 2005	13	1.3	70	14.4	5	70	42.4%	-1.40 [-2.61, -0.19]
Kantorova 2004	7.7	7.3	72	10.1	9.8	71	21.2%	-2.40 [-5.24, 0.44]
Levy 1996	8.7	6.9	32	7.8	12	35	10.4%	0.90 [-3.74, 5.54]
Solouki 2009	7.67	7.2	61	6.16	8.04	68	23.1%	1.51 [-1.12, 4.14]
Total (95% CI)			**273**			**282**	**100.0%**	**-0.54 [-2.20, 1.13]**

Heterogeneity: $Tau^2 = 1.33$; $Chi^2 = 6.59$, df = 4 (P = 0.16); $I^2 = 39\%$
Test for overall effect: Z = 0.63 (P = 0.53)



No significant difference :CI (-2.20-1.13) p=53

4) *Clostridium difficile* infection

No trials reported on *C. Difficile* infection

Findings

'Significantly ↓ risk of both **1^0** outcomes with PPIs

- Clinically important GI bleeding – RR 0.36 (0.19-0.68)
- Overt UGI bleeding – RR 0.35 (0.21-0.59)

'*No* significant ↓ risk of **2^0** outcomes with PPIs vs H_2RA'

Nosocomial pneumonia – RR 1.06 (0.73-1.52)

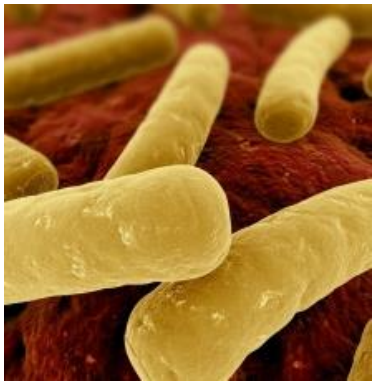
ICU mortality – RR 1.01 (0.83-1.24)

ICU length of stay – RR 0.54 (-2.20-1.13)

CLOSTRIDIUM DIFFICILE INFECTION

C. difficile : Microbiology

- Gram positive spore forming bacillus (rods)
- Obligate anaerobe
- Part of the GI Flora in
  - 1-3% of healthy adult
  - 70% of children < 12 months
- Some strains produce toxins A & B
- Toxins-producing strains cause *C. diff* Infection (CDI)
- CDI ranges from mild, moderate, to severe and even fatal illness



Clostridium Difficile colitis - more virulent than ever

- incidence, deaths, and excess health care costs are at historic highs
  - +/- 1 billion dollars/year
- 3x increase in decade - now 500,000 infections and 29,000 deaths per year.
- More deaths than even MRSA infections.

