LET’S TALK ABOUT … DIARRHEA
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THE PROBLEM
A 9 year old boy flies through his heart transplant for myocarditis only to be readmitted one week after discharge with fever and diarrhea. The diagnosis is *C. difficile* infection (CDI). He responds quickly to metronidazole with no further episodes. Another transplant recipient won’t be so lucky and will end up in the ICU with a third recurrence.

*C. difficile* is now the most common cause of healthcare associated, infectious diarrhea. It is also community acquired in 11-28% and rising. Since 2000, the world has also seen the emergence of hyper virulent strains such as BI/NAP1/027 that are associated with increased incidence, severity, and mortality. Virulence factors are likely the production of a binary toxin, increased production of toxins A and B, hyper sporulation, and resistance to fluoroquinolones. CDI is more common in SOT recipients with an incidence up to 31% in lung transplants. To make matters worse, standard antibiotics are ineffective in 8-36%, CDI recurs up to 25% after the first episode, and no antibiotic kills the spores.

THE ANSWERS?
Antibody seems to be important. Adult heart transplant recipients in Spain underwent serial screening of serum IgG post transplant and were given IVIG when the IgG fell below 400 mg/dl or they developed severe infections. Overall, there was a significant decrease in CDI from 20% to 6% and IgG <400 was the only independent risk for CDI by multivariate analysis. In another study, adult patients with CDI on standard treatment of metronidazole or oral vancomycin were given fully human monoclonal antibodies against toxin A and toxin B in a multi center, double blind, RCT that looked at the prevention of recurrence, effect on duration and severity of initial episode of infection and duration of hospitalization. The recurrence rate was significantly reduced in the treatment group from 25% to 7% and the time to recurrence was also significantly longer. There were no differences however, in the duration and severity of the initial episode. There is a vaccine on the horizon. An adjuvanted *C. difficile* toxoid vaccine was shown to be safe and immunogenic in healthy adult and elderly populations in a Phase I trial. A Phase II trial is underway to look at the primary prevention of the first episode of CDI in high risk adults 40-75 years of age (Clinicaltrials.gov NCT00772343 and NCT 01230957).

Are there any new promising drugs for treatment? Fidaxomicin is a macrocyclic antibiotic that is bactericidal for *C. difficile*. It has minimal systemic absorption which leads to high fecal concentration and has limited activity against normal gut flora. A Phase 3 prospective, multi center, double-blind, randomized, non inferiority study compared treatment of 596 adults with CDI with either 10 days of fidaxomicin or vancomycin. Endpoints were clinical cure at end of treatment, recurrence within 4 weeks after treatment, and global cure which was resolution without recurrence. There was no difference in clinical cure (fidaxomicin 88% vs. vancomycin 86%) but fidaxomicin had a significantly higher rate of resolution of diarrhea without recurrence (75% vs 64%). Overall, there were fewer recurrences in the fidaxomicin group but this was restricted to those infected with any strain other than BI/NAP1/027. As with any new antibiotic, cost benefit analysis will be important to determine the role of fidaxomicin.
in the treatment of CDI particularly in the SOT population.

Just a brief note on diagnosis of CDI. Many laboratories use an enzyme immunoassay to detect toxin in stool probably because this method is relatively easy, cheap and fast. EIA can have a poor positive predictive value for true disease however, and is now considered a less optimal tool by some groups. An alternative method for diagnosis that is gaining recognition is an assay that detects glutamate dehydrogenase in stool followed by a second step to detect toxin if the GDH is positive. The sensitivity ranges from 85-95% and specificity from 89-99% with a high negative predictive value. Labs that use this type of assay report that up to 80% of stool samples sent for C. difficile testing are negative on the simple GDH screen and need no further work up. Finally, on the horizon are toxin gene detection tests that have outstanding sensitivity and specificity but are still expensive.

CONCLUSIONS

- IVIG replacement when serum IgG <400 mg/dl might decrease CDI in SOT
- Treatment with human monoclonal antibodies to reduce recurrence appears promising
- A vaccine for primary prevention is being studied in humans
- Fidaxomicin had a significantly higher rate of resolution of diarrhea without recurrence than vancomycin
- EIA for toxin is considered sub optimal for diagnosis by some groups
- Consider for diagnosis
  - 2 step assay with initial GDH screen followed by confirmation if positive or
  - Toxin gene amplification methods

Disclosure Statement: The author has no conflicts of interest to disclose.

References: