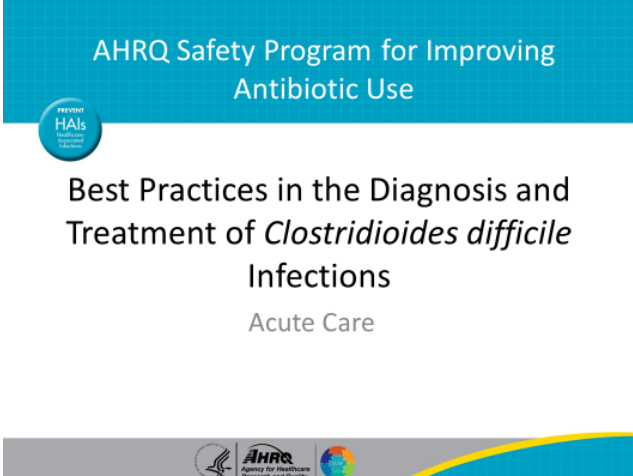
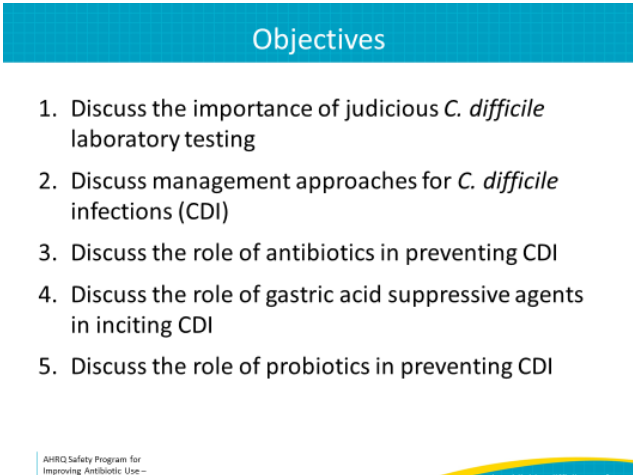


AHRQ Safety Program for Improving Antibiotic Use



Best Practices in the Diagnosis and Treatment of *Clostridioides difficile* Infections Acute Care

Slide Title and Commentary	Slide Number and Slide
<p>Best Practices in the Diagnosis and Treatment of <i>Clostridioides difficile</i> Infections Acute Care</p> <p>SAY:</p> <p>This presentation will address “Best Practices in the Diagnosis and Treatment of <i>Clostridioides difficile</i> Infections.”</p>	<p>Slide 1</p> 
<p>Objectives</p> <p>SAY:</p> <p>By the end of this presentation, participants will be able to—</p> <ul style="list-style-type: none"> • Discuss the importance of judicious <i>Clostridioides difficile</i> or <i>C. difficile</i> laboratory testing • Discuss management approaches for <i>C. difficile</i> infections or CDI • Discuss the role of antibiotics, gastric acid suppressive agents, and probiotics in inciting or preventing <i>C. difficile</i> infections 	<p>Slide 2</p> 



Slide Title and Commentary

The Four Moments of Antibiotic Decision Making

SAY:

As we discuss the diagnosis and treatment of CDI, we will continue to use the Four Moments of Antibiotic Decision Making framework.

As a reminder, the Four Moments include:

Moment 1: Does my patient have an infection that requires antibiotics?

Moment 2: Have I ordered appropriate cultures before starting antibiotics? What empiric therapy should I initiate?

Moment 3: A day or more has passed. Can I stop antibiotics? Can I narrow therapy or change from intravenous to oral therapy?

Moment 4: What duration of antibiotic therapy is needed for my patient's diagnosis?

The Four Moments of Antibiotic Decision Making

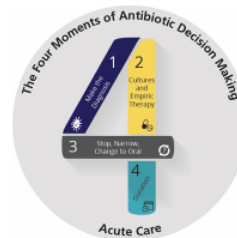
SAY:

We will begin with Moment 1, "Does my patient have an infection that requires antibiotics?"

Slide Number and Slide

Slide 3

The Four Moments of Antibiotic Decision Making



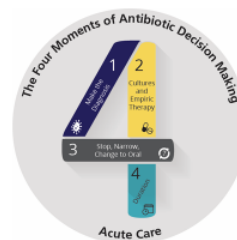
AHRQ Safety Program for Improving Antibiotic Use – Acute Care

1. Does my patient have an infection that requires antibiotics?
2. Have I ordered appropriate cultures before starting antibiotics? What empiric therapy should I initiate?
3. A day or more has passed. Can I stop antibiotics? Can I narrow therapy or change from IV to oral therapy?
4. What duration of antibiotic therapy is needed for my patient's diagnosis?

Clostridioides difficile 3

Slide 4

The Four Moments of Antibiotic Decision Making



AHRQ Safety Program for Improving Antibiotic Use – Acute Care

1. Does my patient have an infection that requires antibiotics?

Clostridioides difficile 4

Slide Title and Commentary

Factors Contributing to CDI

SAY:

Colonization of the intestinal tract with *C. difficile* occurs via the fecal-oral route. This process is facilitated by antibiotic use. Antibiotics disrupt the barrier function of normal colonic flora, providing a niche for *C. difficile* to multiply and produce toxins. *C. difficile* releases two toxins that mediate disease: toxin A and toxin B. Toxin B appears to be the more clinically important toxin. CDI has not been shown to occur in the absence of toxin B production. These toxins lead to inflammation and diarrhea. Antibodies to the toxins, however, can be protective. Asymptomatic carriers often demonstrate higher serum levels of antibodies against *C. difficile* toxins compared to patients who develop clinical disease. As will be discussed later in the presentation, monoclonal antibodies commercially available against *C. difficile* toxin appear to reduce the recurrence rate of CDI.

Case Definition of CDI

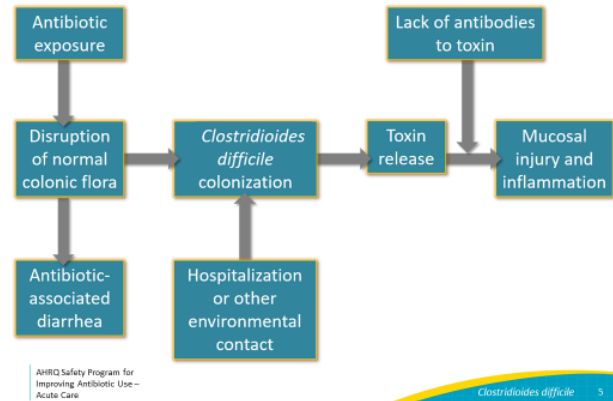
SAY:

The case definition of CDI is as follows as of April 2019: At least three unformed stools within a 24-hour period and either a positive stool test for the *C. difficile* toxin or colonoscopic or histopathologic findings compatible with pseudomembranous colitis. Presence of the *C. difficile* organism in the absence of toxin production should not be considered an infection.

