C.Difficile Associated Diarrhea Overview & Management

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Learning Objectives

1. Recognize the increasing incidence of C.difficile associated diarrhea (CDAD) and its risk factors

2. Recognize the severity of disease associated with the NAP1 strain and its risk factors

3. Describe severity criteria useful in choosing appropriate empiric therapy

4. Describe the appropriate monitoring parameters and strategies for management of patients with C.difficile

5. Address commonly asked questions encountered by pharmacists regarding CDAD

Definition

According to the IDSA guidelines, a case definition of CDI includes:

1) Presence of diarrhea, defined as passage of 3 or more unformed stools in 24 or fewer consecutive hours

2) A stool test result positive for the presence of toxigenic C.difficile or its toxins or colonoscopic or histopathologic findings demonstrating pseudomembranous colitis

Rarely (<1%) a symptomatic patient will present with ileus and colonic distension with minimal or no diarrhea.

Cohen SH, Gerding DN, Johnson S, et al. Clinical practice guidelines for Clostridium difficile infection in adults: 2010 update by the society for healthcare epidemiology of America (SHEA) and the infectious diseases society of America (IDSA). Infect Control Hosp Epidemiol. 2010;31(5):431-55.

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Epidemiology

Pathogenesis

Risk Factors

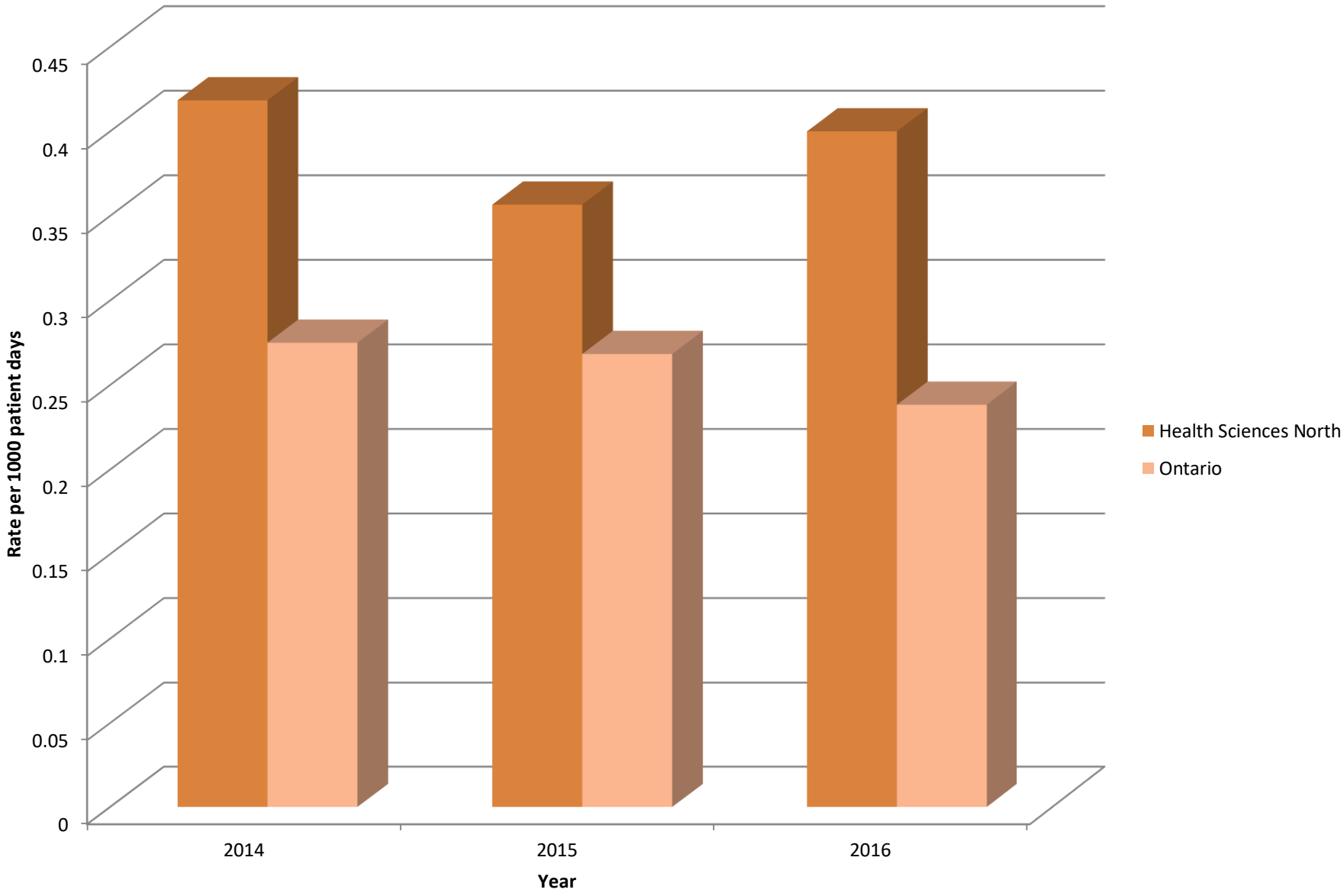
BACKGROUND

Epidemiology

- 400% higher incidence in the US between 2004-2014 compared to the previous decade.[1]
- In Canada, the rate per 1000 patient admissions has gone up from 4.51 in 2007 to 5.35 in 2011.[2]
- Higher incidence has been seen in the elderly population (close to 10x more)[3]
- Mortality rate for HA-CDI was 5.3% in 2011.[2]
  - Includes directly and indirectly related death, 30 days after Hospital acquired C.Diff infection (HA-CDI)

