Is metronidazole still good for *Clostridioides difficile* infection?

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19th June 2025

Shift in the treatment paradigm of *C. difficile* infection (CDI)

Category	IDSA/SHEA 2021	ESCMID 2021	ASID 2025	ACG 2021
Initial episode, non-severe	Fidaxomicin 200 mg PO 12 hourly for 10 days (STD) preferred OR vancomycin 125 mg PO 6 hourly for 10 days (alternative). If above agents are unavailable: metronidazole 500 mg PO 8 hourly for 10–14 days.	Fidaxomicin STD preferred OR vancomycin 125 mg PO 6 hourly for 10 days (alternative). If above agents are unavailable: metronidazole 500 mg PO 8 hourly for 10 days. If high risk of recurrence, especially elderly hospitalized, consider fidaxomicin extended-pulsed regimen (EPFX): 200 mg PO 12 hourly for 5 days followed by 200 mg PO every other day for 20 days or adjunctive bezlotoxumab if fidaxomicin not a/v.	First line: Vancomycin 125 mg orally/enterally four times daily for 10 days Second-line: Metronidazole 400 mg PO 8 hourly for 10 days. if access to vancomycin is not possible High-risk patients: Fidaxomicin 200 mg orally two times daily for 10 days	Vancomycin 125 mg PO 6 hourly for 10 days OR fidaxomicin STD Metronidazole 500 mg PO 8 hourly for 10 days may be considered for low-risk patients
Severe	Fidaxomicin STD OR vancomycin 125 mg PO 6 hourly for 10 days and adjunctive bezlotoxumab for primary CDI if other risk factors for recurrence (age ≥65 years, immunocompromised host) or if episode in prior 6 months.	Fidaxomicin STD OR vancomycin 125 mg PO 6 hourly for 10 days.	Vancomycin 125 mg orally/enterally four times daily for 10 days Oral therapy not possible OR refractory disease: Tigecycline Refractory: Rescue FMT	Vancomycin 125 mg PO 6 hourly for 10 days OR fidaxomicin STD
Severe-complicate fulminant	Vancomycin 500 mg 6 hourly PO or by nasogastric tube and metronidazole 500 mg IV 8 hourly AND consider vancomycin per rectum if ileus present.	Fidaxomicin STD OR vancomycin 125 mg PO 6 hourly for 10 days and consider IV tigecycline 100 mg load, then 50 mg 12 hourly. Consult a surgeon.	Vancomycin + intravenous metronidazole +/- tigecycline Consider rescue FMT Consider surgical intervention	Vancomycin up to 500 mg 6 hourly PO for the first 48–72 hours. Combination therapy with metronidazole 500 mg IV 8 hourly can be considered. For patients with an ileus, the addition of vancomycin enemas (500 mg every 6 hours) may be beneficial

Metronidazole vs vancomycin for CDI
RCT prior to 2000 vs since 2000

Outcomes	No. of Participants (No. of Studies)	Percentage Resolution	Relative Effect[a] (95% CI)	*P* Value	Quality of Evidence (GRADE)[b]	Reference, First Author
Direct comparisons of metronidazole and vancomycin						
Resolution of diarrhea at end of (10 days) treatment	RCTs prior to 2000: 156 (2)	95 (MTR) 98 (VAN)	RR, 0.97 (.91–1.03)	.4		Teasley [168] Wenisch [310]
	RCTs since 2000: 687[c] (3)	75 (MTR) 85 (VAN)	RR, 0.89 (.82–.96)	.002		Zar [188] Johnson [170]
	All RCTs: 843 (5)	78 (MTR) 87 (VAN)	RR, 0.89 (.85–.96)	.0008	⊕⊕⊕⊕ High	
Resolution of diarrhea at end of treatment without CDI recurrence ~1 month after treatment	RCTs prior to 2000: 156 (2)	85 (MTR) 84 (VAN)	RR, 1.0 (.90–1.2)	1.0		Teasley [168] Wenisch [310]
	RCTs since 2000: 687[c] (3)	59 (MTR) 70 (VAN)	RR, 0.84 (.74–.94)	.002		Zar [188] Johnson [170]
	All RCTs: 843 (5)	63 (MTR) 73 (VAN)	RR, 0.87 (.79–.96)	.003	⊕⊕⊕⊕ High	

RCTs published since 2000

- Metronidazole was inferior to oral vancomycin for clinical cure in patients with CDI (P = .002)
- Metronidazole was inferior to oral vancomycin for resolution of diarrhea at end of treatment without CDI recurrence 21–30 days after treatment (P = .002).

