Clostridioides difficile
Treatment Update, Risk Factors and Antibiotic Stewardship

Teresa Lubowski, Pharm. D., B.S.
October 12, 2022

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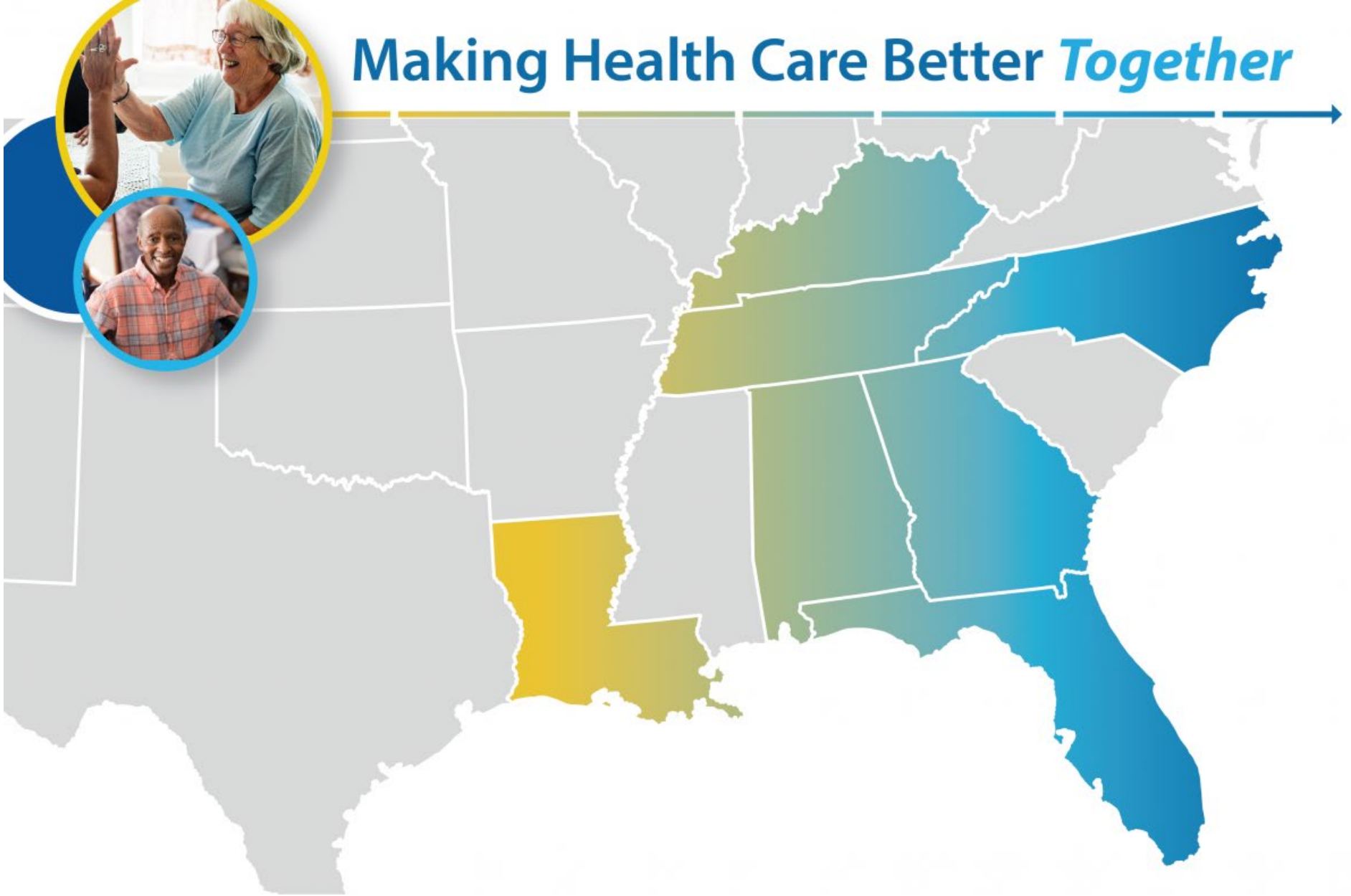

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Treatment Update, Risk Factors and Antibiotic Stewardship

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This material was prepared by IPRO, a Quality Innovation Network-Quality Improvement Organization under contract with the Centers for Medicare & Medicaid Services (CMS), an agency of the U.S. Department of Health and Human Services. The content presented does not necessarily reflect CMS policy.

