Critically Ill Patients With *Clostridium difficile* Infection: Are 2 Antibiotics Better Than One?

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(See the Major Article by Rokas et al on pages 934–41.)

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There is a dearth of evidence about how best to manage critically ill patients with *Clostridium difficile* infection (CDI) [1–3]. The study by Rao et al in this issue of *Clinical Infectious Diseases* provides some information that reinforces weakly graded recommendations in treatment guidelines that currently advocate combination therapy with oral vancomycin and intravenous metronidazole in preference to vancomycin monotherapy in patients with life-threatening CDI [1–4]. This is more in hope than knowledge of a possible effectiveness gain from using 2 antibiotics rather than one, noting also the general lack of evidence for superiority of combination therapy [5]. Encouragingly, Rao et al found that combination therapy was associated with a survival advantage in retrospective CDI cases that were (partly) matched according to illness severity [4]. This is more in hope than knowledge of a possible effectiveness gain from using 2 antibiotics rather than one, noting also the general lack of evidence for superiority of combination therapy [5]. Encouragingly, Rao et al found that combination therapy was associated with a survival advantage in retrospective CDI cases that were (partly) matched according to illness severity [4]. Notably, however, CDI clinical outcomes (other than possible CDI-related mortality, which was not specifically measured) and length of stay in the intensive care unit (ICU) or hospital did not differ between the 2 treatment groups. It should be noted that the study had weak power to detect such differences.

Retrospective data analyses are of course fraught with potential for confounding. In this study, for example, 4 times more patients in the combination therapy group received concurrent vancomycin per rectum, and twice as many combination therapy recipients received a higher dosage of vancomycin [4]. Despite attempts to match for illness severity, there were differences in comorbidities between the treatment groups that could drive outcome; renal disease was more common in those receiving combination therapy. Notably, combination therapy became more common during the 5-year study observation period. A key issue also is the accuracy of the diagnosis of CDI. We know that CDI defined by the presence of free toxin in feces correlates significantly with severity markers, mortality, and CDI-related complications, in contrast to patients for whom only polymerase chain reaction (PCR) for toxin gene(s) is used for diagnosis [6, 7]. Two different methods were used by Rao et al, but no details are provided about which patients were diagnosed by toxin detection vs PCR [4]. Thus, it is possible that some patients with diarrhea were mistakenly diagnosed with CDI, thus reducing the chance to detect a treatment effect.

Mixing data on CDIs that result in ICU admission or transfer as opposed to those diagnosed after entry contributes to the heterogeneity of epidemiologic data in this setting. For example, in the study by Rao et al, 70% of the patients had a diagnosis of CDI after admission to the ICU. Retrospective cohort studies have typically found that 0.5%–5% of patients acquire CDI during an ICU stay [8–11]. Mortality rates among ICU patients with CDI are typically around 20%–25%, but such data do not distinguish between deaths due to CDI vs other causes [8, 9, 11].

A key concern is that the results of Rao et al’s ICU-based study could be extrapolated to other groups of CDI patients. On the contrary, adding oral metronidazole to oral vancomycin cannot be condoned given the lack of evidence to support better outcomes. Two recent, small (<80 patients in each) retrospective studies have examined response rates in monotherapy vs metronidazole plus vancomycin in patients with severe CDI [12] or CDI associated with hematological malignancy [13]. Neither demonstrated any evidence of superiority for combination treatment. In one study, there were significantly more complications in the combination therapy group; the reasons were unclear, but confounding could not be excluded given the study design [12]. An in vitro study did not show synergy for the combination of metronidazole and vancomycin against...
C. difficile [14]. Given the poor pharmacokinetics of metronidazole with respect to drug delivery to the distal gut lumen, it is not surprising that combination treatment has generally been found not to be advantageous. Indeed, increasing evidence suggests that vancomycin [15] (and thus likely fidaxomicin) [16] is superior to metronidazole on an intent-to-treat basis, as well as for more severe CDI cases [17]. Furthermore, there are theoretical risks that oral combination therapy will be more deleterious to the gut microbiome and thus may increase the risk of recurrent CDI. One of the explanations for the superiority of fidaxomicin in preventing recurrent CDI is that it is less inhibitory to gut microflora [18, 19]. It is also likely that using both vancomycin and metronidazole to treat CDI, each of which is a risk factor for overgrowth by glycopeptide-resistant enterococci [20, 21], will be more selective for these problematic potential pathogens.

There remain many unanswered questions about how best to manage life-threatening CDI and CDI in those who are critically ill; sometimes these are synonymous but not necessarily so. Optimal antibiotic dosages, routes of administration, and duration remain unclear. As discussed previously [16], CDI severity scores would be helpful in knowing when to escalate therapy. A recent study described a simple C. difficile severity score (CDSS), comprising 3 binary variables (age ≥65 years, peak serum creatinine level ≥2 mg/dL, and peak peripheral white blood cell count ≥20 000 cells/µL) [22]. The CDSS was validated across patients in 2 hospitals, and scores of 0, 1, 2, or 3 were associated with severe clinical outcomes of CDI in 4.7%, 13.8%, 33.3%, and 40.0% of cases, respectively. Thus, a randomized study comparing treatment regimens in patients at risk of worse outcome is potentially feasible, although not straightforward. Confounders for poor outcome, notably including frailty, comorbid illnesses, and concomitant antibiotics, would need to be considered in such a trial.

In summary, there is a case to support the limited use of combination therapy with oral/per rectal vancomycin and intravenous metronidazole in critically ill patients with CDI. Given that ventilated and sedated patients are likely to have impaired gut motility, intravenous metronidazole may simply be overcoming the suboptimal drug delivery of orally administered vancomycin in this select group of patients with CDI. Thus, a possible benefit of using 2 antibiotics rather than one applies to specialized but not generalized CDI cases. Hopefully, as more therapeutic choices become available, an approach of giving 2 antibiotics to critically ill patients with CDI, in the hope that at least one will arrive in the distal gut, will be superseded by better treatment options.

Note

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