UTAH SOCIETY OF HEALTH–SYSTEM PHARMACISTS

Annual Meeting
August 18, 2018

Poll Everywhere Audience Response

ACPE requires active learning and most prefer real-time participation rather than a graded post-test

We are utilizing Poll Everywhere software for this process.

You may join to participate by 3 different ways:

Text Messaging: Text ushp to 22333

Web Browser: Go to PollEv.com/ushp

Poll Everywhere app: Download app and join ushp presentation

For each question, you can click on the correct answer in Web Browser or App or text correct answer to 22333

Updated IDSA Guidelines for the Treatment of *C. difficile* Infection

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Disclosure

- I have no conflicts of interest to disclose.
- I will discuss the use of Fecal Microbiota Transplantation for the treatment of *C. difficile* infection.
- I will also discuss the dosing of rifaximin (Xifaxan®) in pediatric patients.
- No other off-label drug uses

Learning Objectives

At the conclusion of this activity, ***pharmacists*** should be able to successfully:

1. Evaluate and contrast new recommendations for drug treatment of *C. difficile* infection, particularly related to metronidazole and fidaxomicin.

2. Summarize the evidence supporting those changes, with an emphasis on long-term outcomes.

3. Formulate and defend a treatment recommendation to a provider, using the best available evidence from the new guidelines.

4. Teach a patient about *C. difficile* risk factors, therapy options and possible results.

Learning Objectives

At the conclusion of this activity, ***pharmacy technicians*** should be able to successfully:

1. Describe the mechanism and impact of *C. difficile* infection.

2. Identify medications in current use for the treatment of *C. difficile.*

3. Explain why antibiotic use is the most important modifiable risk in developing this infection.

Why should I care about *C. difficile*?

- Estimated annual incidence in US: 453,000 in 2011; 29,000 deaths
- Since 2000, CDI-attributable mortality: 4.5%-5.7% (endemic), 6.9%-16.7% (epidemic)
- Per episode, for acute-care hospitals: $3427-$9960 (2012 dollars)
- Extrapolates to $1.2-$5.9 billion annual acute care costs

Reference(s): 1

Preliminaries

Abbreviations

- Vancomycin (Vancocin®) = Vancomycin (Vancocin®) PO/PR
- CDI: *Clostridium difficile* infection
- FMT: Fecal Microbiota Transplantation (sometimes Fecal Matter Transplant)

Structure of Guidelines

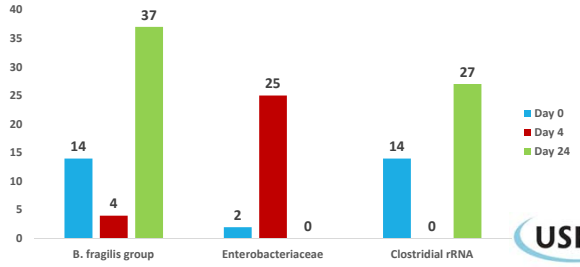
1. Epidemiology
2. Diagnosis
3. Infection Prevention
   1. Antibiotic Stewardship
   2. PPIs and Probiotics
4. Treatment
   1. Adults
   2. Pediatrics
5. Unanswered Questions

Background

- Since 2016, ~~*Clostridium difficile*~~
  - NOW *Clostridioides difficile*
- Why the change?
  - Improved sequencing
  - Phenotype/biochemistry
- *C. difficile* colitis first described in 1970's
  - Broad-spectrum agents
  - Disruption of normal bowel flora

Reference(s): 2-4

Bacterial clones in a random stool sample Before, during and after Augmentin



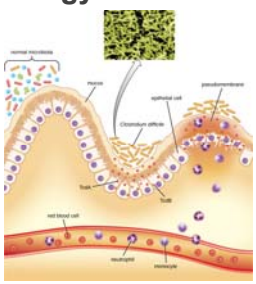
Reference(s): 5

Toxigenic *C. difficile*

- Toxin A
  - Inflammation →
  - Fluid secretion →
  - Mucosal injury
- Toxin B
  - Opens cell junctions
  - Essential to toxigenic activity
- NAP1/BI/027
  1. "Hypervirulent"
  2. Binary toxin
  3. Increase in toxin production
  4. Fluoroquinolone resistance