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Teresa Lubowski completed a B.S degree in Pharmacy at the Albany College of Pharmacy, a Pharm D. degree at the University of New York at Buffalo and a 2 year research/antibiotic stewardship fellowship in infectious diseases at the Hartford Hospital in Connecticut. She has professional pharmacy experience including institutional practice and antibiotic stewardship in multiple states, quality improvement, antibiotic stewardship experience in the outpatient setting, field and headquarters experience in pharmaceutical industry and teaching, administration and research experience in academia. Currently, Dr. Lubowski is the Lead for the HQIC Antibiotic Stewardship Work Group, Director Quality Improvement and Medication Safety and Co Lead for the CMS Quality Improvement initiative for IPRO. She has been working in Quality improvement for the past 6.5 years.

Clostridioides difficile - CDC Urgent Threat - 2019

- *C. difficile* is a spore-forming, anaerobic, gram-positive bacillus
- The bacteria secrete exotoxins - Toxin A and Toxin B
- It is a common cause of antibiotic-associated diarrhea (AAD) and accounts for 15% to 25% of all episodes of AAD
- The spectrum of disease ranges from diarrhea to toxic megacolon and death
- *C. difficile* caused an estimated 12,800 deaths in 2017
- C. difficile infections are more common and tend to be more severe in older people
- Patients with infection exhibit clinical symptoms and test positive for the *C. diff* organism or its toxin

CDC Antibiotic Resistance Threats in U.S. 2019 https://www.cdc.gov/drugresistance/pdf/threats-report/2019-ar-threats-report-508.pdf

https://www.cdc.gov/cdiff/clinicians/faq.html#:~:text=diff%3F-,C.,of%20all%20episodes%20of%20AAD

Pathophysiology

Typically, *C. difficile* produces two types of toxins: Toxin A and Toxin B

- **Toxin A:**
- Over 70% of *C. difficile* strains
- Leads to intestinal secretion, mucosal injury and inflammation
- **Toxin B:**
- Found in all *C. difficile* strains
- Leads to damage in the intestinal walls

Goudarzi, M., Seyedjavadi, S. S., Goudarzi, H., Mehdizadeh Aghdam, E., & Nazeri, S. (2014). *Clostridium difficile infection: Epidemiology, pathogenesis, risk factors, and therapeutic options*. Scientifica.

Tonna, I., & Welsby, P. D. (2005, June 1). *Pathogenesis and treatment of clostridium difficile infection*. Postgraduate Medical Journal

Risk Factors for *Clostridioides difficile* Infection

- The risk for disease increases in patients/residents with:
  - Antibiotic exposure (e.g., fluoroquinolones, third/fourth generation cephalosporins, clindamycin, carbapenems)
  - Gastrointestinal surgery/manipulation
  - A long length of stay in healthcare settings
  - A serious underlying illness
  - Immunocompromising conditions
  - Advanced age

https://www.cdc.gov/cdiff/clinicians/faq.html#:~:text=diff%3F-,C.,of%20all%20episodes%20of%20AAD

Antibiotic Classes and *Clostridioides difficile*

Class	Association with C-Difficile Infection
Clindamycin, Ampicillin, Amoxicillin, Cephalosporins (second generation and higher), Fluoroquinolones, Carbapenems	Very Common
Other Penicillins, Sulfonamides, Trimethoprim, Macrolides	Somewhat Common
Aminoglycosides, Bacitracin, Metronidazole, Teicoplanin, Rifampin, Chloramphenicol, Tetracyclines, Daptomycin, Tigecycline	Uncommon