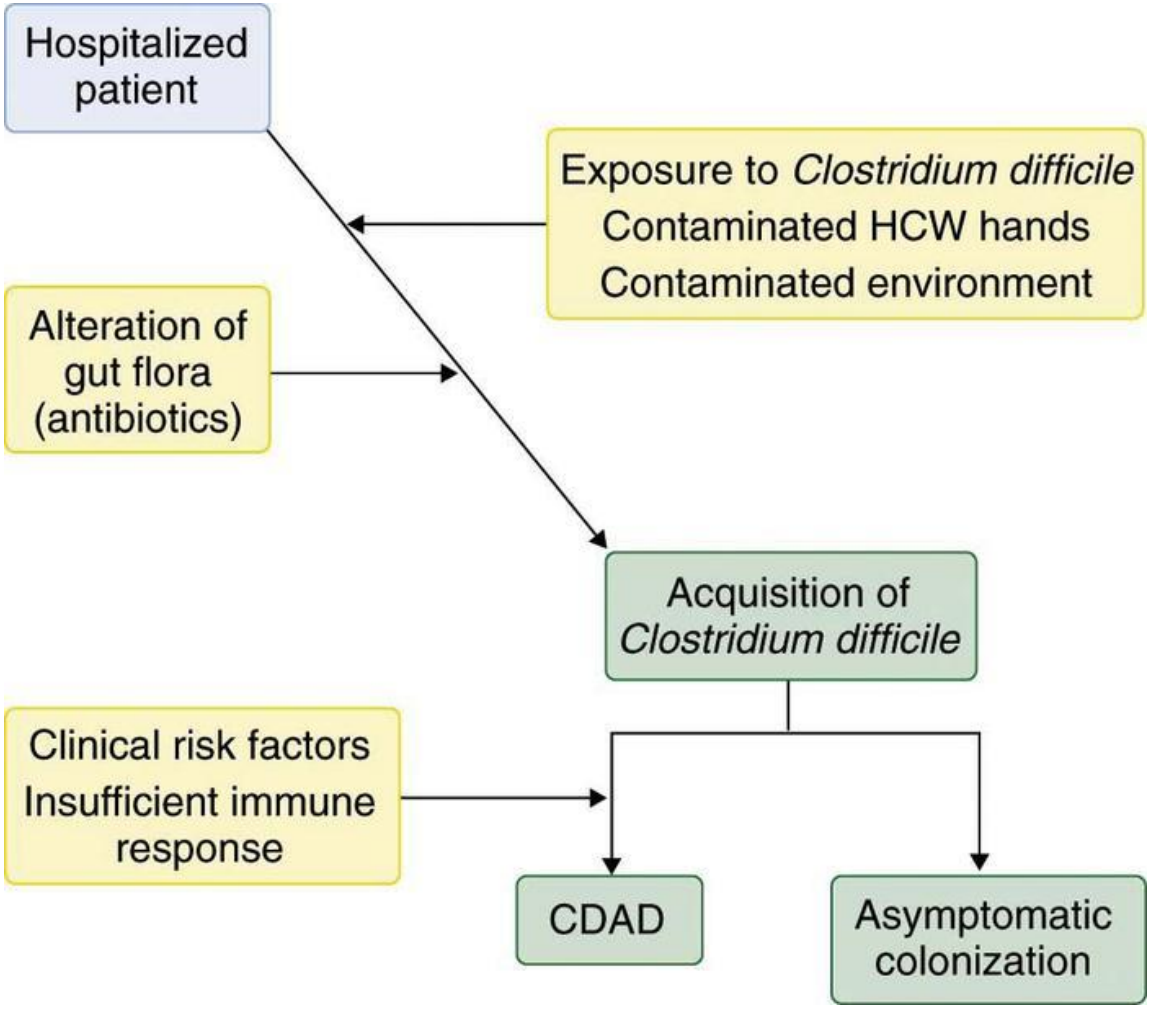
1. Mullane K. Fidaxomicin in Clostridium difficile infection: latest evidence and clinical guidance. Ther Adv Chronic Dis. 2014;5(2):69-84.
2. Available at: http://www.phac-aspc.gc.ca/nois-sinp/projects/cdad-eng.php. Accessed August 8, 2016.
3. Pépin J, Valiquette L, Alary ME, et al. Clostridium difficile-associated diarrhea in a region of Quebec from 1991 to 2003: a changing pattern of disease severity. CMAJ. 2004;171(5):466-72.

Comparing Provincial & HSN average annual C.difficile rates



Available at: http://www.hqontario.ca/System-Performance/Hospital-Care-Sector-Performance?_ga=1.4262458.824277335.1429659185. Accessed August 13, 2016.

Pathogenesis



http://www.clevelandclinicmeded.com/medicalpubs/diseasemanagement/infectious-disease/clostridium-difficile-infection/. Accessed August 1, 2016.