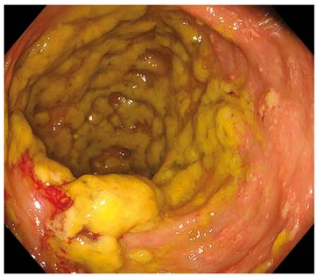
Reference(s): 6

Pathophysiology



Reference(s): 6

Imaging



Reference(s): 7

Clinical Diagnosis

- Which patients to test?
- Adults
  1. Unexplained **AND**
  2. New-onset **AND**
  3. ≥ 3 unformed stools in 24 hrs
- Pediatrics
  - ≤ 12 mos old = DO NOT TEST
  - 1-2 yrs = only if other causes for diarrhea ruled out
  - > 2 yrs = prolonged/worsening diarrhea, contact with healthcare

Reference(s): 1, 8

Question 1

Choose the toxin that is NOT seen in *C. difficile* infections.

A. Binary toxin

B. Toxin B

C. Tetrodotoxin

D. Toxin A

Laboratory Methods

Detection Techniques

- GDH enzyme: glutamate → α-ketoglutarate + ammonia
- EIA – Enzyme Immunoassay
- NAAT – Nucleic Acid Amplification Test

- Is *C. difficile* here?
- Is *C. difficile* producing toxin?
- Is *C. difficile* producing LOTS of toxin?

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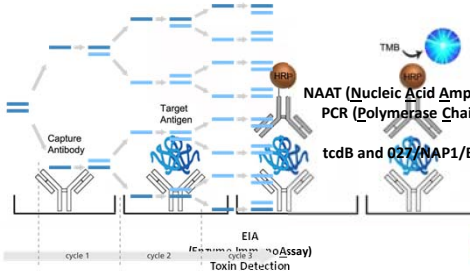
Reference(s): 10

Detection Techniques



NAAT (Nucleic Acid Amplification Test)
PCR (Polymerase Chain Reaction)

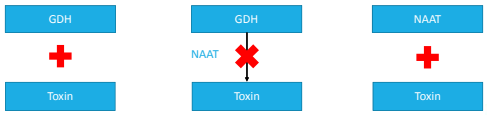
tcdB and 027/NAP1/BI detection

USHP

Reference(s): 11-12

Detection Algorithms

- What tests should we use?
  - Single step: NAAT
  - Multistep: GDH + toxin, GDH + toxin, mediated by NAAT, NAAT + toxin
- Multi-step algorithm recommended



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Reference(s): 1

Repeat Testing

- Adult and pediatric patients
  - Within 7 days of original episode: No
  - Asymptomatic patients: No
- Confounders
  - Asymptomatic carriage
  - Bacterial shedding

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Reference(s): 1

Infection Prevention

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Infection Prevention Specifics

- Topics
  - Isolation
  - Personal protective equipment
  - Device and room cleaning
- Hand hygiene
  - Soap and water over alcohol

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Reference(s): 1

Stewardship is Good Practice

[It] is sufficiently obvious that desirable effects outweigh undesirable effects that no direct evidence is available because no one would be foolish enough to conduct a study addressing the implicit clinical question. Typically, such recommendations are supported by a great deal of indirect evidence, but teasing out the nature of the indirect evidence would be challenging and a waste of time and energy.

Reference(s): 1, 13

Stewardship Ideas

- Targets
  - Fluoroquinolones
  - Clindamycin
  - Cephalosporins
  - Broad-spectrum agents
- Methods
  - Formulary restriction
  - Prospective audit and feedback
  - Use and duration

Reference(s): 14

PPIs and Probiotics

- Proton pump inhibitors / histamine H_2-receptor blockers
  - Epidemiologic association
  - Surrogate markers for disease severity?
  - No recommendation
- Probiotics
  - Inconsistent data
  - No recommendation

Reference(s): 1

Question 2

Antimicrobial stewardship of which classes would be most helpful in controlling CDI?