Longo D.L. NEJM 2015;372:1539-48

IDSA and SHEA 2021 Focused Update
Initial Episode

- Preferred - Fidaxomicin 200mg given twice daily for 10 days
- Alternative - Vancomycin 125mg given four times daily by mouth for 10 days
- Alternative for non-severe infection if above NOT available - Metronidazole 500mg three times daily by mouth for 10-14 days

  Non Severe- Non-severe definition: WBC < 15,000 cell/µL or creatinine <1.5 mg/dL
- Implementation of the above depends upon available resources

Johnson et al. Clinical Practice Guidelines by IDSA and SHEA: 2021 Focused Update. Clinical Infectious Disease 2021

IDSA and SHEA 2021 Focused Update
First CDI Recurrence

- Preferred - Fidaxomicin 200mg twice daily for 10 days OR twice daily for five days followed by once every other day for 20 days.
- Alternative - Vancomycin Tapered and Pulsed Regimen: example: 125mg four times daily for 10-14 days, two times daily for seven days, once daily for seven days and then every two to three days for two to eight weeks.
- Alternative - Vancomycin 125mg four times for 10 days—consider a standard course of Vancomycin if Metronidazole was used for the treatment of the first episode.
- Adjunctive Treatment - Bezlotoxumab 10mg/kg given IV once with antibiotics (data with Fidaxomicin are limited; use with caution in patients with congestive heart failure)

Johnson et al. Clinical Practice Guidelines by IDSA and SHEA: 2021 Focused Update. Clinical Infectious Disease 2021

Fidaxomicin and Recurrence

- Narrow spectrum of activity with less impact on normal bowel flora
- Activity against gram-positive aerobic and anaerobic bacteria
- More microbiome preservation compared to vancomycin
- Bactericidal against *C. difficile,* vancomycin is bacteriostatic
- Superior to vancomycin in the treatment of patients with cancer with higher cure rates and fewer recurrences

Bezlotoxumab (Zinplava)

- FDA approved 2016
- First humanized monoclonal antibody against *C. difficile* Toxin B for prevention of recurrent CDI in high-risk adults in conjunction with standard antibiotics.
- Administered as a one-time infusion of 10mg/kg over 60 minutes
- Long half-life of 18 days
- Warning and precaution: Heart Failure
- Adverse effects include: nausea, pyrexia, headache

Johnson et al. Clinical Practice Guidelines by IDSA and SHEA: 2021 Focused Update. Clinical Infectious Disease 2021

Ziplava FDA label- accessed 9-29-22,

IDSA and SHEA 2021 Focused Update
Second or Subsequent CDI Recurrence

- Fidaxomicin 200mg twice daily for 10 days OR twice daily for five days followed by once every other day for 20 days
- Vancomycin by mouth in a tapered and pulsed regimen
- Vancomycin 125mg four times daily by mouth for 10 days followed by Rifaximin 400mg three times daily for 20 days
- Fecal microbiota transplantation (FMT)
- Adjunctive Treatment - Bezlotoxumab 10mg/kg given IV once with antibiotics (data with Fidaxomicin are limited; use with caution in patients with congestive heart failure).