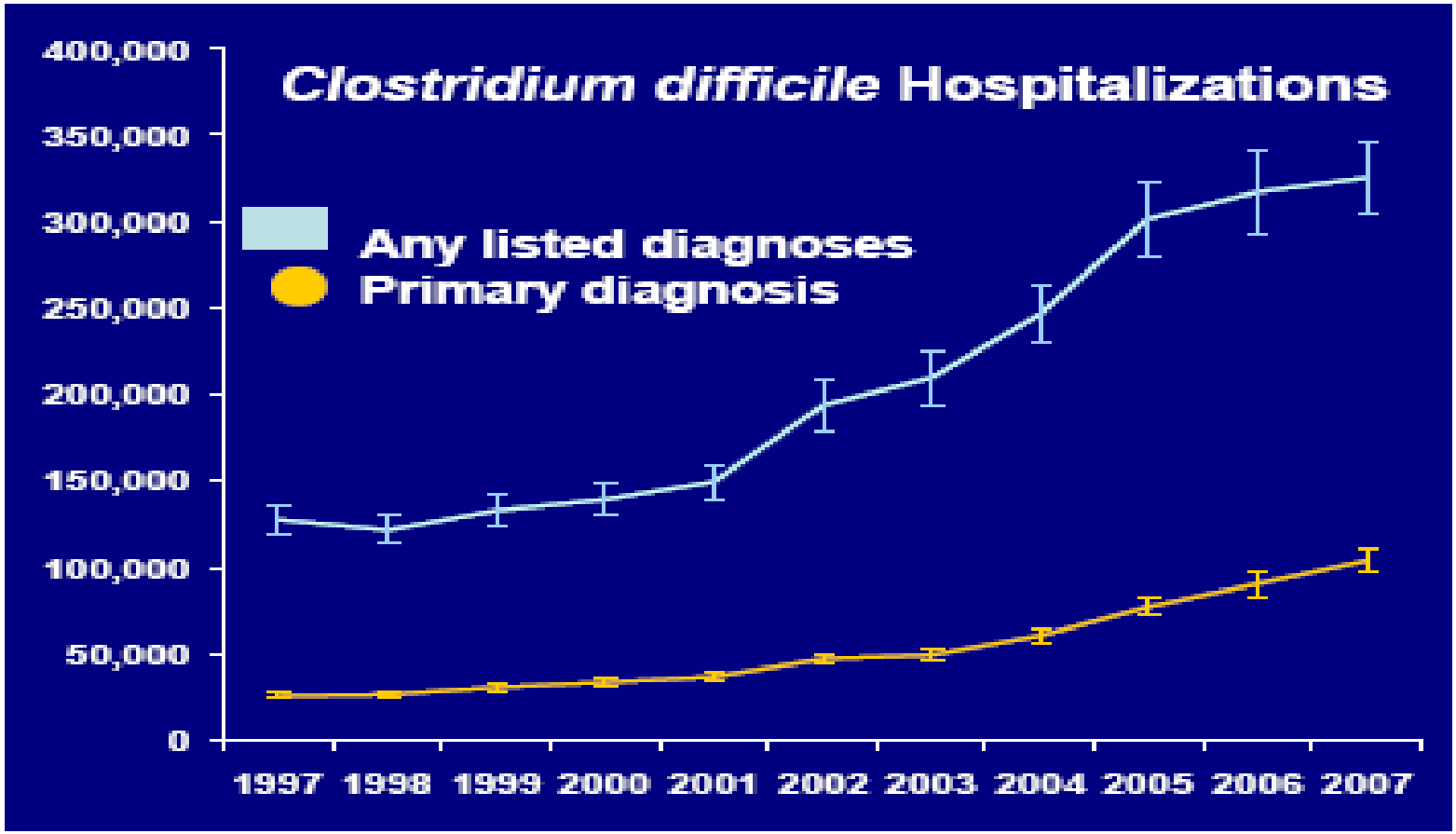
C. difficile: Background

- **#1 cause** of increase - over use of antibiotics
  - A common cause of nosocomial antibiotic-associated diarrhea (AAD)
- **#2 cause** – appearance of a more virulent *C.diff* strain associated with risk of greater mortality
- **#3 cause-** increased relapse rate – 20% of cases have at least one relapse- difficult to treat
- **#4 cause-** overdiagnosis???

C. difficile: Background

- Most common infectious cause of acute diarrheal illness in LTCFs
- The only nosocomial organism that is anaerobic and forms spores
  - survive> 5 months and hard to destroy
- Pathogenesis is mainly due to toxins production
- Infective dose is < 10 spores

CDI: Impact


Clostridium difficile Hospitalizations
Any listed diagnoses
Primary diagnosis
400,000
350,000
300,000
250,000
200,000
150,000
100,000
50,000
0
1997
1998
1999
2000
2001
2002
2003
2004
2005
2006
2007

C. difficile : Transmission

- Fecal – oral route
  - Contaminated hands of healthcare workers
  - Contaminated environmental surfaces.
- Person to person in hospitals and LTCFs
- Reservoir:
  - Human: colonized or infected persons
  - Contaminated environment
- *C. diff* spores can survive for up 5 months on environmental surfaces.

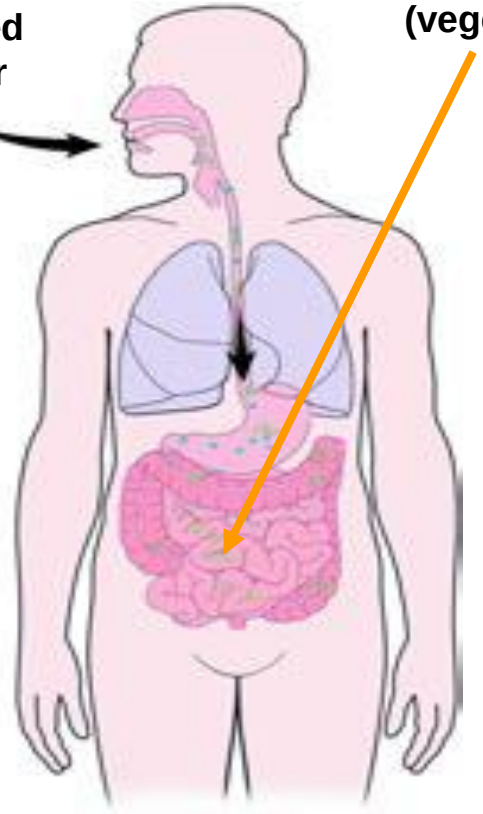
Importance of Spores

- Resistant to heat, drying, pressure, and many disinfectants
- Resistant to all antibiotics because antibiotics only kill or inhibit actively growing bacteria
- Spores survive well in hospital environment
- Spores are not a reproductive form, they represent a survival strategy