Choose all that apply

A. Aminoglycosides

B. Fluoroquinolones

C. Streptogramins

D. Cephalosporins

Treatment

Definitions

- Non-severe
  - Leukocytosis with white blood cell count <15,000 cells/mL
  - Serum creatinine <1.5 mg/dL
- Severe
  - Leukocytosis with white blood cell count >15,000 cells/mL

OR

  - Serum creatinine ≥1.5 mg/dL
- Fulminant
  - Hypotension or shock, ileus, megacolon

Reference(s): 1

Initial Episode - Adult

- Stop the causative agent!
  - If possible, choose an alternative.
- Non-severe or Severe
  1. Oral vancomycin (Vancocin®) 125 mg PO QID x 10 days
  2. Fidaxomicin (Dificid®) 200 mg PO BID x 10 days
  - No preference
- Non-severe only
  - Metronidazole (Flagyl®) 500 mg PO Q8H
  - Access is the question

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Initial Episode - Adult

- Why move away from metronidazole (Flagyl®)?
  - No trials comparing metronidazole (Flagyl®) and fidaxomicin (Dificid®)!
  - Direct comparisons
    - Metronidazole (Flagyl®) and vancomycin (Vancocin®)
    - Vancomycin (Vancocin®) and fidaxomicin (Dificid®)

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Initial Episode - Adult

Outcomes	# Participants	% Resolution	Relative Effect (95% CI)	p Value	Quality of Evidence (GRADE)
Direct comparison of fidaxomicin (Dificid®) and vancomycin (Vancocin®)					
Resolution of diarrhea at the end of treatment	1105	88 (FDX) 86 (VAN)	RR, 0.9 (0.98-1.1)	0.36	High
Resolution of diarrhea at the end of treatment without CDI recurrence ~1 month after treatment	1105	71 (FDX) 57 (VAN)	RR, 1.2 (1.1-1.4)	<0.0001	High
Direct comparison of metronidazole (Flagyl®) and vancomycin (Vancocin®)					
Resolution of diarrhea at the end of treatment without CDI recurrence ~1 month after treatment	843	63 (MTR) 73 (VAN)	RR, 0.87 (0.79-0.96)	0.003	High

FDX = fidaxomicin (Dificid®)
MTR = metronidazole (Flagyl®)
VAN = vancomycin (Vancocin®)

Summary of all available trials published.
Conducted by guideline preparers.

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Reference(s): 1

Fulminant/Recurrent - Adult

Oral vancomycin (Vancocin®) 500 mg PO QID x 10 days

CONSIDER

Ileus: vancomycin (Vancocin®) 500 mg PR QID x 10 days

PLUS

Metronidazole (Flagyl®) 500 mg IV Q8H x 10 days

Surgical management is definitive therapy.

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Reference(s): 1

1st Recurrence - Adult

Oral vancomycin (Vancocin®) tapered and pulsed
125 mg PO QID x 10 days, BID x 7 days, daily x 7 days, every 2-3 days for 2-8 weeks

OR

Fidaxomicin (Dificid®) 200 mg PO BID x 10 days instead of oral vancomycin (Vancocin®) x 10 days

OR

If metronidazole (Flagyl®) initially, then oral vancomycin (Vancocin®) x 10 days

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Reference(s): 1

≥ 2nd Recurrence - Adult

Vancomycin (Vancocin®) tapered and pulsed

OR

Vancomycin (Vancocin®) 125 mg PO QID x 10 days, followed by rifaximin (Xifaxan®) 400 mg PO TID x 20 days

OR

Fidaxomicin (Dificid®) 200 mg PO BID x 10 days

OR

Fecal Microbiota Transplantation (FMT)