Risk Factors

- Age greater than 65
- Recent antibiotic use
  - As far back as last 2-3 months
- Recent hospitalization
  - Along with length of stay
- Gastric acid suppression
  - PPIs, Antacids, H2RAs
- Immunosuppression
  - Steroid use, Chemotherapy, HIV
- Inflammatory bowel disease
  - Higher incidence in Ulcerative Colitis vs Crohn's Disease[2]
- Manipulation of GI tract (surgery), including tube feeding

1. Cohen SH, Gerding DN, Johnson S, et al. Clinical practice guidelines for Clostridium difficile infection in adults: 2010 update by the society for healthcare epidemiology of America (SHEA) and the infectious diseases society of America (IDSA). Infect Control Hosp Epidemiol. 2010;31(5):431-55.
2. Trifan A, Stanciu C, Stoica O, Girleanu I, Cojocariu C. Impact of Clostridium difficile infection on inflammatory bowel disease outcome: a review. World J Gastroenterol. 2014;20(33):11736-42.

NAP1/BI/027 Strain

- Hypervirulent strain that has up to 20 times more toxin production than normal due to a gene mutation
- Found to be resistant to Fluoroquinolones, which has led to it's correlation with Fluoroquinolone use[1]
- Led to an outbreak in Quebec in the early 2000s, with an overall mortality rate of 16%.[2,3]
- Subgroup analysis showed no difference in outcomes for those aged less than 60 but more severe outcomes in older patients.[1]

1. Loo VG, Poirier L, Miller MA, et al. A predominantly clonal multi-institutional outbreak of Clostridium difficile-associated diarrhea with high morbidity and mortality. N Engl J Med. 2005;353(23):2442-9.
2. Pépin J, Valiquette L, Alary ME, et al. Clostridium difficile-associated diarrhea in a region of Quebec from 1991 to 2003: a changing pattern of disease severity. CMAJ. 2004;171(5):466-72.
3. Pépin J, Valiquette L, Cossette B. Mortality attributable to nosocomial Clostridium difficile-associated disease during an epidemic caused by a hypervirulent strain in Quebec. CMAJ. 2005;173(9):1037-42.

NAP1 and Mortality

	NAP1/027	Other types	Total
Death and ICU admissions	39 **(12.5%)**	41 **(5.9%)**	80
No severe outcomes	272 **(87.5%)**	656 **(94.1%)**	928
Total	311	697	

P = 0.0003 (Chi-Square test)

Loo VG, Poirier L, Miller MA, et al. A predominantly clonal multi-institutional outbreak of Clostridium difficile-associated diarrhea with high morbidity and mortality. N Engl J Med. 2005;353(23):2442-9.

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Diagnosis

Severity

Treatment

DIAGNOSIS/MANAGEMENT

Diagnosis

Test	Sensitivity (%)	Specificity (%)	Advantages	Disadvantages
PCR toxin gene detection	92-97	100	• Highly sensitive and specific • Fast (1-2 hours)	• Cost
ELISA toxin test	65-85	95-100	• Fast (2-6h) • Easy to do • High specificity	• Not very sensitive
Cytotoxin assay	80-90	99-100	• High sensitivity & specificity	• Takes 24-48h • Needs tissue culture facility • Only detects toxin B
Stool Culture	90-100	98-100	• Allows strain typing	• 2-5 days • Labor intensive • Non-specific

C.Difficile toxin is very unstable at room temperature and may be undetectable within 2 hours of collection if not promptly refrigerated or tested, giving a false negative.[3]

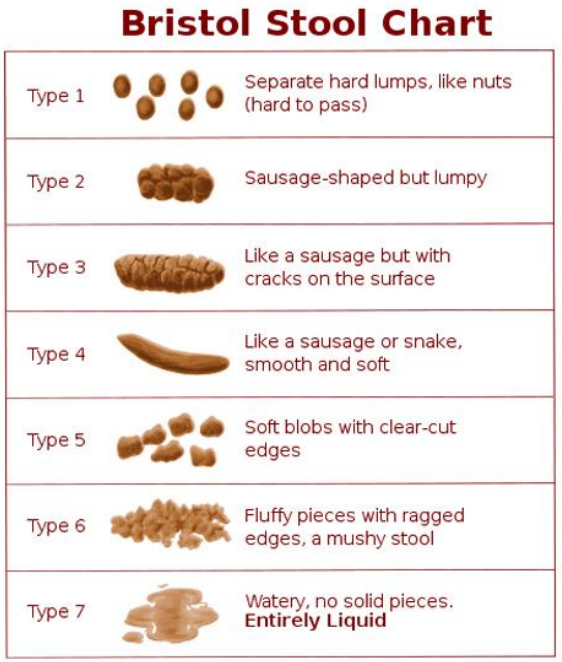
1. Poutanen SM, Simor AE: *Clostridium difficile*–associated diarrhea in adults. *CMAJ* 2004;171:51-58.
2. Cohen SH, Gerding DN, Johnson S, et al: Clinical practice guidelines for *Clostridium difficile* infection in adults: 2010 updated by the Society for Healthcare Epidemiology of America (SHEA) and the Infectious Disease Society of America (IDSA). *Infect Control Hosp Epidemiol* 2010;31:431-455.
3. Available at: http://www.cdc.gov/hai/organisms/cdiff/cdiff_faqs_hcp.html. Accessed August 14, 2016.