CDI: Pathogenesis

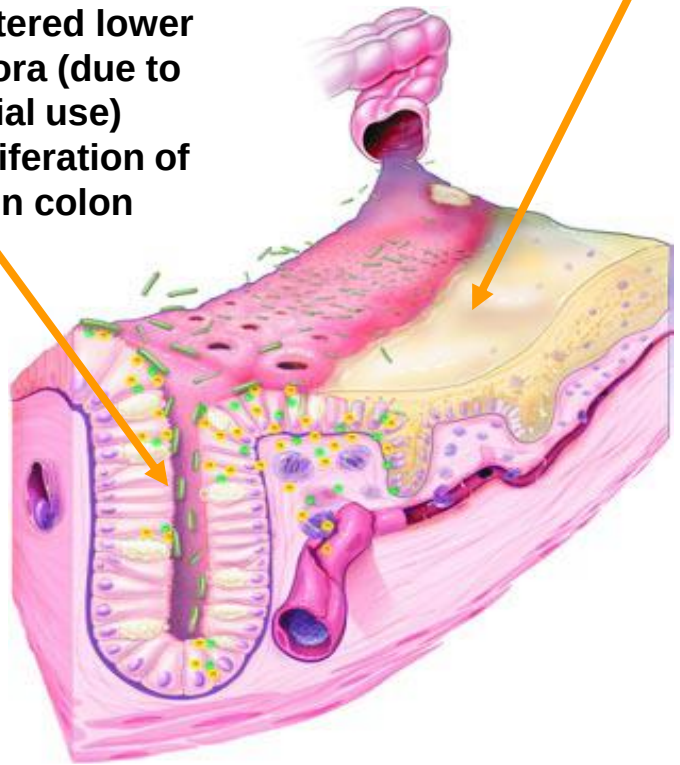
Step 1- Ingestion of spores transmitted from other patients

