



Central
Health

What's the deal with C. difficile?

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Disclosure

- None to declare

Objectives

- After attending this session, the participant:
 - Should be familiar with the microbiology, and transmission of *C. difficile* infection (CDI).
 - Should be able to diagnose the condition based on laboratory data.
 - Will be able to identify risk factors for CDI and offer suggestions on how to reduce modifiable risk factors.
 - Will be able to offer recommendations on how to optimally treat first episode and recurrent CDI.
 - Will gain insight into how to integrate the treatment of CDI into an antimicrobial stewardship program intervention.

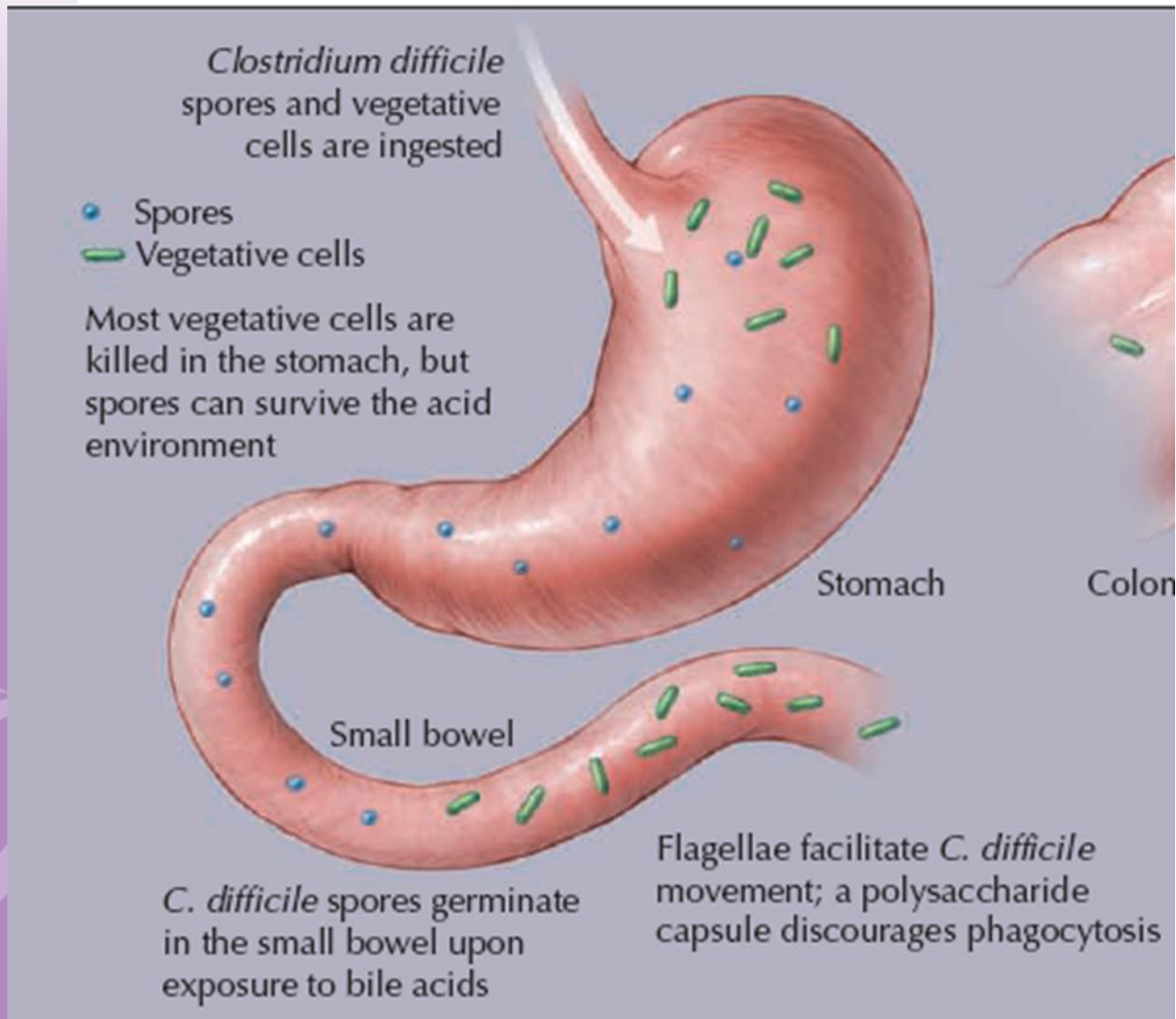
Microbiology