Diagnosis

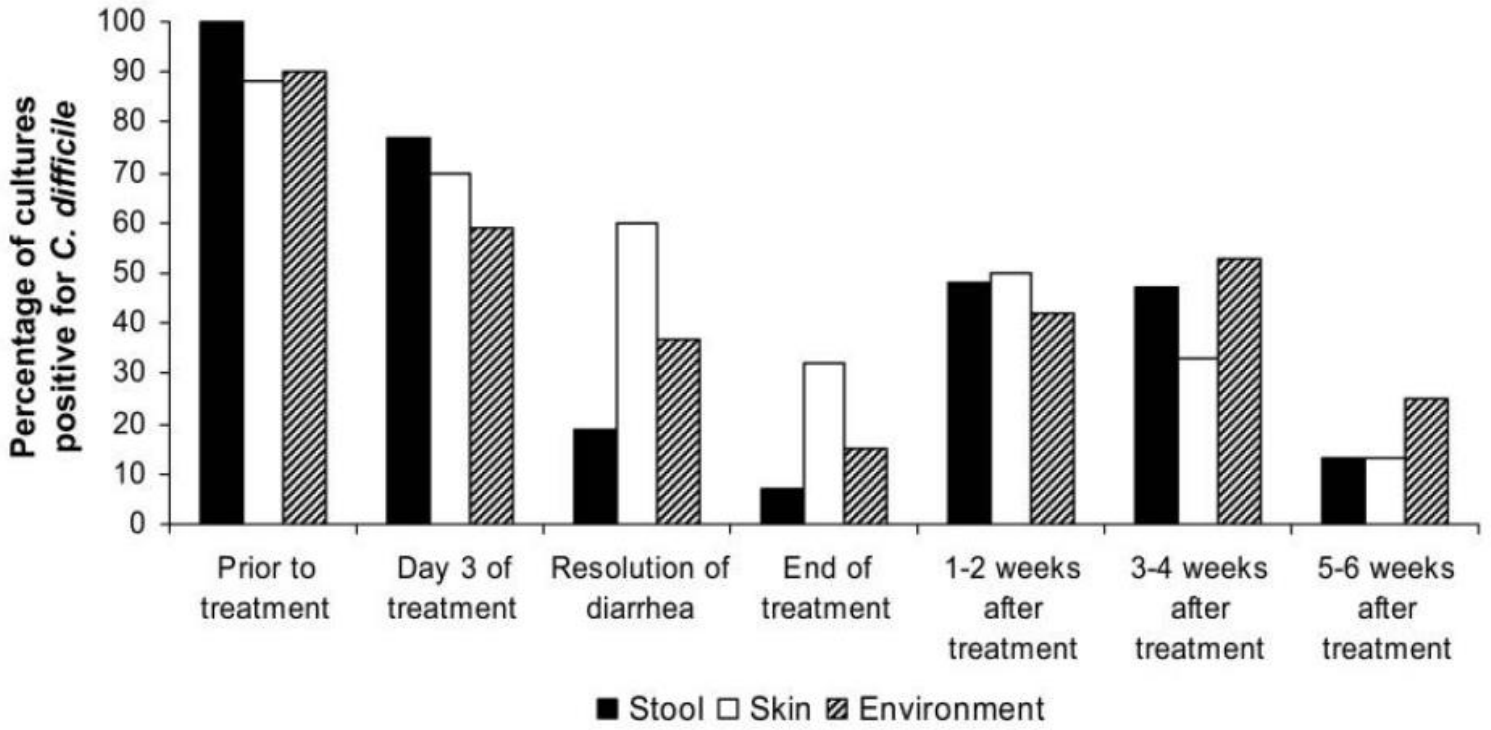
- Patient must have unformed stools (symptomatic) for it to be sent for culturing
  - a stool specimen that takes the shape of the container it is put in and is equivalent to types 5-7 on the Bristol stool chart.

- Asymptomatic patients should not be tested because as many as 20-50% of adults in a healthcare environment can be carriers[2]

- Test of cure should not be performed as a successfully treated patient can still shed toxin in the stool for many weeks



1. Cohen SH, Gerding DN, Johnson S, et al. Clinical practice guidelines for Clostridium difficile infection in adults: 2010 update by the society for healthcare epidemiology of America (SHEA) and the infectious diseases society of America (IDSA). Infect Control Hosp Epidemiol. 2010;31(5):431-55.
2. Riggs MM, Sethi AK, Zabarsky TF, Eckstein EC, Jump RL, Donskey CJ. Asymptomatic carriers are a potential source for transmission of epidemic and nonepidemic Clostridium difficile strains among long-term care facility residents. Clin Infect Dis. 2007;45(8):992-8.



Percentage of stool, skin and environmental cultures positive for C.difficile among 52 patients with C.diff infection. The numbers of patients who had samples cultured at each time point were 52 before treatment, 48 on day 3 of treatment, 43 after resolution of diarrhea, 28 at the end of treatment, 22 at 1–2 weeks after treatment, 15 at 3–4 weeks after treatment, and 8 at 5–6 weeks after treatment.

Sethi AK, Al-nassir WN, Nerandzic MM, Bobulsky GS, Donskey CJ. Persistence of skin contamination and environmental shedding of Clostridium difficile during and after treatment of C. difficile infection. Infect Control Hosp Epidemiol. 2010;31(1):21-7.

