18.09.10 월요 집담회

Clostridium difficile Infection (CDI)

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N ENGL J MED 372;16 NEJM.ORG APRIL 16, 2015

The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

Dan L. Longo, M.D., *Editor*

Clostridium difficile Infection

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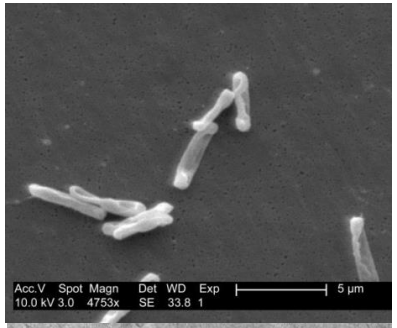
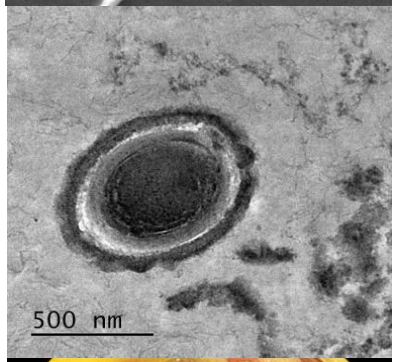
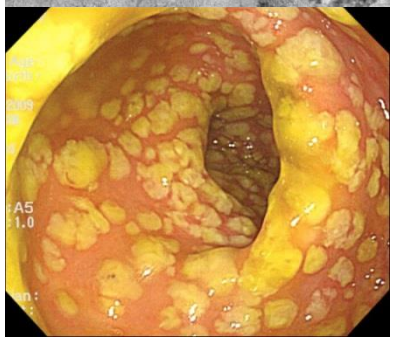
Clostridium difficile infection (CDI)

- Anaerobic gram (+), spore-forming, toxin(TcdA&TcdB)-producing bacillus
- Transmitted among humans through the fecal–oral route
- In the US, most frequently reported nosocomial pathogen

- Asymptomatic carrier
- Diarrhea, medicated by TcdA and TcdB, mild to severe
  : leading to colonocyte death, loss of intestinal barrier function, and neutrophilic colitis
- Colitis or pseudomembranous colitis(PMC)
- Recurrent







N ENGL J Med 2015;372:1539-48

Clostridium difficile infection (CDI)

- Associated with severe illness, infection-related mortality of 5% and all-cause mortality of 15 to 20 %

- **Mild** : afebrile, no notable laboratory abnormalities
- **Moderate** : WBC >15000/mm3, BUN or Cr levels above baseline
- **Severe** : bloody diarrhea, PMC, ileus, BT>38.9°C, WBC >20000/mm3, albumin <2.5mg/dl, AKI
- **Complicated :** toxic megacolon, peritonitis, respiratory distress, hemodynamic instability

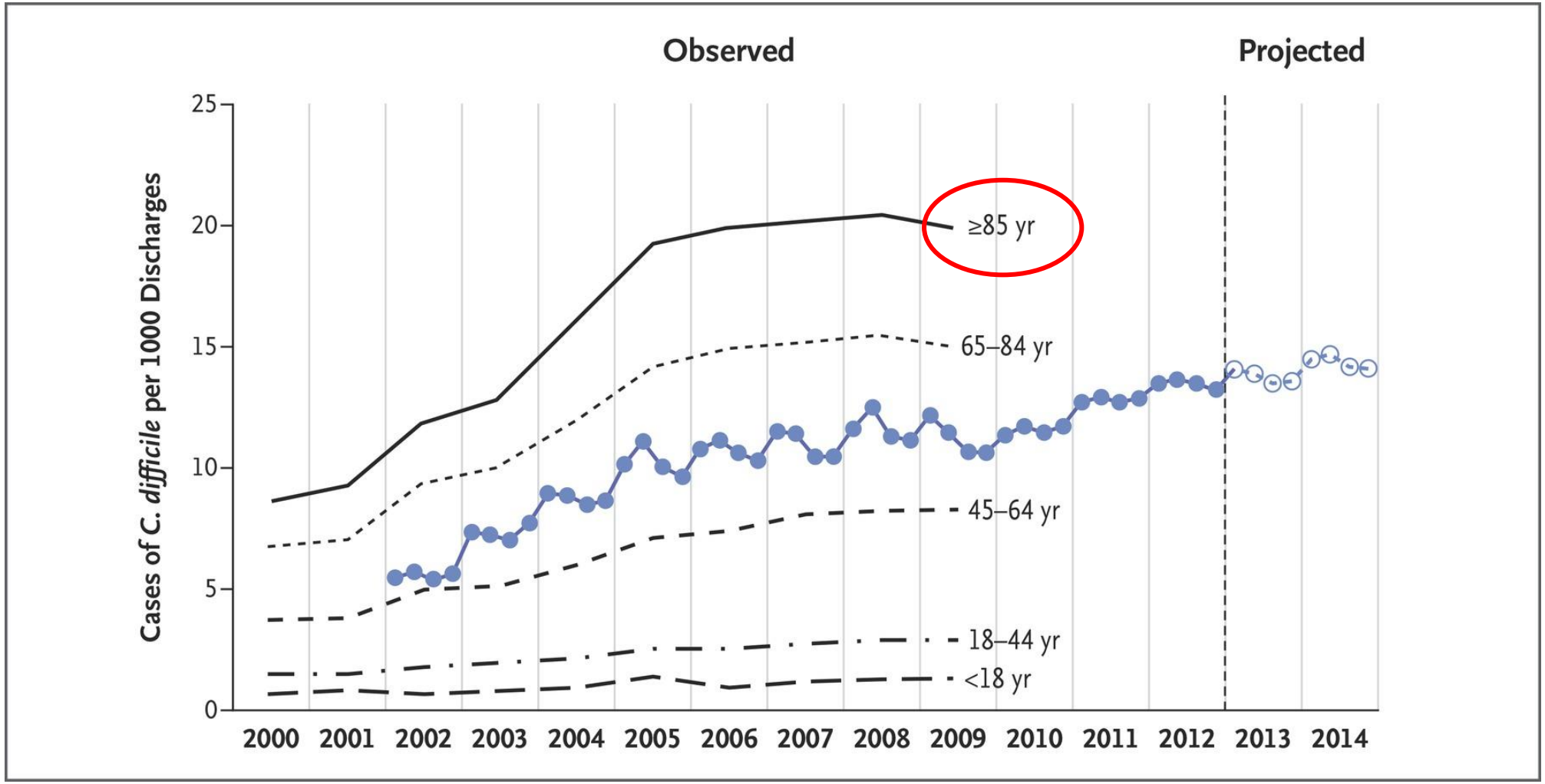
N ENGL J Med 2015;372:1539-48

Clostridium difficile infection (CDI)

- **Community-acquired *C.difficile***
  : in a person who had no overnight stay in a health care facility within 12 weeks before infection

- **Nosocomial infection**
  : events collected >3 days after admission to the facility

Incidence of nosocomial CDI



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Risk factors of CDI

- **Antibiotic use : most important**
- Advanced age : severity increase as age increase
- Inflammatory bowel disease
- Chemotherapy
- Chronic kidney disease
- Immunodeficiency
- Organ transplantation
- Acid suppression (PPI use) : uncertain