Slide Number and Slide

Slide 5

Factors Contributing to CDI^{1,2}



Slide 6


Case Definition of CDI³


- ≥3 unformed stools in a 24-hour period and positive stool test for *C. difficile* toxin
- OR**
- Colonoscopic or histopathologic findings compatible with pseudomembranous colitis



AHRQ Safety Program for Improving Antibiotic Use – Acute Care

Clostridioides difficile 6

Slide Title and Commentary	Slide Number and Slide
<p><i>C. difficile</i> Clinical Spectrum</p> <p>SAY:</p> <p>Asymptomatic carriage with <i>C. difficile</i> is common. In healthy infants under 1 year of age, the prevalence of <i>C. difficile</i> colonization has been described as between 10 and 60 percent in various studies. Reasons for the high prevalence of <i>C. difficile</i> in infants are unclear. Despite higher rates of colonization, clinically apparent disease in infants is uncommon. Based on animal models, it has been proposed that the absence of toxin receptors is the main reason for the rarity of clinical disease in human infants.</p> <p>By 2 years of age, the risk of colonization is the same as healthy adults—at about 3 percent. The risk of colonization has been shown to increase linearly with the duration of hospital stay; 10–20 percent of hospitalized patients test positive for <i>C. difficile</i> toxin.</p> <p>The most common clinical presentation of <i>C. difficile</i> infection is watery diarrhea. Additional findings include lower abdominal pain, cramping, and nausea. Low-grade fevers occur in approximately 15 percent of patients. Leukocytosis may be present and on average the serum white blood cell count is approximately 15,000 cells per microliter.</p> <p>Severe or fulminant colitis may present with severe abdominal pain, a possible ileus, lactic acidosis, hypoalbuminemia, and/or significant leukocytosis.</p>	<p>Slide 7</p> <p><i>C. difficile</i> Clinical Spectrum</p> <ul style="list-style-type: none"> • Asymptomatic colonization <ul style="list-style-type: none"> – 10–60% of healthy infants under 1 year of age⁴⁻⁶ – 3% of healthy adults¹ – 10–20% of hospitalized patients¹ • Watery diarrhea¹ <ul style="list-style-type: none"> – Most common presentation – Lower abdominal pain, cramping, nausea, low-grade fever (15%), and leukocytosis (average ~15,000 cells/microL) • Severe or fulminant colitis¹  <p><small>AHRQ Safety Program for Improving Antibiotic Use – Acute Care</small></p> <p><small><i>Clostridioides difficile</i> 7</small></p>

Slide Title and Commentary	Slide Number and Slide
<p>Severe and Fulminant CDI</p> <p>SAY:</p> <p>As of April 2019, there is no consensus for what defines severe versus fulminant CDI. The 2018 Infectious Diseases Society of America and Society for Healthcare Epidemiology of America guidelines recommend considering CDI as severe when a leukocytosis of greater than 15,000 cells per milliliter is present or the serum creatinine is greater than 1.5 mg/dL. Fulminant CDI is generally defined as CDI requiring ICU admission because of hypotension, intestinal perforation, or toxic megacolon. Patients with fulminant CDI who survive the infection may require a colectomy.</p> <p>Prompt surgical consultations are recommended for all cases of severe or fulminant CDI. Abdominal imaging is important to evaluate for the presence of toxic megacolon, bowel perforation, or other findings warranting surgical intervention.</p>	<p>Slide 8</p> <p style="text-align: center;">Severe and Fulminant CDI⁷</p> <ul style="list-style-type: none"> • 2018 IDSA/SHEA guidelines state CDI is severe when— <ul style="list-style-type: none"> – Leukocytosis greater than 15,000 cells per milliliter or serum creatinine greater than 1.5 mg/dL • Fulminant CDI defined as CDI requiring ICU admission because of— <ul style="list-style-type: none"> – Hypotension – Intestinal perforation – Toxic megacolon • Obtain abdominal imaging and prompt surgical consultation <p><small>AHRQ Safety Program for Improving Antibiotic Use – Acute Care</small></p> <p style="text-align: right;"><small><i>Clostridioides difficile</i> 8</small></p>
<p>Ribotype 027 (NAP1) Strain</p> <p>SAY:</p> <p>The NAP1 or ribotype 027 strain is a hypervirulent strain of <i>C. difficile</i> that has become increasingly recognized since the early 2000s. This strain is associated with frequent, severe, refractory disease that is more likely to relapse than non-NAP1 strains. This may be because the NAP1 strain generally produces large quantities of toxin.</p>	<p>Slide 9</p> <p style="text-align: center;">Ribotype 027 (NAP1) Strain^{8,9}</p> <ul style="list-style-type: none"> • Associated with frequent, severe, refractory disease that is more likely to relapse compared to non-NAP1 strains <ul style="list-style-type: none"> – Toxin production 16–23-fold greater than wild-type strains • Fluoroquinolone (FQ) use has been associated with the emergence of the NAP1 strain¹⁰ <ul style="list-style-type: none"> – Reduction in FQ use in the United Kingdom has been associated with dramatic reductions in CDI due to NAP1.  <p><small>AHRQ Safety Program for Improving Antibiotic Use – Acute Care</small></p> <p style="text-align: right;"><small><i>Clostridioides difficile</i> 9</small></p>

Slide Title and Commentary

Recurrent CDI

SAY:

Recurrent CDI is defined as a resolution of CDI symptoms, followed by subsequent reappearance of symptoms after treatment has been discontinued. It is helpful to forewarn patients that they may have loose stools and symptoms consistent with irritable bowel syndrome for some time after completing CDI treatment, particularly if still receiving antibiotics. This is usually not indicative of recurrent of CDI. Patients should be retested to confirm the patient indeed has CDI by testing specifically for the presence of toxin and not just simply the presence of the organism, as persistence of the organism may occur in the absence of toxin production.

Up to 30 percent of patients experience recurrent CDI within 30 days of treatment. It may not occur immediately after discontinuing antibiotics. CDI recurrences have been shown to present as late as 3 months after the discontinuation of CDI treatment.

The risk of another episode increases with each successive recurrence. Recurrent symptoms may be due to a relapse of the initial infecting strain or a reinfection with a new strain, although the former is more common. Among 102 patients with recurrent CDI, isolates obtained 2 to 8 weeks apart were identical in 88 percent of cases.

The Four Moments of Antibiotic Decision Making

SAY:

Moment 2 reminds us to ensure appropriate testing has occurred once a patient has clinical signs or symptoms suggestive of an infection.

Slide Number and Slide

Slide 10

Recurrent CDI

- Resolution of CDI symptoms followed by reappearance of symptoms after treatment has been discontinued¹¹
- ~30% of patients experience recurrent CDI within 30 days of treatment¹¹
- Recurrent symptoms may be due to relapse of the initial infecting strain or reinfection with a new strain^{12,13}



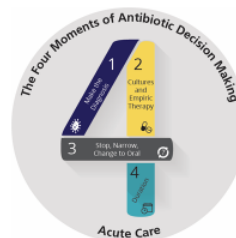
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Slide 11

The Four Moments of Antibiotic Decision Making

1. Does my patient have an infection that requires antibiotics?
2. Have I ordered appropriate cultures before starting antibiotics? What empiric therapy should I initiate?



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Clostridioides difficile 11

Common Laboratory Testing Approaches

SAY:

Several diagnostic tests are available to identify *C. difficile* infection. The enzyme immunoassay can identify toxin A and B production. It is relatively easy to perform, and results return within 4 hours. The major drawback with this test is that it has limited sensitivity.

There are nucleic acid tests that identify the genes that produce toxin A and B. These are very sensitive, but they cannot distinguish whether the genes are activated and making toxin or present but inactive. Thus, there is concern that they will detect large portions of patients with asymptomatic colonization—likely leading to overdiagnosis and overtreatment.