Determining severity

As per the 2010 IDSA guidelines:

- Mild to moderate if WBC 15,000 cells/µL or lower AND SCr level less than 1.5x baseline
- Severe if WBC >15,000 cells/µL OR SCr level greater than or equal to 1.5x baseline
- Severe, complicated if presence of hypotension/shock, ileus, megacolon

****Criteria based on expert opinion.**

Cohen SH, Gerding DN, Johnson S, et al. Clinical practice guidelines for Clostridium difficile infection in adults: 2010 update by the society for healthcare epidemiology of America (SHEA) and the infectious diseases society of America (IDSA). Infect Control Hosp Epidemiol. 2010;31(5):431-55.

Since then..

1) Zilberberg MD, Shorr AF, Wang L, Baser O, Yu H. **Development and Validation of a Risk Score for Clostridium difficile Infection in Medicare Beneficiaries: A Population-Based Cohort Study**. J Am Geriatr Soc. 2016;

2) Dubberke ER, Yan Y, Reske KA, et al. **Development and validation of a Clostridium difficile infection risk prediction model**. Infect Control Hosp Epidemiol. 2011;32(4):360-6.

3) Van werkhoven CH, Van der tempel J, Jajou R, et al. **Identification of patients at high risk for Clostridium difficile infection: development and validation of a risk prediction model in hospitalized patients treated with antibiotics**. Clin Microbiol Infect. 2015;21(8):786.e1-8.

4) Tanner J, Khan D, Anthony D, Paton J. **Waterlow score to predict patients at risk of developing Clostridium difficile-associated disease**. J Hosp Infect. 2009;71(3):239-44.

Severity Criteria

- ❑ Age greater than 65
- ❑ Immunosuppression (HIV with CD4 less than $50x10^6$, solid organ or stem cell transplant, neutropenia, systemic steroids equivalent to prednisone 20 mg daily)
- ❑ Temperature greater than 38°C
- ❑ Increase in SCr greater than 50% from baseline or significantly decreased urine output
- ❑ WBC greater than 15 x 10^9/L
- ❑ Albumin less than 30 g/dL
- ❑ Abdominal examination consistent with peritonitis

Mild to Moderate Disease

Patient meets less than 2 severity criteria

+

Patient is stable with no signs of shock*

Severe Disease

Patient meets 2 or more severity criteria

+

Patient is stable with no signs of shock*

Complicated/Fulminant Disease

Patient is hemodynamically unstable or has signs of shock*

OR

Patient has ileus or toxic megacolon

*Shock: SBP less than 90 mm Hg or SBP decrease greater than 40 mm Hg from baseline, urine output less than 0.5 mL/kg/h, decreased level of consciousness, serum lactate greater than 2 mmol/L

Available at: http://www.antimicrobialstewardship.com/sites/default/files/article_files/clostridium_difficile_infection_protocol_march2016.pdf. Accessed August 8, 2016.

Treatment

Mild/Moderate Disease

Metronidazole 500 mg PO/NG three times daily for 10-14 days
*IV if unable to take enteral medication, PO/NG preferred

Severe Disease

Vancomycin 125 mg PO/NG four times daily for 10-14 days

+/-

Metronidazole 500 mg IV three times daily for 1-14 days

Complicated/ Fulminant Disease

Vancomycin 125 mg PO/NG four times daily for 14 days

AND

Metronidazole 500 mg IV three times daily for up to 14 days

+/-

Vancomycin 500 mg in approximately 100 mL NS per rectum four times daily as retention enema, retain for 60 minutes