Risk factors of recurrent CDI

- Advanced age
- Severe initial episode of CDI
- Ongoing use of antibiotics

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Pathogenesis of CDI

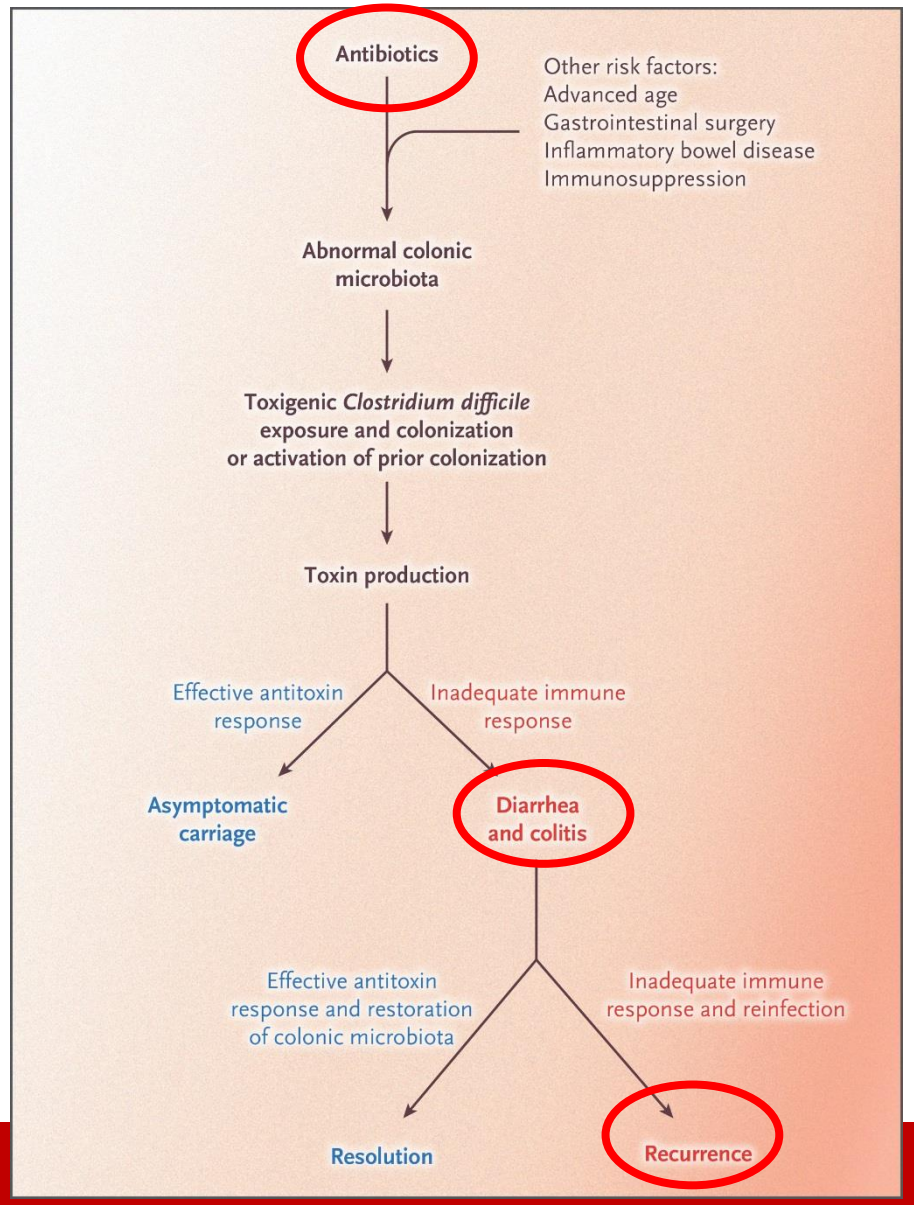

Table 1. Antibiotic Classes and Their Association with *Clostridium difficile* Infection.*

Class	Association with *C. difficile* Infection
Clindamycin	Very common
Ampicillin	Very common
Amoxicillin	Very common
Cephalosporins	Very common
Fluoroquinolones	Very common
Other penicillins	Somewhat common
Sulfonamides	Somewhat common
Trimethoprim	Somewhat common
Trimethoprim–sulfamethoxazole	Somewhat common
Aminoglycosides	Uncommon
Bacitracin	Uncommon
Metronidazole	Uncommon
Teicoplanin	Uncommon
Rifampin	Uncommon
Chloramphenicol	Uncommon
Tetracyclines	Uncommon
Carbapenems	Uncommon
Daptomycin	Uncommon
Tigecycline	Uncommon

* Specific antibiotics are listed if their association with *C. difficile* infection differs from that of most other antibiotics in their class.

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B1/NAP1/027 strain

- High-level fluoroquinolone resistance
- Efficient sporulation
- Markedly high toxin production
- Mortality rate 3 times higher than less virulent strains

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Diagnosis of CDI

- Enzyme immunoassay for toxins in stool : rapid, easily performed
- DNA-based test that identify microbial toxin genes in unformed stool
  : higher sensitivity, specificity, and can detect BI/NAP1/027 strain
- Stool culture : not widely available

- Sequential testing with PCR & enzyme immunoassay
- But, in clinical practice, in patient with diarrhea
  either enzyme immunoassay or PCR (+) -> should prompt treatment

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Diagnosis of CDI

- Stool testing for *C.difficile* toxins should be confined to patients **with diarrhea**

- Posttreatment testing has **no role** in confirming eradication
- After resolution of symptoms, many successfully treated patients will continue to test (+) for weeks or months

- Ongoing or recurrent diarrhea, after initial treatment, stool testing can be helpful in differentiating recurrent CDI from postinfectious IBS or IBD

Severity of CDI

- Old age
- Comorbidity
- Immunocompromised state
- Organ failure(Respiratory failure, Hypotension)
- Severe leukocytosis(>15,000/mm3),
- Renal dysfunction(Cr >2.3 mg/dL or X1.5 of base line)
- Hypoalbuminemia(<2.5 mg/dL)
- Pancolitis
- Toxic megacolon
- Bowel perforation

N Engl J Med 2005;353:2442-9.
CMAJ 2004;171:466-72.
Clin Infect Dis 2010;50:194-201
World J Gastroenterol 2009;15:1554- 80
Infect Control Hosp Epidemiol 2010;31:431- 55.

Treatment of CDI

- Metronidazole(MTZ) 500mg q8hr
- Oral vancomycin(VAN) 125mg-500mg q6hr
- Mild to moderate infection : MTZ = VAN
- Severe infection : MTZ < VAN
- **Recent data : overall superiority of VAN**

- More frequent side effects of MTZ
- Decreasing cost of generic VAN

➔ **Increasing use of VAN**

2017 update by IDSA and SHEA
Initial CDI: oral VAN or FDX > MTZ

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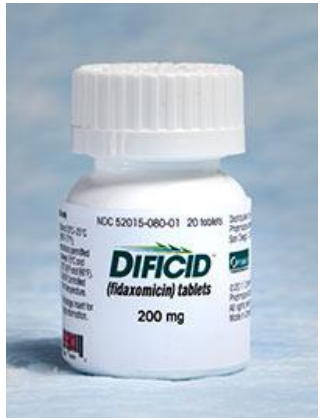
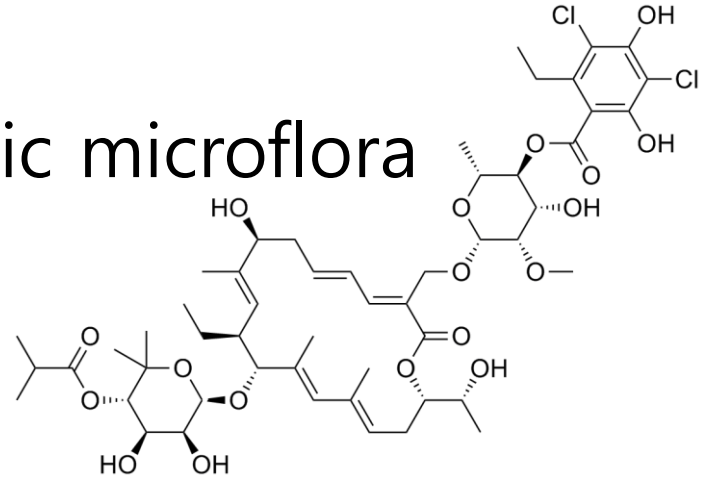
Treatment of CDI