Glutamate dehydrogenase is an enzyme produced by all *C. difficile* isolates. It is rapid, relatively inexpensive, and easy to perform. It has very good sensitivity for detecting the presence of *C. difficile* but its specificity is poor because it does not distinguish strains that do or do not produce toxin.

Finally, the cytotoxin assay is considered the “gold standard” for *C. difficile* detection. The test is performed by adding a prepared stool sample to a monolayer of cultured cells. If *C. difficile* toxin is present, it exerts a cytopathic effect. This test has a sensitivity approaching 100 percent, but it is time consuming to perform and results take up to 48 hours. Some laboratories perform “two-step” tests which initially look for the presence of the organism, followed by testing for the toxin if the organism is present. For example, initial testing may look for the production of glutamate dehydrogenase, and if present, then EIA testing for toxins A and B is performed. Or the initial test might be a nucleic acid test followed by the EIA to evaluate for toxin production.

The 2018 IDSA/SHEA guidelines suggest that a nucleic acid test alone is reasonable if there are established criteria for stool testing for *C. difficile* in a facility—for example, only testing unformed stools. But in the absence of these institutional recommendations, the guidelines recommend using a multistep testing algorithm.

Slide 12

Common Laboratory Testing Approaches^{2,14}

Assay	Benefits	Disadvantages
Enzyme immunoassay (EIA) toxins A and B	Results ≤ 4 hours; easy to perform, inexpensive; specific (75–100%)	Least sensitive technique (63–94%)
Nucleic acid testing (NAAT)	Results ≤ 3 hours; sensitive (85–95%) and specific (89–99%)	Expensive; overly sensitive, requires trained personnel
Glutamate dehydrogenase immunoassays	Results ≤ 1 hour; sensitive (>94%); inexpensive; good initial screening test	Specificity: 58–68%; does not identify toxin production
Cytotoxin assay (tissue culture)	Sensitive (up to 100%) and specific (>95%)	Results take up to 48 hours; labor intensive

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Additional Tips Related to Laboratory Testing

SAY:

Keeping in mind the high rates of asymptomatic colonization with *C. difficile*, particularly in patients with recent or active health care exposure, it is important to obtain *C. difficile* testing for patients with a high clinical suspicion for CDI. Testing should be limited to patients with at least three unformed stools within the past 24 hours and without a reasonable alternative explanation, with an exception being fulminant disease with ileus.

At least one study showed that screening and isolating asymptomatic *C. difficile* carriers reduced the incidence of CDI, but there were some limitations with this study. It spanned over a decade, so other changes that occurred during this time period may have impacted outcomes, including the improved institutional hand hygiene compliance over time. Improvements in antibiotic use over time were not evaluated in this study. Similar studies need to be performed to better understand the pros and cons of screening and isolating asymptomatic carriers. As of April 2019, identifying asymptomatic carriers is not considered standard practice. One concern with this approach is that patients with asymptomatic colonization may unnecessarily receive *C. difficile* therapy.

One of the most common reasons people have loose stools in the hospital setting is laxative use. In one study conducted in an academic medical center, 44 percent of patients with positive nucleic acid testing for *C. difficile* received laxatives within the previous 48 hours.

It is important to confirm a patient has not recently received a laxative prior to sending *C. difficile* testing. Also, tests of cure are not necessary. Once a patient has responded to antibiotic therapy, retesting for *C. difficile* is not needed as asymptomatic colonization can persist in the absence of disease.

Because of the high prevalence of *C. difficile* colonization in infants and the very low likelihood of *C. difficile* clinical infection in infants under a year of age, testing for *C. difficile* is discouraged in this age group. Many institutions have expanded this to limit testing for

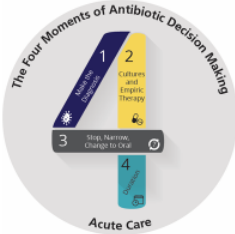
Slide 13


Additional Tips Related to Laboratory Testing

- Testing limited to patients with diarrhea
 - ≥ 3 unformed stools per day
- Confirm patient has not received a laxative within the prior 48 hours before sending testing
- No indication for a test of cure
 - Over 60% of patients with favorable clinical responses continue to test positive
- Infants <1 year of age should not be routinely tested
 - Testing children <2 years old is also strongly discouraged
- Consider placing restrictions on the ordering of *C. difficile* testing
 - No repeat testing within 7 days
 - No testing of formed stool samples

AHRQ Safety Program for
Improving Antibiotic Use –
Acute Care



Slide Title and Commentary	Slide Number and Slide
<p>children under 2 years of age. Some laboratories require approval by an infectious diseases clinician prior to pursuing <i>C. difficile</i> testing in young children.</p> <p>Other mechanisms that have been successfully used to limit unnecessary testing of <i>C. difficile</i> include not testing for <i>C. difficile</i> more than once in 7 days, having automatic popups in the electronic health record reminding clinicians to ensure that a patient is not receiving a laxative prior to sending <i>C. difficile</i> testing, or laboratory refusal to test formed stool samples for <i>C. difficile</i>.</p>	
<p>The Four Moments of Antibiotic Decision Making</p> <p>SAY:</p> <p>The second portion of Moment 2 as well as Moments 3 and 4 focus on antibiotic therapy. Empiric therapy is not recommended for CDI, unless there is a high suspicion for CDI and the presentation is fulminant, particularly if significant delays are anticipated while awaiting laboratory confirmation. As there are generally not opportunities for de-escalation of CDI therapy and the duration of therapy is relatively standardized, Moments 3 and 4 can be combined for CDI management.</p>	<p>Slide 14</p> <p>The Four Moments of Antibiotic Decision Making</p>  <ol style="list-style-type: none"> 1. Does my patient have an infection that requires antibiotics? 2. Have I ordered appropriate cultures before starting antibiotics? What empiric therapy should I initiate? 3. A day or more has passed. Can I stop antibiotics? Can I narrow therapy or change from IV to oral therapy? 4. What duration of antibiotic therapy is needed for my patient's diagnosis? <p>AHRQ Safety Program for Improving Antibiotic Use – Acute Care</p> <p><i>Clostridioides difficile</i> 14</p>

Slide Title and Commentary	Slide Number and Slide
<p>Treatment Principles</p> <p>SAY:</p> <p>A number of treatment principles should be considered.</p> <p>First, do not treat asymptomatic patients with a positive <i>C. difficile</i> test. Always confirm that the patient has signs and symptoms consistent with CDI before prescribing therapy.</p> <p>Second, if possible, discontinue any antibiotic therapy the patient is receiving that is not being administered to treat CDI. Continuing additional antibiotic agents may decrease clinical response and increase CDI recurrence rates.</p> <p>If additional antibiotics are needed because of proven infection, or in a situation where it is not entirely clear if a patient has sepsis from an abdominal source or CDI, select the narrowest agent possible. Avoid agents with a strong association with CDI such as third- and fourth-generation cephalosporins, fluoroquinolones, or clindamycin. As there are some data suggesting the risk of CDI is lower with tetracyclines compared with most other antibiotic classes, consider a tetracycline (such as doxycycline or tigecycline) if appropriate based on the clinical scenario.</p> <p>Discontinue gastric acid suppression medications whenever possible. Additionally, avoid antimotility agents as some studies suggest that these agents could lead to poor outcomes.</p>	<p>Slide 15</p> <p>Treatment Principles</p> <ul style="list-style-type: none"> • Do not treat asymptomatic patients with a positive <i>C. difficile</i> test <ul style="list-style-type: none"> – Confirm symptoms consistent with CDI exist prior to prescribing therapy • If possible, discontinue any antibiotic therapy not specifically treating CDI • If additional antibiotic therapy is necessary: <ul style="list-style-type: none"> – Select the narrowest agent possible – Avoid agents with a strong association with CDI – Consider a tetracycline if appropriate • Discontinue gastric acid suppression medications • Avoid antimotility agents  <p><small>AHRQ Safety Program for Improving Antibiotic Use – Acute Care</small></p> <p><small><i>Clostridioides difficile</i> 15</small></p>