Rifaximin (Xifaxan) Facts

- Rifamycin antibiotic
- Dosing for a second or subsequent CDI recurrence = 400mg three times daily for 20 days following oral vancomycin.
- A course of Rifaximin after successful treatment might reduce recurrence by 50%
- Used as Post-Vancomycin “chaser” strategy for recurrent CDI
- Potential for resistance

Major et al. Follow on rifaximin for the prevention of recurrence following standard therapy. Gut 2019

Fecal Microbiota Transplant (FMT)- FDA Alerts

- FDA Alert 3-12-2020 - Safety alert for the risk of serious adverse events likely due to transmission of pathogenic organisms. Transmission of enteropathogenic E. coli causing infection in FMT recipients. Need for donor screening and risk/benefit discussions with patients
- FDA Alert 8-22-22 - FDA informs health care providers and patients of the potential risk of transmission of the monkeypox virus through FMT products. Recommendation for donor screening and risk/benefit discussions with patients

https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/safety-alert-regarding-use-fecal-microbiota-transplantation-and-additional-safety-protections-0

https://www.fda.gov/safety/medical-product-safety-information/fecal-microbiota-transplantation-safety-alert-risk-serious-adverse-events-likely-due-transmission

IDSA and SHEA 2021 Focused Update
Fulminant CDI

- Definition of fulminant *C. difficile* = hypotension or shock, ileus, megacolon
- Vancomycin 500mg four times daily by mouth or nasogastric tube. If ileus, consider adding rectal installation of vancomycin
- Intravenously administered metronidazole (500mg every eight hours) should be administered together with oral or rectal vancomycin, particularly if ileus is present

Vancomycin and Fidaxomicin Facts

- Vancomycin (capsules)
  - Good Rx- Initial Episode Treatment= $263.29
  - Precautions: nephrotoxicity, ototoxicity
  - Clinical serum concentrations have been reported
  - Monitor renal function (during and following treatment)
  - Adverse effects include: nausea, abdominal pain, hypokalemia
- Fidaxomicin (Dificid)
  - Good Rx- Initial Episode Treatment= $4401.26
  - Adverse effects include: nausea, vomiting, abdominal pain, GI hemorrhage, anemia, neutropenia
  - Only one indication, minimal absorption

GoodRx accessed 9-8-22, Dificid package insert, accessed 9-28-22, Vancocin package insert, accessed 9-28-22

Probiotics and Proton Pump Inhibitors and *Clostridioides difficile*

- "Although there is an epidemiologic association between proton pump inhibitor (PPI) use and CDI, and unnecessary PPIs should always be discontinued, there is insufficient evidence for discontinuation of PPIs as a measure for preventing CDI (no recommendation)." IDSA 2017 Update.

- There are insufficient data at this time to recommend the administration of probiotics for primary prevention of CDI outside of clinical trials *(no recommendation)*. IDSA 2017 Update

McDonald et al. Clinical Practice Guidelines for Clostridium difficile. Clinical Infectious Disease 2018;66 (7): e1-48.

C. difficile and Antimicrobial Stewardship (AS)

- Antimicrobial stewardship has proven to be the most effective way to decrease *C. difficile* rates.
- Hospital-based AS studies have demonstrated a reduction of *C. difficile* incidence by 24-60%.
- Antibiotic risks include the use of short-term perioperative antibiotics.
- The number of antibiotics and duration of therapy increase *C. difficile* risk.
- Risk can persist for as long as three months after antibiotic discontinuation.

Turner et al. Hospital Infection Control: Clostridioides difficile. Clin Colon Rectal Surgery 2020; 33:98-108
Webb et al. Antibiotic exposure and risk for hospital-associated CDI.AAC 2020; 64: 169