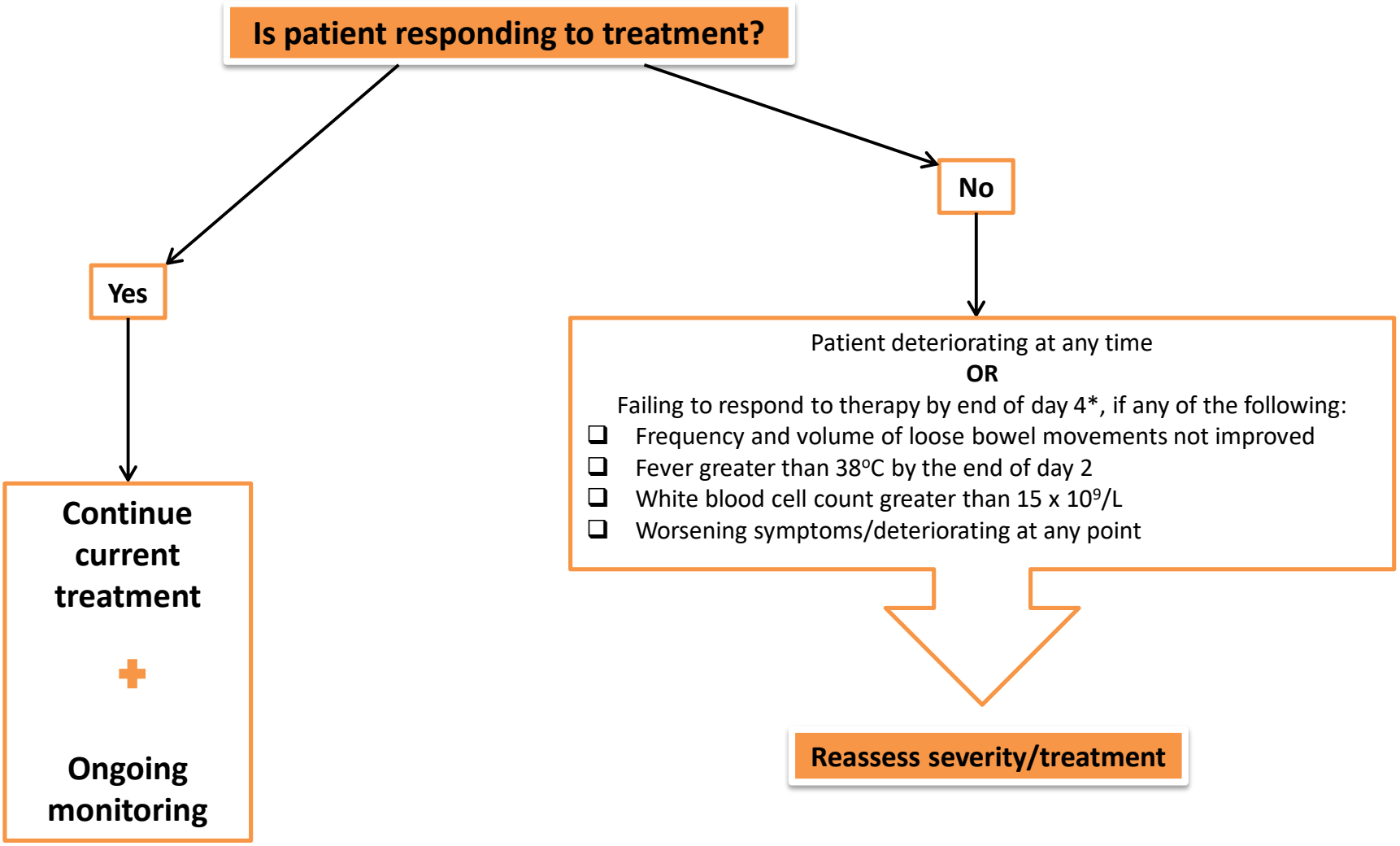
Monitoring

- ❑ **Vital signs (Temp, BP)**
- ❑ **Electrolytes**
- ❑ **CBC**
- ❑ **Creatinine**
- ❑ **Albumin**
- ❑ **Lactate**
- ❑ **Frequency of bowel movements**

Reassess the need for following therapies:

- **Concurrent antibiotics for active infection. If required, possible to switch to lower risk antibiotics?**
- **Concurrent acid suppression (PPIs, H2RAs, Antacids)**
- **Discontinue antidiarrheal/antiperistaltic agents**
  - Want the toxin to be flushed out of the colon
  - Metronidazole achieves higher concentration in the colon in presence of diarrhea
- **Discontinue/reassess narcotics and bowel regimens**

Response to Treatment



Available at:
http://www.antimicrobialstewardship.com/sites/default/files/article_files/clostridium_difficile_infection_protocol_march2016.pdf. Accessed August 8, 2016.

Treatment for recurrence

- First recurrence is treated with the same regimen as the initial episode but stratified by disease severity. **(C-III)**
- Do not use Metronidazole beyond first recurrence or for long term chronic therapy due to risk for cumulative neurotoxicity. **(B-II)**
- For second or later recurrence, use Vancomycin therapy using a tapered and/or pulse regimen as the preferred strategy. **(B-III)**

Cohen SH, Gerding DN, Johnson S, et al. Clinical practice guidelines for Clostridium difficile infection in adults: 2010 update by the society for healthcare epidemiology of America (SHEA) and the infectious diseases society of America (IDSA). Infect Control Hosp Epidemiol. 2010;31(5):431-55.

Pulse regimen

- Vancomycin 125 mg PO q6h for 10-14 days then,125 mg PO BID for 7 days followed by 125 mg PO daily for 7 days, and then 125 mg every 2-3 days for 2-8 weeks.[1]

- Vancomycin 125 mg PO q6h for 10 days, followed by 125 mg PO daily pulsed every 3 days for 10 doses.[2]

Purpose of the pulse regimen is to allow the spores to germinate and then kill the vegetative form of C.difficile as spores are not eradicated by antibiotics.

1. Cohen SH, Gerding DN, Johnson S, et al. Clinical practice guidelines for Clostridium difficile infection in adults: 2010 update by the society for healthcare epidemiology of America (SHEA) and the infectious diseases society of America (IDSA). Infect Control Hosp Epidemiol. 2010;31(5):431-55.
2. Surawicz CM, Brandt LJ, Binion DG, et al. Guidelines for diagnosis, treatment, and prevention of Clostridium difficile infections. Am J Gastroenterol. 2013;108(4):478-98.

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Intervention Template

Purpose

APPLYING THE ALGORITHM

Intervention Template

Intervention name: FNA **Get code: SRCDI**

Date:

Current treatment:

C diff PCR:

a) Age > 65?
b) Immunocompromised?
c) Fever (> 38)?
d) SCr increased more than 50% from baseline or reduced urine output?
e) WBC > 15?
f) Albumin < 30?
g) Peritonitis?

1 point for each of above AND positive PCR:

Score 0-1 = Mild/mod = Flagyl 500 mg PO q8h x 10-14 days.

Score 2+ = Severe = Vanco 125 mg PO q6h x14 days +/- Flagyl 500 mg IV q8hr x 1-14 days.