Step 2- Germination into growing (vegetative) form

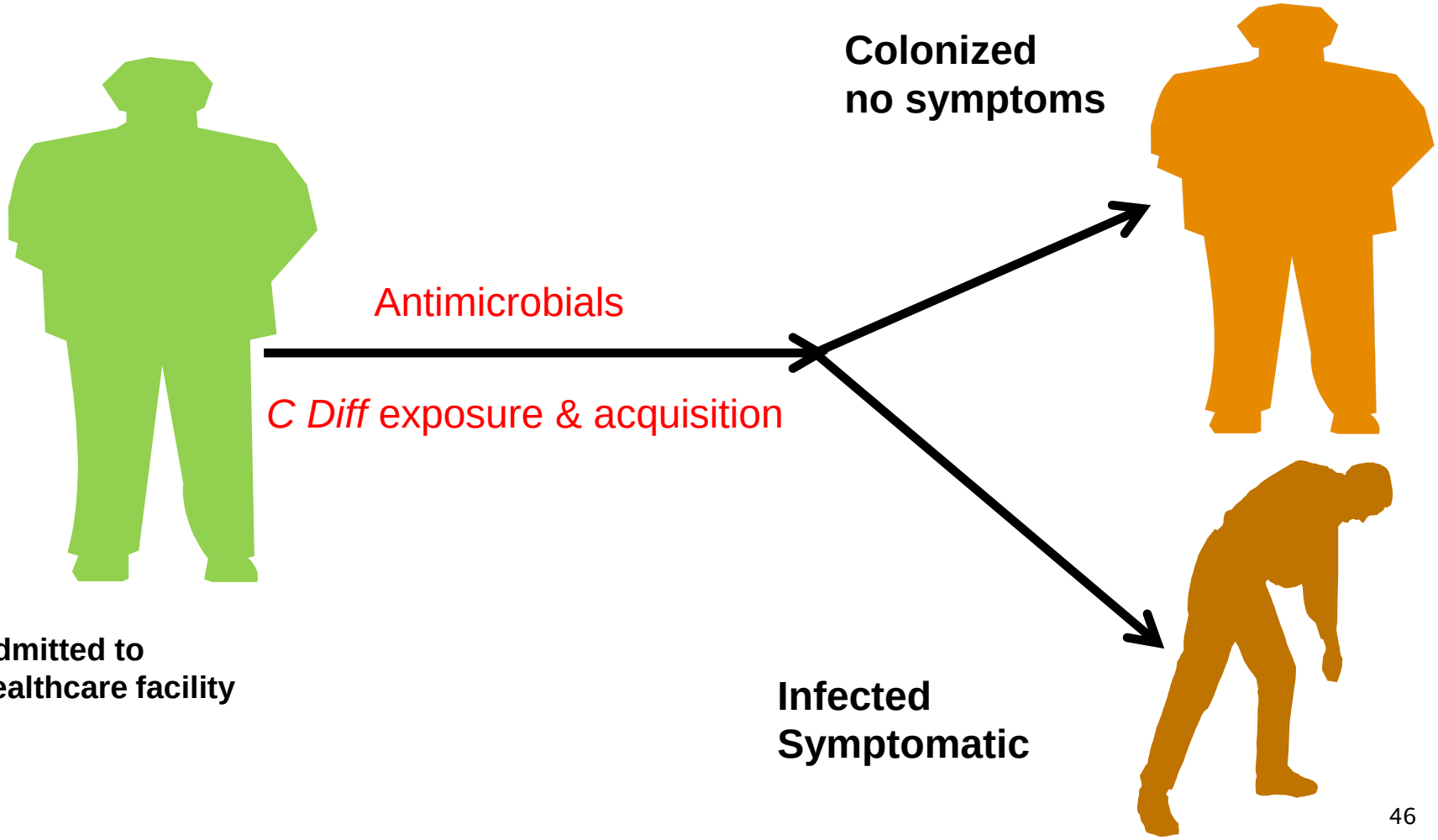


Step 3 - Altered lower intestine flora (due to antimicrobial use) allows proliferation of *C. difficile* in colon

Step 4 . Toxin B & A production leads to colon damage +/- pseudomembrane



CDI Pathogenesis



CDI: Risk Factors

- Exposure to antimicrobials (prior 2-3 months)
- Exposure to healthcare (prior 2-3 months)
- Infection with toxogenic strains of *C. difficile*
- Old age > 64 years
- Underlying illness
- Immunosuppression & HIV
- Chemotherapy (immunosuppression & antibiotic-like activities)
- Tube feeds and GI surgery
- Exposure to gastric acid suppression meds ??

Clinical Manifestations

- Illness caused by toxin-producing strains of *C. difficile* ranges from
  - Asymptomatic carriers = Colonized
  - Mild or moderate diarrhea
  - Pseudo membranous colitis that can be fatal
- A median time between exposure to onset of CDI symptoms is of 2–3 days
- Risk of developing CDI after exposure ranges between 5-10 days to 10 weeks

CDI: Pathogenesis

Case Study 1

- 60 years old male admitted to hospital for community acquired pneumonia, treated with levofloxacin and discharged
- 7 days later, seen at another hospital because of 5 kg weight gain over last few days (“my abdomen has never been so big”) and hypertension (213/106)
  - Afebrile, WBC of 8.5, albumin 3.1, creatinine 0.9, no diarrhea noted
  - Admitted, treated for hypertension and ciprofloxacin given to complete treatment for CAP; discharged 3 days later

Case Study 1 (cont'd)

Day 1	Presents to ER 3 days after discharge • Fever (37,9), diarrhea, generally feeling ill, no abdominal pain • WBC 27.8K, albumin 2.9, creatinine 1.2 • Admitted with *C. difficile* colitis listed as a possible dx, but not treated (except for levofloxacin)
Day 2	10 stools/day, altered mental status • *C. difficile* EIA positive; put on metronidazole 500 mg TID

Case Study 1 (cont'd)

Day 3	Transferred to SICU, anuric, abdominal pain, distension, developed cardiac complications, ventilated, renal failure. Poor prognosis and colectomy ruled out following surgical consult • Oral and rectal vancomycin added • WBC > 30K, albumin 2.3, creatinine 3.1
Day 4	WBC 59.6K, toxic megacolon
Day 5	WBC 88K, made DNI/DNR, died

Historical Perspective

- In the 1960s it was noted that patients on antibiotics developed diarrhea[1]
  - "staphylococcal colitis"
    - Originally thought to be caused by *S. aureus* and treated with oral bacitracin
    - Stool cultures routinely ordered for *S. aureus*
- Early 1970s, a new explanation
  - "clindamycin colitis"
    - Severe diarrhea, pseudomembranous colitis, and occasional deaths documented in patients on clindamycin

"Antibiotic Associated Pseudomembranous Colitis Due to Toxin-Producing Bacteria"

- Bartlett and co-workers demonstrated cytotoxicity in tissue culture and enterocolitis in hamsters from stool isolates from patients with pseudomembranous colitis
  - Isolate was *C. difficile*
- *Bacillus difficilis* (now confirmed as *C. difficile*) was cultured from healthy neonates (with difficulty, hence the name) in 1935[2]

Quiz Time

Q. Why did it take so long to associate the organism *C. difficile* with the disease?

A. Organism was (is) found in healthy infants

Q. Why do antibiotics sometimes cause diarrhea (unrelated to *C. difficile*)?

A. Disrupt the intestinal flora which plays a major role in digestion of food

Role of Antibiotics

- All antibiotics (including metronidazole and vancomycin) are associated with CDI
- High-risk group
  - Clindamycin
  - Cephalosporins/penicillins/beta-lactams
  - Fluoroquinolones
- Alteration of normal colonic flora thought to favor growth of *C. difficile*
  - Antibiotics do not know they are suppose to kill/inhibit only the “bad guys”