Slide Title and Commentary	Slide Number and Slide
<p>Treatment of Initial Episode</p> <p>SAY:</p> <p>In the past, metronidazole was advocated for mild to moderate cases of CDI, but the 2018 IDSA/SHEA guidelines recommend enteral vancomycin 125 mg by mouth 4 times a day or fidaxomicin 200 milligrams twice a day for mild, moderate, or severe disease. For children, either oral metronidazole or oral vancomycin are considered reasonable options for nonsevere cases. There are no randomized controlled trials evaluating the comparative efficacy of these agents for CDI in children. For children with an initial episode of severe CDI, oral vancomycin is recommended over oral metronidazole.</p> <p>Of note, intravenous vancomycin has no effect on CDI because of its minimal excretion into the colon. The liquid formulation of vancomycin compounded from powder which is intended for intravenous administration can be safely and effectively administered as oral vancomycin. This approach is more cost effective than using the standard oral vancomycin formulation, especially while a patient is hospitalized.</p>	<p>Slide 16</p> <p>Treatment of Initial Episode¹⁵⁻¹⁸</p> <p>Enteral vancomycin (125 mg PO four times daily) or fidaxomicin</p> <ul style="list-style-type: none"> • Rates of resolution of primary CDI similar between these two agents • Cost of fidaxomicin should be considered in decision process • Intravenous formulation of vancomycin administered enterally is a cost-savings approach of drug administration • For children: Either metronidazole or vancomycin (10 mg/kg/dose PO four times daily) recommended for nonsevere episodes <p>Limit duration of CDI therapy to 10 days</p> <ul style="list-style-type: none"> • Can extend to 14 days if resolution has not occurred by day 10 • CDI-targeted therapy does not need to continue for the duration of concomitant antibiotic therapy <p>AHRQ Safety Program for Improving Antibiotic Use – Acute Care Clostridioides difficile 16</p>
<p>Treatment of Fulminant Disease</p> <p>SAY:</p> <p>In cases of fulminant CDI, vancomycin in higher dosages (500 mg instead of 125 mg) is recommended although there is a lack of evidence of a clear benefit with this increased dose. Intravenous metronidazole should also be considered for fulminant CDI, particularly if an ileus prevents the delivery of oral agents to the colon. If an ileus is present, vancomycin can also be administered per rectum as a retention enema, along with intravenous metronidazole. It is anticipated that IV metronidazole is likely to achieve therapeutic concentrations in an inflamed colon. For fulminant CDI, early surgical consultation is essential.</p>	<p>Slide 17</p> <p>Treatment of Fulminant Disease³</p> <ul style="list-style-type: none"> • Oral vancomycin preferred for both children and adults <ul style="list-style-type: none"> – Adults: 500 mg orally 4 times per day – Children: 10 mg/kg/dose orally 4 times per day • If ileus present, vancomycin can also be administered per rectum as a retention enema, along with intravenous metronidazole • Early surgical consultation is essential! <p>AHRQ Safety Program for Improving Antibiotic Use – Acute Care Clostridioides difficile 17</p>

Slide Title and Commentary

Treatment of Recurrent CDI

SAY:

A first recurrence of CDI in adults can be treated with either oral vancomycin as a tapered and pulse regimen or a 10-day course of fidaxomicin. Although the risk of recurrence may be lower with fidaxomicin compared with a tapered and pulse regimen of vancomycin, medication costs should be factored into this decision.

The theoretical benefit of a tapered and pulse vancomycin regimen that extends over several weeks is that it may keep growth of *C. difficile* under control while allowing normal flora to repopulate. A commonly used prolonged tapered and pulse regimen consists of 125 mg of oral vancomycin 4 times per day for 10 to 14 days, followed by twice a day for a week, then once a day for a week, and then every 2 to 3 days for 2 to 8 weeks.

If metronidazole was used for the primary episode, it is recommended that a first recurrence of CDI is treated with a standard 10-day course of vancomycin.

For children, oral vancomycin is recommended for a first recurrence.

Fecal microbiota transplantations should be considered for both children and adults with multiple CDI recurrences.

Slide Number and Slide

Slide 18


Treatment of Recurrent CDI³

Recurrences	Treatment
First recurrence of CDI in adults	<ul style="list-style-type: none">• EITHER enteral vancomycin as a tapered and pulse regimen• OR a 10-day course of fidaxomicin<ul style="list-style-type: none">– Risk of recurrences may be lower with fidaxomicin vs. enteral vancomycin (61% vs. 71%) but cost should be considered¹⁶• OR a 10-day course of vancomycin if oral metronidazole was used for the first CDI episode
First recurrence of CDI in children	<ul style="list-style-type: none">• Enteral vancomycin for a 10-day course

Fecal microbiota transplantations should be considered for patients with multiple CDI recurrences

AHRQ Safety Program for Improving Antibiotic Use – Acute Care

Clostridioides difficile 18

Slide Title and Commentary	Slide Number and Slide
<p>Fecal Microbiota Transplantation</p> <p>SAY:</p> <p>The colon harbors a stable community of microorganisms which exist in symbiosis with the host. Antibiotics lead to the selective removal of bacteria that serve as a barrier to colonization with <i>C. difficile</i>. Fecal microbiota transplantations or FMTs promote intestinal diversity similar to what was present prior to antibiotic exposure.</p> <p>There are a number of observational and randomized controlled trials that have evaluated the efficacy of FMTs. Treatment success in these studies range from 50 to 100 percent when used for patients with recurrent CDI. The highest success rates appear to be associated with instillation of feces via colonoscopy rather than the nasogastric route.</p>	<p>Slide 19</p> <p>Fecal Microbiota Transplantation¹⁹⁻²³</p> <ul style="list-style-type: none"> • Colon harbors a stable community of microorganisms which exist in symbiosis with the host • Antibiotics lead to selective removal of bacteria that serve as a barrier to colonization with <i>C. difficile</i> • FMT promotes intestinal diversity similar to what was present prior to antibiotic exposure • Observational and randomized controlled trials: <ul style="list-style-type: none"> – Treatment success rates ranges from 50% to almost 100% for recurrent CDI – Highest success rates associated with instillation of feces via the colon  <p>AHRQ Safety Program for Improving Antibiotic Use – Acute Care</p> <p><i>Clostridioides difficile</i> 19</p>
<p>Monoclonal Antibodies</p> <p>SAY:</p> <p>Monoclonal antibodies against <i>C. difficile</i> toxin appear to reduce the recurrence rate of CDI. Bezlotoxumab is a monoclonal antibody directed against toxin B that was approved by the Food and Drug Administration in 2016 as adjunctive therapy for patients with a previous history of CDI who are receiving antibiotic treatment for CDI and who are at high risk for recurrence. Bezlotoxumab together with standard therapy has been associated with lower recurrence rates than standard therapy alone—17 percent versus 28 percent. The role of monoclonal antibodies to prevent and treat CDI recurrences is still being defined as of April 2019.</p>	<p>Slide 20</p> <p>Monoclonal Antibodies</p> <ul style="list-style-type: none"> • Monoclonal antibodies against <i>C. difficile</i> toxin appear to reduce the recurrence rate of CDI²⁴ • Bezlotoxumab²⁵ <ul style="list-style-type: none"> – Monoclonal antibody that binds to toxin B – Received Food and Drug Administration approval in 2016 for the secondary prevention of CDI in high-risk patients • Randomized controlled trials <ul style="list-style-type: none"> – Bezlotoxumab + standard therapy = lower recurrence rates than standard therapy alone (17% vs. 28%) • The role of monoclonal antibodies to prevent and treat CDI recurrence is still being defined <p>AHRQ Safety Program for Improving Antibiotic Use – Acute Care</p> <p><i>Clostridioides difficile</i> 20</p>