- Anaerobic gram-positive, spore-forming, toxin-producing bacillus
- "difficult clostridium" because of difficulty related to its isolation and growth on conventional media
- Two forms: spore and vegetative
 - Spore: outside the colon
 - resistant to heat, acid, and antibiotics.
 - Vegetative: inside the colon
 - fully functional, toxin-producing, susceptible to killing by antimicrobial agents.

Transmission

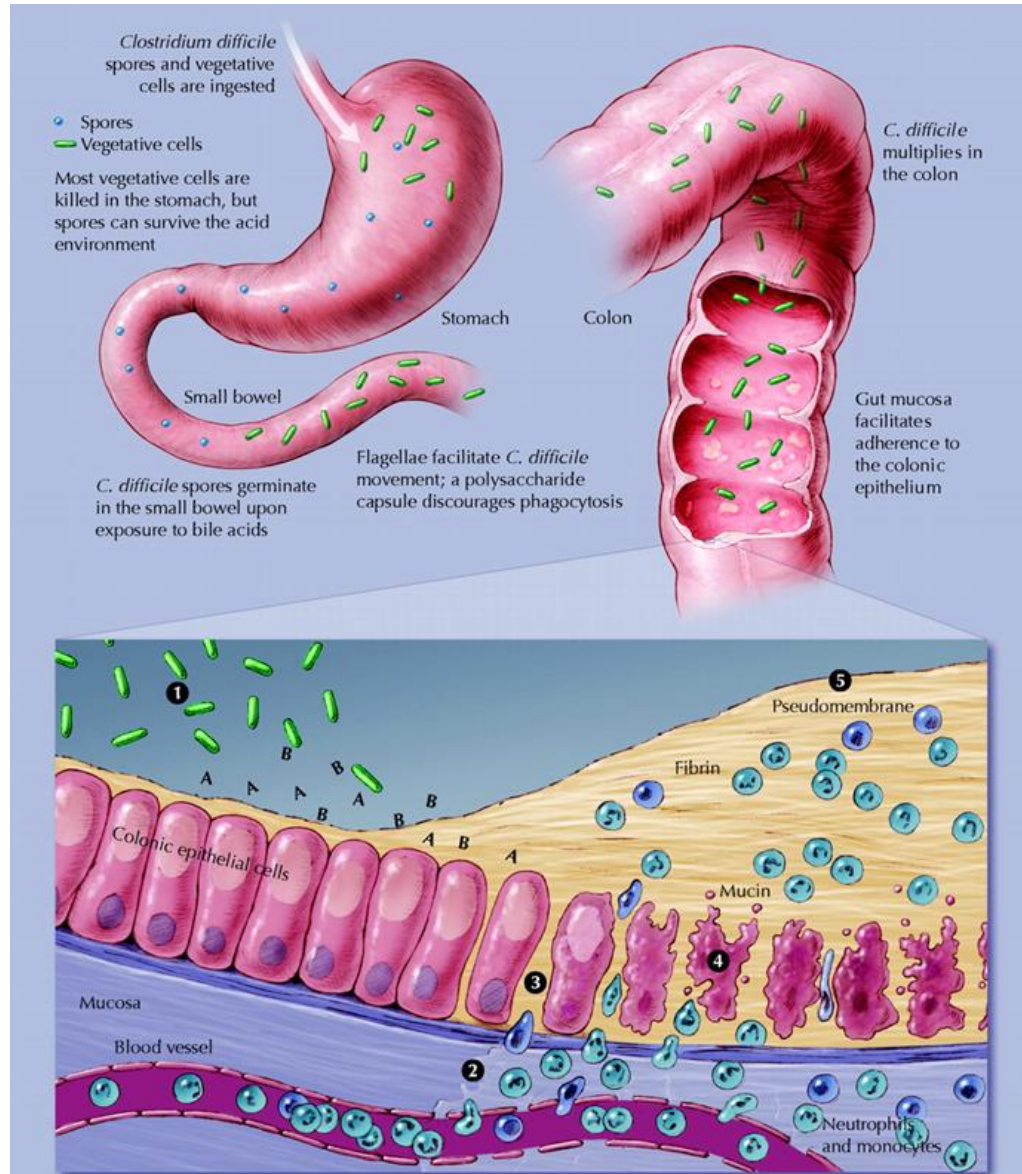
- Patients with *C. difficile* carriage are a reservoir for environmental contamination +/- clinical infection.
- Highly transmissible via the fecal-oral route by ingestion of spores.
- Cultured readily from the hospital environment, (hands, clothing, and stethoscopes of healthcare workers)
- Infection is also transmitted readily between hospital roommates.