Antimicrobials Predisposing to CDI

Very commonly related	Less commonly related	Uncommonly related
Clindamycin Ampicillin Amoxicillin Cephalosporins Fluoroquinolons	Sulfa Macrolides Carbapenems Other penicillins	Aminoglycosides Rifampin Tetracycline Chloramphincol

- Among symptomatic patients with CDI:
  - 96% received antimicrobials within the 14 days before onset
  - 100% received an antimicrobial within the previous 3 months
- 20% of hospitalized patients are colonized with *C. diff*

Pathogenesis
Historical Perspective

- Most CDI were mild
  - Diarrhea was main symptom
  - Pseudomembranous colitis and toxic megacolon were rare
  - Discontinuing antibiotics worked in many cases
  - High response rate to metronidazole and vancomycin

CDI: Symptoms

- Asymptomatic colonization
- Diarrhea
  - mild → moderate → severe
- Abdominal pain and distension
- Fever
- Pseudomembranous colitis
- Toxic megacolon
- Perforated colon → sepsis → death

Markers of Severe Disease

- Leukocytosis
  - Prominent feature of severe disease
  - Rapidly elevating WBC
  - Up to >100 K
- >10 BM/day
- Albumin < 2.5
- Creatinine 2x baseline
- Hypertension
- Pseudomembranous colitis
- Toxic megacolon
- Severe distension and abdominal pain

TESTING AND PREVENTION OF CDAD

CDI: Testing

Test		Advantage	Disadvantage
Testing Toxins	Enzyme immuno-assay (EIA)	• Detects toxin A or both A & B • Rapid (same day)	Less sensitive 63-94%
	Tissue culture cytotoxicity assay	Provides specific and sensitive results for *C. diff* 67-100%	-Detect toxin B -Technical expertise -Expensive -24-48 hours
Organism ID	Glutamate Dehydrogenase	Rapid, sensitive, may prove useful as a triage or screening tool	Not specific, toxin testing required to verify diagnosis
	PCR	Rapid, sensitive, detects presence of toxin gene	Expensive Special equipment
	Stool culture	Most sensitive test available when performed appropriately	False-positive results if isolate is not tested for toxin labor-intensive; requires 48–96 hours

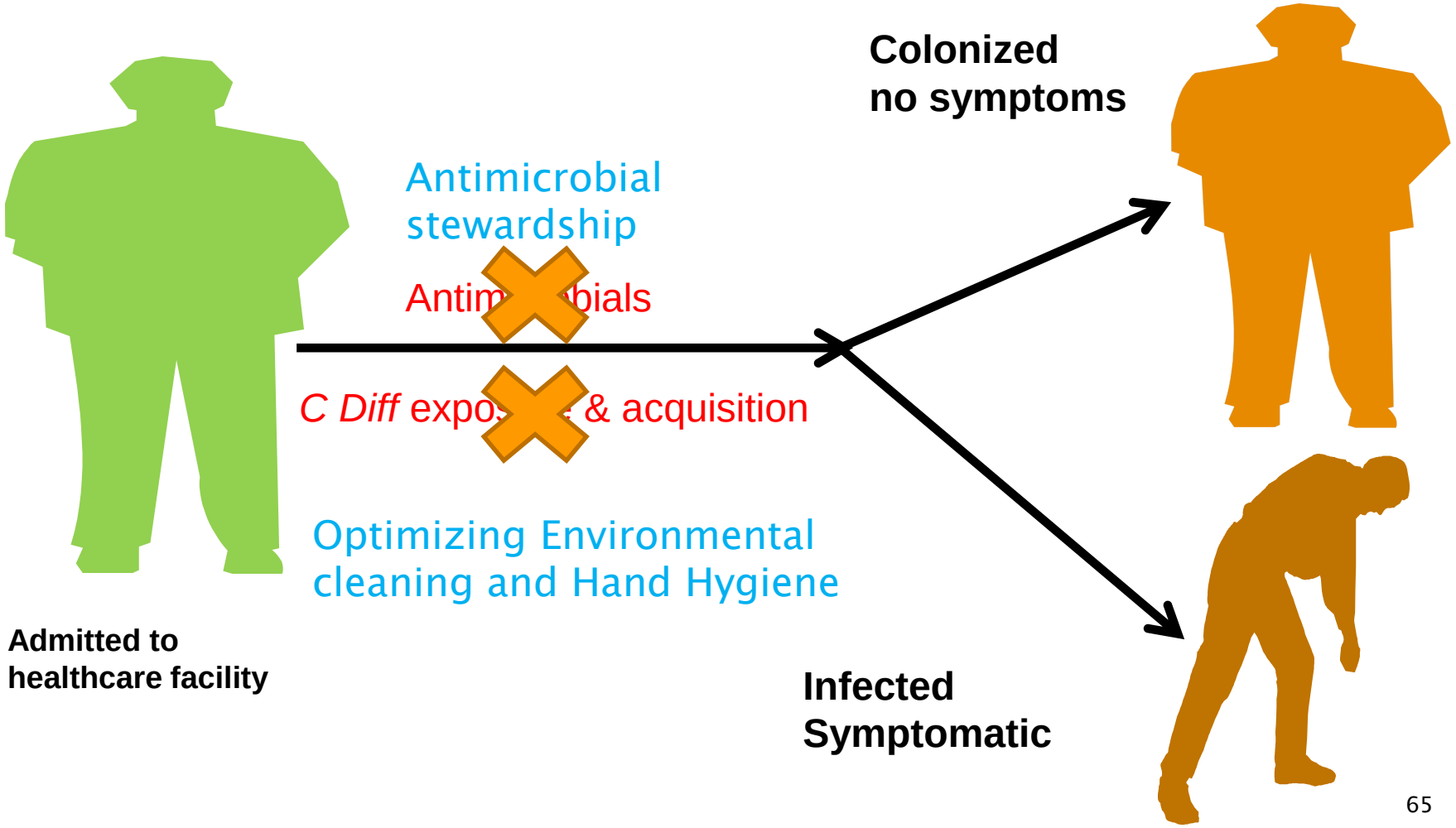
Best Strategy for *C. difficile* Testing