Slide Title and Commentary

Select Modifiable Risk Factors

SAY:

Some nonmodifiable risk factors place people at increased risk of CDI. These include elderly age, inflammatory bowel disease, solid organ transplant recipient, or Hirschsprung's disease in young children.

Some important modifiable risk factors alter a patient's risk of developing CDI including antibiotic use, gastric acid suppression, probiotic use, and infection control practices. Although the role of lapses in infection control practices is well recognized in the transmission of CDI, this presentation will not review the role of infection prevention practices in limiting the spread of *C. difficile*.

To observe a demonstrable decrease in CDI rates, a multifaceted approach is generally necessary that starts with judicious testing for *C. difficile* as well as appropriate antibiotic use, judicious gastric acid suppression use, and infection prevention practices. The reference on this slide by Abbett and colleagues, published in *Infection Control and Hospital Epidemiology* in 2009, includes a checklist that reviews modifiable risk factors, including enhanced isolation practices and laboratory notification procedures, which successfully reduced the incidence of CDI by 40 percent at a tertiary-care hospital.

Clostridioides difficile and Antibiotics

SAY:

Virtually all antibiotics can increase the propensity for the development of CDI, but the greatest risk exists with third- and fourth-generation cephalosporins, fluoroquinolones, and clindamycin. The risk is highest when patients are receiving antibiotics, but the risk remains elevated up to 12 weeks later. Some data suggest that tetracyclines such as doxycycline or tigecycline may be protective as they have some activity against *C. difficile* growth and appear to inhibit toxin production. It also appears they have minimal effects on a number of healthy gut flora.

Slide Number and Slide

Slide 21

Select Modifiable Risk Factors²⁶

- Antibiotic use
- Gastric acid suppression
- Probiotics
- Infection control practices
 - Hand hygiene
 - Contact precautions
 - Environmental cleaning



AHRQ Safety Program for
Improving Antibiotic Use –
Acute Care

Clostridioides difficile 21

Slide 22

C. difficile and Antibiotics

- Virtually all antibiotics can increase the propensity for development of CDI
- Greatest risk^{10,27}
 - Third- and fourth-generation cephalosporins (OR 5.68)
 - Fluoroquinolones (OR 5.50)
 - Clindamycin (OR 16.80)
 - Risk highest while receiving antibiotics but still elevated up to 12 weeks later
- Doxycycline/tigecycline may be protective²⁸
 - Active against *C. difficile* growth and inhibits toxin production
 - Minimal effects on a number of gut flora




AHRQ Safety Program for
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Acute Care


Clostridioides difficile 22

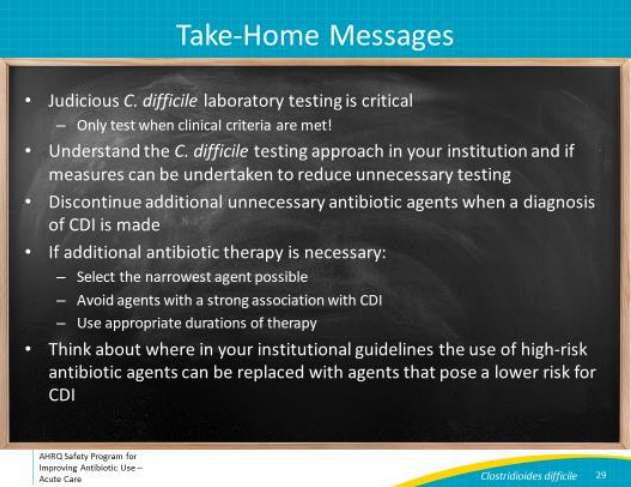
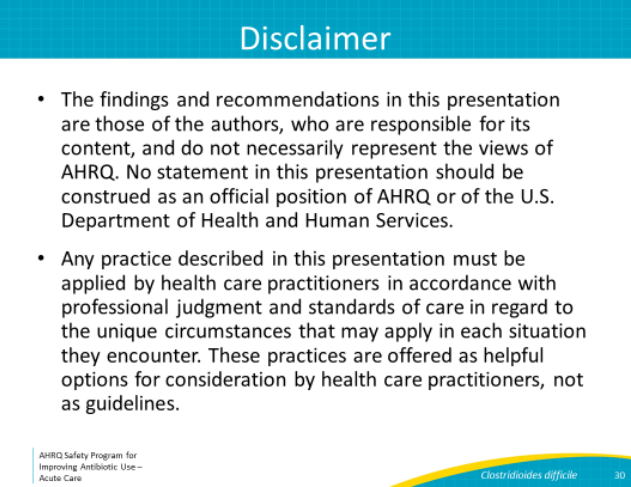
Slide Title and Commentary	Slide Number and Slide
<p>CDI Reductions Associated With Reduction in Cephalosporins and FQ</p> <p>SAY:</p> <p>A large quasi-experimental study was undertaken to assess the impact of national antibiotic stewardship and infection control programs on CDI rates in Scotland, evaluating data from over 1 million patients. Stewardship activities included empiric guidelines recommending against the use of agents such as fluoroquinolones, clindamycin, and cephalosporins and finding suitable replacement agents. Approval was needed for use of these agents and susceptibilities of these agents were not routinely provided. In addition, improvements in infection control practices occurred. These interventions led to a 68 percent reduction of CDI in Scottish hospitals.</p>	<p>Slide 23</p> <p>CDI Reductions Associated With Reduction in Cephalosporins and FQ</p> <ul style="list-style-type: none"> • Quasi-experimental study to assess the impact of national antibiotic stewardship and infection control programs on CDI rates in Scotland in 1997–2012²⁹ • Antibiotic stewardship program <ul style="list-style-type: none"> – Empiric guidelines recommending against the use of fluoroquinolones, clindamycin, cephalosporins, and amoxicillin/clavulanate – Approval required for use of these agents – Susceptibilities of these agents not routinely provided • Hand hygiene campaign and monthly auditing of environmental cleaning • 68% reduction in CDI in hospitals <p>AHRQ Safety Program for Improving Antibiotic Use – Acute Care</p> <p><i>Clostridioides difficile</i> 23</p>