- **Fidaxomicin(FDX) 200mg q12hr**
  : Poorly absorbed, bactericidal, macrocyclic antibiotic with activity against specific anaerobic gram (+) bacteria
  : Cure rate for acute infection was nearly equivalent to VAN
  : Reducing the risk of recurrence
  : Less disruption of the normal colonic anaerobic microflora
  : Higher cost



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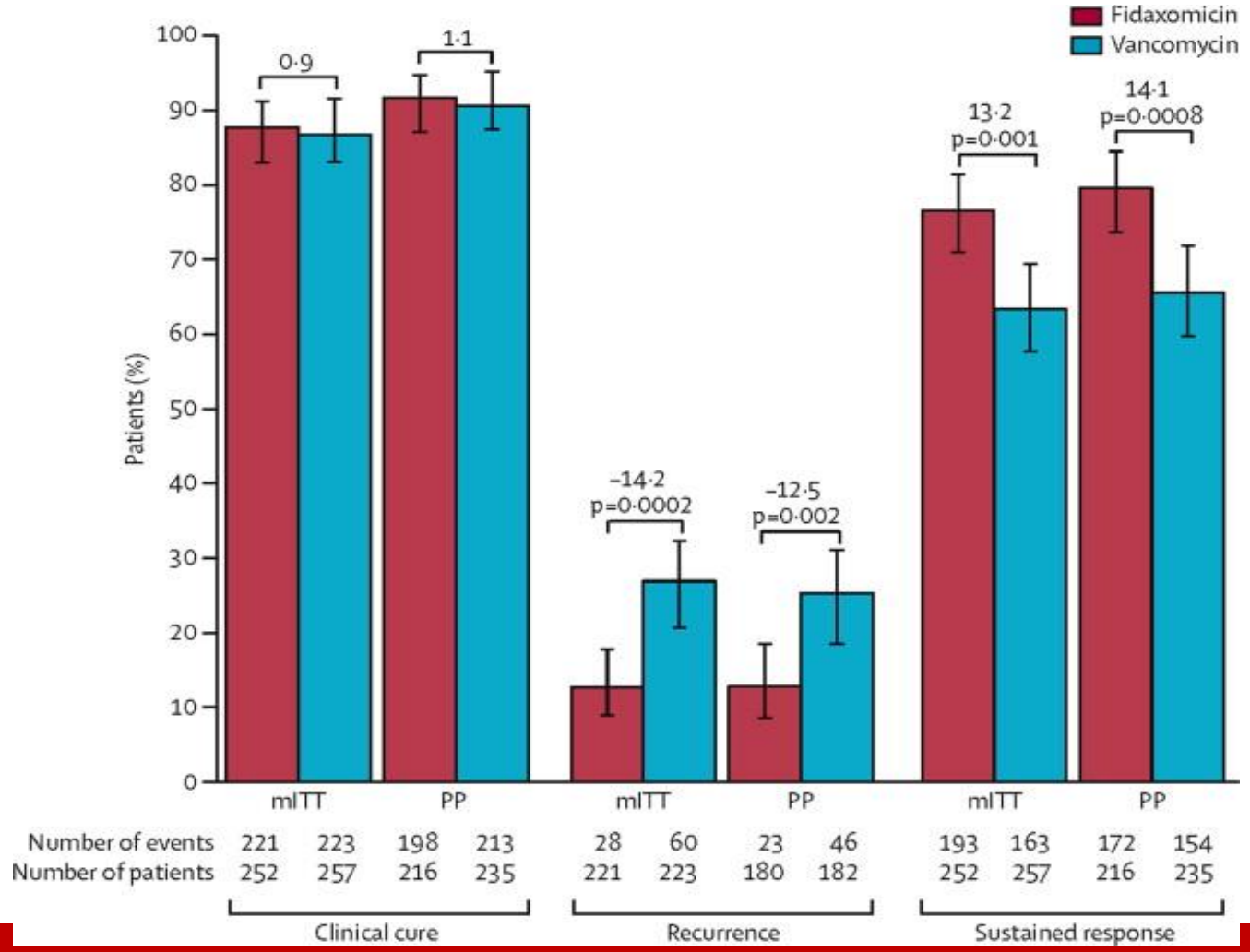
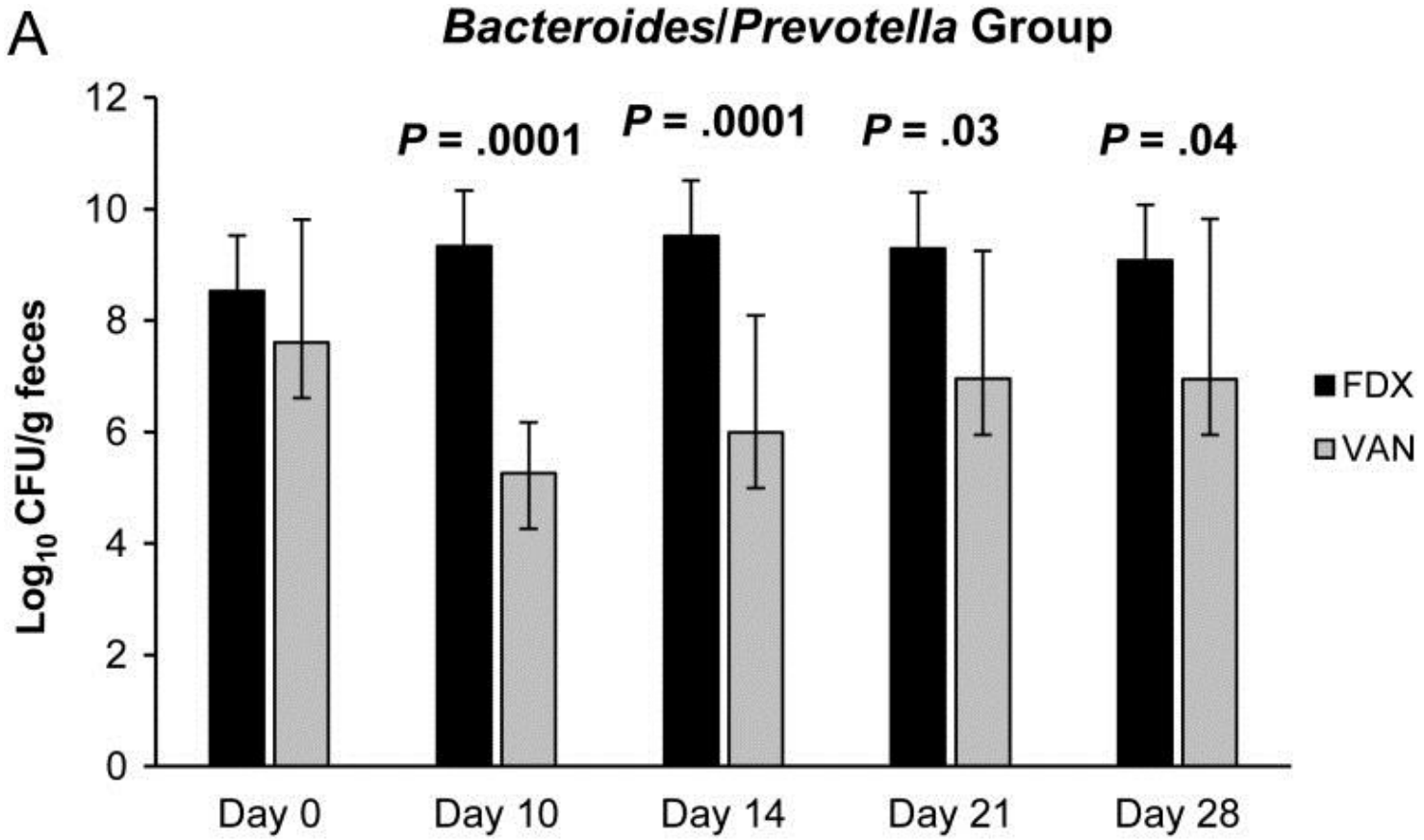
Fidaxomicin *VS.* vancomycin for CDI in Europe, Canada, and the USA: a double-blind, non-inferiority, RCT



