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Commentary

Which trials do we need? Fidaxomicin plus either intravenous metronidazole or tigecycline versus vancomycin plus either intravenous metronidazole or tigecycline for fulminant *Clostridioides difficile* infection

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Background

The main international guidelines for the management of *Clostridioides difficile* (*C. difficile*) infection (CDI) diverge on the suggested treatment of its fulminant form [1–4]. As some authors pointed out [5], the therapeutic choices that are proposed by current guidelines [1–4] were based on few retrospective observational studies with several biases (Table 1).

Fulminant CDI accounts for up to 3–8% of the cases [6,7] with an estimated mortality ranging from 20% to 80% [4], but these figures are influenced by notable heterogeneity in the underlying cohorts, some of them quite dated, not mirroring the medical and surgical advancements over the years. Anyway, one of the most ample cohorts of fulminant cases (199 patients) from the United States (1996–1997) reported a 34.7% in-hospital mortality [8]. Multiple factors impact clinical outcomes: on one hand, comorbidities and some ribotypes (such as RT027/ST1, whose distribution varies worldwide and whose incidence apparently decreased in the last decades) may contribute to higher death rate, whereas combination treatment and improved testing sensitivity could reduce mortality [9].

At any rate, no clinical trial to date addressed the medical treatment of fulminant CDI. There are some potential explanations for this lack of high-quality data informing recommendations in this setting: the severity of the clinical entity, making it difficult to recruit patients for a randomized study, and the differences in definition across guidelines, although all agree on some defining elements of complicated/fulminant infections such as hypotension or shock, ileus or megacolon [1–3].

Fidaxomicin has become the drug of choice for initial non-severe CDI, whereas for fulminant CDI in the absence of comparative data fidaxomicin and vancomycin are placed equally in the last European guidelines update [1], but other guidance still put vancomycin as reference drug [2,3] as shown in Table 1. Another unsettled issue is the role of combination therapy, with either metronidazole or tigecycline via intravenous (i.v.) route: actually, monotherapy based on vancomycin seems not inferior to combination regimens including metronidazole, with a minimal mortality difference (−3%) even in favour of the former over the latter (95% CI, −23% to 18%) [10]. On the other hand, a meta-analysis showed high clinical cure rates when resorting to tigecycline, up to 79%, although drawing upon primary studies not exclusively focusing on severe CDI and without making comparisons [11]. As a matter of fact, all guidelines agree on the possibility of adding a

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Table 1
Suggested treatment by the main international society guidelines

Severe-complicated or "fulminant" CDI	ESCMID 2021	IDSA/SHEA 2021	ACG 2021	WSES 2019
	Fidaxomicin STD[a] or vancomycin 125 mg orally 6 hourly for 10 days and consider i.v. tigecycline 100 mg load, then 50 mg 12 hourly Consult a surgeon. Consider FMT when refractory	Vancomycin 500 mg 6 hourly orally or via nasogastric tube and metronidazole 500 mg i.v. 8 hourly and consider vancomycin per rectum if ileus.	Vancomycin 500 mg 6 hourly orally or via nasogastric tube; consider i.v. metronidazole 500 mg 8 hourly and consider vancomycin per rectum if ileus. Consider FMT when refractory.	Vancomycin 500 mg 6 hourly orally and/or per enema in combination with i.v. metronidazole 500 mg 8 hourly. Consult a surgeon.

[a] Standard Therapeutic Dose.
ACG, American College of Gastroenterology; CDI, *Clostridioides difficile* infection; ESCMID, European Society of Clinical Microbiology and Infectious Diseases; FMT, faecal microbiota transplantation; IDSA, Infectious Diseases Society of America; i.v., intravenous; SHEA, Society for Healthcare Epidemiology of America; STD, standard dose; WSES, World Society of Emergency Surgery.

systemic drug to the backbone usually orally administered, although the decision to opt for a combination regimen remains on a case-by-case basis [1–3].

From a pharmacological perspective, since the moment it became available for clinical use, fidaxomicin appeared to have many advantageous features as opposed to vancomycin: they both reach very high concentrations in the stool, but only fidaxomicin has a minimal effect on intestinal microbiota, inhibit sporulation, and displays antimicrobial activity on spores [12].

