UWTASP
tele-antimicrobial stewardship program

November 2, 2021

Infectious Diarrhea: There's DIFFinitely Some Updates

Project ECHO

Guideline Update

Clinical Practice Guideline by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA): 2021 Focused Update Guidelines on Management of *Clostridioides difficile* Infection in Adults

Stuart Johnson,[1,2] Valéry Lavergne,[3,4] Andrew M. Skinner,[1,2] Anne J. Gonzales-Luna,[5] Kevin W. Garey,[5] Ciaran P. Kelly,[6] and Mark H. Wilcox[7]

Johnson S et al. Clin Infect Dis. 2021

Initial CDI Episode

2017

- **VAN** 125 mg PO QID x 10 days OR
- **FDX** 200 mg PO BID x 10 days

- Alternative for non-severe CDI, if above agents are unavailable: **MET** 500 mg PO TID x 10-14 days

VS

2021

- **Preferred:** **FDX** 200 mg PO BID x 10 days
- **Alternative:** **VAN** 125 mg PO QID x 10 days
- Alternative for non-severe CDI, if above agents are unavailable: **MET** 500 mg PO TID x 10-14 days

FDX: Fidaxomicin
VAN: Vancomycin
MET: Metronidazole

Johnson S et al. Clin Infect Dis. 2021

"Implementation Depends on Available Resources"

"The panel suggests the use of fidaxomicin as the preferred therapy for an initial CDI episode to improve sustained response after therapy but recognizes that vancomycin remains an acceptable alternative if fidaxomicin is not available."

Johnson S et al. Clin Infect Dis. 2021

Key Differences

Vancomycin

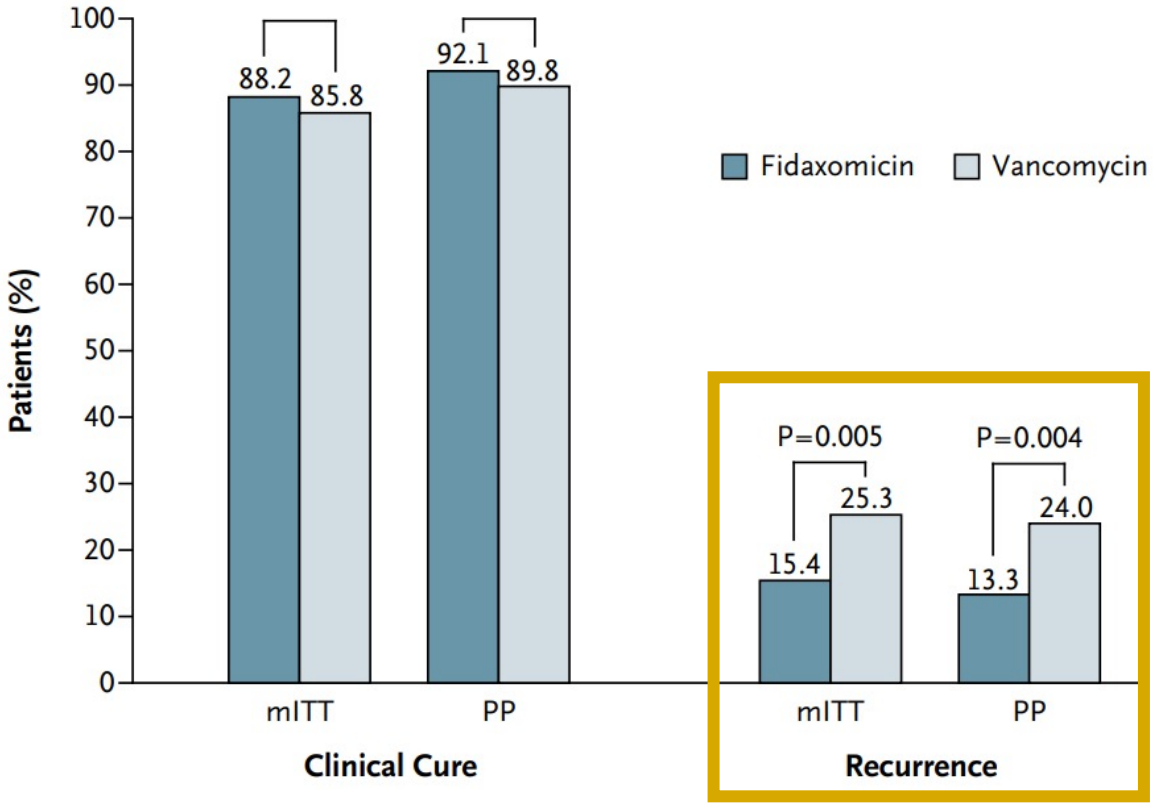
- Tricyclic glycosylated peptic antibiotic
- Inhibits bacterial cell wall synthesis
- Gram-positive anaerobes; impacts indigenous bowel flora
- Minimal systemic absorption
- Multiple treatment indications
- AWP $62