Fig. 1: Pathogenesis of *Clostridium difficile*-associated diarrhea in adults.



Susan M. Poutanen, and Andrew E. Simor CMAJ
2004;171:51-58

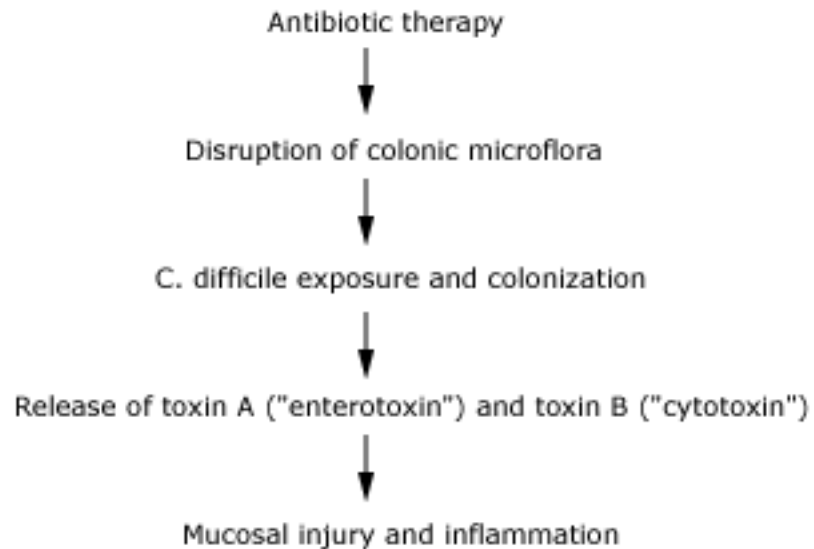
Fig. 1: Pathogenesis of *Clostridium difficile*-associated diarrhea in adults.



C. difficile vegetative cells produce toxins A and B and hydrolytic enzymes (1). Local production of toxins A and B leads to production of tumour necrosis factor-alpha and proinflammatory interleukins, increased vascular permeability, neutrophil and monocyte recruitment (2),

opening of epithelial cell junctions (3) and epithelial cell apoptosis (4). Local production of hydrolytic enzymes leads to connective tissue degradation, leading to colitis, pseudomembrane formation (5) and watery diarrhea.

Pathogenesis of *Clostridium difficile* diarrhea



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Laboratory Diagnosis

- Enzyme immunoassay (EIA) for *C. difficile* toxins A and B
 - Most *C. difficile* strains produce both toxins A and B
 - Sensitivity of EIA for toxins A and B is about 75 percent; the specificity is high (up to 99 percent)
- EIA for *C. difficile* glutamate dehydrogenase (GDH)
 - GDH antigen is an essential enzyme produced constitutively by all *C. difficile* isolates
 - its detection cannot distinguish between toxigenic and nontoxigenic strains