McDonald LC et al. 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). Clin Infect Dis. 2018 Mar 19;66(7):e1-e48.

Vancomycin is superior for treating patients with severe CDI in a RCT

Patient population

- Oct 1994 to Jun 2002
- Inpatients from Saint Francis Hospital
- Criteria for inclusion:
  - diarrhea (defined as ⩾3 nonformed stools in 24 h) and C. difficile toxin A demonstrated in the stool within 48 h after study entry or
  - pseudomembranous colitis found on endoscopic examination or
  - clinically suspected to have CDI, and they were dropped from the study if the toxin A assay result was negative and if no pseudomembranous colitis was demonstrated on endoscopic examination (if performed)

Cure

Disease severity	No. of patients cured/ no. of patients treated (%)			P^a
	Mtz group	Vm group	Total	
Mild	37/41 (90)	39/40 (98)	76/81 (94)	.36
Severe	29/38 (76)	30/31 (97)	59/69 (86)	.02
All	66/79 (84)	69/71 (97)	135/150 (90)	

NOTE. Mtz, metronidazole; Vm, vancomycin.

[a] *P* values were calculated using Fisher's exact test.

Relapse

Disease severity	No. of patients who experienced relapse/no. of patients who were cured (%)			P^a
	Mtz group	Vm group	Total	
Mild	3/37 (8)	2/39 (5)	5/76 (7)	.67
Severe	6/29 (21)	3/30 (10)	9/59 (15)	.30
All	9/66 (14)	5/69 (7)	14/135 (10)	.27

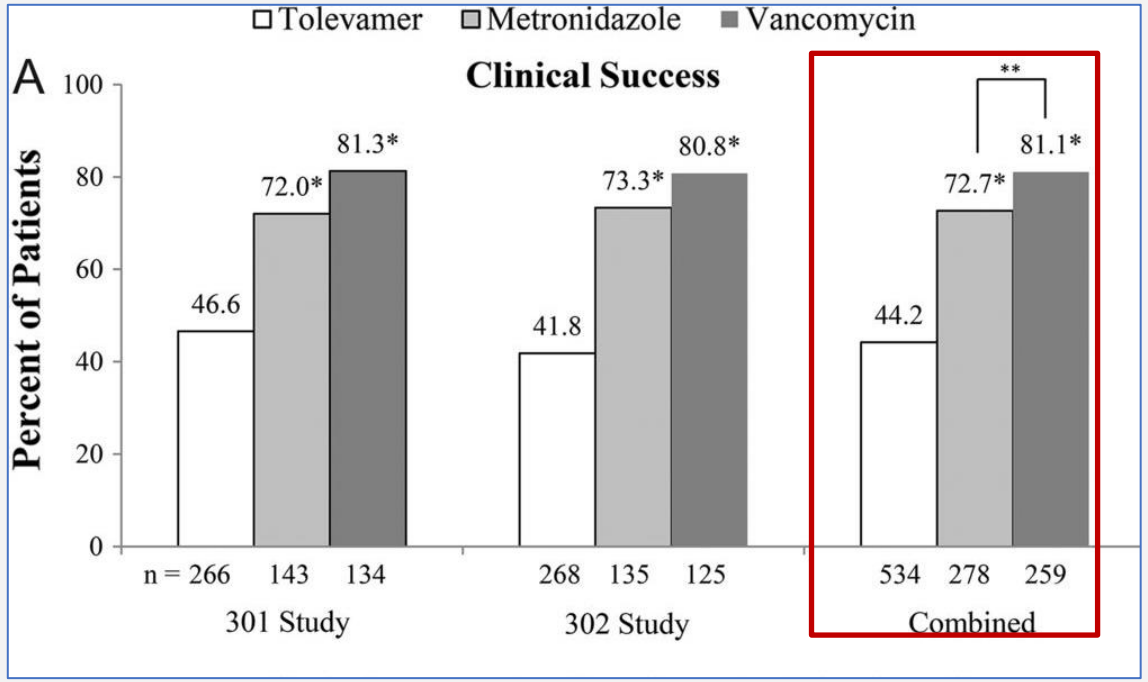
NOTE. Mtz, metronidazole; Vm, vancomycin.

[a] *P* values were calculated using Fisher's exact test.

Zar FA, Bakkanagari SR, Moorthi KM, Davis MB. A comparison of vancomycin and metronidazole for the treatment of Clostridium difficile-associated diarrhea, stratified by disease severity. Clin Infect Dis. 2007 Aug 1;45(3):302-7.