Lancet infect Dis. 2012; 12:281-289

Fidaxomicin preserves the intestinal microbiome during and after treatment of CDI



Clin Infect Dis. 2012;55 Suppl 2:S132-42

Treatment of CDI

Table 2. Treatment of *Clostridium difficile* Infection.*

Severity	Clinical Manifestations	Treatment
Asymptomatic carrier	No symptoms or signs	No treatment indicated
Mild†	Mild diarrhea (3 to 5 unformed bowel movements per day), afebrile status, mild abdominal discomfort or tenderness, and no notable laboratory abnormalities	Predisposing antibiotic cessation, hydration, monitoring of clinical status, and either administration of metronidazole (500 mg three times per day) or close outpatient monitoring without the administration of antibiotics
Moderate	Moderate nonbloody diarrhea, moderate abdominal discomfort or tenderness, nausea with occasional vomiting, dehydration, white-cell count >15,000/mm^3, and blood urea nitrogen or creatinine levels above baseline	Consideration of hospitalization and cessation of predisposing antibiotics; hydration, monitoring of clinical status, and either administration of oral metronidazole (500 mg three times per day) or first-line therapy with oral vancomycin (125 mg four times per day for 14 days)

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Treatment of CDI

Table 2. Treatment of *Clostridium difficile* Infection.*

Severe	Severe or bloody diarrhea, pseudomembranous colitis, severe abdominal pain, vomiting, ileus, temperature >38.9°C, white-cell count >20,000/mm^3, albumin level <2.5 mg/dl, and acute kidney injury	Hospitalization; oral or nasogastric vancomycin (500 mg four times per day) with or without intravenous metronidazole (500 mg three times per day), or oral fidaxomicin (200 mg twice a day for 10 days) instead of vancomycin if the risk of recurrence is high
Complicated	Toxic megacolon, peritonitis, respiratory distress, and hemodynamic instability	Antibiotics as for severe infection, and surgical consultation for subtotal colectomy or a diverting ileostomy with vancomycin colonic lavage; consideration of fecal microbial transplantation or additional antibiotics

Recurrent CDI

- Risk of CDI recurrence
  : ranges from 20 % after initial episode to 60% after multiple prior recurrences

- Re-exposure to or reactivation of spores in patients, who have impaired immune response to infection and weakened barrier function of the colonic microbiota

Treatment of recurrent CDI

- **First recurrence**
  : VAN for 10-14 days

- **Second recurrence**
  : FDX or VAN tapered and pulsed regimen
  : Fecal microbial transplantation (FMT)

N ENGL J Med 2015;372:1539-48

Special Article

DOI: 10.3947/ic.2010.42.6.323
Infect Chemother 2010;42(6):323-361

소화기계 감염 진료지침 권고안

대한감염학회 · 대한화학요법학회 · 대한임상미생물학회

Clinical Guideline for the Diagnosis and Treatment of Gastrointestinal Infections

The Korean Society of Infectious Diseases, Korean Society for Chemotherapy, The Korean Society of Clinical Microbiology

6. 원인이 된 항생제는 가능하면 빨리 중지한다(A-II).
7. 중증 혹은 합병증을 동반한 *C. difficile* 관련 설사가 의심되면 경험적 치료를 시작한다(C-III).
8. 대변 독소검사가 음성일 때 치료 시작, 중지, 지속 여부는 개별화하여 임상의가 판단한다(C-III).
9. 장운동 억제제는 가능하면 사용하지 않는다. 증상이 불명확해지고 독성큰결장증을 촉진할 수 있다(C-III).
10. 경증-중등도 *C. difficile* 관련 설사는 초치료로 metronidazole (500 mg 경구, 일일 3회, 10-14일)을 권장하고(A-I), 중증 *C. difficile* 관련 설사 초치료로 vancomycin (125 mg 경구, 1일 4회, 10-14일)을 고려한다(B-I).
11. 중증 및 합병증이 동반된 *C. difficile* 관련 설사는 경구 vancomycin (장폐색증이 있으면 직장으로 투여)±주사용 metronidazole을 고려하나 권장 근거가 부족하다. Vancomycin의 용량은 500 mg 경구 혹은 코위영양관으로 6시간마다, 직장내 투여의 경우 500 mg (생리식염수 약 100 mL과 혼합)을 6시간마다 투여하고, metronidazole은 500 mg을 정맥내로 8시간마다 투여한다(C-III).
12. 중증 환자에서 결장 절제술을 고려할 수 있다. 말초 백혈구 수 (>50,000/mm^3)와 혈청 lactate 수치(>5 mmol/L) 상승이 수술전후 사망률과 관련되어 있다(B-II).
13. *C. difficile* 관련 설사 첫 재발은 통상적으로 초치료와 같은 항생제 사용을 권장하지만(A-II), 초치료 때와 마찬가지로 중증도에 따라 접근한다(C-III).
14. 2회 이상의 재발이나 장기간 치료가 필요할 때 metronidazole은 신경독성 가능성이 있어 고려하지 않는다(B-II).
15. 2회 이상 재발의 경우 다양한 용법, 용량의 vancomycin 사용을 고려한다(B-III).

Fecal microbial transplantation (FMT)