Moreover, despite not being in a statistically significant fashion, in the few studies addressing death as an outcome in case of CDI fidaxomicin showed a better profile than vancomycin, as emerged from a recent meta-analysis: odds ratio for mortality 0.86, ranging the confidence interval from 0.64 to 1.15 (eight studies, 1951 patients) [13]. Therefore, in light of the absence of available trials, we propose to compare fidaxomicin and vancomycin in combination with either i.v. tigecycline or metronidazole.

Study design

This would be a multicentric, double-blind randomized controlled trial (RCT).

Hypothesis

To evaluate the superiority of combination therapy with oral fidaxomicin with either i.v. tigecycline or metronidazole compared to oral vancomycin with either i.v. tigecycline or metronidazole in patients with fulminant CDI.

Participants

Inclusion criteria

1. Adults (aged at least 18 years old).
2. Diagnosis of CDI according to the combination of consistent clinical findings (i.e. diarrhoea as at least three episodes of loose stools in 24 hours) and microbiological evidence of *C. difficile*-free toxins using enzyme immunoassay without any alternative reasonable explanation of symptomatology or a consistent clinical picture compatible with a positive nucleic acid amplification test, or positive toxigenic *C. difficile* culture or pseudomembranous colitis as diagnosed during endoscopy [1].
3. Diagnosis of fulminant CDI during the first 48 hours, defined as per the European Society of Clinical Microbiology and Infectious Diseases guidelines, specifically as a CDI complicated with hypotension, septic shock, elevated serum lactate levels, ileus, toxic megacolon, bowel perforation, or any fulminant course of disease [1].
4. Signed informed consent by the patient or a legal representative (in case of patients unable to give their consent or under tutorship).

Exclusion criteria

1. Allergy or intolerance or any contraindication to the drugs under investigation.
2. Life expectancy is less than 24 hours.

Randomization

Patients will be randomly assigned in a 1:1:1:1 ratio to receive one of the following regimens: vancomycin plus i.v. metronidazole (reference), vancomycin plus i.v. tigecycline, fidaxomicin plus i.v. metronidazole and fidaxomicin plus i.v. tigecycline.

Patients will be randomly assigned according to a randomization list prepared in advance for each site. The sequence will be generated using blocks of eight patients and will be made accessible using an online randomization platform.

Intervention

The study will divide the patients into four arms. Group A will receive fidaxomicin 200 mg twice a day orally (or through the nasogastric tube) in combination with metronidazole 500 mg three times a day via the i.v. route (group A), group B will receive fidaxomicin 200 mg three times a day (same routes as above) in combination with tigecycline 50 mg twice a day orally via i.v. route after a loading dose equal to 100 mg, group C will receive vancomycin 125 mg four times a day orally (or through the nasogastric tube) in combination with metronidazole 500 mg three times a day via i.v. route, finally, group D will receive vancomycin 125 mg four times a day (same routes as above) in combination with tigecycline 50 mg twice a day via i.v. route after a loading dose equal to 100 mg. In case of ileus, the patient should be also treated with an attempt of intraluminal (coloscopic per enema) delivery of the drugs (see European guidelines [1]): vancomycin (500 mg in saline solution, every 6 hours) or fidaxomicin (200 mg every 12 hours) according to the allocation arm. The duration of therapy will be 10 days. Fig. 1 shows a flow chart.

Primary outcome

A 30-day all-cause mortality after randomization.

Secondary outcomes

1. Necessity of undergoing surgery (colectomy or diverting loop ileostomy).
2. A 90-day all-cause mortality after randomization.
3. CDI attributable mortality.