Laboratory Diagnosis

- Polymerase chain reaction (PCR) testing
 - detect toxin A and B genes; highly sensitive and specific
 - the sensitivity of PCR is greater than enzyme immunoassay
 - Potential for false positive results
 - GDH and EIA for toxins A and B + PCR

Risk Factors

- Antibacterial therapy
 - Treatment during the previous 3 months
 - Multiple antibacterial agents
- Older age (≥ 65 years)
- Severe underlying illness
- Immunocompromised patients
 - Immunosuppressive drugs
 - HIV infection
 - Antineoplastic agents
- Tube feeding and gastrointestinal surgery
- Gastrointestinal medications, including gastric acid reduction therapy
- ICU stay
- Prolonged hospitalization (median periods of 20 days)

Modifying Risk Factors

- Antimicrobial Stewardship
- PPI, H2 antagonists

Antibiotics as a Risk Factor

Antibiotic Class	Odds Ratio
Clindamycin	16.80
Cephalosporins/monobactams/carbapenems	5.68
Fluoroquinolones	5.50
Penicillins	2.71
Macrolides	2.65
Trimethoprim/sulfamethoxazole	1.81
Tetracycline	0.92

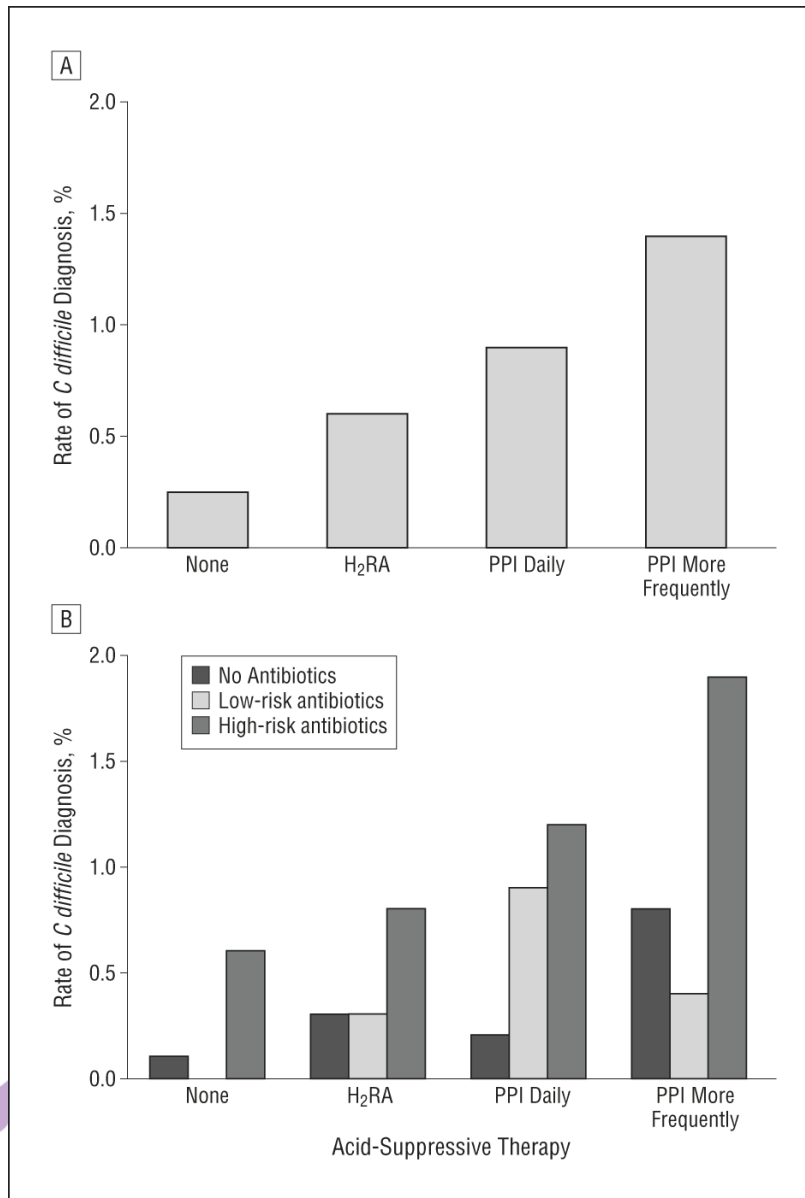
Thomas Glück, MD reviewing Brown KA et al. Antimicrob Agents Chemother 2013 May. Deshpande A et al. J Antimicrob Chemother 2013 Apr 25.