Slide Title and Commentary	Slide Number and Slide
<p>How Can We Reduce the Use of High Risk Agents?</p> <p>SAY:</p> <p>What are some ways we can reduce the use of high-risk antibiotic agents? Keeping in mind the elevated risk of CDI with antibiotics such as ceftriaxone, cefepime, clindamycin, and fluoroquinolones, use of these agents should be limited as much as possible.</p> <p>Think about infectious processes where these agents are commonly used in your facility and consider alternative agents. For example, ceftriaxone is commonly used for the treatment of community-acquired pneumonia. Consider replacing it in your local community-acquired pneumonia guidelines with ampicillin or ampicillin/sulbactam. Ceftriaxone is also commonly used for cystitis. The reality is most cystitis in the hospital is really asymptomatic bacteriuria. Before prescribing treatment, confirm that the patient has urinary symptoms. Further, intravenous therapy generally is not needed for cystitis. If treatment appears necessary, consider 5 days of nitrofurantoin, 3 days of trimethoprim/sulfamethoxazole, or 7 days of cephalexin for cystitis.</p> <p>Cefepime is commonly used for neutropenic fever. Although all antipseudomonal beta-lactam antibiotics have the potential for adverse events, if you are having higher rates of CDI in your oncology wards than expected, consider replacing your standard neutropenic fever beta-lactam with piperacillin/tazobactam. Data for both children and adults suggest the risk of CDI is lower in units where piperacillin-tazobactam is used as the standard neutropenic fever agent compared with other anti-pseudomonal beta-lactams.</p>	<p>Slide 24</p> <p>How Can We Reduce the Use of High-Risk Agents?</p> <ul style="list-style-type: none"> • Ceftriaxone <ul style="list-style-type: none"> – Consider ampicillin or ampicillin/sulbactam for community-acquired pneumonia – Avoid for cystitis <ul style="list-style-type: none"> ○ Most “cystitis in the hospital” is asymptomatic bacteriuria ○ Ask about symptoms before testing and treating ○ Consider nitrofurantoin (5 days), trimethoprim/sulfamethoxazole (TMP/SMX) (3 days), or cephalexin (7 days) for cystitis³⁰ • Cefepime <ul style="list-style-type: none"> – Consider piperacillin/tazobactam for neutropenic fever if elevated CDI rates <p><small>AHRQ Safety Program for Improving Antibiotic Use – Acute Care</small></p> <p><small><i>Clostridioides difficile</i> 24</small></p>

Slide Title and Commentary	Slide Number and Slide
<p>How Can We Reduce the Use of High-Risk Agents?</p> <p>SAY:</p> <p>Clindamycin is frequently used for both nonpurulent and purulent cellulitis. For nonpurulent cellulitis, consider the use of cephalexin. Consider trimethoprim/sulfamethoxazole or doxycycline for mild purulent cellulitis when methicillin-resistant <i>Staphylococcus aureus</i> is a consideration. Rates of resistance to clindamycin for both methicillin-susceptible and -resistant <i>S. aureus</i> have increased in many parts of the county, making clindamycin a poor choice for purulent cellulitis in these areas.</p> <p>Fluoroquinolones should be avoided for cystitis and intra-abdominal infections whenever possible. Additionally, consider limiting their use for community-acquired pneumonia to patients with severe penicillin allergies.</p> <p>And, in general, always remember to stop or de-escalate antibiotic therapy whenever possible when reviewing Moment 3, and limit the duration of antibiotic therapy to what is appropriate for the condition you are treating when considering Moment 4.</p>	<p>Slide 25</p> <p>How Can We Reduce the Use of High-Risk Agents?</p> <ul style="list-style-type: none"> • Clindamycin <ul style="list-style-type: none"> – Consider cephalexin for nonpurulent cellulitis – Consider trimethoprim/sulfamethoxazole or doxycycline for mild purulent cellulitis • Fluoroquinolones <ul style="list-style-type: none"> – Avoid for cystitis – Limit use for community-acquired pneumonia to severe penicillin allergies • Overall <ul style="list-style-type: none"> – De-escalate therapy whenever possible – Limit durations of therapy <p><small>AHRQ Safety Program for Improving Antibiotic Use – Acute Care</small></p> <p><small><i>Clostridioides difficile</i> 25</small></p>


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<p>Gastric Acid Suppression</p> <p>SAY:</p> <p>Proton-pump inhibitors and histamine receptor antagonists have been associated with an increased risk of CDI in both pediatric and adult studies.</p> <p>In an observational study including 650 children with CDI, children with CDI had 22 times the odds of having recently receiving PPIs within the previous 90 days than children without CDI. Based on the results of three meta-analyses including over 45 observational studies of adults, adults with CDI had about twice the odds of having recently received PPIs than adults without CDI.</p> <p>Evaluating Centers for Disease Control and Prevention data from 2009 to 2011, which included a relatively large percentage of community-associated CDI cases, 36 percent did not report antibiotic exposure in the preceding 12 weeks. However, among patients without reported antibiotic exposure, 31 percent received proton pump inhibitors. The increased risk of CDI is likely due to a decrease in the protective effect of stomach acid. This decreased protective effect allows the entry and survival of <i>C. difficile</i> in the upper gastrointestinal tract.</p> <p>The relationship between the route and duration of gastric acid suppressive agents and CDI is unknown. Although some debate exists regarding the true impact of gastric acid suppressive agents on CDI, as with all medications, their use should be limited to when they are clearly necessary.</p>	<p>Slide 26</p> <p>Gastric Acid Suppression³¹⁻³⁴</p> <ul style="list-style-type: none"> • Proton-pump inhibitors (PPIs) and histamine 2 receptor antagonists <ul style="list-style-type: none"> – Associated with an increased risk of CDI in studies of children and adults • Likely due to breaches in the protective effect of stomach acid facilitating the entry and survival of <i>C. difficile</i> in the upper gastrointestinal tract • Relationship between the risk of CDI and route and duration of gastric acid suppressive agents is unknown • Limit gastric acid suppressive agent use whenever possible  <p>AHRQ Safety Program for Improving Antibiotic Use – Acute Care</p> <p><i>Clostridioides difficile</i> 26</p>