- Testing should be performed only on diarrheal stool
- Testing asymptomatic patients is not indicated
- Testing for cure is not recommended

Best Strategy for *C. difficile* Testing

- For clinical use: two-step testing uses initially EIA detection of GDH for screening followed by cytotoxicity assay or toxigenic culture for confirmation
- Gold standard is stool culture followed by toxigenic culture assay
- Toxin is very unstable, degrades at room temperature, and undetectable within 2 hours (false negative results)

CDI Pathogenesis



Antimicrobial stewardship

- Regardless of setting, ~ 50% antibiotic use is "inappropriate"
- The best CDI preventative measure
  - Decrease in number of patients at risk (susceptible)
  - Decrease in number of patients with CDI (reservoirs)

Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America Guidelines for Developing an Institutional Program to Enhance Antimicrobial Stewardship

Timothy H. Dellit,[1] Robert C. Owens,[2] John E. McGowan, Jr.,[3] Dale N. Gerding,[4] Robert A. Weinstein,[5] John P. Burke,[6] W. Charles Huskins,[7] David L. Paterson,[8] Neil O. Fishman,[9] Christopher F. Carpenter,[10] P. J. Brennan,[9] Marianne Billeter,[11] and Thomas M. Hooton[12]

Antimicrobial stewardship

- Recommendations:
  - Minimize the frequency and duration of antimicrobial therapy
  - Decrease the number of antimicrobial agents prescribed,
  - Targeted antimicrobials should be based on the local epidemiology and the *C. difficile* strains
  - Restrict the use of cephalosporin and clindamycin
  - Audit and feedback targeting broad-spectrum antibiotics

Prevention Strategies

- Contact Precautions for duration of diarrhea
- Hand hygiene (HH) in compliance with CDC/WHO
- Cleaning and disinfection of equipment and environment
- Laboratory-based alert system for immediate notification of positive test results
- Educate HCP, housekeeping, admin staff, patients, families, visitors, about CDI

TREATMENT OF CDAD

Treatment of Mild to Moderate Disease

- Stop antibiotic(s) if medically reasonable
- Metronidazole
  - Oral or IV, 500 mg TID for 10-14 days is standard therapy
  - 5–20% failure rate
  - 20% relapse rate
  - Can use a full 2nd course for failure/relapse but beyond 2 courses, switch to vancomycin
  - Failures not due to metronidazole resistance

Initial Treatment Options for CDI

- Historical response (96%) and relapse rates (20%) similar between metronidazole and vancomycin[1]
- More recently, efficacy of metronidazole for severe disease called into question[2-4]
- Recent prospective trials report vancomycin to be superior to metronidazole in severe CDI[5-7]

Initial Treatment Options for CDI

Metronidazole 250 mg QID or 500 mg TID	• May be administered PO or IV • Development of resistance rare • Historical first-line agent
Vancomycin 125 mg QID	• Effective in enteral (oral or rectal) form only • Typically reserved for severe disease, those failing to respond to metronidazole, or cases in which metronidazole is contraindicated

Metronidazole vs Vancomycin

- Zar et al[1] classified patients as mild or severe CDI
- In mild disease, vancomycin was slightly better than metronidazole (98% vs 90%)
  - Not statistically significant
- In severe disease, vancomycin was significantly better than metronidazole (97% cure vs 76% cure)

Clinical Success by Disease Severity: Tolevamer Phase III Results

Defining CDI Disease Severity

Mild CDI	3–5 BM/day WBC ≤15,000/mm^3 Mild abdominal pain due to CDI
Moderate CDI	6–9 BM/day WBC 15,001 to 20,000/mm^3 Moderate abdominal pain due to CDI
Severe CDI	≥ 10 BM/day WBC ≥20,001/mm^3; Severe abdominal pain due to CDI

Any one of the 3 defining characteristics assigns a patient to the more severe category.