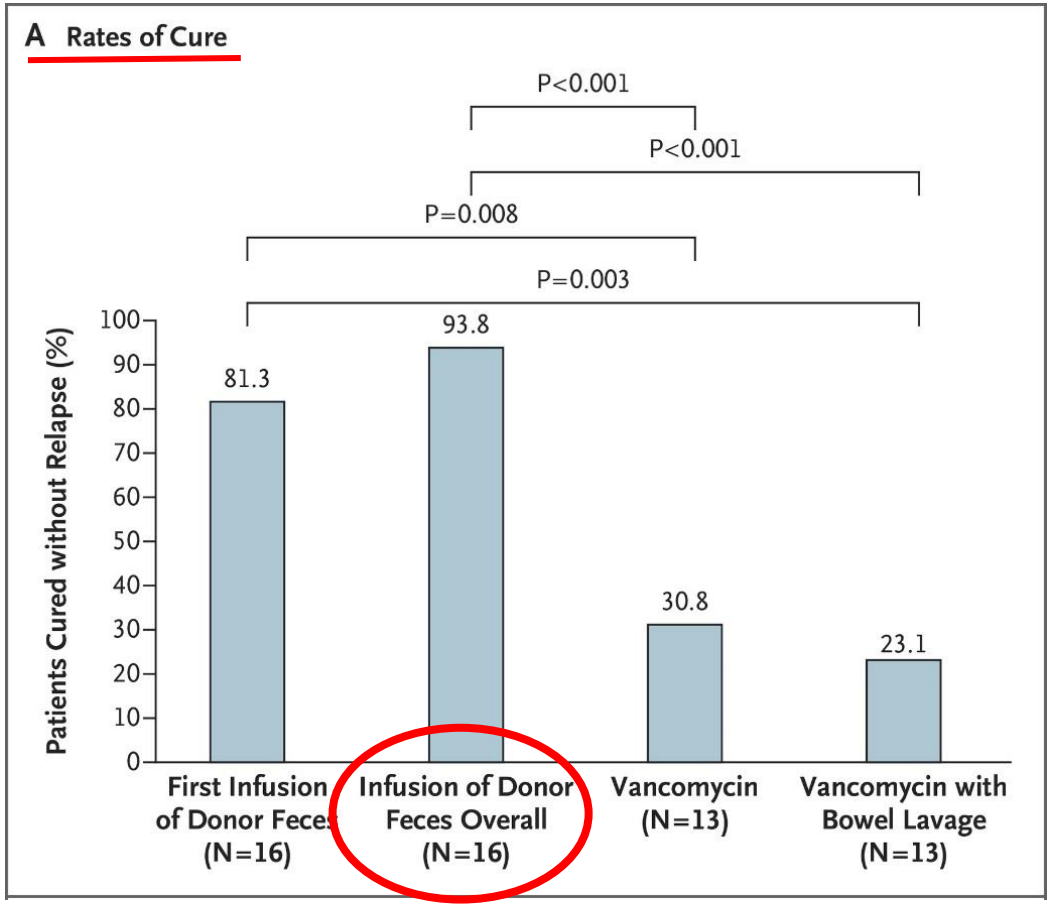
- Human colonic microbiota provides colonization resistance against bacterial pathogen
- Exposure to antibiotics -> rapid decline in fecal microbial diversity
- Stopping administration of antibiotics -> eliminate *C.difficile* from colon and allow microbiota to recover (12wks or longer)

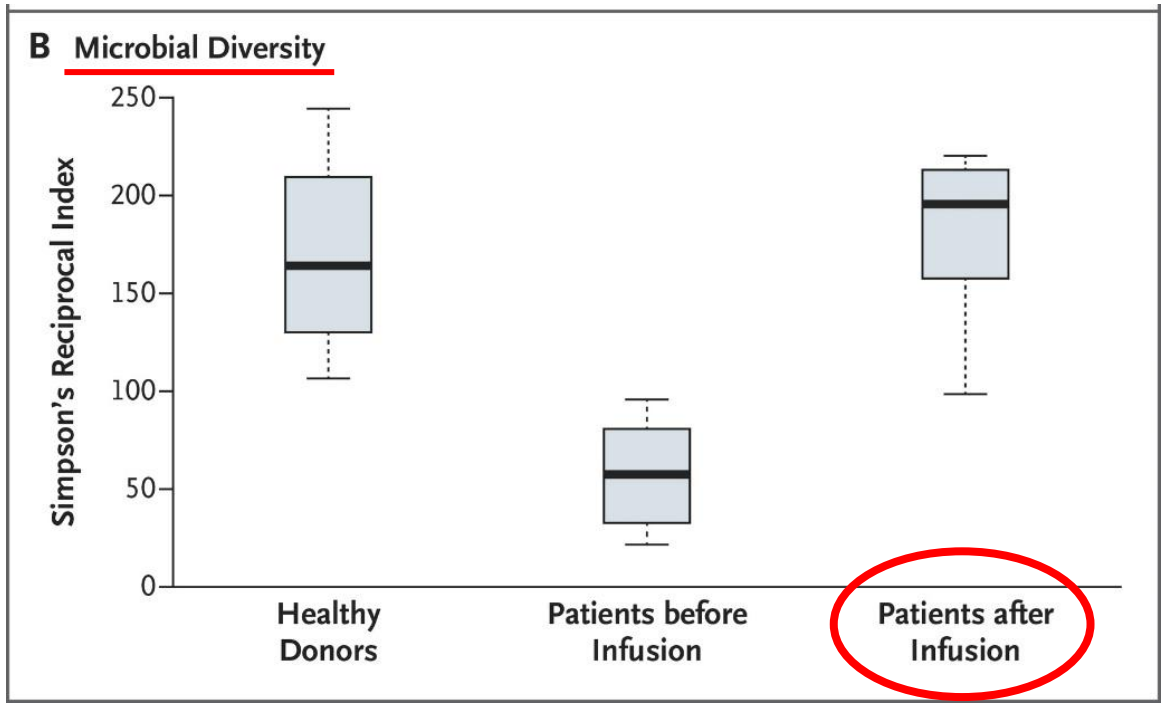
- Oral or rectal transplantation of feces from healthy, pretested donor
- Phyla Bacteroidetes and Firmicutes are critical components

  but, precise components of fecal microbiome are not known

N ENGL J Med 2015;372:1539-48

FMT





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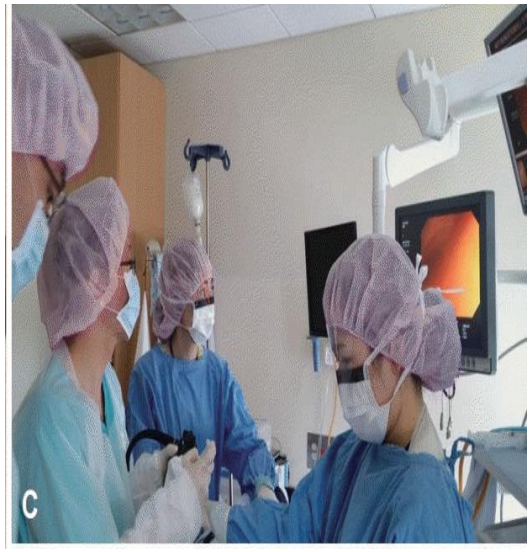
FMT



History

1. Has the donor received antibiotics within the past 3 months?
2. Has the donor been incarcerated, gotten any tattoos or body piercings within the past 3 months?
3. Does the donor have a history of chronic diarrhea, constipation, IBD, IBS, colorectal polyps or cancer, immunocompromised, morbid obesity, metabolic syndrome, atopy, or chronic fatigue syndrome?
4. Does the recipient have any allergies? If so, the donor must not ingest these items for several days before FMT.