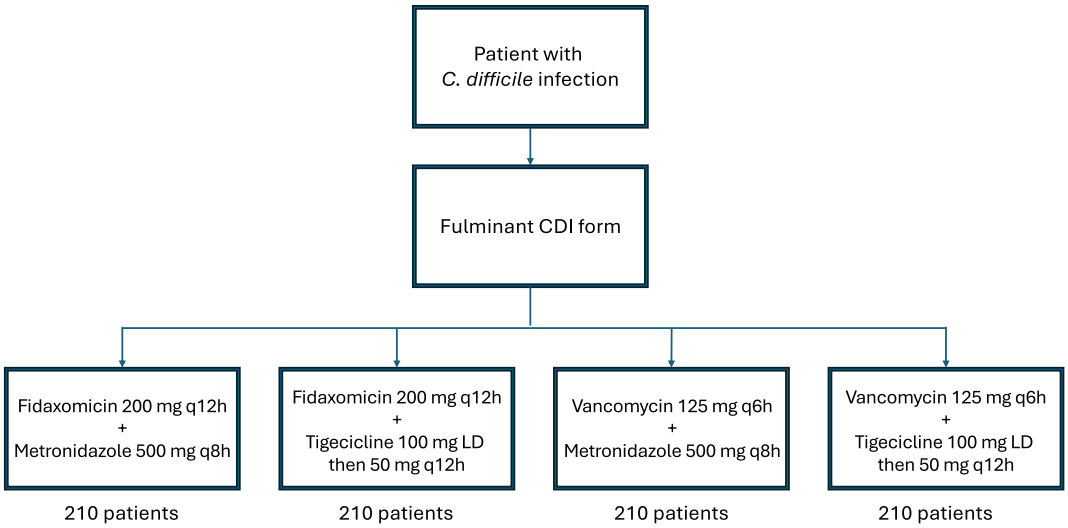

Fig. 1. Flow chart for patients' randomization. CDI, *Clostridioides difficile* infection; LD, loading dose.

4. Recurrence of CDI after resolution in survivors (<4 weeks after treatment).
5. Bacteraemia or fungemia during the first 30 days of observation
6. Adverse effects attributable to study drugs.
7. Length of hospital stay.
8. Length of Intensive Care Unit stay.

Sample size and statistical analysis plan

This RCT will be reported according to the proper checklist for multi-arm parallel-group randomized trials [14].

A tentative calculation of the required sample size for such a trial has been made by resorting to a Shiny web application built upon the R package "*multiarm*" [15], factoring in a binary primary outcome (mortality) and the presence of three experimental treatments compared to standard treatment.

The assumptions are the following: $\alpha = 0.05$ (significance level), $\beta = 0.2$ (power), $\delta_1 = 0.15$ (percentage of interesting treatment difference threshold), $\pi_0 = 0.80$ (percentage of response among controls), meaning 80% of participants alive in the reference group, using familiar Dunnett correction as well as equal allocation across arms. The output would be a total of 840 patients, 210 in each arm. The entire output underlying the calculation is presented in the Appendix S1.

The rationale for these figures is the following: estimates of mortality in fulminant CDI do not come from rock-solid evidence and often rely on old data, but the range emerging from the literature is 30–40% [16]. We lowered the anticipated death rate in the reference arm to 20% in light of global medical advancements and considering that the sickest patients will likely be dead before enrollment. A 10% absolute mortality benefit is a reasonable trade-off between implausible too-optimistic expectations and a minimal clinical difference so small as to not justify a very large RCT.

Outcomes will be primarily analysed according to an intention-to-treat principle. A per-protocol evaluation will be performed additionally.

Subgroup analyses will be carried out considering if the current episode is primary or a recurrence and whether patients suffer from ileus (so receiving intraluminal administration of fidaxomicin or vancomycin) or not.

Limitations and conclusions

We are fully aware of the difficulties of recruiting patients with fulminant CDI and of the pitfalls regarding the design and the assessment of a multi-arm trial in this setting, wherein even the computation of a plausible sample size is made difficult by the lack of high-quality data precisely informing on the mortality burden.

Nevertheless, in light of the highly varying approach to this clinical entity, we posit that a study comparing at once multiple options could provide important answers we need to shed new light on the problem and better inform the next guidelines. In the preferable scenario, it could provide the single best regimen for fulminant CDI. Otherwise, it could single out two regimens that might be further addressed in future dedicated two-arm RCTs.

An international effort linking many centres by creating a dedicated network may facilitate the task [12]. Finally, given the lower rate of fulminant forms, a main concern would be the lower number of patients enrolled per year by each centre. This problem could be overcome, for example, with a 5-year international multicentric trial.

Author contributions

G.P., G.G., and A.E.M. participated in conceptualization. G.P. and A.E.M. participated in writing the original draft. G.P. and A.E.M. participated in reviewing and editing. G.P., C.I., G.G., A.C., and A.E.M. participated in visualization, validation, and supervision.

Transparency declaration

Potential conflict of interest

The authors declare that they have no conflicts of interest.

Financial report

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cmi.2024.09.017.