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Reference(s): 1

>1 Recurrence – Adult and Pediatric

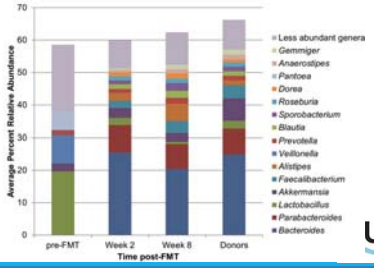
Fecal Microbiota Transplantation

Reference(s): 15, 16

Fecal Microbiota Transplantation

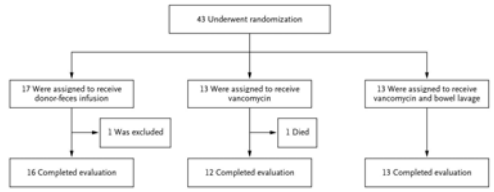
Increased diversity

Marked change in proportions



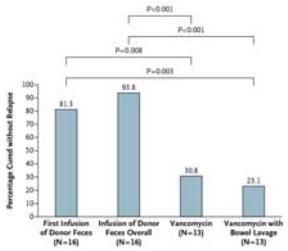
Reference(s): 17

Fecal Microbiota Transplantation



Reference(s): 18

Fecal Microbiota Transplantation



Reference(s): 18

Question 3

A hospitalist asks you for a discharge recommendation for treatment of his patient's CDI. The patient is completing a 7-day course of levofloxacin for a UTI. She contracted the infection during this admission, and has never had *C. difficile* before. If needed, she can pay for PO vancomycin (Vancocin®). However, she would prefer to use a cheaper alternative if possible. What would you recommend?

A. PO metronidazole (Flagyl®)

B. PO vancomycin (Vancocin®)

C. PO vancomycin (Vancocin®), only after failing PO metronidazole (Flagyl®)

D. PO fidaxomicin (Dificid®)

Initial Episode - Pediatric

- Non-severe
  1. Oral vancomycin (Vancocin®) 10 mg/kg/dose PO QID x 7-10 days

  OR

  2. Metronidazole (Flagyl®) 7.5 mg/kg/dose PO TID-QID x 10 days
     - No preference
- Severe/Fulminant
  1. Oral vancomycin (Vancocin®) PO/PR 10 mg/kg/dose PO QID x 7-10 days

  AND / OR

  2. Metronidazole (Flagyl®) IV TID-QID x 10 days

Reference(s): 1

1st Recurrence - Pediatric

Vancomycin (Vancocin®) PO tapered and pulsed (up to 12 weeks)

OR

Metronidazole (Flagyl®) PO x 10 days

No preference

Reference(s): 1

≥ 2nd Recurrence - Pediatric

Vancomycin (Vancocin®) PO tapered and pulsed (up to 12 weeks)

OR

Vancomycin (Vancocin®) 125 mg PO QID x 10 days, followed by rifaximin (Xifaxan®) 400 mg PO TID x 20 days

OR

Fecal Microbiota Transplantation (FMT)

Reference(s): 1

Question 4

A 9 year-old boy with recurrent CDI is admitted to your floor. While doing the medication reconciliation, you find that his parents are frustrated with this readmission. He has already taken courses of vancomycin (Vancocin®) and metronidazole (Flagyl®).

They ask you about alternatives to drug therapy, like "Poo in a Pill". What options would you discuss?

A. FMT is first-line therapy and more likely to clear CDI than other interventions.

B. FMT could be reasonable, but only if antibiotics, probiotics and surgery have failed.

C. FMT is not preferred, but is helpful in some patients, such as the immunosuppressed.

D. FMT can be effective, used only after antibiotic therapy fails.

Conclusions

- Upgrades
  - Clarity of roles of fidaxomicin (Dificid®) and metronidazole (Flagyl®)
  - Recommendations for pediatric patients
  - Highlights role for antibiotic stewardship
- Needs
  - Prevention strategies
  - Role of PPIs, probiotics
  - Fidaxomicin in pediatric patients
  - Bezlotoxumab (Zinplava™)
  - New PCR-based laboratory platforms

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