Metronidazole was inferior to vancomycin in 2 RCTs (clinical success)

- Two identical multicenter RCTs (91 sites in the United States and Canada and 109 sites in Europe, Australia, and Canada) between 2005 and 2007
- Patients were randomly assigned in a 2:1:1 ratio to receive tolevamer (9 g loading dose followed by 3 g every 8 hours for 14 days), vancomycin (one 125-mg capsule every 6 hours for 10 days), or metronidazole (one 375-mg capsule every 6 hours for 10 days).
- BI strain: 136 patients in the 301 study [34%] vs 40 patients in the 302 study [11%] among those with isolates typed; P < .001

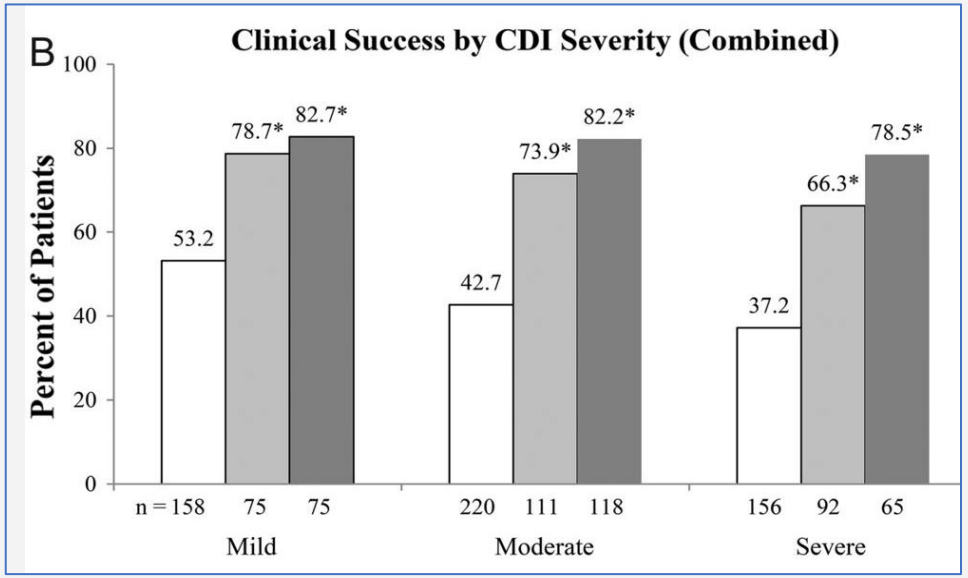


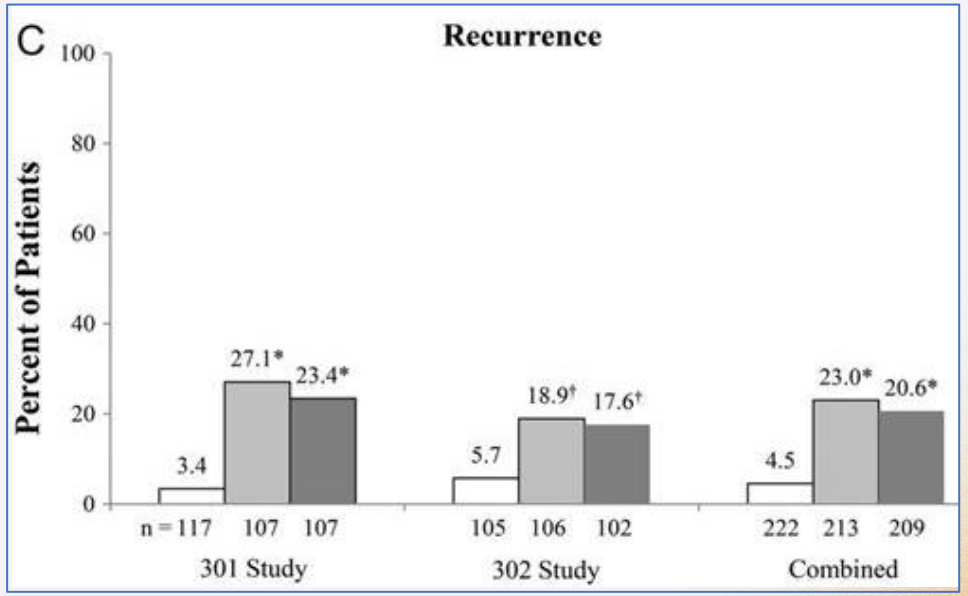
*P < .001 for comparisons between tolevamer and metronidazole and between tolevamer and vancomycin. **P = .020 for comparison between metronidazole and vancomycin.