References

[1] van Prehn J, Reigadas E, Vogelzang EH, Bouza E, Hristea A, Guery B, et al. European Society of Clinical Microbiology and Infectious Diseases: 2021 update on the treatment guidance document for Clostridioides difficile infection

in adults. Clin Microbiol Infect 2021;27(Suppl 2):S1–21. https://doi.org/10.1016/j.cmi.2021.09.038.
[2] Johnson S, Lavergne V, Skinner AM, Gonzales-Luna AJ, Garey KW, Kelly CP, et al. 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. Clin Infect Dis 2021;73:e1029–44. https://doi.org/10.1093/cid/ciab549.
[3] Sartelli M, Di Bella S, McFarland LV, Khanna S, Furuya-Kanamori L, Abuzeid N, et al. 2019 update of the WSES guidelines for management of *Clostridioides (Clostridium) difficile* infection in surgical patients. World J Emerg Surg 2019;14:8. https://doi.org/10.1186/s13017-019-0228-3.
[4] Kelly CR, Fischer M, Allegretti JR, LaPlante K, Stewart DB, Limketkai BN, et al. ACG clinical guidelines: prevention, diagnosis, and treatment of Clostridioides difficile Infections. Am J Gastroenterol 2021;116:1124–47. https://doi.org/10.14309/ajg.0000000000001278.
[5] Pipitone G, Granata G, Sartelli M, Gizzi A, Imburgia C, Cascio A, et al. Intravenous metronidazole for fulminant Clostridioides difficile infection. Clin Microbiol Infect 2023;29:656–7. https://doi.org/10.1016/j.cmi.2023.01.026.
[6] van der Wilden GM, Chang Y, Cropano C, Subramanian M, Schipper IB, Yeh DD, et al. Fulminant Clostridium difficile colitis: prospective development of a risk scoring system. J Trauma Acute Care Surg 2014;76:424–30. https://doi.org/10.1097/ta.0000000000000105.
[7] Di Bella S, Sanson G, Monticelli J, Zerbato V, Principe L, Giuffre M, et al. *Clostridioides difficile* infection: history, epidemiology, risk factors, prevention, clinical manifestations, treatment, and future options. Clin Microbiol Rev 2024;37:e0013523. https://doi.org/10.1128/cmr.00135-23.
[8] Sailhamer EA, Carson K, Chang Y, Zacharias N, Spaniolas K, Tabbara M, et al. Fulminant Clostridium difficile colitis: patterns of care and predictors of mortality. Arch Surg 2009;144:433–9. https://doi.org/10.1001/archsurg.2009.51. discussion 9–40.
[9] Davies KA, Ashwin H, Longshaw CM, Burns DA, Davis GL, Wilcox MH, et al. Diversity of Clostridium difficile PCR ribotypes in Europe: results from the European, multicentre, prospective, biannual, point-prevalence study of Clostridium difficile infection in hospitalised patients with diarrhoea (EUCLID), 2012 and 2013. Euro Surveill 2016;21. https://doi.org/10.2807/1560-7917.es.2016.21.29.30294.
[10] Pipitone G, Granata G, Sartelli M, Gizzi A, Imburgia C, Marsala L, et al. On the use of intravenous metronidazole for severe and complicated Clostridioides difficile infection: a review and meta-analysis. Infez Med 2024;32:20–4. https://doi.org/10.53854/liim-3201-3.
[11] Kechagias KS, Chorepsima S, Triarides NA, Falagas ME. Tigecycline for the treatment of patients with Clostridium difficile infection: an update of the clinical evidence. Eur J Clin Microbiol Infect Dis 2020;39:1053–8. https://doi.org/10.1007/s10096-019-03756-z.
[12] 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;124:118–23. https://doi.org/10.1016/j.ijid.2022.09.013.
[13] Stabholz Y, Paul M. The effect of antibiotic therapy for Clostridioides difficile infection on mortality and other patient-relevant outcomes: a systematic review and meta-analysis. Clin Microbiol Infect 2024;30:51–8. https://doi.org/10.1016/j.cmi.2023.09.002.
[14] Juszczak E, Altman DG, Hopewell S, Schulz K. Reporting of multi-arm parallel-group randomized trials: extension of the CONSORT 2010 statement. JAMA 2019;321:1610–20. https://doi.org/10.1001/jama.2019.3087.
[15] Grayling MJ, Wason JM. A web application for the design of multi-arm clinical trials. BMC Cancer 2020;20:80. https://doi.org/10.1186/s12885-020-6525-0.
[16] Carlson TJ, Gonzales-Luna AJ, Garey KW. Fulminant Clostridioides difficile infection: a review of treatment options for a life-threatening infection. Semin Respir Crit Care Med 2022;43:28–38. https://doi.org/10.1055/s-0041-1740973.