Donor stool testing

1. *Clostridium difficile* toxin
2. Stool culture
3. Stool ova and parasites
4. *Giardia* stool antigen
5. *Helicobacter pylori* stool antigen
6. *Cryptosporidium* antigen test
7. *Isospora* (acid fast stain)
8. Rotavirus

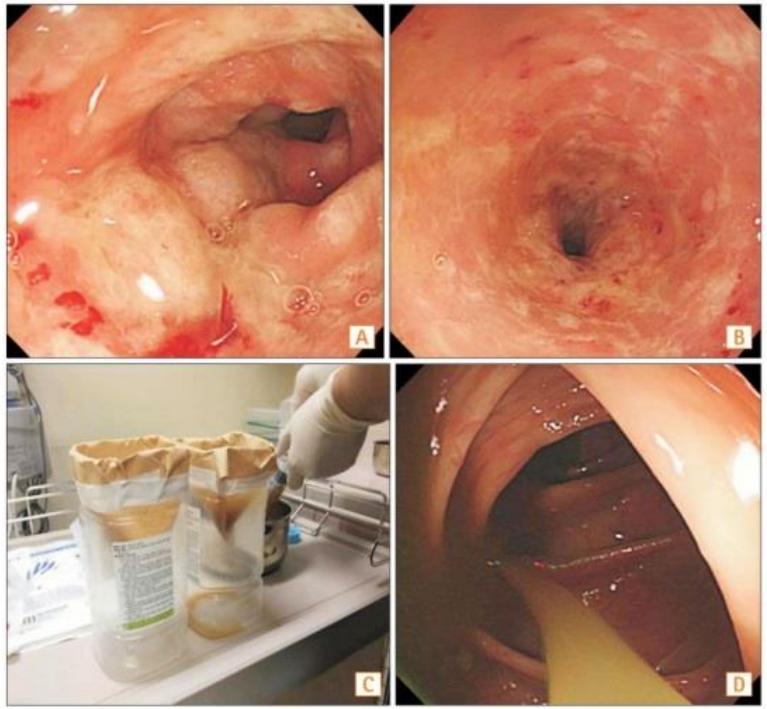
Donor serologic testing

1. Hepatitis A IgM
2. Hepatitis B surface antigen
3. Antibodies to hepatitis B surface antigen
4. Hepatitis C antibody
5. HIV type 1 and 2 antibody
6. Syphilis

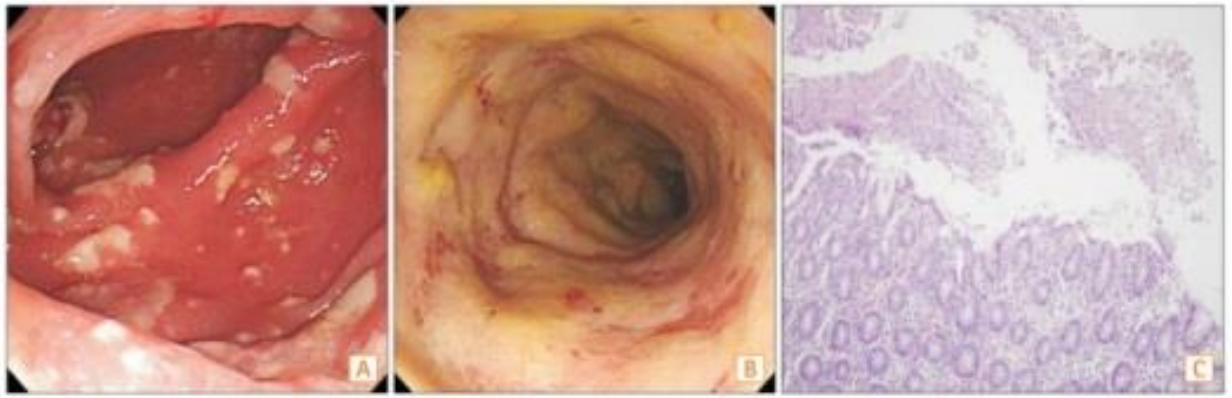
Clin Endosc 2016 March 9

FMT in refractory PMC

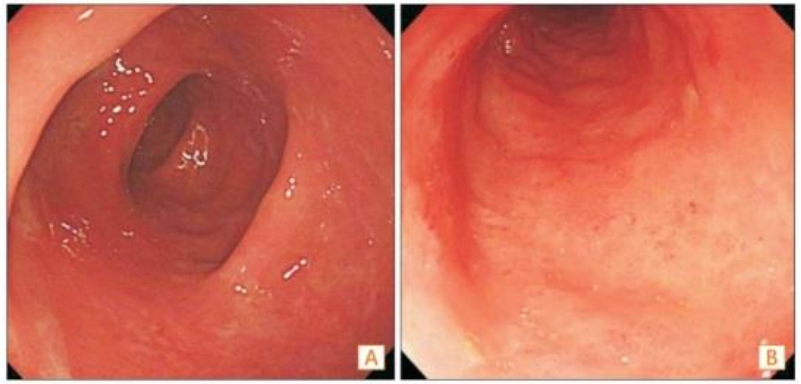
69/F
PMC by colonoscopy
Metronidazole 10 days and vancomycin 4 weeks



Colonoscopic findings on the day of the procedure and fecal microbial transplantation



Initial colonoscopic and pathologic findings



Colonoscopic findings one month after FMT

Treatment of recurrent CDI

Table 2. Treatment of *Clostridium difficile* Infection.*

Severity	Clinical Manifestations	Treatment
First recurrence		Oral vancomycin (125 mg four times per day for 14 days) or oral fidaxomicin (200 mg twice a day for 10 days)
Second or further recurrence		Vancomycin in a tapered and pulsed regimen‡, fecal microbial transplantation, or fidaxomicin (200 mg twice a day for 10 days)

* Some data are from Debast et al.[54] and Cohen et al.[55]

† *C. difficile* infection should be considered mild only if it occurs in outpatients.

‡ A tapered and pulsed regimen involves the administration of vancomycin as follows: 125 mg four times a day for 1 week, 125 mg three times a day for 1 week, 125 mg twice a day for 1 week, 125 mg daily for 1 week, 125 mg once every other day for 1 week, and 125 mg every 3 days for 1 week.

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Prevention

- Absence of an effective vaccine

- Infection control
  : Antibiotic stewardship
  : Prevention of spread in health care facilities
  : Probiotics (?)

Prevention

- Minimizing antibiotic use

- Washing with soap and water, reduce number of viable *C.difficile* spores (**not** alcohol-based hand sanitizer)
- Patients with known or suspected *C.difficile* should be isolated
- Wear gloves and gowns, postdischarge disinfection

- Probiotics : uncertain effect on the prevention of CDI

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Clinical Infectious Diseases

IDSA GUIDELINE

Clinical Practice Guidelines for *Clostridium difficile* Infection in Adults and Children: 2017 Update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA)

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CID 2018: 66 (1 April) , 2017 update by IDSA and SHEA
Clinical guidelines for Clostridium difficile infection

I. How are CDI cases best defined?

Recommendation

1. To increase comparability between clinical settings, use available standardized case definitions for surveillance of (1) healthcare facility-onset (HO) CDI; (2) community-onset, healthcare facility– associated (CO-HCFA) CDI; and (3) community-associated (CA) CDI

(good practice recommendation)

II. What is the minimal surveillance recommendation for institutions with limited resources?

Recommendation

1. At a minimum, conduct surveillance for HO-CDI in all inpatient healthcare facilities to detect elevated rates or outbreaks of CDI within the facility

(weak recommendation, low quality of evidence)

II. What is the best way to express CDI incidence and rates?

Recommendation

1. Express the rate of HO-CDI as the number of cases per 10 000 patient-days. Express the CO-HCFA prevalence rate as the number of cases per 1000 patient admissions

(good practice recommendation)

IV. How should *CDI surveillance* be approached in settings of *high endemic rates or outbreaks*?

Recommendation

1. Stratify data by patient location to target control measures when CDI incidence is above national and/or facility reduction goals or if an outbreak is noted

(weak recommendation, low quality of evidence)

VI. What is the *preferred population for C. difficile testing*, and should efforts be made to achieve this target?

Recommendation

1. Patients with unexplained and new-onset ≥3 unformed stools in 24 hours are the preferred target population for testing for CDI

(weak recommendation, very low quality of evidence)

Diagnosis of CDI

Table 3. Summary of Available Tests for *Clostridium difficile* Infection, in Decreasing Order of Sensitivity

Test	Sensitivity	Specificity	Substance Detected
Toxigenic culture	High	Low[a]	*Clostridium difficile* vegetative cells or spores
Nucleic acid amplification tests	High	Low/moderate	*C. difficile* nucleic acid (toxin genes)
Glutamate dehydrogenase	High	Low[a]	*C. difficile* common antigen
Cell culture cytotoxicity neutralization assay	High	High	Free toxins
Toxin A and B enzyme immunoassays	Low	Moderate	Free toxins

[a]Must be combined with a toxin test.

