Treatment of First Recurrences of Clostridium difficile–Associated Disease: Waiting for New Treatment Options

Thomas J. Louie
Infection Prevention and Control, Foothills Medical Center, Calgary, Alberta, Canada

(See the article by Pepin et al. on pages 758–64)

In this issue of the journal, Pepin et al. [1] have reported on the outcomes of treatment of 463 first recurrences of Clostridium difficile–associated disease (CDAD) during the period of 1991 through mid-2005, spanning the period prior to and during the outbreak of infection with the C. difficile ribotype 027/NAP-1 pulsotype strain in Sherbrooke, Quebec. Almost two-thirds of the recurrences occurred in the outbreak period 2003–2005. A major question arising in the infectious diseases community is whether and when to abandon the use of metronidazole as first-line therapy for C. difficile diarrhea, both for initial and recurrent episodes in the face of the changing epidemiology of this re-emerging infectious disease [2, 3]. Earlier this past year, Pepin et al. [4] and Musher et al. [5] reported their recent findings of higher relapse rates and delayed or suboptimal responses for metronidazole treatment of initial episodes of CDAD. The implication by extrapolation was that metronidazole should be abandoned in favor of vancomycin. The accompanying editorial by Gerding [6] cautioned that these clinical experiences are still subject to uncontrolled biases, that carefully conducted randomized trials are required to resolve the relative merits or deficiencies of treatments, and that metronidazole should remain the agent of choice for the majority of cases of initial treatment.

In this current report, Pepin et al. [1] reexamine the issue of treatment choices for first recurrences. Outcomes focused on (1) the risk of an additional recurrence of CDAD and (2) the development of complicated CDAD (defined as megacolon, perforation, colectomy, shock, and all-cause death within 30 days). The findings demonstrate that the risks of recurrence for metronidazole and vancomycin therapy are similarly high (36.5%–40%) and are unaffected by the treatment of the prior episode, and the risk of recurrence before the outbreak period does not differ from the risk during the outbreak period. The implication is that neither therapy is helpful in restoration of the microbial flora that is severely impaired in relapsing cases of CDAD [7]. Age and duration of hospitalization were found to be risk factors favoring a second recurrence of disease.

In the analysis of recurrence, it was concluded that reinfection rather than relapse of CDAD was more likely on the basis of longer duration of hospitalization. In the presence of an outbreak of CDAD in which spores of the outbreak strain become dominant in the hospital, the traditional definitions of endogenous relapse of infection with the same strain or exogenous reinfection with a different strain (or strains) become much less incisive, because this disease perpetuates itself via intestinal and environmental persistence of spores. A simple designation of recurrence seems appropriate in these circumstances.

With respect to the equally important (and perhaps more important) end point of development of complicated disease, it was observed that advancing age, a leukocyte count of >20 × 10^9 cells/L, and renal insufficiency were risk factors favoring a poorer outcome. A complicated course supervened in 12 (7%) of 171 vancomycin-treated episodes, compared with 15 (13%) of 115 metronidazole-treated episodes (P = .12). (According to table 2 in the article by Pepin and colleagues, combined therapy with both vancomycin and metronidazole appeared to result in a higher likelihood of a complicated course; this was also shown in the initial infection study [8], and the complicated course was much more likely associated with the initiation of combination therapy for patients who were severely ill, rather than the development of severe disease as a result of combined therapy.) It was concluded that there was a tendency for vancomycin to be less likely to be accompanied by a complicated course, but the
the order of 55%–89%. Tissue culture de-
time and high specificity, sensitivity is in toxins A/B offer a rapid turnaround
ficile
and although EIAs for detection of is the prompt initiation of therapy. De-
vancing complications. The first priority
of relapse/recurrence runs the risk of de-
severe morbidity/mortality should rank
two end points for therapy, prevention of
complications, all patients treated for
CDAD should be closely monitored daily
for adverse outcomes, especially during
the first week of therapy. In the absence
of severe leukocytosis, renal insufficiency,
and advanced age, for patients who appear
to have disease of mild-to-moderate severity,
metronidazole remains first-line therapy. This likely applies to the majority
of patients. For those with risk factors for severe disease or who are deemed to
be suboptimal responders to metronidazole,
vancomycin is the current practical alter-
native. Treatment with vancomycin is tar-
geted at attaining a clinical response, with
no added benefit over metronidazole in
terms of recurrence.

At present, there are few attractive choices or strategies for the treatment of relapsing disease. It is not certain whether
tapering the dose of vancomycin, which is
commonly practiced, is effective for pre-
vention of recurrences. Although it has
been demonstrated that vancomycin suppresses the gram-negative anaerobic fecal flora (as well as the expected suppression of infection with most gram-positive organisms) [9], a detailed sequential sampling of microfloral shifts during metron-
idazole therapy of primary CDAD is not
available. Nevertheless, the presumption is that both first-line therapies suppress the normal flora, accounting for or contrib-
uting to relapse/recurrences. Limited data
on bacitracin and fusidic acid for treat-
ment of initial infection reveal that van-
comycin and metronidazole have com-
parable response and relapse rates [10–
12], and neither appears to be a better
alternative for recurrent infections. The
mechanisms of relapse have not been in-
vestigated and do not necessarily involve
the same process between agents. In a limited study, teicoplanin was shown to be
associated with a lower relapse rate, but
this agent is not used in the United States
[13].

Of the new therapies that might offer
selective suppression of C. difficile while
preserving components of the normal flora, televamer (a liquid polystyrene
preparation that binds and neutralizes C. difficile toxins A/B) [14], ticamicin B
complex (PAR-101; formerly OPT-80)
[15], rifaximin [16, 17], and nitazoxanide
[18] appear to have potential normal flora
sparring effects. Ingestion of oligofructose
to enhance the growth of bifidobacteria
has recently been shown to reduce recur-
rent disease [19]. Confirmatory studies
should be available to verify these capa-
bilities in the next 1–2 years.

This study verifies that metronidazole
and vancomycin treatment of first recur-
cences of CDAD are associated with the
same potential for subsequent (second)
recurrences, and it revealed a trend toward
a lower frequency of complicated out-
comes for vancomycin treatment. These
findings are of temporary utility while the
results of new therapies are awaited.

Acknowledgments

Potential conflicts of interest. T.J.L. has re-
ceived recent research funding from Optima
Pharma (for a clinical trial investigation), Gen-
zyme (for a clinical investigation), ActivBiotics (for a clinical trial), and Bristol-Myers Squibb.

References

758–64 this issue).
2433–41.
3. Loo VG, Poirier L, Miller MA, et al. A pre-
dominantly clonal multi-institutional out-
break of Clostridium difficile-associated diar-
rhea with high morbidity and mortality. N Engl J Med 2005; 353:
2442–9.
4. Pepin J, Alary M-E, Vaisseau L, et al. Increas-
ing risk of relapse after treatment of Clo-

766 • CID 2006:42 (15 March) • EDITORIAL COMMENTARY