Fidaxomicin

- Macrocyclic antibiotic
- Inhibits RNA synthesis
- Gram-positive anaerobes; less impact on indigenous bowel flora
- Minimal systemic absorption
- Only treatment indication id *C. difficile*
- AWP $3,360

Fidaxomicin vs Vancomycin #1

- Phase 3, double-blind, RCT
- FDX 200mg BID vs PO VAN 125mg 4x daily
- Treatment duration: 10 days



Conclusions:

- Similar initial clinical cure
- Lower recurrence with fidaxomicin

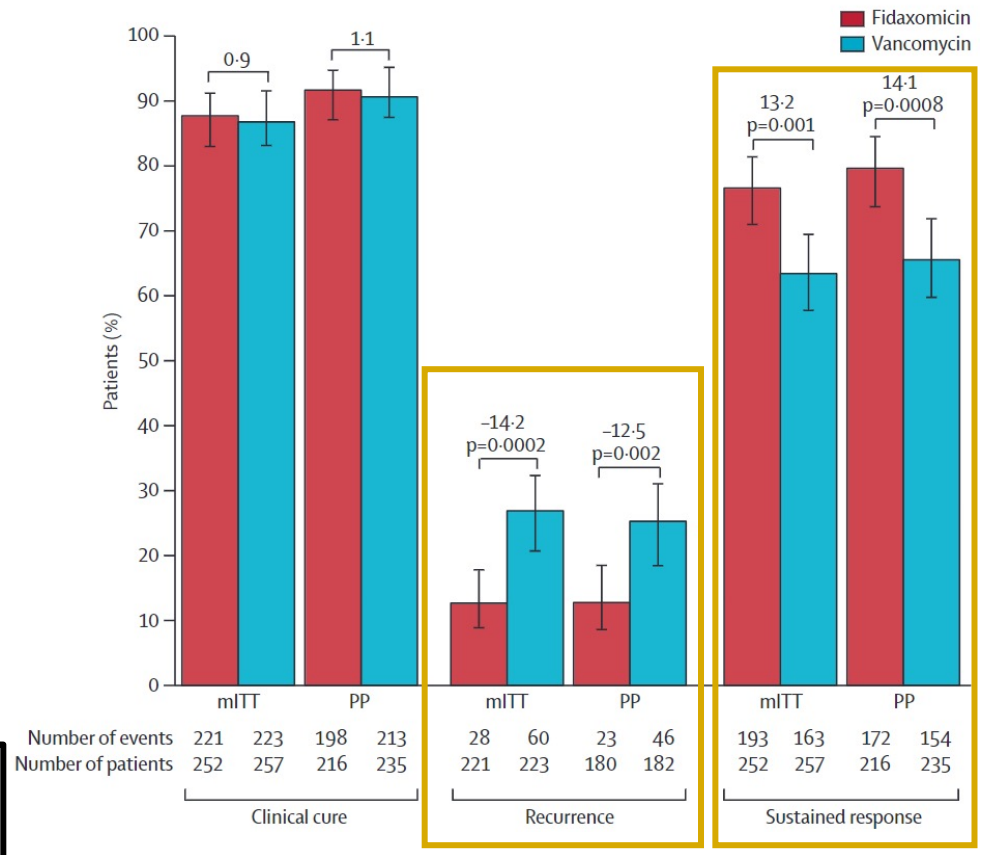
*Clinical cure: resolution of symptoms and no need for further therapy

**Recurrence: diarrhea and a positive result on a stool toxin test within 4 weeks after treatment

Louie T et al. N Engl J Med. 2011;364:422-431.

Fidaxomicin vs Vancomycin #2

- Double-blind, non-inferiority, RCT
- FDX 200mg BID vs PO VAN 125mg 4x daily
- Treatment duration: 10 days



Conclusions:

- Similar initial clinical cure
- Lower recurrence with FDX
- Sustained response with FDX

*Clinical cure: resolution of diarrhea and no further need for treatment

**Recurrence: 30 days after treatment

***Sustained response: 4 weeks after treatment

Cornely O et al. Lancet Infect Dis. 2012;12(4):281-289.