CID 2018: 66 (1 April) , 2017 update by IDSA and SHEA
Clinical guidelines for Clostridium difficile infection

VII. What is the *best-performing method* (ie, in use positive and negative predictive value) for detecting patients at increased risk for clinically significant *C. difficile* infection in commonly submitted stool specimens?

Recommendation

1. Use a stool toxin test as part of a multistep algorithm (ie, glutamate dehydrogenase [GDH] plus toxin; GDH plus toxin, arbitrated by nucleic acid amplification test [NAAT]; or NAAT plus toxin) rather than a NAAT alone for all specimens received in the clinical laboratory when there are no preagreed institutional criteria for patient stool submission

VIII. What is the *most sensitive method* of diagnosis of CDI in stool specimens from patients likely to have CDI based on clinical symptoms?

Recommendation

1. Use a NAAT alone or a multistep algorithm for testing (ie, GDH plus toxin; GDH plus toxin, arbitrated by NAAT; or NAAT plus toxin) rather than a toxin test alone when there are preagreed institutional criteria for patient stool submission

(weak recommendation, low quality of evidence)

IX. What is the *role of repeat testing*, if any? Are there asymptomatic patients in whom repeat testing should be allowed, including test of cure?

Recommendation

1. Do **not** perform repeat testing (within 7 days) during the same episode of diarrhea and do **not** test stool from asymptomatic patients, except for epidemiological studies

   (strong recommendation, moderate quality of evidence)

X. Does detection of fecal lactoferrin or another *biologic marker* improve the diagnosis of CDI over and above the detection of toxigenic *C. difficile* Can such a subset predict a more ill cohort?

Recommendation

1. There are insufficient data to recommend use of biologic markers as an adjunct to diagnosis

(no recommendation)

XIII. Should private rooms and/or dedicated toilet facilities be used for isolated patients with CDI?

- ***Recommendations***

1. Accommodate patients with CDI in a private room with a dedicated toilet to **decrease transmission** to other patients. If there is a limited number of private single rooms, prioritize patients with stool incontinence for placement in private rooms

(strong recommendation, moderate quality of evidence)

XIII. Should *private rooms* and/or *dedicated toilet* facilities be used for isolated patients with CDI?

- ***Recommendations***

2. If cohorting is required, it is recommended to **cohort** patients infected or colonized with the same organism(s) that is, do not cohort patients with CDI who are discordant for other multidrug-resistant organisms such as methicillin-resistant *Staphylococcus aureus* or vancomycin-resistant *Enterococcus*

(strong recommendation, moderate quality of evidence)

XIV. Should *gloves and gowns* be worn while caring for isolated CDI patients?

Recommendation

1. Healthcare personnel **must** use gloves
   (strong recommendation, high quality of evidence)
   and gowns on entry to a room of a patient with CDI and while caring for patients with CDI

(strong recommendation, moderate quality of evidence)

XV. *When* should isolation be implemented?

Recommendation

1. Patients with suspected CDI **should be** placed on preemptive contact precautions pending the *C. difficile* test results if test results cannot be obtained on the same day

(strong recommendation, moderate quality of evidence).

XVI. *How long* should isolation be continued?

Recommendations

1. Continue contact precautions for at least 48 hours **after** diarrhea has resolved

   (weak recommendation, low quality of evidence)

2. Prolong contact precautions **until discharge** if CDI rates remain high despite implementation of standard infection control measures against CDI

   (weak recommendation, low quality of evidence)

XVII. What is the recommended *hand hygiene method* (assuming glove use) when caring for patients in isolation for CDI?

Recommendations

1. In routine or endemic settings, perform hand hygiene **before and after** contact of a patient with CDI and **after** removing gloves with either soap and water or an alcohol-based hand hygiene product

(strong recommendation, moderate quality of evidence)

XVII. What is the recommended *hand hygiene method* (assuming glove use) when caring for patients in isolation for CDI?

Recommendations

2. **In CDI outbreaks or hyperendemic** (sustained high rates) settings, perform hand hygiene with soap and water preferentially instead of alcohol-based hand hygiene products before and after caring for a patient with CDI given the increased efficacy of spore removal with soap and water

(weak recommendation, low quality of evidence)

XVII. What is the recommended *hand hygiene method* (assuming glove use) when caring for patients in isolation for CDI?

Recommendations

3. Handwashing with soap and water is **preferred** if there is direct contact with feces or an area where fecal contamination is likely (eg, the perineal region)

(good practice recommendation)

XVIII. Should patient bathing interventions be implemented to *prevent CDI*?

Recommendation

1. **Encourage** patients to wash hands and shower to reduce the burden of spores on the skin

   (good practice recommendation)

XIX. Should noncritical devices or equipment be dedicated to or specially cleaned after being used on the isolated patient with CDI?

Recommendation

1. Use disposable patient equipment when possible and ensure that reusable equipment is thoroughly cleaned and disinfected, preferentially with a sporicidal disinfectant that is equipment compatible

(strong recommendation, moderate quality of evidence)

XX. What is the role of manual, terminal disinfection using a *C. difficile* sporicidal agent for patients in isolation for CDI?

Recommendation

1. Terminal room cleaning with a sporicidal agent should be considered in conjunction with other measures to prevent CDI during endemic high rates or outbreaks, or if there is evidence of repeated cases of CDI in the same room

   (weak recommendation, low quality of evidence)

XXI. Should *cleaning adequacy* be evaluated?

Recommendation

1. Incorporate measures of cleaning effectiveness to ensure quality of environmental cleaning

   (good practice recommendation)

XXII. What is the role of *automated terminal disinfection* using a method that is sporicidal against *C. difficile*?

1. There are limited data at this time to recommend use of automated, terminal disinfection using a sporicidal method for CDI prevention

   (no recommendation)

XXIII. What is the role of *daily sporicidal disinfection*?

Recommendation

1. Daily cleaning with a sporicidal agent should be considered in conjunction with other measures to prevent CDI during outbreaks or in hyperendemic (sustained high rates) settings, or if there is evidence of repeated cases of CDI in the same room

(weak recommendation, low quality of evidence)

XXIV. Should *asymptomatic carriers* of *C. difficile* be identified and isolated if positive?

Recommendation

1. There are **insufficient data** to recommend screening for asymptomatic carriage and placing asymptomatic carriers on contact precautions

   (no recommendation)

XXV. What is the role of *antibiotic stewardship* in controlling CDI rates?

Recommendations

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)

XXV. What is the role of *antibiotic stewardship* in controlling CDI rates?

Recommendations

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)

XXVI. What is the role of *proton pump inhibitor* restriction in controlling CDI rates?

Recommendation

1. 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)

XXVII. What is the role of *probiotics* in primary prevention of CDI?

Recommendation

1. There are **insufficient data** at this time to recommend administration of probiotics for primary prevention of CDI outside of clinical trials

   (no recommendation)

XXVIII. What are *important ancillary treatment* strategies for CDI?

Recommendations

1. Discontinue therapy with the inciting antibiotic agent(s) as soon as possible, as this may influence the risk of CDI recurrence

(strong recommendation, moderate quality of evidence)

XXVIII. What *are important ancillary treatment* strategies for CDI?

Recommendations

2. Antibiotic therapy for CDI should be started empirically for situations where a substantial **delay in laboratory** confirmation is expected, or **for fulminant CDI**

(weak recommendation, low quality of evidence)

XXIX. What are the *best treatments of an initial CDI* episode to ensure resolution of symptoms and sustained resolution 1 month after treatment?