Johnson S, Louie TJ, Gerding DNet al.. Vancomycin, metronidazole, or tolevamer for Clostridium difficile infection: results from two multinational, randomized, controlled trials. Clin Infect Dis 2014; 59: 345–54.

Trend towards superiority for vancomcyin over metronidazole for clinical success & recurrence

- Clinical success of vancomycin vs metronidazole
  - Mild: 4% more (P = .54)
  - Moderate: 8.3% more (P = .14)
  - Severe: 12.2% more (P = .059)





*P < .001 for comparisons between tolevamer and metronidazole and between tolevamer and vancomycin. †P < .05 for comparisons between tolevamer and metronidazole and between tolevamer and vancomycin.

Johnson S, Louie TJ, Gerding DNet al.. Vancomycin, metronidazole, or tolevamer for Clostridium difficile infection: results from two multinational, randomized, controlled trials. Clin Infect Dis 2014; 59: 345–54.

Cochrane review in 2017

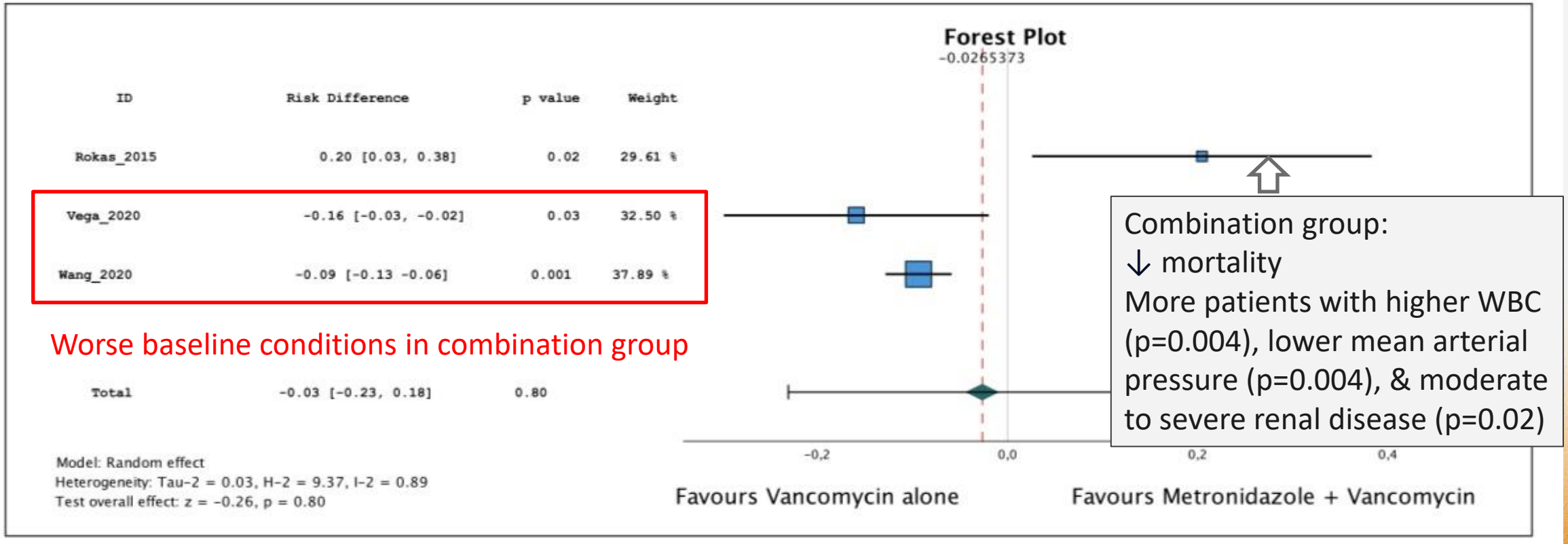
- 22 randomised controlled trials reviewed
- Vancomycin was found to be more effective than metronidazole for achieving symptomatic cure.
- 72% (318/444) of metronidazole patients achieved symptomatic cure compared to 79% (339/428) of vancomycin patients (RR 0.90, 95% CI 0.84 to 0.97; moderate quality evidence).
- The differences in effectiveness between these antibiotics were not too large.

Nelson RL, Suda KJ, Evans CT. Antibiotic treatment for Clostridium difficile-associated diarrhoea in adults. Cochrane Database Syst Rev. 2017 Mar 3;3(3):CD004610.