First CDI Recurrence

2017

- **VAN** 125 mg PO QID x 10 days if **MET** was used for initial episode
- Prolonged tapered and pulsed **VAN** if standard regimen was used for initial episode
- **FDX** 200 mg PO BID x 10 days if **VAN** was used for initial episode

VS

2021

- **Preferred:** **FDX** 200 mg PO BID x 10 days OR **FDX** 200 mg PO BID x 5 days, then once every other day x 20 days
- **Alternative:** **VAN** PO in a tapered and pulsed regimen
- **Alternative:** **VAN** 125 mg PO QID x 10 days
- **Adjunctive treatment:** **Bezlotoxumab** 10 mg/kg IV x once during administration of SOC antibiotics

FDX: Fidaxomicin MET: Metronidazole
VAN: Vancomycin SOC: Standard of care

Johnson S et al. Clin Infect Dis. 2021

Second or Subsequent CDI Recurrence

2017

- **VAN** PO in a tapered and pulsed regimen
- **VAN** 125 mg PO QID x 10 days followed by **rifaximin** 400 mg TID x 20 days
- **FDX** 200 mg PO BID x 10 days
- Fecal microbiota transplantation

VS

2021

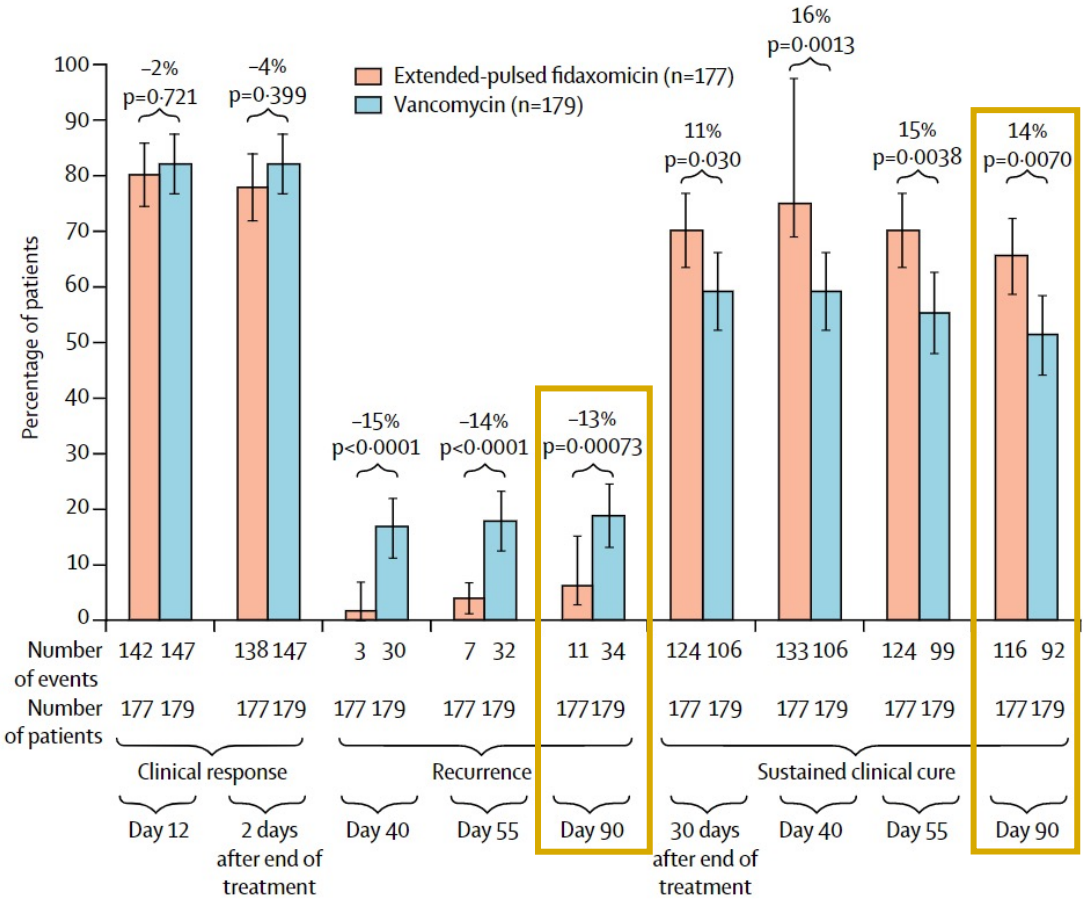
- **FDX** 200 mg PO BID x 10 days OR **FDX** 200 mg PO BID x 5 days, then once every other day x 20 days
- **VAN** PO in a tapered and pulsed regimen
- **VAN** 125 mg PO QID x 10 days followed by **rifaximin** 400 mg TID x 20 days
- **Fecal microbiota transplantation**
- Adjunctive treatment: **Bezlotoxumab** 10 mg/kg IV x once during administration of SOC antibiotics

