Antibiotic stewardship and *Clostridium difficile* infection

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Medical Director of Adult Antimicrobial Stewardship

Disclosures

- Consultant: Genentech, Actelion
Learning objectives

- To recognize the importance of antibiotic stewardship
- To formulate an approach to improve antibiotic use for a defined problem
- To assess the success of a stewardship intervention
- To outline an approach to CDI diagnosis and management

Outline

- Introduction to stewardship
- Stewardship case
- CDI
A story…

- Find someone sitting next to you
- **2 minutes:** Think about a time where you think antibiotic management could have gone better. Please share with the person sitting next to you and share what factors contributed
- Then, summarize with 1-2 words and write down
  - E.g. Treated viral infection with antibiotics due to pressure from patient → Family pressure, treatment of non-bacterial infection

Factors contributing to imperfect antibiotic management
87% of physicians agree that AMR is a public health problem, but…

<table>
<thead>
<tr>
<th>Factor</th>
<th>Mean rank (1 = highest)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efficacy of drug to treat CAP</td>
<td>1.8</td>
</tr>
<tr>
<td>Severity of illness</td>
<td>3.1</td>
</tr>
<tr>
<td>Previous experience with the antibiotic</td>
<td>4.0</td>
</tr>
<tr>
<td>Side effects</td>
<td>4.4</td>
</tr>
<tr>
<td>Ease of use</td>
<td>4.8</td>
</tr>
<tr>
<td>Cost</td>
<td>4.5</td>
</tr>
<tr>
<td>Risk of contributing to the problem of antibiotic resistance</td>
<td>5.5</td>
</tr>
</tbody>
</table>


Risk avoidance depends on the clinical population

Almost 40% of inpatients receive antibiotics on a given day

- In 2006, 63.5% of patients at 35 University Health System Consortium hospitals received at least one dose of antibiotics during their hospitalization

30% of inpatient antibiotic use is unnecessary

- 58% received ≥ 1 day of unnecessary antibiotics

  - Redundant coverage 10%
  - Spectrum not indicated 4%
  - Noninfectious or nonbacterial 33%
  - Colonization or contamination 16%
  - Duration too long 34%
  - Adjustment not made 3%
But why do we care?

New vancomycin resistance in patient with recurrent MSSA bloodstream infection

78 year old woman with ESRD on HD via tunneled catheter

- Severe beta-lactam allergy
- Additional vancomycin allergy

<table>
<thead>
<tr>
<th>Date</th>
<th>Susceptibility</th>
<th>Daptomycin</th>
<th>Nafcillin</th>
<th>Vancomycin</th>
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<tr>
<td>1/2017</td>
<td>MIC &lt;=0.5 S</td>
<td>&lt;=0.5 S</td>
<td>0.5 S</td>
<td>&lt;=0.5 S</td>
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<tr>
<td>5/2018</td>
<td>MIC 4 / 2 I</td>
<td>4 I</td>
<td>0.5 S</td>
<td>4* / 2 I</td>
</tr>
</tbody>
</table>

*E-test

Chaz Langelier, MD, PhD
Antimicrobial resistance stats

23,000 annual deaths

> 2 million illnesses


Attributable mortality of MDROs

Sir Alexander Fleming

The time may come when penicillin can be bought by anyone in the shops. Then there is the danger that the ignorant man may easily underdose himself and, by exposing his microbes to non-lethal quantities of the drug, educate them to resist penicillin.

-Nobel lecture, 1945

The prevailing attitude

“[it] is time to close the book on infectious diseases and declare the war against pestilence won”

--Surgeon General William H. Stewart, 1960s
“Last resort” antibiotics are endangered

Tracking the mcr genes

About This Map

https://www.cdc.gov/drugresistance/biggest-threats/tracking/mcr.html

http://chicago-mosaic.medill.northwestern.edu/antibiotic-resistance-superbugs/
Timeline of drug development

Clinical development

- Pre-human research
- Phase I
- Phase II
- Phase III

IND review → NDA/BLA review

FDA filing, approval, launch preparation

Year 0
Year 5
Year 10

What can we do?

...
What is antibiotic stewardship?

Interventions designed to optimize the appropriate use of antimicrobials

- Decrease antibiotic resistance, AE, costs
- Improve patient outcomes


A brief survey

- Does your hospital have an antibiotic stewardship program?
- Do you know what the program does?
- Has the program ever been helpful for you?
But what exactly does that mean?

https://www.cdc.gov/antibiotic-use/healthcare/implementation/core-elements.html

What does a stewardship program look like?
Does it work?