Severe-complicate CDI

Meta-analysis of 3 retrospective studies comparing vancomycin vs vancomycin + metronidazole

- Non-significant mild risk difference of 2.7% in favor of vancomycin monotherapy (−0.027, 95% CI: −0.23, 0.18) (p= 0.8)
- The studies exhibited significant heterogeneity (I^2=89%)



Worse baseline conditions in combination group

Combination group:
↓ mortality
More patients with higher WBC (p=0.004), lower mean arterial pressure (p=0.004), & moderate to severe renal disease (p=0.02)

Pipitone G, Granata G, Sartelli M, Gizzi A, Imburgia C, Marsala L, Cascio A, Iaria C. On the use of intravenous metronidazole for severe and complicated Clostridioides difficile infection: a review and meta-analysis. Infez Med. 2024 Mar 1;32(1):20-24.

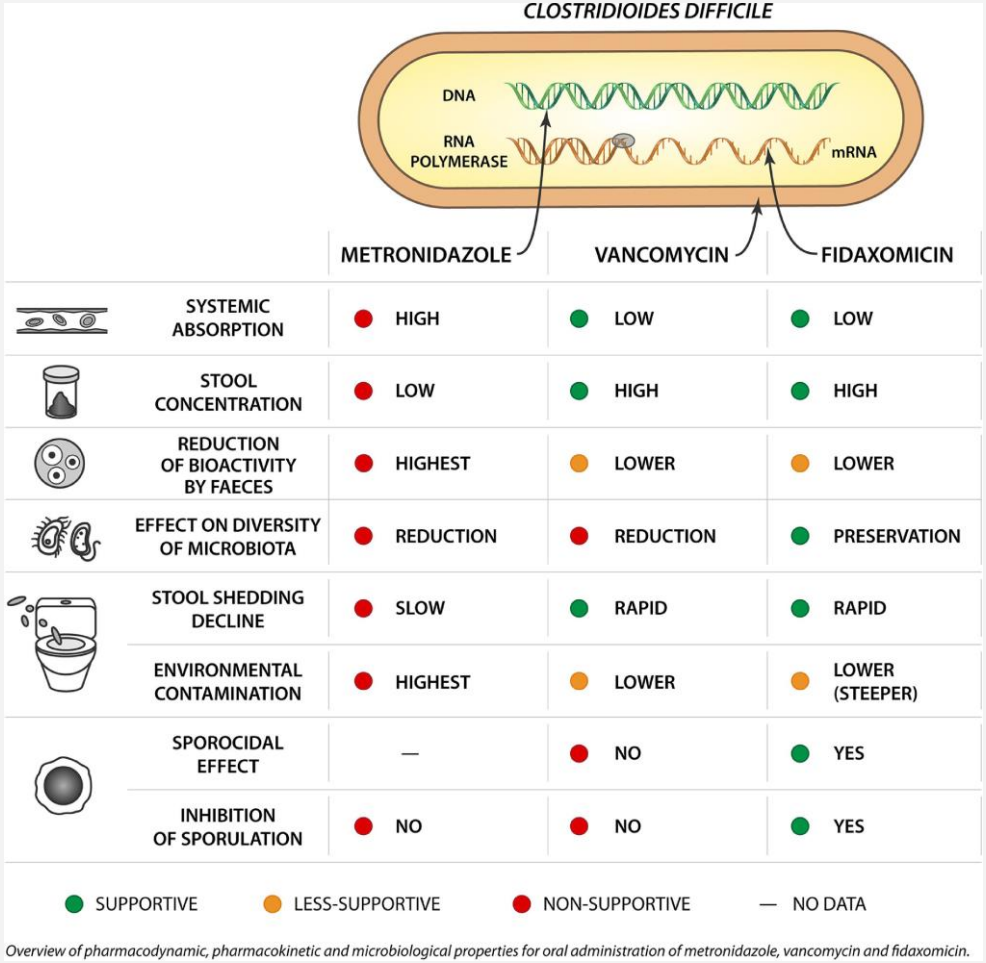
Possible causes account for the superiority of vancomycin to metronidazole

1. Emergence of hypervirulent epidemic strain (NAP1/B1/027) in North America, Europe and Australia

2. Emergence of metronidazole resistance
   - Higher MIC reported for ribotypes 001, 027, 106, and 356
   - Ribotype 955 with resistance to metronidazole