FDX: Fidaxomicin MET: Metronidazole
VAN: Vancomycin SOC: Standard of care

Johnson S et al. Clin Infect Dis. 2021

Extended-pulsed Fidaxomicin

- Phase 3b/4, RCT, parallel, superiority, open-label trial
- FDX 200mg BID on days 1-5, then once daily on alternate days 7-25 vs PO VAN 125mg 4x daily on days 1-10



Guery B et al. Lancet Infect Dis. 2018;18(3):296-307.

Extended-pulsed Fidaxomicin

Clinical Outcomes for the Modified Full Analysis Set

Recurrence of *C difficile* infection				
At day 40	3 (2%)	30 (17%)	0·09 (0·03–0·29)	<0·0001
At day 55	7 (4%)	32 (18%)	0·20 (0·08–0·46)	<0·0001
At day 90	11 (6%)	34 (19%)	0·29 (0·14–0·60)	0·00073
Sustained clinical cure 30 days after end of treatment				
n (%)	124 (70%)	106 (59%)	1·62 (1·04–2·54)	0·030
OR by baseline stratification				
C difficile infection severe *vs* non-severe	..	..	0·57 (0·36–0·91)	0·019
Presence *vs* absence of cancer	..	..	0·59 (0·35–1·01)	0·053
Age group ≥75 years *vs* <75 years	..	..	0·83 (0·53–1·30)	0·414
Previous *C difficile* infection occurrences (2 *vs* 0)	..	..	0·69 (0·26–1·80)	0·444
Previous *C difficile* infection occurrences (1 *vs* 0)	..	..	0·61 (0·33–1·11)	0·105
Sustained clinical cure 30 days after end of treatment				
Presence of *C difficile* PCR ribotype 027¶	20 (80%) [n=25]	9 (41%) [n=22]	..	0·0059
Absence of *C difficile* PCR ribotype 027‖	104 (68%) [n=152]	97 (62%) [n=157]	..	0·221

Conclusions:

- Similar initial clinical cure
- Lower recurrence with fidaxomicin
- Sustained response of CDI with fidaxomicin

Guery B et al. Lancet Infect Dis. 2018;18(3):296-307.

ISDA vs ACG (American College of Gastroenterology) Recommendations

Initial CDI Episode

ACG

- **VAN** 125 mg PO QID x 10 days
  OR FDX 200 mg PO BID x 10 days
- Alternative for non-severe CDI, if above agents are unavailable: **MET** 500 mg PO TID x 10 days
- Severe and fulminant CDI: FMT can be considered for CDI refractory to antibiotic therapy

VS

IDSA

- Preferred: **FDX** 200 mg PO BID x 10 days
- Alternative: **VAN** 125 mg PO QID x 10 days
- Alternative for non-severe CDI, if above agents are unavailable: **MET** 500 mg PO TID x 10-14 days

FDX: Fidaxomicin MET: Metronidazole
VAN: Vancomycin FMT: Fecal Microbiota Transplantation

Kelly C et al. The American Journal of Gastroenterology. 2021.
Johnson S et al. Clin Infect Dis. 2021

Recurrent CDI Episode

ACG

- **VAN** PO in a tapered and pulsed regimen after initial course with VAN, FDX, or MET
- **FDX** 200 mg PO BID x 10 days after an initial course of **VAN** or **MET**
- **Bezlotoxumab** can be considered if high risk for recurrence

VS

IDSA

- Preferred: **FDX** 200 mg PO BID x 10 days
- Alternative: **VAN** 125 mg PO QID x 10 days
- Alternative for non-severe CDI, if above agents are unavailable: **MET** 500 mg PO TID x 10-14 days

FDX: Fidaxomicin
VAN: Vancomycin
MET: Metronidazole
FMT: Fecal Microbiota Transplantation

Kelly C et al. The American Journal of Gastroenterology. 2021.
Johnson S et al. Clin Infect Dis. 2021

So...What's Next?