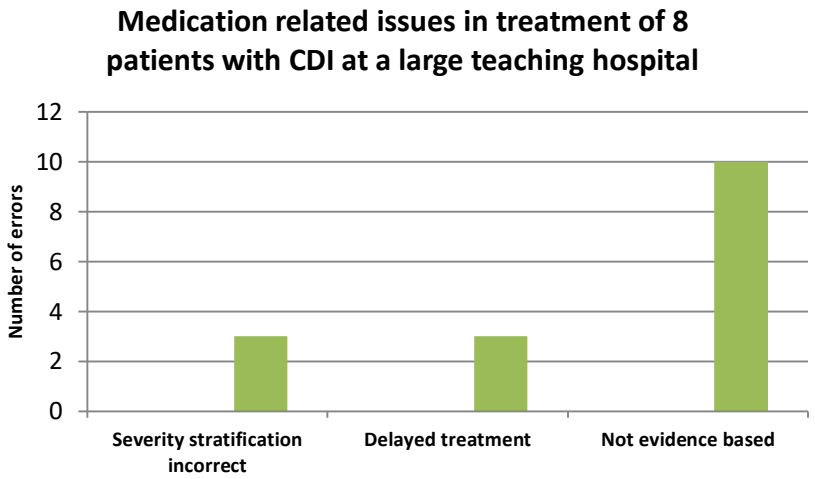
Ileus/toxic megacolon/shock = Complicated = Vanco 125 mg PO q6h x 14 days AND Flagyl 500 mg IV up to 14 days +/- vanco retention enema 500 mg in 100 mL NS PR QID (retain for 60 mins)

Suggestions:

Plan/FU:

Purpose

- Pharmacist's involvement early in the CDI process is critical for timely interventions on medication related issues
- We want to be able to gather stats on the number of patients we intervene on to change therapy
- Also how many patients are started on the correct regimen according to severity



- Ultimately want to transition this into a pre printed order or an automatic substitution

Available at:
http://www.cshp.ca/programs/cshp2015/virtualposters/2015/posters/files/posters/cshp2015_2015_poster_16_poster.pdf

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FREQUENTLY ENCOUNTERED QUESTIONS BY PHARMACISTS

Questions

1. Are certain antibiotics more likely to cause C.difficile infection?

2. How soon can we repeat PCR testing after a negative test result?

3. Do probiotics have any role for treatment or prevention of C.difficile infection?

Antibiotics and C.difficile Risk

- Any antibiotic can potentially cause a C.difficile infection
- No head to head RCTs out there comparing antibiotics and their risk for C.difficile infection
- Most if not all data comes from retrospective or observational studies, thus lots of confounders
- **Highly dependent on prescribing trends! More you use, more likely to see CDI**

Frequently associated
Fluoroquinolones
Clindamycin
Cephalosporins
Penicillins (broad spectrum)
Occasionally associated
Macrolides
Septra
Rarely associated
Aminoglycosides
Tetracyclines
Metronidazole
Vancomycin

Table adapted from UptoDate

	Slimings and Riley (2014) Hospital associated	Brown et al. (2003) Community associated	Deshpande et al. (2013) Community associated
Description of Meta-analysis	13 Case control studies and 1 cohort study 3202 cases 15,938 patients	6 Case control studies and 1 cohort study 2578 cases	8 case control studies Cases not reported 30,184 patients
Clindamycin	OR: 1.57 (CI: 2.04-4.02)	OR: 16.8 (CI: 7.48-37.76)	OR 20.43 (CI: 8.50-49.09)
Cephalosporins	OR: 1.97 (CI: 1.21-3.23) Subgroup 1st gen – OR 1.36 (CI 0.92-2) 2nd gen – OR 2.23 (CI 1.47-3.37) 3rd gen – OR 3.20 (CI 1.80-5.71)	OR: 5.68 (CI: 2.12-15.23)	OR: 4.47 (CI: 1.60-12.50)
Quinolones	OR: 1.66 (CI: 1.17-2.35)	OR: 5.50 (CI: 4.26-7.11)	OR: 5.65 (CI: 4.38-7.28)
Penicillins	No significant association seen Pip-Taz/Amoxi-clav subgroup OR 1.54 (CI 1.05-2.24)	OR: 2.71 (CI: 1.75-4.21)	OR: 3.25 (CI: 1.89-5.57)
Macrolides	No significant association seen	OR: 2.65 (CI: 1.92-3.64)	OR: 2.55 (CI: 1.91-3.39)
Septra	OR: 1.78 (CI: 1.04-3.05)	OR: 1.81 (CI: 1.34-2.43)	OR: 1.84 (CI: 1.48-2.29)
Carbapenems	OR: 1.84 (CI: 1.26-2.68)	---	---
Tetracyclines	No significant association seen	No significant association seen	No significant association seen
Aminoglycosides	No significant association seen	---	---

Abbreviations: Odds Ratio (OR), 95% Confidence interval (CI)

Available at: https://www.nice.org.uk/advice/esmpb1/chapter/Key-points-from-the-evidence

Does Doxycycline Protect Against Development of *Clostridium difficile* Infection?