3. Pharmacological characteristics of vancomycin and metronidazole

Comparison of metronidazole, vancomycin, and fidaxomicin



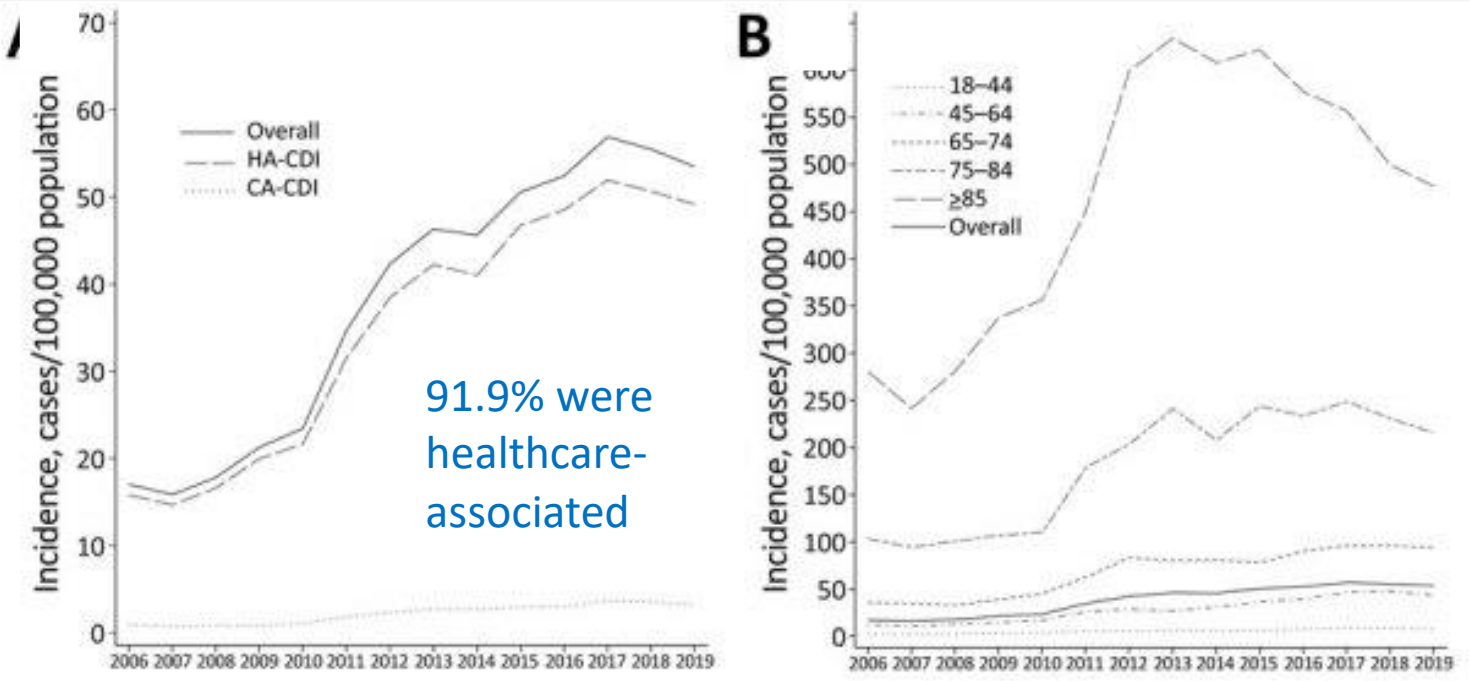
Overview of pharmacodynamic, pharmacokinetic and microbiological properties for oral administration of metronidazole, vancomycin and fidaxomicin.

Krutova M, Wilcox M, Kuijper E. Clostridioides difficile infection: are the three currently used antibiotic treatment options equal from pharmacological and microbiological points of view? Int J Infect Dis. 2022 Nov;124:118-123.

Epidemiology is different in Hong Kong

Burden of disease in Hong Kong, 2006 to 2019

Lower risk of recurrence



- ~A quarter of cases <65 years old
- 30-day mortality:
  - Decreasing trend: 20.1% in 2015 to 16.8% in 2019
  - Risk factors: advanced age and metastatic tumor
- 60-day recurrence:
  - Increased from 7.8% (2006 to 2014) to ~11% (2015 to 2019)
  - Predictors: healthcare-associated CDI, use of quinolones or broad-spectrum antibiotics within 8 weeks before diagnosis of CDI
- <0.1% required surgical intervention