MDRO incidence rate w/ ASP: 0.49 (0.35-0.68)
CDI incidence rate w/ ASP: 0.68 (0.53-0.88)

Take-home

- Antibiotic decisions are challenging, and unsuitable antibiotic use is common
- Antibiotic resistance is a major problem
- Antibiotic stewardship is one tool that can help
  - Requires resources and coordination
  - Proven to improve outcomes
But how does it really work? *A case-based approach*

Outline

- Introduction to stewardship
  - Stewardship case
  - CDI
You return from a great Hospital Medicine CME lecture…

- You have just taken home the following nuggets of information:
  1. Non-purulent cellulitis: Use a narrow-spectrum β-lactam (cefazolin)
  2. GNR antibiotics for SSTIs: Rarely indicated
  3. Treatment duration for cellulitis: 5 days

- You think that your group could decrease vancomycin and GNR coverage for SSTI and shorten therapy, and you want to spearhead the effort

Some questions

- How can you confirm this is a problem? (5 minutes)
Metrics

Use
- By indication
- Which providers?
- Which agents?
- # of starts
- Duration

Outcomes
- Mortality
- Sepsis
- MDRO rates
- CDI rates

Costs
- High-cost agents
- Highly utilized
- Outliers

Two main components to measuring antibiotic use

Usage
- DDD: Defined daily doses
- DOT: Days of therapy
- LOT: Length of therapy

Pt volume
- Number of admissions
- Number of patient days
- Number of days present
Days of therapy (DOT)

- # of days of individual antibiotics, based on administration

<table>
<thead>
<tr>
<th>Day</th>
<th>1</th>
<th>2</th>
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</thead>
<tbody>
<tr>
<td>Cefepime</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vancomycin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DOT</td>
<td>2</td>
<td>2</td>
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</tbody>
</table>

<table>
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<tr>
<th>Day</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
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<tbody>
<tr>
<td>Ampicillin</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>Gentamicin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DOT</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>1</td>
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</table>

Length of therapy (LOT)

- Number of days a patient receives any antibiotics

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<thead>
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<td></td>
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<tr>
<td>DOT</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>LOT</td>
<td>1</td>
<td>1</td>
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<td>Gentamicin</td>
<td></td>
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</tr>
<tr>
<td>DOT</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>LOT</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
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</table>
Defined daily dose

- Average dose/day (adult) for a drug used for its main indication
- Based on purchasing, dispensing, or administration records
- Defined by WHO
- Total antibiotic usage (grams) for adult inpatients/DDD (from WHO)=DDD/yr
- Rx: Levofloxacin 750 mg po daily x 7 days=(0.75 g dose/0.5 g DDD) x 7 days
  = 1.5 DDD x 7= 10.5 DDD

Antibiotic Use and Resistance (AUR) module

- CDC’s NHSN module
  - Antimicrobial days/days present by month
  - Data source: eMAR or barcode administration data
- Standardized Antibiotic Administration Ratio (SAAR)
  - Observed use compared to expected
  - Risk adjustment based on hospital bed #, ICU beds, teaching status
### Pros/cons of consumption metrics

<table>
<thead>
<tr>
<th>Metric</th>
<th>Advantage</th>
<th>Disadvantage</th>
</tr>
</thead>
</table>
| Expenditure | • Easy to get  
• Administrators want $$$ | • Less accurate  
• Affected by changes in cost, formulary |
| DOT | • Most accurate  
• Preferred by CDC, NHSN | • Difficult to obtain/calculate  
• Favors monotherapy over dual  
• Accurate for renal failure/dose adj |
| LOT | • Reflects duration | • Cannot compare specific drugs |
| DDD | • Easy to obtain  
• Benchmark | • Inaccurate for peds, renal populations  
• WHO-defined values may not reflect doses used locally |
| SAAR | • Benchmarking | • Risk adjustment inadequate (e.g. transplant population, CMI)  
• Only compatible with certain EMRs |