C. difficile and Antimicrobial Stewardship

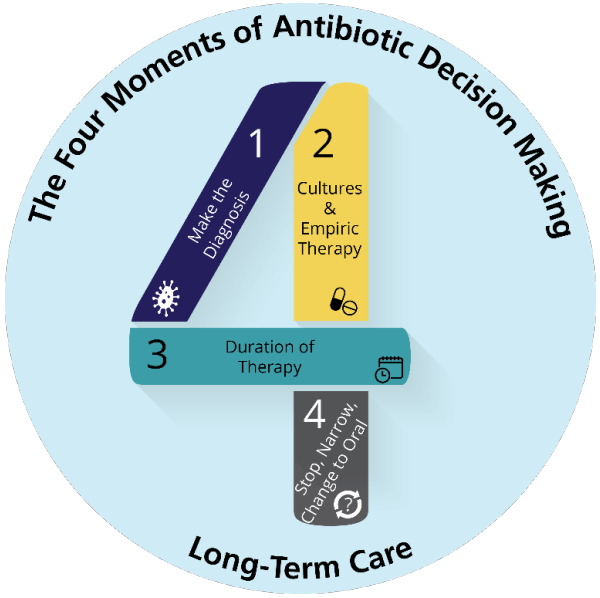
- Discontinue therapy with the inciting antibiotic as soon as possible
- The disruption of the intestinal microbiota by antibiotics is long-lasting, and the risk of CDI increases both during therapy and in the three-month period following the cessation of therapy
- Both longer exposure to antibiotics and exposure to multiple antibiotics increase the risk for CDI

IDSA Recommendations on Antibiotic Stewardship in Controlling *C. difficile* Rates

1. Minimize the frequency and duration of high-risk antibiotic therapy and the number of antibiotic agents prescribed, to reduce CDI risk *(strong recommendation, moderate quality of evidence)*.
2. Implement an antibiotic stewardship program *(good practice recommendation)*.
3. Antibiotics to be targeted should be based on the local epidemiology and the *C. difficile* strains present. Restriction of fluoroquinolones, clindamycin, and cephalosporins (except for surgical antibiotic prophylaxis) should be considered *(strong recommendation, moderate quality of evidence)*.

McDonald et al. Clinical Practice Guidelines for C. difficile 2017 Update. CID 2018; e1-e48

The Four Moments of Antibiotic Decision Making



1. Does the resident have symptoms that suggest an infection? Can we try symptomatic treatment and active monitoring?
2. What type of infection is it? Have we collected appropriate cultures and diagnostic tests before starting antibiotics? What empiric therapy should we initiate?
3. What duration of antibiotic therapy is needed for the resident's diagnosis?
4. It's been two to three days since we started antibiotics. Re-evaluate the resident and review the results of diagnostic tests. Can we stop antibiotics? Can we narrow therapy?

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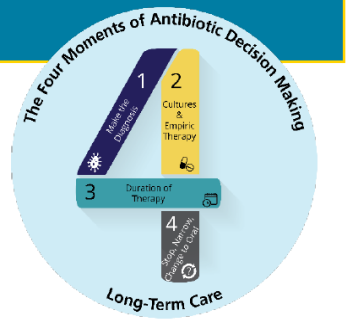
AHRQ Activities of AS Team

- Establish and review antibiotic use protocols
- Monitor antibiotic use
- Track antibiotic use data
- Recommend approaches to improve antibiotic use
- Obtain, review, and distribute the antibiogram
- Review *Clostridioides difficile* infection rates and recommend improvement approaches
- Perform proactive risk assessments to determine areas in which harm related to antibiotic prescribing could be avoided with intervention
- Review the antibiogram and recommend improvement approaches
- Develop, review, and distribute materials to prescribing clinicians, nursing staff, and residents/family members regarding optimal antibiotic prescribing
- Provide feedback to prescribers about antibiotic prescribing practices
- Review approaches employed by the contracted microbiology lab for reporting culture and susceptibility data

Talking With Residents and Family Members About Antibiotics

The last time this happened, the doctor prescribed an antibiotic and my family member got better.

Can't we do that again… just in case?



Five potential health problems can occur as a result of taking an antibiotic.