Acid Suppression

- Gurian et al. (1982) demonstrated that gastric juices killed *C. difficile* and neutralized its toxin in a dose dependent manner.

Gurian L, Ward TT, Katon RM. Possible foodborne transmission in a case of pseudomembranous colitis due to *Clostridium difficile*: influence of gastrointestinal secretions on *Clostridium difficile* infection. *Gastroenterology*. 1982;83(2):465-469.

Acid Suppression



Arch Intern Med. 2010;170(9):784-790.
doi:10.1001/archinternmed.2010.89

Treatment Regimens (Non-severe)

- Initial Therapy
 - Metronidazole 500 mg PO TID X 10-14 days or
 - Metronidazole 250 mg PO QID X 10 -14 days or
 - Metronidazole 500 mg IV TID X 10-14 days
 - If oral route is not feasible
 - Fecal concentrations in the therapeutic range are achievable drug's biliary excretion and increased exudation across the intestinal mucosa during CDI

Treatment Regimens (Non-severe)

- Metronidazole
 - Peripheral neuropathy (dose-dependent)
 - Nausea
 - Metallic taste

Treatment Regimens (Non-severe)

- Initial Therapy
- Pregnant, breastfeeding, or intolerant/allergic to metronidazole:
 - Vancomycin 125 mg PO QID X 10-14 days
 - No difference in 125 mg vs 500 mg
 - PO vancomycin is not absorbed systemically and achieves high levels in the colon
 - IV vancomycin has no effect on *C. difficile* colitis since the antibiotic is not excreted significantly into the colon

Treatment Regimens (Severe)

- No consensus definition for severe CDI
- Guideline parameters for severe CDI include
 1. WBC >15,000 cells/microL
 2. Serum creatinine level ≥ 1.5 times the premorbid level
- NAP1 strain (Quebec outbreak)
 - 11% of cases was associated with shock, colectomy, megacolon, perforation, or death.

Treatment Regimens (Severe)

- Oral vancomycin is the preferred therapy
- Zar et al., 2007:
 - Prospective, randomized, double-blind, placebo-controlled trial
 - N=172
 - Patients with 2 points were considered to have severe CDI
 - One point each for:
 - age >60 years
 - temperature >38.3C,
 - albumin level <2.5 mg/ dL
 - peripheral WBC count >15,000 cells/mm
 - Two points for endoscopic evidence of pseudomembranous colitis or in ICU

Treatment Regimens (Severe)

- Alternatives to vancomycin:
 - Fidoxamicin 200 mg PO BID
 - Additional data needed for efficacy in severe disease
 - Metronidazole 500 mg PO TID or 250 mg PO QID
- Ileus:
 - Metronidazole 500 mg IV q8h
 - Intracolonic vancomycin

Treatment Regimens (Severe)

- PO vancomycin + IV metronidazole
- 88 ICU patients w/CDI
 - 44 PO vancomycin
 - 44 PO vanco + IV metronidazole
- Mortality 36.4% monotherapy and 15.9% combination (P = .03)
- clinical success, length of stay, and length of ICU stay did not differ

Treatment regimens

Initial Recurrence

- “complete abatement of CDI symptoms while on appropriate therapy, followed by subsequent reappearance of diarrhea and other symptoms after treatment has been stopped.”
- Occurs in approximately 25% of cases treated with metronidazole or vancomycin
- Most present within one to three weeks after discontinuing antibiotic therapy (up to 2-3 months)