#### Vanco DOT Trends

![Graph showing Vanco DOT Trends](image-url)
Antibiotic intensity IV only

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>DOT/1000 Patient-Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>vancomycin</td>
<td>156.7</td>
</tr>
<tr>
<td>ceftazolin</td>
<td>80.4</td>
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<tr>
<td>piperacillin-tazobactam</td>
<td>60.1</td>
</tr>
<tr>
<td>ceftriaxone</td>
<td>57.0</td>
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<tr>
<td>ceftazolin</td>
<td>52.6</td>
</tr>
<tr>
<td>meropenem</td>
<td>52.4</td>
</tr>
<tr>
<td>metronidazole</td>
<td>50.7</td>
</tr>
<tr>
<td>ampicillin-sulbactam</td>
<td>50.4</td>
</tr>
<tr>
<td>levofloxacin</td>
<td>49.5</td>
</tr>
<tr>
<td>amoxicillin</td>
<td>49.5</td>
</tr>
<tr>
<td>ciprofloxacin</td>
<td>49.5</td>
</tr>
<tr>
<td>clindamycin</td>
<td>49.5</td>
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<tr>
<td>linezolid</td>
<td>49.5</td>
</tr>
<tr>
<td>aztreonam</td>
<td>49.5</td>
</tr>
<tr>
<td>azithromycin</td>
<td>49.5</td>
</tr>
<tr>
<td>cefoxitin</td>
<td>49.5</td>
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<tr>
<td>daptomycin</td>
<td>49.5</td>
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<tr>
<td>doxycycline</td>
<td>49.5</td>
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<tr>
<td>ceftazidime</td>
<td>49.5</td>
</tr>
<tr>
<td>tobramycin</td>
<td>49.5</td>
</tr>
<tr>
<td>nitrofurantion</td>
<td>49.5</td>
</tr>
</tbody>
</table>

Confidential
Humbly engage with stakeholders

- Leaders
- Champions
- Outliers
- Multiple disciplines

Find out:
- What drives practice
- What guidance they want
- What data

Some questions

✓ How can you confirm this is a problem?
- What approaches can you use to start this effort? (5 minutes)
Opportunities for stewardship

Diagnostic work-up for suspected infection
Guidelines
Diagnostic stewardship
Rapid diagnostics

Empirical Rx started
Guidelines
Antibiogram
Computerized decision support
Allergy testing
Formulary restriction
Prospective audit and feedback
Automatic stops

Definitive therapy
PAF
Time-out
Guidelines
Cascade reporting
Pharmacy interventions

Some questions

✓ How can you confirm this is a problem?
✓ What approaches can you use to start this effort?
  ▪ What resources might you need? (5 minutes)
Published resources

- IDSA and other society guidelines
- CDC
- Primary literature
- EIN, ASN, other programs
- Pharmacists

You complete your guideline. What next?
Some questions

- How can you confirm this is a problem?
- What approaches can you use to start this effort?
- What resources might you need?
  - List three approaches to implementation/dissemination
    (5 minutes)

Spreading the news

<table>
<thead>
<tr>
<th>Approach</th>
<th>Pros</th>
<th>Cons</th>
</tr>
</thead>
<tbody>
<tr>
<td>EHR/order sets/CDS</td>
<td>Hardwired</td>
<td>Not everyone uses order sets</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Alert fatigue</td>
</tr>
<tr>
<td>In-person education</td>
<td>Impactful</td>
<td>Does not reach everyone</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Diminishing returns</td>
</tr>
<tr>
<td>Deputize local leaders</td>
<td>Extend reach</td>
<td>May not reach everyone</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Unclear what gets passed on</td>
</tr>
<tr>
<td>Email</td>
<td>Far-reaching</td>
<td>No one reads it!</td>
</tr>
<tr>
<td>Hard copies/cards</td>
<td>Convenient</td>
<td>Need to keep track for updating</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Environmental impact</td>
</tr>
</tbody>
</table>
Computerized decision support

Usual care (N = 123) vs. CDS (N = 123)

- Ward-level randomization
- Appropriate empirical antibiotic for MDI
  - FDR: 64%
  - LOS by 1 day
  - Cost
  - Spectrum ↔
  - Mortality
  - 73%

Reinforcement: Prospective audit with feedback

- Vanco started for SSTI
- Reviewed by pharmacist
- Feedback to team
Real-world example: Prospective audit and feedback

[Image of a medical chart with patient information and antimicrobial orders.]

Real-world example: Prospective audit and feedback

[Image of a consultation note with a detailed medical report and recommendations.]

UCSF
Data to support PAF

Patients on medical wards on antibiotics < 24h (N = 246)

Usual care (N = 123)

Blinded adjudication of abx appropriateness

PAF on D1 and D3-4 (N = 123)

Appropriateness D3-4

29%

↓3 days of antibiotics

45%


Peer comparison for URI Rx

“You are not a top performer”

Some questions

✓ How can you confirm this is a problem?
✓ What approaches can you use to start this effort?
✓ What resources might you need?
✓ List three approaches to implementation/dissemination
  ▪ How will you monitor success?