1. **Allergic reactions**
   People may develop a rash or swelling. Allergic reactions don't happen often, but when they do they can cause people to feel pretty uncomfortable.
2. **Side effects**
   Most antibiotics cause only mild side effects, such as stomach upset. But side effects vary a lot from person to person, and from antibiotic to antibiotic.
3. **Interactions with other medications**
   Some antibiotics interact with certain drugs. Medications such as antacids, the anticoagulant warfarin (e.g., Coumadin®), blood pressure medications, or antidiabetic medications can interact with antibiotics. Some interactions can be harmful, for example by causing organ damage.
4. **Infection with *Clostridioides difficile* or *C. diff*.**
   C. diff is bacteria that can cause diarrhea, pain or cramping in the stomach, weight loss, fever, and dehydration. Someone is much more likely to get a *C. diff* infection after taking antibiotics. Once a person has *C. diff*, he or she can get it again more easily.
5. **Antibiotic resistance**
   Antibiotics kill bacteria. Sometimes not all of the bacteria are killed. The strongest ones are left to grow and spread. A person can get sick again, and this time the bacteria will be harder to kill because the bacteria are resistant to the antibiotics. In other words, the more often you use an antibiotic, the greater the chance that the antibiotic won't kill the bacteria.
   As bacteria become more resistant to antibiotics, it becomes harder to find effective antibiotics. Your family member may also have to be put in isolation to prevent resistant bacteria from spreading to other residents.

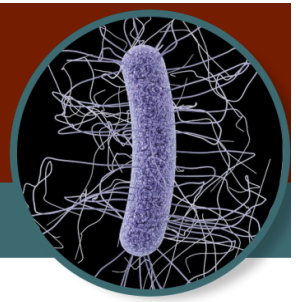
The best way to reduce these risks is to only use antibiotics when necessary.

AHRQ Agency for Healthcare Research and Quality

AHRQ Pub. No. 17(21)-0029
June 2021

Accessible version: https://www.cdc.gov/cdiff/what-is.html

THE PROGRESSION OF A *C. DIFF* INFECTION



C. diff is a bacterium (germ) that causes diarrhea and colitis (an inflammation of the colon). *C. diff* infections can be life-threatening.

***C. diff* can affect anyone. Most cases of *C. diff* infection occur while you're taking antibiotics or not long after you've finished taking antibiotics. Other risk factors include:**

- Previous infection with *C. diff* or known exposure to the germs
- Being 65 or older
- Recent stay at a hospital or nursing home
- A weakened immune system, such as people with HIV/AIDS, cancer, or organ transplant patients taking immunosuppressive drugs

If you have signs or symptoms, see a doctor.

- The doctor will review your signs and symptoms and order a lab test.
- If it's positive, you'll take an antibiotic for 10 days.

After you've recovered, you could still be colonized.

- The germs will be in your body, but you won't feel sick. So you won't need treatment.
- But you can still spread it to others, so always practice good hand hygiene.
- Tell all of your healthcare providers that you've had *C. diff*.

Some people get *C. diff* over and over again.

- For those with repeat infections, fecal microbiota transplants have shown promising results.

***C. diff* develops within a few days or up to several weeks after you take antibiotics. Symptoms can include:**

- Diarrhea
- Fever
- Stomach tenderness or pain
- Loss of appetite
- Nausea

You might be admitted to the hospital.

- Your healthcare providers will use precautions such as wearing gloves and gowns to prevent the spread of *C. diff*.

About 1 in 6 people who get *C. diff* infection will get it again in the subsequent 2-8 weeks.

- If you have symptoms again, see your doctor.

***C. diff* is contagious, but you can keep others from getting it.**

- Wash your hands with soap and water every time you use the bathroom and always before you eat.
- Try to use a separate bathroom if you have diarrhea.
- Take showers and use soap.

cdc.gov/cdiff

U.S. Department of Health and Human Services
Centers for Disease Control and Prevention

Questions?