Treatment Regimens

Initial Recurrence

- Treatment of the first recurrence (non-severe) of CDI is usually with the same regimen as for the initial episode (i.e., metronidazole)
- Multiple recurrences
 - Avoid metronidazole (due to potential neurotoxicity and hepatic toxicity)
 - Vancomycin (pulse tapered fashion)
 - 500 mg PO daily X 7/7 then 250 mg PO daily X 7/7 then 125 mg PO daily X 7/7 then 125 mg every third day X 21/7
 - Fidoxamicin 200 mg PO BID X 10/7
 - Rifaximin

Antibiotics

- Fidaxomicin
 - Macrolide antibiotic
 - Absorption: Oral: Minimal systemic absorption
 - Distribution: Largely confined to the gastrointestinal tract
 - concentrations in feces substantially exceed the 90% MIC of *C. difficile*.
 - Fidaxomicin is bactericidal against gram-positive anaerobes and gram-positive aerobes (including *C. difficile* NAP1/B1/027 strain)
 - Not active against gram-negative aerobes or gram-negative anaerobes

Antibiotics

- Rifaximin
 - rifamycin-based non-systemic antibiotic that has effect against *C. difficile*
 - 200 to 400 mg PO 2 to 3 times daily X 14/7
 - Prior exposure to rifamycins may be a risk factor for resistant isolates
 - Possesses *in vitro* susceptibility to *C difficile* but does not kill other enteric flora

Response Times

- Resolution of fever – within first 2 days
- Resolution of diarrhea- within 2-4 days
- Symptoms for patients infected with NAP1 strains may take longer
- Failure to respond to metronidazole in 5 to 7 days necessitates change to vancomycin.

Other Considerations

- Discontinue opioids
- Discontinue laxatives, stool softeners, pro-motility agents
- Discontinue anti-diarrheals

Anti-infective guidelines for community-acquired infections. Toronto: MUMS Guideline Clearinghouse; 2013

CDI Audit

- April 1, 2014 to March 31, 2015
- 12 inpatients identified as having CDI
 - Was the optimal antimicrobial regimen ordered?
 - Was the precipitating antibiotic discontinued?
 - Was concurrent proton pump inhibitor discontinued?
 - Was concurrent opioid discontinued?
 - Were concurrent anti-diarrheals discontinued?
 - Were concurrent stool softeners and laxatives discontinued?

CDI Audit

Initial Treatment Regimen Ordered	Number of Patients	Number of patients who met criteria for antibiotic regimen*	
		Met Criteria	Did not meet Criteria
Metronidazole 500 mg PO BID	4	0	4
Metronidazole 500 mg IV BID	2	0	2
Metronidazole 500 mg PO TID	3	1	2
Vancomycin 125 mg PO QID	2	1	1
Vancomycin 250 mg PO QID	1	0	1
TOTAL	12	2	10

*based on mild to moderate disease (WBC less than $15 \times 10^9/L$ and SCr less than 1.5 X baseline): first line: metronidazole 500 mg PO TID or 250 mg PO QID and severe disease (WBC greater than or equal to $15 \times 10^9/L$ and SCr greater than or equal to 1.5 X baseline) first line: vancomycin 125mg PO QID.

17% of patients had antibiotic treatment consistent with the 2013 Anti-Infective Guidelines

CDI Audit

Potentially Exacerbating Medication	Number of prescriptions for the medication that could exacerbate CDI	Number of orders to discontinue potentially exacerbating medication	Number of prescriptions to continue potentially exacerbating medication (i.e., order not discontinued)
Precipitating antibiotic	9	3/9 (33%)	6/9 (66%)
Acid suppression agent	9	0 (0%)	9/9 (100%)
Opioids	4	0 (0%)	4/4 (100%)
Anti-diarrheals	0	n/a	n/a
Stool softeners and laxatives, or promotility agents	3	0	3/3 (100%)
TOTAL	25	3 (12%)	22 (88%)

12% of medications which could exacerbate CDI were discontinued.