Prognostic Factors For Recurrent CDI

Summary of findings: recurrent CDI
Higher age (>65-70 years)
Previous recurrence of CDI (<3 months)
Healthcare-associated CDI
Prior hospitalization (<3 months)
Proton pump inhibitors started during/after CDI diagnosis

Limitations:

- Quality of evidence was low to moderate
- Majority retrospective studies
- Moderate to high risk of bias

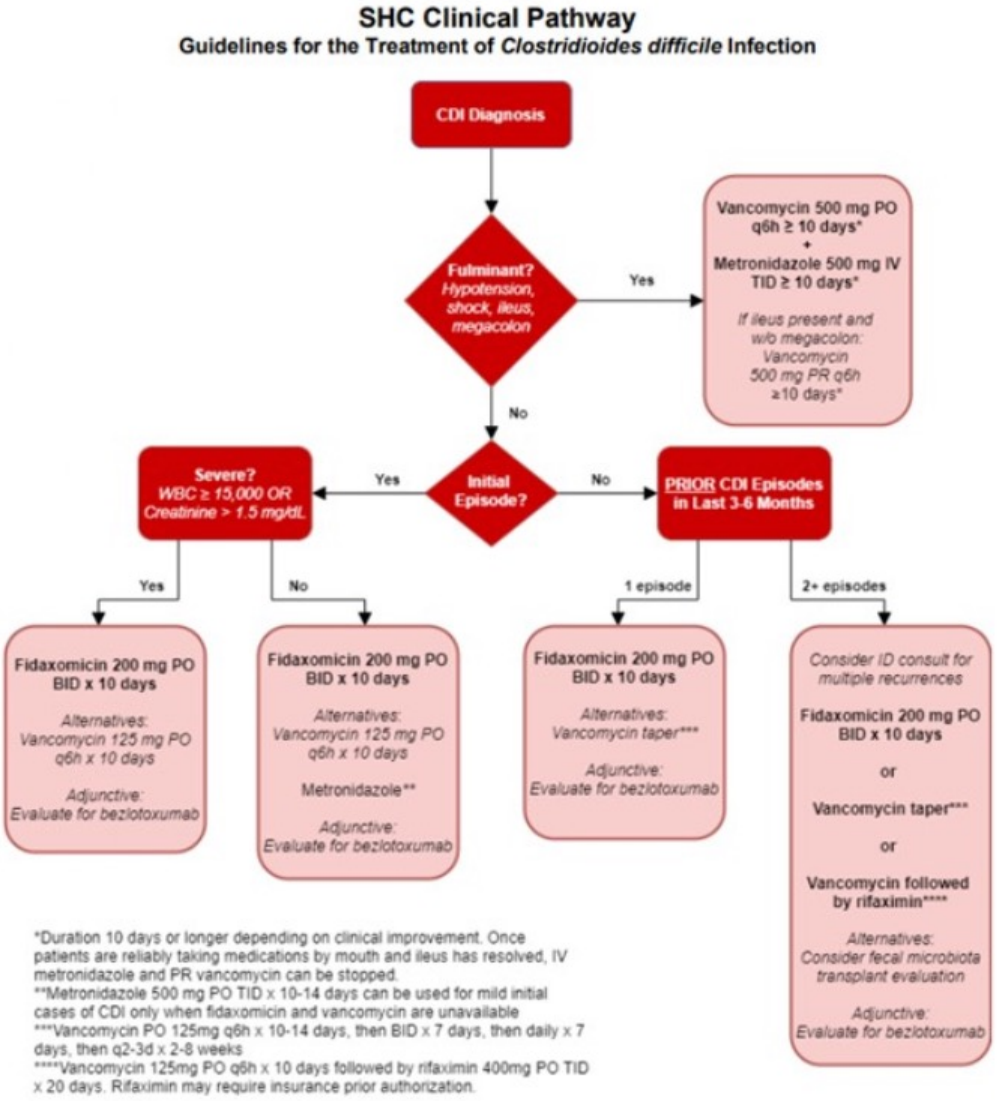
Rossen T et al. Clin Microbiol Infection: Journal Pre-proof. Accepted Sep 2021

Cost Analysis

ARR: 10-14% ⇨ NNT: 7-10

- Cost to prevent one recurrence rate
  - 7 x $3,360 (AWP FDX) = $23,530
  - 10 x $3,360 (AWP FDX) = $33,600

Stanford Health Care



Conclusions

- Fidaxomicin versus vancomycin
  - Similar initial clinical cure
  - Lower recurrence with fidaxomicin
  - Sustained response of CDI with fidaxomicin

- **IDSA:** fidaxomicin is preferred over vancomycin for initial and first CDI recurrence

- **AJG:** fidaxomicin AND vancomycin preferred for initial and recurrent CDI episode

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