Nursing Home and Partnership for Community Health:
CMS 12th SOW GOALS

OPIOID UTILIZATION AND MISUSE

Promote opioid best practices

•

Reduce opioid adverse drug events in all settings

PATIENT SAFETY

Reduce hospitalizations due to c. diff

•

Reduce adverse drug events

•

Reduce facility acquired infections

CHRONIC DISEASE SELF-MANAGEMENT

Increase instances of adequately diagnosed and controlled hypertension

•

Increase use of cardiac rehabilitation programs

•

Reduce instances of uncontrolled diabetes

•

Identify patients at high-risk for kidney disease and improve outcomes

CARE COORDINATION

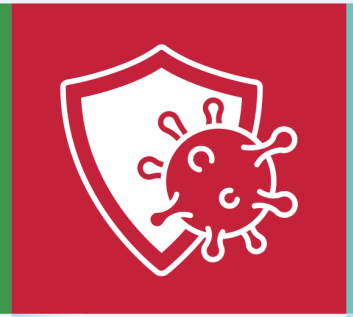
Convene community coalitions

•

Reduce avoidable readmissions, admissions to hospitals and preventable emergency department visits

•

Identify and promote optimal care for super utilizers



COVID-19

Support nursing homes by establishing a safe visitor policy and cohort plan

•

Provide virtual events to support infection control and prevention

•

Support nursing homes and community coalitions with emergency preparedness plans

IMMUNIZATION

Increase influenza, pneumococcal, and COVID-19 vaccination rates

TRAINING

Encourage completion of infection control and prevention trainings by front line clinical and management staff

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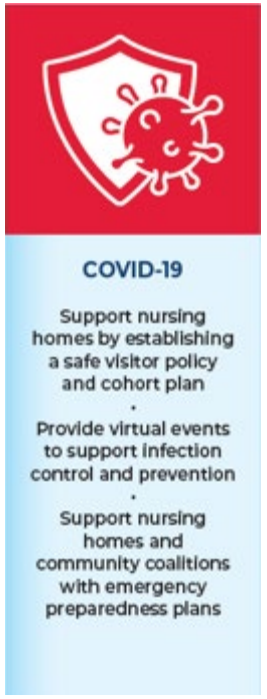
Scan the QR codes or Click the Links to Complete the Assessments!

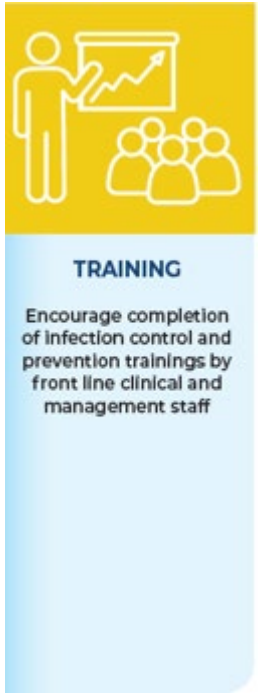
CMS requested Alliant Health Solutions, your QIN-QIO, to work with select nursing homes to understand emerging healthcare needs in nursing homes. Alliant Health Solutions is engaging nursing home leadership on each of these key areas to ensure plans are in place to achieve and maintain health quality and equity!

Please scan the QR codes below and complete the assessments.



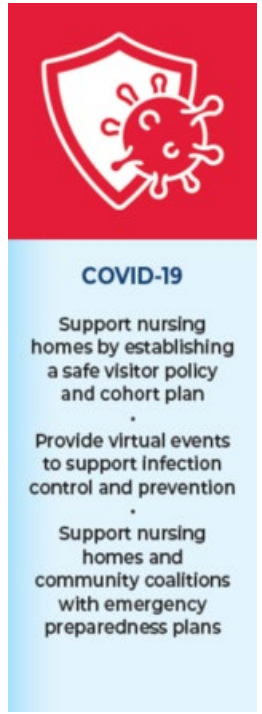
Nursing Home Emergency Preparedness Program (NH EPP) Self-Assessment

https://bit.ly/AHS_NHEPPAssessment



Nursing Home Infection Prevention (NHIP) Initiative Training Assessment

https://bit.ly/NHIPAssessment



Nursing Home Safe Visitor Policy and Cohorting Plan Verification

https://bit.ly/SafeVisitorVerification

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