CDI Audit: Intervention 1 (July 2015)



Attach Patient Label here

REGIONAL ANTIMICROBIAL STEWARDSHIP COMMITTEE C. DIFFICILE INFECTION (CDI) INTERVENTION FORM

This patient has been identified as (Pharmacist to check ONE):

- C. difficile Antigen AND Toxin A/B Positive C. difficile toxin DNA positive

Pharmacy suggests:

- No change in antibiotics Change _____ (metronidazole or vancomycin) to:
- Metronidazole 500 mg PO TID X 14 days
 - Rationale: _____
 - Vancomycin 125 mg PO QID X 14 days
 - Rationale: _____

Prescriber to consider:

- ✓ Discontinue precipitating antibiotics.
- ✓ Discontinue proton pump inhibitors (PPI's may increase risk of CDI due to acid suppression)
- ✓ Discontinue narcotics (may reduce clearance of pathogen)
- ✓ Discontinue anti-diarrheals (may reduce clearance of pathogen)
- ✓ Discontinue stool softeners and laxatives (may exacerbate diarrhea)

**ANY CHANGES MUST BE MADE ON THE PHYSICIAN ORDER FORM
THIS NOTE IS TO BE RETURNED TO PHARMACY UPON REVIEW BY PRESCRIBER**

Pharmacist: _____ Date: _____ Time: _____

Physician: _____ Date: _____ Time: _____

ANTIBIOTIC INTERVENTION

CDI Audit:

Intervention 2 (July 2015)

Treatment guidelines added to positive C. difficile toxin and/or antigen reports.

Recommended Treatment:

Mild to moderate (WBC < $15 \times 10^9/L$ and SCr < 1.5 x baseline):

- Metronidazole 500mg PO TID or 250mg PO QID x 10-14 days

Severe (WBC $\geq 15 \times 10^9/L$ and SCr ≥ 1.5 x baseline):

- Vancomycin 125mg PO QID x 10-14 days

CDI Audit 2016

- Second Audit Period: July 1, 2015 to December 31, 2015
- Total inpatients with positive *C. difficile* toxin AND antigen OR either positive toxin or antigen PLUS positive PCR: 13

CDI Audit 2016

Initial Treatment Regimen Ordered	Number of Patients	Number of patients who met criteria for antibiotic regimen?*	
		Yes	No
Metronidazole 500 mg PO BID	1	0	1
Metronidazole 500 mg PO TID	5	5	0
Metronidazole 250 mg PO QID	1	1	0
Metronidazole 500 mg PO q6h	1	0	1
Vancomycin 125 mg PO QID + Metronidazole 250 mg PO QID	1	0	1
Vancomycin 125 mg PO QID Metronidazole 500 mg IV TID	1	1	0
Vancomycin 250 mg PO QID	1	0	1
TOTALS	11	7 (64%)	4 (36%)

*based on mild to moderate disease (WBC < 15 X 10⁹/L and SCr < 1.5 X baseline): first line: metronidazole 500 mg PO TID or 250 mg PO QID and severe disease (WBC ≥ 15 X 10⁹/L and SCr ≥ 1.5 X baseline): vancomycin 125 mg PO QID.

In the two cases where both metronidazole and vancomycin were used, Meditech profiles were reviewed more closely to determine if cases clinically appeared “mild to moderate” or “severe”.

Total inpatients included in Treatment Regimen Audit: 11/13 (2/13 patients had no bloodwork taken to classify infection as “Mild to moderate” or “Severe”)

64% of patients had antibiotic treatment consistent with the 2013 Anti-Infective Guidelines (improved by 47%!)

CDI Audit

Potentially Exacerbating Medication	Number of prescriptions for the medication that could exacerbate CDI	Number of orders to discontinue potentially exacerbating medication	Number of prescriptions to continue potentially exacerbating medication (i.e., order not discontinued)
Precipitating antibiotic	5	0(0%)	5/5 (100%)
Acid suppression agent	5	1/5 (20%)	4/5 (80%)
opioids	2	0 (0%)	2/2 (100%)
anti-diarrheals	2	0 (0%)	2/2 (100%)
stool softeners and laxatives, or promotility agents	2	1/2(50%)	1/2(50%)
TOTAL	16	2/16 (13%)	14(88%)

13% of medications which could exacerbate CDI were discontinued (no change!)



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Questions?