PDSA
Take-home

- Stewardship can and should be done locally
- Data is key
- Engage stakeholders
- Use published resources
- Be strategic about implementation and monitoring
Outline

- Introduction to stewardship
- Stewardship case
  - CDI

Outline

- Brief background and epidemiology
- Diagnosis
- Management—mild, uncomplicated disease
- Management—moderate-severe disease
- Management—recurrent/relapsed disease
- Management—fulminant disease
- Prevention
One of CDC’s 3 “Urgent Threats”

https://www.cdc.gov/drugresistance/biggest_threats.html

Duration, number, and intensity of antibiotics affect risk for CDI

Antibiotic use affects the population risk

- Risk for CDI if prior room occupant got antibiotics = HR 1.22 (1.02-1.45)

Diagnostic testing

Glutamate dehydrogenase Ag (GDH)
- Bacterial detection
- Sn but not Sp

Enzyme immunoassay (EIA)
- Protein detection
- ↓ Sensitivity
- ↑ Specificity

Polymerase chain reaction (PCR):
- Toxin-producing gene
- ↑ Sensitivity
- ↓ Specificity
CDI overdiagnosis

- 21% +PCR
- Of these, 44% + toxin
- Toxin-/PCR+
  - ↓ bacterial load
  - ↓ abx
  - ↓ diarrhea
- No CDI-complications


MANAGEMENT
**Treatment scenario #1.** 63 y/o F recently treated for a UTI with levofloxacin, now having watery stools 4x/day, fever to 38.3, WBC 11K, Cr 1.0. Other vitals stable. PCR positive for *C. difficile* toxin. With what should you treat her?

A. Vancomycin 125 mg po qid  
B. Vancomycin 500 mg po qid  
C. Metronidazole 500 mg po tid  
D. Fidaxomicin 200 mg po bid

---

**Initial uncomplicated CDI, severe or non-severe**

- VAN 125 mg po QID x 10 days (up to 14) (strong, high)  
- FDX 200 mg PO twice daily x 10 days (strong, high)  
  - Favor in patients at high risk for recurrence  
- If above agents are unavailable, can consider metronidazole x 10-14 days (weak, high)

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McDonald LC et al. CID. cix1085. https://doi.org/10.1093/cid/cix1085
RCTs metronidazole vs. vancomycin

- Similar findings for study of MTZ vs VAN vs tolevamer
- Cure not differential with regard to levels of severity

New evidence to support vancomycin

- aRR death VAN vs MT:Z
  - Any severity: 0.86 (0.74 to 0.98)
  - Severe: 0.79 (0.65 to 0.97)
- NNT to prevent 1 death, severe CDI: 25
What about fidaxomicin?

- Bottom line vs. VAN: Similar cure (~88%), lower recurrence (13-15% vs. 25-27%)
- Unclear role in multiply recurrent or severe disease

<table>
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<tr>
<th>Strain</th>
<th>Cure</th>
<th>Relapse</th>
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<tbody>
<tr>
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<td>Same</td>
</tr>
<tr>
<td>Non-epidemic</td>
<td>Same</td>
<td>↓</td>
</tr>
<tr>
<td>Concomitant abx</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Prior CDI</td>
<td>Same</td>
<td>↓</td>
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</table>

<table>
<thead>
<tr>
<th></th>
<th>FDX</th>
<th>VAN</th>
<th>MTZ</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$2800</td>
<td>$250-680</td>
<td>$22</td>
</tr>
</tbody>
</table>


Additional considerations

- Stop unnecessary antibiotics
- Shorten antibiotic courses
- Narrow antibiotic spectrum
- Stop acid-suppressive medications when possible (though low quality evidence)
- No anti-peristaltic agents until acute sx improve
Take-home

- For initial treatment of non-fulminant CDI, VAN 125 mg po QID x 10-14 days for most patients
- Role of fidaxomicin unclear
  - Consider if ↑ risk of relapse or need CA

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**Treatment scenario #2:** You are seeing a 62 y/o F who has takes chronic amoxicillin/clavulanic acid for suppression of Enterococcal osteomyelitis and has developed her second bout of C. difficile colitis. Her first episode was treated with VAN x 10 days. Her WBC count is 9 and Cr is 0.3. With what should you treat her?