Slide Title and Commentary	Slide Number and Slide
<p>Probiotics</p> <p>SAY:</p> <p>Probiotics include microorganisms that may reduce the risk of colonization by pathogenic bacteria. They are becoming increasingly available as capsules and dairy-based food supplements. Several meta-analyses have indicated probiotics may be effective at preventing CDI when given to patients receiving antibiotics. However, randomized trial data have not shown the same benefit.</p> <p>There have also been several meta-analyses that have included randomized trials that suggest a benefit of probiotics when administered to patients with mild to moderate CDI. Similar data are not available for patients with severe CDI.</p>	<p>Slide 27</p> <p style="text-align: center;">Probiotics³⁴</p> <ul style="list-style-type: none"> • Include microorganisms that may reduce the risk of colonization by pathogenic bacteria • Becoming increasingly available as capsules and dairy-based food supplements • Prevention of CDI <ul style="list-style-type: none"> – Several meta-analyses indicate probiotics may be effective at preventing CDI when given to patients receiving antibiotics – No randomized trials have shown a benefit with probiotics in preventing CDI • Treatment of CDI <ul style="list-style-type: none"> – Meta-analysis of RCTs suggest a benefit of probiotics for mild-moderate CDI therapy – Data not available for severe CDI  <p><small>AHRQ Safety Program for Improving Antibiotic Use – Acute Care</small></p> <p style="text-align: right;"><small><i>Clostridioides difficile</i> 27</small></p>
<p>Bottom Line With Probiotics</p> <p>SAY:</p> <p>The role of probiotics in preventing and treating CDI is evolving. They are not routinely recommended as of April 2019.</p> <p>There continue to be gaps in knowledge regarding the right strains, dosages, frequency, and duration of probiotics for both the prevention and treatment of CDI. There are not current requirements to demonstrate safety or manufacturing consistencies of probiotics to consumers. Probiotics generally seem associated with little harm and may have a benefit for immunocompetent patients. But they may cause harm if administered to immunocompromised patients. There have been cases of probiotic-associated bacteremia or fungemia in immunocompromised patients as well as premature neonates. Although the role of probiotics in the prevention or treatment of CDI is still not clear, it is important to remember that encouraging probiotic use is not a standalone intervention if you are trying to make changes in your facility to reduce CDI rates.</p>	<p>Slide 28</p> <p style="text-align: center;">Bottom Line With Probiotics</p> <ul style="list-style-type: none"> • Role of probiotics in preventing and treating CDI is evolving and currently not routinely recommended • Right strain(s), dosage, duration unknown • No requirement to demonstrate safety or manufacturing consistencies of probiotics to consumers • Likely little harm and may have a benefit for generally immunocompetent patients <ul style="list-style-type: none"> – Cases of probiotic-associated bacteremia or fungemia have been reported, particularly in immunocompromised patients and premature neonates • Encouraging probiotic use is not a standalone intervention to reduce CDI. <p><small>AHRQ Safety Program for Improving Antibiotic Use – Acute Care</small></p> <p style="text-align: right;"><small><i>Clostridioides difficile</i> 28</small></p>

Slide Title and Commentary	Slide Number and Slide
<p>Take-Home Messages</p> <p>SAY:</p> <p>A few take-home points are worth reemphasizing.</p> <p>First, judicious <i>C. difficile</i> laboratory testing is critical. Only test stool for <i>C. difficile</i> when clinical criteria are met!</p> <p>Make sure you understand the <i>C. difficile</i> testing approach used in your institution and work with your microbiology laboratory and other important stakeholders to determine if measures can be undertaken to reduce unnecessary testing.</p> <p>It is critical to discontinue additional unnecessary antibiotic agents when a diagnosis of CDI is made. If additional antibiotic therapy is necessary, make sure to select the narrowest antibiotic agent(s) possible, avoid using agents with a strong association with CDI (such as ceftriaxone, cefepime, clindamycin, and fluoroquinolones), and limit the duration of antibiotic therapy to the lowest effective duration.</p> <p>Also, think about where in your institutional guidelines the use of high-risk antibiotic agents can be replaced with agents that pose a lower risk for CDI.</p>	<p>Slide 29</p> 
<p>Disclaimer</p> <p>SAY:</p> <p>The findings and recommendations in this presentation are those of the authors, who are responsible for its content, and do not necessarily represent the views of AHRQ. No statement in this presentation should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.</p> <p>Any practice described in this presentation must be applied by health care practitioners in accordance with professional judgment and standards of care in regard to the unique circumstances that may apply in each situation they encounter. These practices are offered as helpful options for consideration by health care practitioners, not as guidelines.</p>	<p>Slide 30</p> 

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<p>References</p>	<p>Slide 31</p> <p style="text-align: center;">References</p> <ol style="list-style-type: none"> 1. Bartlett JG. <i>Clostridium difficile</i> Infection. Infect Dis Clin N Am. 2017 Sep;31(3):489-95. PMID: 28779831. 2. Tamma PD, Sandora TJ. <i>Clostridium difficile</i> infection in children: current state and unanswered questions. J Pediatric Infect Dis Soc. 2012 Sep;1(3):230-43. PMID: 23687578. 3. McDonald LC, Gerding DN, Johnson S, et al. Clinical practice guidelines for <i>Clostridium difficile</i> infection in adults and children: 2018 update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA). Clin Infect Dis. 2018 Mar 19;66(7):987-94. PMID: 29562266. 4. Rousseau C, Poillane I, De Pontual L, et al. <i>Clostridium difficile</i> carriage in healthy infants in the community: a potential reservoir for pathogenic strains. Clin Infect Dis 2012 Nov;55(9):1209-15. PMID: 22843784. 5. Enoch DA, Butler MJ, Pai S, et al. <i>Clostridium difficile</i> in children: colonisation and disease. J Infect 2011 Aug;63(2):105-13. PMID:21664931. 6. Jangl S, Lamont JT. Asymptomatic colonization by <i>Clostridium difficile</i> in infants : implications for disease in later life. J Pediatr Gastroenterol Nutr 2010 Jul; 51(1):2-7. PMID: 20512057. <p>AHRQ Safety Program for Improving Antibiotic Use – Acute Care Clostridioides difficile 31</p>
<p>References</p>	<p>Slide 32</p> <p style="text-align: center;">References</p> <ol style="list-style-type: none"> 7. Cohen SH, Gerding DN, Johnson S, et al. Clinical practice guidelines for <i>Clostridium difficile</i> 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 May;31(5):431-55. PMID: 20307191. 8. McDonald L, Killgore GE, Thompson A, et al. An epidemic, toxin gene-variant strain of <i>Clostridium difficile</i>. N Engl J Med 2005 Dec 8;353(23):2433-41. PMID: 16322603. 9. See I, Mu Y, Cohen J, et al. NAP1 strain type predicts outcomes from <i>Clostridium difficile</i> infection. Clin Infect Dis. 2014 May;58(10): 1394-400. PMID: 24604900. 10. Tabak YP, Srinivasan A, Yu KC, et al. Hospital-level high-risk antibiotic use in relation to hospital-associated <i>Clostridioides difficile</i> infections: retrospective analysis of 2016-2017 data from US hospitals. Infect Control Hosp Epidemiol. 2019 Sep 16:1-7. [Epub ahead of print] PMID: 31522695. 11. Kelly CP. Can we identify patients at high risk of recurrent <i>Clostridium difficile</i> infection? Clin Microbiol Infect. 2012 Dec;18 Suppl 6:21-7. PMID: 23121551. 12. Wilcox MH, Fawley WN, Settle CD, et al. Recurrence of symptoms in <i>Clostridium difficile</i> infection—relapse or reinfection? J Hosp Infect. 1998 Feb;38(2):93-100. PMID: 9522287. 13. Kamboj M, Khosa P, Kaltsas A, et al. Relapse versus reinfection: surveillance of <i>Clostridium difficile</i> infection. Clin Infect Dis. 2011 Nov;53(10):1003-6. PMID: 21976462. <p>AHRQ Safety Program for Improving Antibiotic Use – Acute Care Clostridioides difficile 32</p>
<p>References</p>	<p>Slide 33</p> <p style="text-align: center;">References</p> <ol style="list-style-type: none"> 14. Bagdasarjan N, Rao K, Malani PN. Diagnosis and treatment of <i>Clostridium difficile</i> in adults: a systematic review. JAMA. 2015 Jan 27;313(4):398-408. PMID: 25626036. 15. Zar FA, Balkanagari SR, Moorthi KM, et al. A comparison of vancomycin and metronidazole for the treatment of <i>Clostridium difficile</i>-associated diarrhea, stratified by disease severity. Clin Infect Dis 2007;45(3): 302-7. PMID: 17599306. 16. Johnson S, Louie TJ, Gerding DN, et al. Vancomycin, metronidazole, or tolevamer for <i>Clostridium difficile</i> infection: results from two multinational, randomized, controlled trials. Clin Infect Dis. 2014 Aug 1;59(3):345-54. PMID: 24799326. 17. Louie TJ, Miller MA, Mullane KM, et al. Fidaxomicin versus vancomycin for <i>Clostridium difficile</i> infection. New Engl J Med. 2011 Feb;364(5):422-31. PMID: 21288078. 18. Cornely OA, Crook DW, Esposito R, et al. Fidaxomicin versus vancomycin for infection with <i>Clostridium difficile</i> in Europe, Canada, and the USA: a double-blind, non-inferiority, randomised controlled trial. Lancet Infect Dis. 2012 Apr;12(4):281-9. PMID: 22321770. 19. van Nood E, Vrieze A, Nieuwdorp M, et al. Duodenal infusion of donor feces for recurrent <i>Clostridium difficile</i>. N Engl J Med. 2013 Jan 31;368(5):407-15. PMID: 23323867. <p>AHRQ Safety Program for Improving Antibiotic Use – Acute Care Clostridioides difficile 33</p>