Recommendations

1. Either **vancomycin or fidaxomicin** is recommended over metronidazole for an initial episode of CDI.
   The dosage is vancomycin 125 mg orally 4 times per day or fidaxomicin 200 mg twice daily for 10 days

   (strong recommendation, high quality of evidence)

XXIX. What are the *best treatments of an initial CDI* episode to ensure resolution of symptoms and sustained resolution 1 month after treatment?

Recommendations

2. In settings where access to vancomycin or fidaxomicin is limited, we suggest using **metronidazole** for an initial episode of nonsevere CDI only *(weak recommendation, high quality of evidence)*

   The suggested dosage is metronidazole 500 mg orally 3 times per day for 10 days. **Avoid** repeated or prolonged courses due to risk of cumulative and potentially irreversible neurotoxicity *(strong recommendation, moderate quality of evidence)*

XXX. What are the best treatments of *fulminant CDI*?

Recommendations

1. For **fulminant CDI***, **vancomycin** administered orally is the regimen of choice *(strong recommendation, moderate quality of evidence)*

   If **ileus** is present, **vancomycin** can also be administered per rectum *(weak recommendation, low quality of evidence)*

*__Fulminant CDI__, previously referred to as severe, complicated CDI, may be characterized by hypotension or shock, ileus, or megacolon.

XXX. What are the best treatments of *fulminant CDI*?

Recommendations

The **vancomycin** dosage is 500 mg **orally** 4 times per day and 500 mg in approximately 100 mL normal saline **per rectum** every 6 hours as a retention enema. **Intravenously administered metronidazole** should be administered together with oral or rectal vancomycin, particularly if **ileus** is present

(strong recommendation, moderate quality of evidence)

The metronidazole dosage is 500 mg intravenously every 8 hours.*

XXX. What are the best treatments of *fulminant CDI*?

Recommendations

2. If **surgical management** is necessary for **severely ill** patients, perform subtotal colectomy with preservation of the rectum
(strong recommendation, moderate quality of evidence).

Diverting loop ileostomy with colonic lavage followed by antegrade vancomycin flushes is an alternative approach that may lead to improved outcomes
(weak recommendation, low quality of evidence).

XXXI. What are the best treatments for *recurrent CDI*?

Recommendations

1. Treat a **first recurrence** of CDI with oral vancomycin as a **tapered and pulsed** regimen rather than a second standard 10-day course of vancomycin

   (weak recommendation, low quality of evidence), OR

2. Treat **a first recurrence** of CDI with a 10-day course of **fidaxomicin** rather than a standard 10-day course of vancomycin

   (weak recommendation, moderate quality of evidence), OR

XXXI. What are the best treatments for *recurrent CDI*?

Recommendations

3. Treat a **first recurrence** of CDI with a standard 10-day course of **vancomycin** rather than a second course of metronidazole if metronidazole was used for the primary episode

(weak recommendation, low quality of evidence)

XXXI. What are the best treatments for *recurrent CDI*?

Recommendations

4. Antibiotic treatment options for patients with **>1 recurrence** of CDI include **oral vancomycin** therapy using a **tapered and pulsed regimen**, *(weak recommendation, low quality of evidence)*

a standard course of oral **vancomycin followed by rifaximin** *(weak recommendation, low quality of evidence)*, or

fidaxomicin *(weak recommendation, low quality of evidence)*.

XXXI. What are the best treatments for *recurrent CDI*?

5. **Fecal microbiota transplantation** is recommended for patients with **multiple recurrences** of CDI who have failed appropriate antibiotic treatments

(strong recommendation, moderate quality of evidence)

XXXI. What are the best treatments for *recurrent CDI*?

6. There are **insufficient data** at this time to recommend extending the length of anti–*C. difficile* treatment beyond the recommended treatment course or restarting an anti–*C. difficile* agent empirically for patients who require continued antibiotic therapy directed against the underlying infection or who require retreatment with antibiotics shortly after completion of CDI treatment, respectively

(no recommendation)

Treatment of CDI

Table 1. Recommendations for the Treatment of *Clostridium difficile* Infection in Adults

Initial episode

Clinical Definition	Supportive Clinical Data	Recommended Treatment[a]	Strength of Recommendation/ Quality of Evidence
Initial episode, non-severe	Leukocytosis with a white blood cell count of ≤15000 cells/mL and a serum creatinine level <1.5 mg/dL	• VAN 125 mg given 4 times daily for 10 days, OR • FDX 200 mg given twice daily for 10 days • Alternate if above agents are unavailable: metronidazole, 500 mg 3 times per day by mouth for 10 days	Strong/High Strong/High Weak/High
Initial episode, severe[b]	Leukocytosis with a white blood cell count of ≥15000 cells/mL or a serum creatinine level >1.5 mg/dL	• VAN, 125 mg 4 times per day by mouth for 10 days, OR • FDX 200 mg given twice daily for 10 days	Strong/High Strong/High
Initial episode, fulminant	Hypotension or shock, ileus, megacolon	• VAN, 500 mg 4 times per day by mouth or by nasogastric tube. If ileus, consider adding rectal instillation of VAN. Intravenously administered metronidazole (500 mg every 8 hours) should be administered together with oral or rectal VAN, particularly if ileus is present.	Strong/Moderate (oral VAN); Weak/Low (rectal VAN); Strong/Moderate (intravenous metronidazole)

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Treatment of CDI

Table 1. Recommendations for the Treatment of *Clostridium difficile* Infection in Adults

Recurrent episode

Clinical Definition	Supportive Clinical Data	Recommended Treatment[a]	Strength of Recommendation/ Quality of Evidence
First recurrence	…	• VAN 125 mg given 4 times daily for 10 days if metronidazole was used for the initial episode, OR	Weak/Low
		• Use a prolonged tapered and pulsed VAN regimen if a standard regimen was used for the initial episode (eg, 125 mg 4 times per day for 10–14 days, 2 times per day for a week, once per day for a week, and then every 2 or 3 days for 2–8 weeks), OR	Weak/Low
		• FDX 200 mg given twice daily for 10 days if VAN was used for the initial episode	Weak/Moderate
Second or subsequent recurrence	…	• VAN in a tapered and pulsed regimen, OR	Weak/Low
		• VAN, 125 mg 4 times per day by mouth for 10 days followed by rifaximin 400 mg 3 times daily for 20 days, OR	Weak/Low
		• FDX 200 mg given twice daily for 10 days, OR	Weak/Low
		• Fecal microbiota transplantation[c]	Strong/Moderate

Abbreviations: FDX, fidaxomicin; VAN, vancomycin.

[a]All randomized trials have compared 10-day treatment courses, but some patients (particularly those treated with metronidazole) may have delayed response to treatment and clinicians should consider extending treatment duration to 14 days in those circumstances.

[b]The criteria proposed for defining severe or fulminant *Clostridium difficile* infection (CDI) are based on expert opinion. These may need to be reviewed in the future upon publication of prospectively validated severity scores for patients with CDI.

[c]The opinion of the panel is that appropriate antibiotic treatments for at least 2 recurrences (ie, 3 CDI episodes) should be tried prior to offering fecal microbiota transplantation.

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