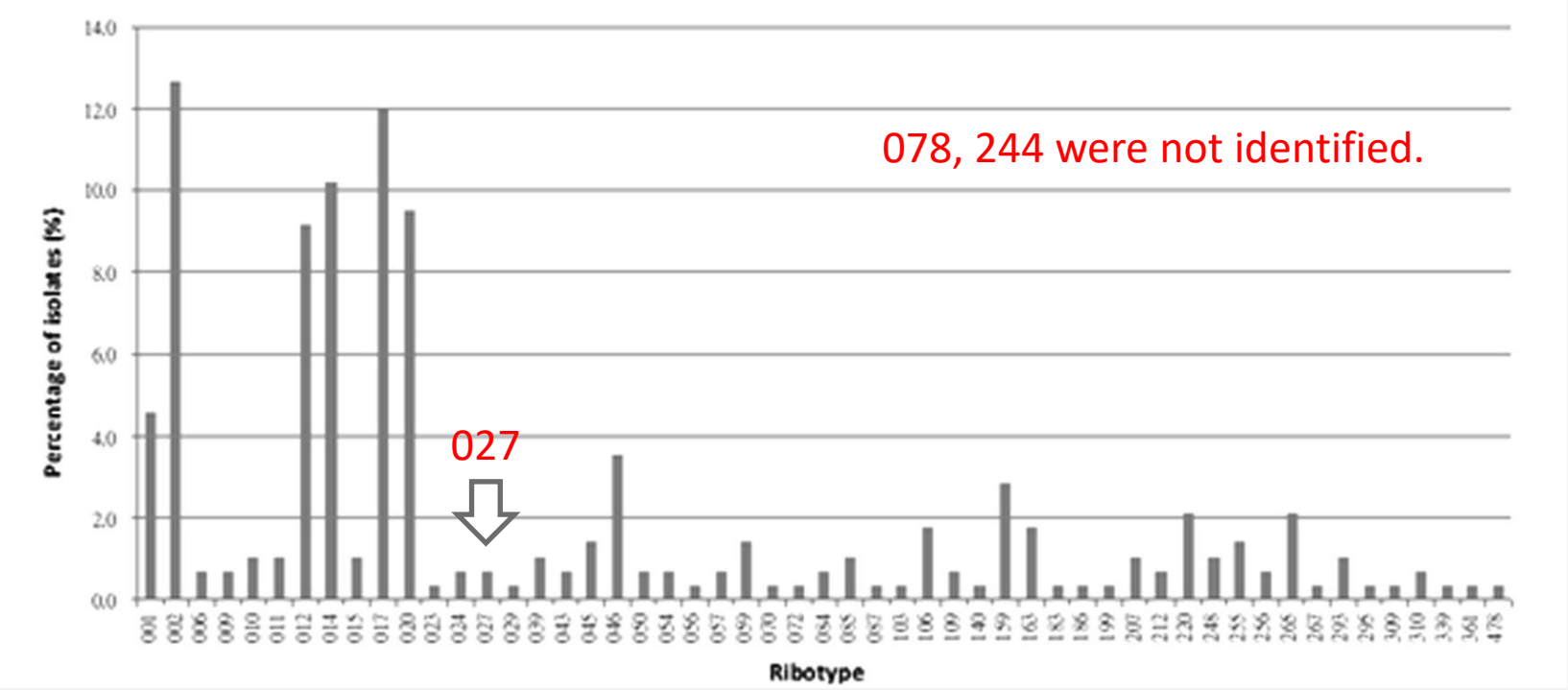
Ho J et al. Disease Burden of Clostridium difficile Infections in Adults, Hong Kong, China, 2006-2014. Emerg Infect Dis. 2017 Oct;23(10):1671-1679. doi: 10.3201/eid2310.170797.

Guo CLT et al. Trends in Incidence and Clinical Outcomes of Clostridioides difficile Infection, Hong Kong. Emerg Infect Dis. 2021 Dec;27(12):3036–44. doi: 10.3201/eid2712.203769.

Hypervirulent strain NAP1/B1/027 & resistance to metronidazole are uncommon in Hong Kong

Ribotype 027 is rare in Hong Kong

- 284 toxigenic C. difficile clinical isolates, collected at the Prince of Wales Hospital, Hong Kong between 2009–2011
- 53 PCR ribotypes were identified
- The five most prevalent ribotypes were 002 (13%), 017 (12%), 014 (10%), 012 (9.2%), and 020 (9.5%).
- All were tested susceptible to metronidazole.



Chow VCY, Kwong TNY, So EWM, Ho YII, Wong SH, Lai RWM, Chan RCY. Surveillance of antibiotic resistance among common Clostridium difficile ribotypes in Hong Kong. Sci Rep. 2017 Dec 8;7(1):17218.