A. MTZ 500 mg po TID x 10 days
B. VAN 125 mg PO QID x 10 days
C. VAN taper
D. FDX 200 mg po BID x 10 days
First recurrence, non-fulminant CDI

- If MTZ used initially → VAN 125 mg po QID x 10 days (weak, low)
- If VAN used initially, two options:
  1. VAN taper (weak, low)
  2. FDX 200 mg po BID x 10 days (weak, mod)

Evidence to support VAN taper

- Treatment outcomes from pts in placebo group with rCDI of 2 RCTs of probiotics (n = 163)
- 29 got VAN tapers of varying stripes
  - Mean 21.5 +/- 10 days
  - 31% recurrence compared to 71% of the 10 pts given standard VAN courses (p = 0.01)
  - Also lower recurrences for VAN pulses
- Small numbers, uncontrolled study
Vancomycin taper

- 125 mg po 4x daily x 14 days
- 125 mg po 2x daily x 7 days
- 125 mg po 1x daily x 7 days
- 125 mg po every other day x 8 days (4 doses)
- 125 mg po every 3 days x 15 days (5 doses)

Risk for recurrent CDI

Treatment scenario #3. This patient returns one month after you have treated her with a 10-day course of PO FDX complaining of ongoing diarrhea. A repeat stool toxin is positive. What do you do?

A. VAN followed by rifaximin  
B. VAN taper  
C. FDX 200 mg PO BID x 10 days  
D. Fecal microbiota transplantation  
E. Any of the above

Second/subsequent recurrence

- VAN taper/pulse (weak, low)  
- VAN 125 mg po QID x 10 days followed by rifaximin 400 mg po TID x 20 days (weak, low)  
- FDX 200 mg PO BID x 10 days (weak, low)  
- FMT (strong, mod)  
  - “appropriate antibiotic treatments for at least 2 recurrences… should be tried prior to offering [FMT]”

FMT

• ↓Diversity w/ rCDI
• Colonization resistance
• Related donors vs. banked stool
• R/o transmissible dz

• Multiple RCTs
• Overall response:
  • Multiple: 92% (89-94)
  • Single: 84% (79-89)

• Colo vs. pill RCT:
  • 12-week cure:
    • Pill: 96%
    • Colo: 96%
    • Diff: 0% (-6.1% to ∞)

Multiple RCTs


Take-home

• rCDI is a challenge
• First recurrence: Stratify by initial rx
  - MTZ→Standard VAN course
  - VAN→VAN taper or FDX
• Subsequently:
  - VAN taper
  - VAN course + rifaximin chaser
  - FDX
  - FMT (try above options first)
**Treatment scenario #4:** 63 y/o F recently treated for a UTI with levofloxacin, now with profuse diarrhea, T 38.7, BP 79/50, HR 140, WBC 30K, Cr 3.2, and lactate 3.7. With what do you treat her?

A. VAN 125 mg po qid  
B. VAN 500 mg po qid  
C. VAN 500 mg PR qid  
D. MTZ 500 mg iv tid  
E. FDX 200 mg po bid  
F. A+C+D  
G. B+C+D

---

**Fulminant CDI**

- Paucity of data for medical approaches, expert opinion
  - VAN 500 mg po QID (strong, moderate)
  - Ileus → VAN 500 mg in 100 cc saline PR QID (weak, low)
  - MTZ IV (strong, moderate)
- Surgical options:
  - Subtotal colectomy (strong, moderate)
  - Alt: Diverting loop ileostomy with colonic lavage (weak, low)

---

McDonald LC et al. CID, cix1085, https://doi.org/10.1093/cid/cix1085
Take-home for severe, complicated CDI

- Use high-dose oral +/- rectal VAN
- Use IV MTZ
- Consider surgical intervention early
  - Consider diverting loop ileostomy
- FMT is promising but need more data, multiple FMTs may be needed
  - Make sure medical therapy has been optimized
- Additional therapies (IVIG, other antibiotics) lack data

---

**Treatment scenario #5.** You are starting your 70 y/o M patient on 4 weeks of ciprofloxacin for prostatitis. He asks you whether he should take probiotics. How do you counsel him?

A. Probiotics will prevent antibiotic-associated diarrhea, including CDI
B. Probiotics will prevent antibiotic-associated diarrhea but not CDI
C. Probiotics are useless
Probiotics for CDI

<table>
<thead>
<tr>
<th>RCT</th>
<th>Meta-analysis</th>
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<tbody>
<tr>
<td>• 0.9% vs. 1.2%</td>
<td>• 0.42 (0.30 0.50)</td>
</tr>
<tr>
<td>• OR CDI: 1.0 (0.8-1.3)</td>
<td>• Studies limiting to initiation w/i 48h on abx had stronger effect size</td>
</tr>
<tr>
<td></td>
<td>• Limits UK study</td>
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<tr>
<td></td>
<td>• IDSA guidelines = insufficient</td>
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</tbody>
</table>


Interventions to prevent CDI

- Antibiotic stewardship
- Vaccine
- Infection Control
- Non-toxigenic C. diff, FMT, and probiotics
- PO VAN
- Passive immunity

Outline

- Introduction to stewardship
- Stewardship case
- CDI

THANK YOU!