Louie T, et al. The 47th Annual ICAAC Meeting, Sept. 17-20, 2007; Chicago, IL. Abstract k-425-a.

Metronidazole vs Vancomycin vs Tolevamer

- Patients stratified as mild, moderate, or severe
- Original goal of study was to evaluate tolevamer as a treatment for CDI

Drug	Mild	Moderate	Severe
Tolevamer	59	46	37
Metronidazole	79	76	65
Vancomycin	85	80	85

Louie et al. ICAAC AbstractK-425-9 2007

Recurrent Clostridium difficile infection

- Rates of recurrence
  - 20% after 1st episode
  - 45% after 1st recurrence
  - 65% after two or more recurrences
- No reports of Metronidazole or Vancomycin resistance following treatment

Original Article

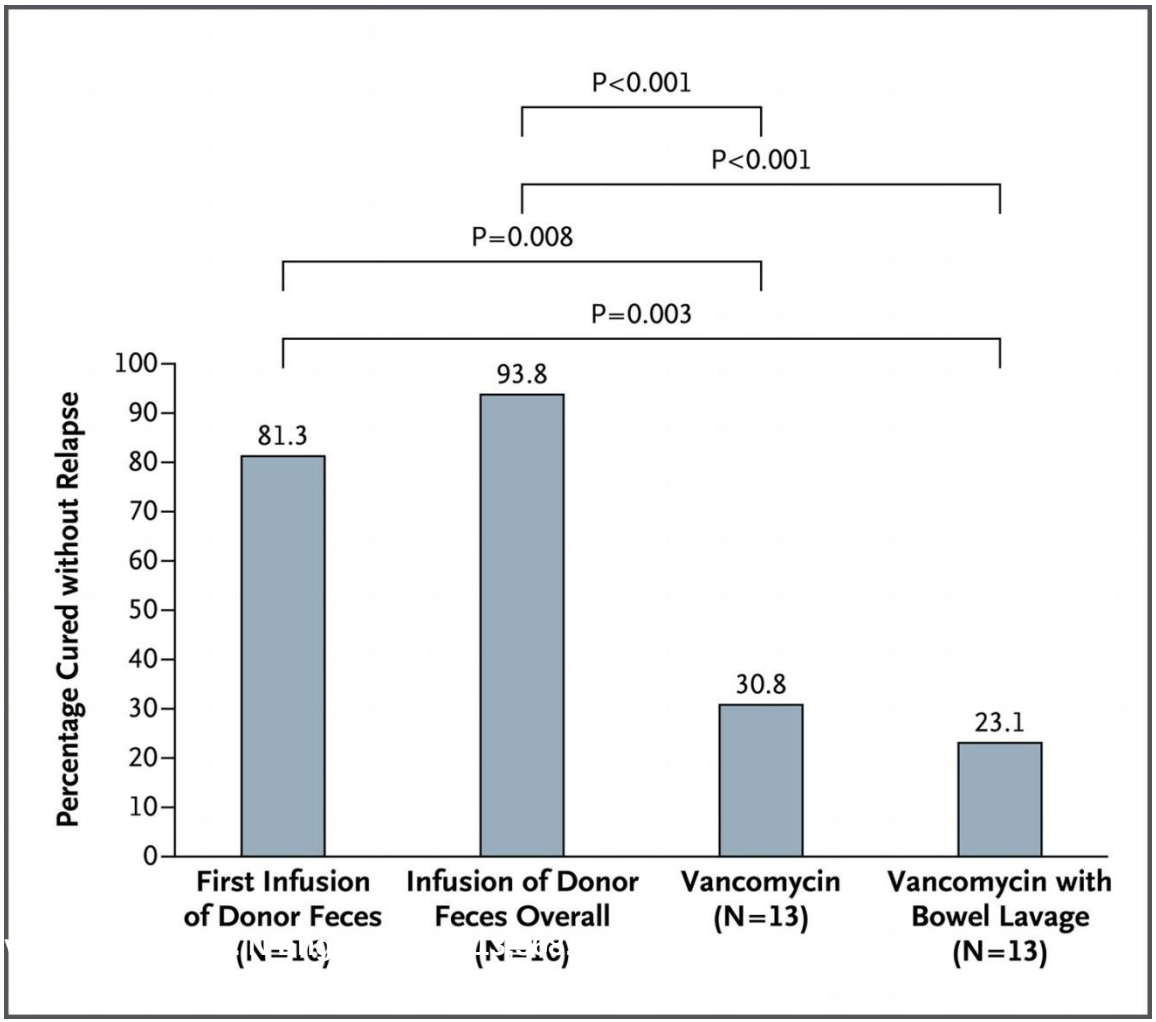
Duodenal Infusion of Donor Feces for Recurrent *Clostridium difficile*