Ribotype distribution in the Asia Pacific Region (2014 to 2015)

All susceptible to metronidazole

QX 239: Associated with recurrence, not reported from HK isolates

Ribotype	No. of isolates (%)									
	AUS	CHN, HKG	IDN, MYS, PHL	JPN	KOR	SGP	TWN	THA	VNM	Total
RT 017	0	9 (18.0)	8 (47.1)	1 (2.2)	13 (14.6)	1 (4.5)	10 (11.4)	19 (50.0)	7 (50.0)	68 (16.4)
RT 014/020	13 (26.0)	4 (8.0)	0	1 (2.2)	6 (6.7)	6 (2.7)	8 (9.1)	7 (18.4)	0	45 (10.9)
RT 018	2 (4.0)	1 (2.0)	0	0	38 (42.7)	0	0	0	0	41 (9.9)
RT 002	3 (6.0)	1 (2.0)	0	12 (26.1)	1 (1.1)	1 (4.5)	20 (22.7)	0	0	38 (9.2)
RT 012	1 (2.0)	6 (12.0)	0	0	2 (2.2)	3 (13.6)	6 (6.8)	2 (5.3)	0	20 (4.8)
RT 369	0	4 (8.0)	0	11 (23.9)	1 (1.1)	0	1 (1.1)	0	0	17 (4.1)
QX 239	0	0	0	15 (32.6)	0	0	0	0	0	15 (3.6)
QX 032	0	1 (2.0)	0	0	3 (3.4)	0	10 (11.4)	1 (2.6)	0	15 (3.6)
RT 001	0	5 (10.0)	1 (5.9)	0	1 (1.1)	1 (4.5)	4 (4.5)	1 (2.6)	0	13 (3.1)
RT 106	1 (2.0)	1 (2.0)	0	1 (2.2)	1 (1.1)	0	8 (9.1)	0	0	12 (2.9)
RT 046	0	2 (4.0)	1 (5.9)	0	4 (4.5)	0	3 (3.4)	0	1 (7.1)	11 (2.7)
RT 056	5 (10.0)	1 (2.0)	0	0	0	0	1 (1.1)	0	0	7 (1.7)
RT 070	3 (6.0)	0	1 (5.9)	0	2 (2.2)	0	0	0	0	6 (1.4)
RT 027	0	1 (2.0)	2 (11.8)	0	0	0	0	0	0	3 (0.7)
RT 078	0	0	0	0	1 (1.1)	0	1 (1.1)	0	0	2 (0.5)
Other	22 (44.0)	14 (28.0)	4 (23.5)	5 (10.9)	16 (18.0)	10 (45.5)	16 (18.1)	8 (21.1)	6 (42.9)	101 (24.4)
Total	50 (100.0)	50 (100.0)	17 (100.0)	46 (100.0)	89 (100.0)	22 (100.0)	88 (100.0)	38 (100.0)	14 (100.0)	414 (100.0)

[a]Abbreviations: AUS, Australia; CHN, China; HKG, Hong Kong; IDN, Indonesia; MYS, Malaysia; PHL, Philippines; JPN, Japan; KOR, Republic of Korea; SGP, Singapore; TWN, Taiwan; THA, Thailand; VNM, Vietnam.

Lew T, Putsathit P, Sohn KM, Wu Y, Ouchi K, Ishii Y, Tateda K, Riley TV, Collins DA. Antimicrobial Susceptibilities of Clostridium difficile Isolates from 12 Asia-Pacific Countries in 2014 and 2015. Antimicrob Agents Chemother. 2020 Jun 23;64(7):e00296-20.

Conclusion

1. Metronidazole still maintains a role in the management of CDI.

2. For initial non-severe episode, metronidazole remains one of the first-line options, particularly for patients with lower risk of recurrence.

3. For fulminant disease, combination therapy of vancomycin + metronidazole is a cautious approach to attain clinical success.

IMPACT Guideline (6th Edition)
Part V: Known pathogen therapy for *Clostridioides difficile*

Drug choice	Alternative	Remarks
Initial non-severe episode: P.O. vancomycin or P.O. metronidazole (preferred for patients at low risk of recurrence)	Severe disease, ileus or toxic megacolon: I.V. metronidazole + P.O. vancomycin ± per rectum vancomycin + consult surgeon	Multiple recurrences: please consult a clinical microbiologist or infectious disease physician regarding options, including vancomycin taper or faecal microbiota transplant.
First recurrence, non-severe: P.O. vancomycin		

https://impact.chp.gov.hk/chapters_5_1.php

Thank you!