Where to Place the New Treatments for Clostridium difficile Infection?

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(See the Major Article by Gupta et al on pages 730–4.)

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To place well-established and newly developed treatments into Clostridium difficile infection (CDI) algorithms, for any given patient the clinician needs to know the probabilities of a first episode, of a cure, and of a recurrence of CDI.

Today we cannot predict who will develop a first CDI episode. This lack of knowledge is a factor in the large sample sizes in vaccine or other primary prevention trials.

We actually do have tools to predict cure at the end of therapy. At time of diagnosis of CDI, the ATLAS score comprising clinical (age, systemic antibiotics) and laboratory factors (leukocyte count, serum albumin, and serum creatinine) accurately predicts the probability to cure the disease.

Various studies have addressed the probability of recurrence and emphasized the following risk factors: age ≥65 years [1], prior CDI episodes [2], treatment with vancomycin (as opposed to fidaxomicin) in nonhypervirulent cases [3, 4], and CDI caused by a BI/NAP1/027 strain [3–5].

In 2010, a phase 2 study compared the probability of recurrent CDI following metronidazole or vancomycin treatment with or without a single infusion of monoclonal antibodies directed toward toxin A and toxin B [6].

Now, in this issue of Clinical Infectious Diseases, Gupta and colleagues provide more interesting data from that study [7]. They report on predictors of recurrence in the 99 placebo-treated patients. Risk of CDI recurrence depends on overall morbidity. In a very sick population successfully treated with the old standards of metronidazole or vancomycin, one expects recurrence rates of about 25%. The study under discussion meets that characteristic, so the analysis is informative.

The authors identify 2 predictors: Whereas endogenous antibodies toward toxin B protect, age ≥65 years increases the risk of recurrence. Unfortunately, we know neither baseline serum creatinine nor serum albumin concentrations nor the absolute leukocyte count of the study population. In addition, data on strain type are missing for 25 patients in the placebo group [6].

All of these factors are likely to become part of a future integrated score predicting recurrence. The scientific community would have to reevaluate any risk score repeatedly to address epidemiologic changes such as the spread of 078 and 244 strains and others yet to come.

The Gupta et al study adds new evidence regarding the importance of endogenous toxin B antibody levels from a prospective clinical trial. Their findings may allow for precision treatment against CDI recurrence. Clinically, it appears obvious to measure endogenous antibody titers upon diagnosis of CDI to estimate the risk of recurrence. If titers are low, one could substitute monoclonal antibodies directed toward toxin B by bezlotoxumab infusion. This calls for a validated, commercially available test. A turnaround time of several days would be sufficient to allow antimicrobial treatment.

Assuming effective prediction of CDI recurrence, one could hypothesize that sustained cure rates could be further optimized by combining fidaxomicin, which has been shown to significantly reduce recurrence rates compared to vancomycin, with a preventive treatment option. Currently the latter includes monoclonal antibodies, nontoxigenic C. difficile strains [8], conventional fecal microbiota transfer [9], and the probiotic SER-109 [10].

Although this strategy may appear to be the best from a medical point of view, reimbursement of combination treatment seems unlikely given the comparatively high cost of new anti-infectives. While the pharmaceutical industry is expected to keep pricing affordable, it also becomes clear that the structure of many healthcare systems does not support prescription of treatments that provide long-term health and economic advantages. Immediate effects achieved during a current, billable hospitalization or outpatient visit are the drivers. Recurrent CDI is a prime example of this phenomenon. While metronidazole...
has the lowest list price of all registered CDI treatments, it is the least cost-effective option, due to its high associated recurrence rate [11].

In conclusion, reliable prediction models allowing for targeted treatment of patients at risk of recurrence are within reach. However, structural hurdles including lack of a commercially available endogenous toxin B antibody test, high pricing, and limited reimbursement of novel CDI therapies may jeopardize successful improvement of patient care.

Note

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