Sarah B. Doernberg,[1] Lisa G. Winston,[1] Daniel H. Deck,[2] and Henry F. Chambers[1]

[1]Department of Internal Medicine, Division of Infectious Diseases, University of California, San Francisco, and [2]Department of Pharmaceutical Sciences, San Francisco General Hospital, California

Background. Receipt of antibiotics is a major risk factor for *Clostridium difficile* infection (CDI). Doxycycline has been associated with a lower risk for CDI than other antibiotics. We investigated whether doxycycline protected against development of CDI in hospitalized patients receiving ceftriaxone, a high-risk antibiotic for CDI.

Methods. We studied adults admitted to an academic county hospital between 1 June 2005 and 31 December 2010 who received ceftriaxone to determine whether the additional receipt of doxycycline decreased the risk of CDI. Patients were followed from first administration of ceftriaxone to occurrence of CDI or administrative closure 30 days later.

Results. Two thousand three hundred five unique patients comprising 2734 hospitalizations were studied. Overall, 43 patients developed CDI within 30 days of ceftriaxone receipt, an incidence of 5.60 cases per 10 000 patient-days. The incidence of CDI was 1.67 cases per 10 000 patient-days in those receiving doxycycline, compared to 8.11 per 10 000 patient-days in those who did not receive doxycycline. In a multivariable model adjusted for age, gender, race, comorbidities, hospital duration, pneumonia diagnosis, surgical admission, and duration of ceftriaxone and other antibiotics, for each day of doxycycline receipt the rate of CDI was 27% lower than a patient who did not receive doxycycline (hazard ratio, 0.73; 95% confidence interval, .56–.96).

Conclusions. In this cohort of patients receiving ceftriaxone, doxycycline was associated with lower risk of CDI. Guidelines recommend this combination as a second-line regimen for some patients with community-acquired pneumonia (CAP). Further clinical studies would help define whether doxycycline-containing regimens should be a preferred therapy for CAP.

Doernberg SB, Winston LG, Deck DH, Chambers HF. Does doxycycline protect against development of Clostridium difficile infection?. Clin Infect Dis. 2012;55(5):615-20.

Repeat PCR Testing

- Micro policy: You must wait a week before you can repeat a C.diff toxin PCR after it comes back negative
- Retrospective cohort study looked at 406 repeat tests in the two weeks after the initial negative
- Only 10 of 406 tests came back positive (2.5%) in the two weeks
- Rate of positives within 1 week was 1.1% while after the 1 week mark it was 5%

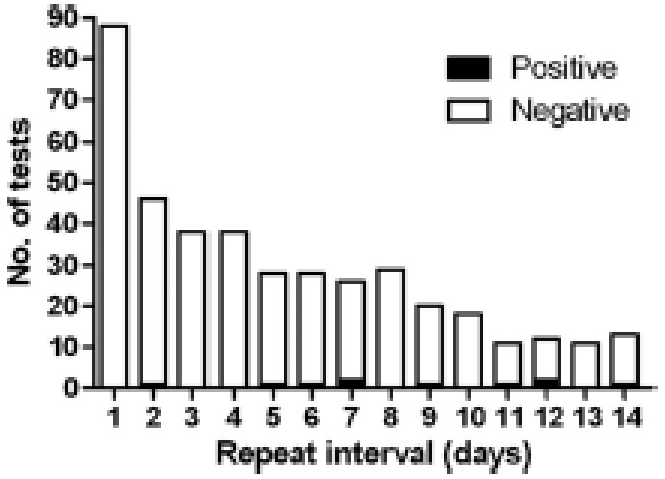

FIG. 1. Results for repeat PCR tests following a negative result. The PCR results per day for all patients who underwent repeat testing 1 to 14 days following a prior negative result are shown.

Repeat testing within a week after a negative result is of little to no clinical value.

Luo RF, Banaei N. Is repeat PCR needed for diagnosis of Clostridium difficile infection?. J Clin Microbiol. 2010;48(10):3738-41

Probiotics

- Limited data out there for treatment, more data pertaining to prevention
- 2012 Meta analysis looking at 20 randomized trials with a total of 3818 patients, concluded probiotics reduce incidence of C.difficile associated diarrhea (CDAD) by 66%[1]
- Common problem with these meta analyses is the heterogeneity between studies as not all studies use the same strain/formulation or dose
- Probiotics are not regulated as tightly as drugs, which makes them more susceptible to manufacturing inconsistencies
- PLACIDE study published in 2013 was a large, well designed RCT with 2941 patients over the age of 65, looking at CDAD prevention using a multistrain preparation of *Lactobacillus acidophilus* and *Bifidobacterium bifidum*[2]
  - Found no significant reduction in CDAD (RR 0.71; 95% CI 0.34-1.47)
- Risks of probiotics include bacteremia/fungemia in severely ill or immunocompromised patients
- Overall, no good data to support use of probiotics in treatment or prevention of CDAD but is an option for patients who can afford it and have no contraindications

1. Johnston BC, Ma SS, Goldenberg JZ, et al. Probiotics for the prevention of Clostridium difficile-associated diarrhea: a systematic review and meta-analysis. Ann Intern Med. 2012;157(12):878-88.
2. Allen SJ, Wareham K, Wang D, et al. Lactobacilli and bifidobacteria in the prevention of antibiotic-associated diarrhoea and Clostridium difficile diarrhoea in older inpatients (PLACIDE): a randomised, double-blind, placebo-controlled, multicentre trial. Lancet. 2013;382(9900):1249-57.

Questions?