Els van Nood, M.D., Anne Vrieze, M.D., Max Nieuwdorp, M.D., Ph.D., Susana Fuentes, Ph.D., Erwin G. Zoetendal, Ph.D., Willem M. de Vos, Ph.D., Caroline E. Visser, M.D., Ph.D., Ed J. Kuijper, M.D., Ph.D., Joep F.W.M. Bartelsman, M.D., Jan G.P. Tijssen, Ph.D., Peter Speelman, M.D., Ph.D., Marcel G.W. Dijkgraaf, Ph.D., and Josbert J. Keller, M.D., Ph.D.

N Engl J Med
Volume 368(5):407-415
January 31, 2013

The NEW ENGLAND JOURNAL of MEDICINE

Rates of Cure without Relapse for Recurrent *Clostridium difficile* Infection.



Case Report

- 79-year-old woman with multiple medical problems admitted to hospital for treatment of community-acquired pneumonia
- Responds slowly to levofloxacin 750 mg daily
- After 6 days
  - Develops diarrhea (9 loose BMs)
  - WBC count: 11,500/mm^3
- Day 7–14 loose BMs, WBC count rises to 19,500/mm^3
- Stool testing for *C. difficile* toxins A and B is requested
- Continued antibiotic therapy for pneumonia is deemed necessary

- How would you manage her care?
  A. Await stool test results and monitor her progress
  B. Empirically start metronidazole PO
  C. Empirically start metronidazole IV
  D. Empirically start vancomycin PO

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Treatment of Severe Disease

- Follow definition of severe disease
  - >10 BM/day, high WBC, low albumin
- This is a life-threatening infection
- Surgical consultation recommended as patient may require a colectomy
- Oral vancomycin drug of choice
  - Dose varies based on severity
  - Can add metronidazole (oral or IV)

Management of Severe CDI

- Early recognition is critical
  - Initiate therapy as soon as diagnosis is suspected
- Manage as for mild CDI plus:
  - Oral vancomycin (125 mg QID for 10 to 14 days) as initial treatment
- If patient is unable to tolerate oral medication, consider intracolonic vancomycin instillation (by enema)
  - 0.5–1 g vancomycin (IV formulation) in 0.1 to 0.5 L of normal saline via rectal (or Foley) catheter
  - Clamp for 60 minutes
  - Repeat every 4–12 hours

Management of Severe, Complicated CDI

- Potential role of intravenous immunoglobulin G (IVIG)[1-6]
  - Antitoxin A IgG predicts clinical outcome of CDI
  - Serum antibodies to toxins A and B are prevalent in healthy populations
- Recent studies in severe disease[5,6]
  - Well tolerated in small numbers of patients
  - Conflicting data regarding outcome improvement (mortality and need for colectomy)
- Often administered when surgery is considered imminent

Treatment for Clostridium difficile - Summary

- Discontinue preciptitatingantibiotics
- Oral Vancomycin125/250 mg qid for 10-14 d
- Oral Metronidazole 500 mg tid or qit for 10-14 d
  - Recent reports of resistance to metronidazole
- IV give both antibiotics together 200 mg bid for 10 d
- Fidaxomicin
- Experimental fecal transplant (enemas)

TEST TIME

I. Which fact is **incorrect** about *C. diff*?

a. Causes 500,000 cases per year
b. Severity of illness has increased last few years
c. Majority of *C. diff* cases are community acquired
d. Relapses are major problem with *C. diff* and may respond to stool transplant

II. Which of the following is **incorrect** regarding medical management of *C. diff*?

a. Oral metronidazole is recommended for mild *C. diff*
b. Oral vancomycin is preferred for moderate or severe *C.diff*
c. Patients with fulminant *C. diff* with ileus should receive intravenous vancomycin

III. Manifestations of fulminant *C. diff* include all the following except:

a. Severe abd pain and worsening diarrhea
b. Hypotension requiring vasopressors
c. Dropping WBCs
d. Respiratory failure requiring intubation
e. Elevated lactate levels
f. Renal failure

IV. New approaches to *C. diff* infection include all of the following except:

- PCR testing for quicker and more sensitive diagnosis – but may result in over-treatment of a carrier state
- Stool transplant for recurrent disease
- Less invasive surgical techniques to improve outcome and allow for earlier intervention
- Fidaxomicin as an inexpensive and effective oral therapy for NAP-1 strain infections