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<p>References</p>	<p>Slide 34</p> <p>References</p> <ol style="list-style-type: none"> 20. Cammarota G, Masucci L, Ianiro G, et al. Randomised clinical trial: faecal microbiota transplantation by colonoscopy vs. vancomycin for the treatment of recurrent <i>Clostridium difficile</i> infection. <i>Aliment Pharmacol Thera</i>. 2015 May;41(9):835-43. PMID: 25728808. 21. Youngster I, Sauk J, Pindar C, et al. Fecal microbiota transplant for relapsing <i>Clostridium difficile</i> infection using a frozen inoculum from unrelated donors: a randomized, open-label, controlled pilot study. <i>Clin Infect Dis</i>. 2014 Jun;58(11):1515-22. PMID: 24762631. 22. Lee CH, Steiner T, Petrof EO, et al. Frozen vs fresh fecal microbiota transplantation and clinical resolution of diarrhea in patients with recurrent <i>Clostridium difficile</i> infection: a randomized clinical trial. <i>JAMA</i> 2016 Jan;315(2):142-9. PMID: 26757463. 23. Kelly CR, Khoruts A, Staley C, et al. Effect of fecal microbiota transplantation on recurrence in multiply recurrent <i>Clostridium difficile</i> infection a randomized trial. <i>Ann Intern Med</i>. 2016 Nov 1;165(9):609-16. PMID: 27547925. 24. Lowy I, Molrine DC, Leav BA, et al. Treatment with monoclonal antibodies against <i>Clostridium difficile</i> toxins. <i>N Engl J Med</i>. 2010 Jan 21;362(3):197-205. PMID: 20089970. <p>AHRQ Safety Program for Improving Antibiotic Use – Acute Care <i>Clostridioides difficile</i> 34</p>
<p>References</p>	<p>Slide 35</p> <p>References</p> <ol style="list-style-type: none"> 25. Wilcox MH, Gerding DN, Poxton IR, et al. Bezlotoxumab for prevention of recurrent <i>Clostridium difficile</i> infection. <i>N Engl J Med</i>. 2017 Jan 26;376(4):305-17. PMID: 28121498. 26. Abbett SK, Yokoe DS, Lipsitz ST, et al. Proposed checklist of hospital interventions to decrease the incidence of healthcare-associated <i>Clostridium difficile</i> infection. <i>Infect Control Hosp Epidemiol</i> 2009 Nov;30(11):1062-9. PMID: 19751156. 27. Brown KA, Khanafar N, Daneman N, et al. Meta-analysis of antibiotics and the risk of community-associated <i>Clostridium difficile</i> infection. <i>Antimicrob Agents Chemother</i>. 2013 May;57(5):2326-32. PMID: 23478961. 28. Doernberg SB, Winston LG, Deck DH, et al. Does doxycycline protect against development of <i>Clostridium difficile</i> infection? <i>Clin Infect Dis</i>. 2012 Sep;55(5):615-20. PMID: 22563022. 29. Lawes T, Lopez-Lozano JM, Nebot, et al. Effect of a national 4C antibiotic stewardship intervention on the clinical and molecular epidemiology of <i>Clostridium difficile</i> infections in a region of Scotland: a non-linear time-series analysis. <i>Lancet Infect Dis</i>. 2017;17(2):194-206. PMID: 27825595. <p>AHRQ Safety Program for Improving Antibiotic Use – Acute Care <i>Clostridioides difficile</i> 35</p>
<p>References</p>	<p>Slide 36</p> <p>References</p> <ol style="list-style-type: none"> 30. Gupta K, Hooton TM, Naber KG, et al. International clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women: a 2010 update by the Infectious Diseases Society of America and the European Society of Microbiology and Infectious Diseases. <i>Clin Infect Dis</i>. 2011 Mar 1;52(5):e103-20. PMID: 21292654. 31. Freedberg DE, Lamouse-Smith ES, Lightdale JR, et al. Use of acid suppression medication is associated with risk for <i>C. difficile</i> infection in infants and children: a population-based study. <i>Clin Infect Dis</i>. 2015 Sep 15;61(6):912-7. PMID: 26060292. 32. Kwok CS, Arthur AK, Anibueze CL, et al. Risk of <i>Clostridium difficile</i> infection with acid suppressing drugs and antibiotics: meta-analysis. <i>Am J Gastroenterol</i>. 2014 Jan;109(1):144. PMID: 22525304. 33. Janarthanan S, Ditah I, Adler DG, et al. <i>Clostridium difficile</i>-associated diarrhea and proton pump inhibitor therapy: a meta-analysis. <i>Am J Gastroenterol</i>. 2012 Jul;107(7):1001-10. PMID: 22710578. 34. Tleyjeh I, Bin Abdulhak A, Riaz M, et al. Association between acid-suppression therapy and <i>Clostridium difficile</i> infection: a contemporary systematic review and meta-analysis. <i>PLoS One</i>. 2012;7(12):e50836. PMID: 23236397. <p>AHRQ Safety Program for Improving Antibiotic Use – Acute Care <i>Clostridioides difficile</i> 36</p>

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References	<p data-bbox="836 218 959 254">Slide 37</p> <div data-bbox="836 260 1468 317" style="background-color: #0099cc; color: white; padding: 5px; text-align: center;">References</div> <p data-bbox="873 348 1419 426">35. Pattani R, Palda VA, Hwang SW, et al. Probiotics for the prevention of antibiotic-associated diarrhea and <i>Clostridium difficile</i> infection among hospitalized patients: systematic review and meta-analysis. Open Med. 2013 May 28;7(2):e56-67. PMID: 24348885.</p> <div data-bbox="873 705 980 741" style="font-size: small;">AHRQ Safety Program for Improving Antibiotic Use – Acute Care</div> <div data-bbox="1227 709 1468 743" style="text-align: right; font-size: small;">  <i>Clostridioides difficile</i> 37 </div>