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Commentary: Of Mice and Men: Eosinopenia and Adverse Outcomes After *Clostridium difficile* Infections

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The spectrum of presentation of *Clostridium difficile* infections (CDIs) ranges from mild requiring oral antibiotics only to fulminant requiring intensive care admission and emergent total abdominal colectomy. Unfortunately, clinical prediction rules for identifying which patients at increased risk for poor outcomes are suboptimal; many have not been validated or have low diagnostic accuracy.¹ Furthermore, none of the available prediction rules include variables with a mechanistic basis. In contrast, Kulaylat et al developed a model based on findings translated from a mouse model.² They hypothesized that admission eosinopenia, defined as a peripheral eosinophil level of 0 k/ μ l, is associated with worsened outcomes. Using both a training and a validation cohort, they determined that eosinopenia is an independent predictor of inpatient mortality (OR 2.01, 95% CI 1.08–3.73). Additionally, it is associated with increased need for admission to a monitored setting, vasopressors, and emergent total colectomy.

A mouse model demonstrated that the *Clostridium difficile* transferase (CDT) toxin suppresses protective colonic eosinophilia and induces apoptosis of blood eosinophils.³ CDT operates through a Toll-like Receptor 2 (TLR2) dependent pathway, and adoptive transfer of TLR2 deficient eosinophils is protective. This animal study provides a compelling rationale for studying the relationship between eosinopenia and outcomes in CDI in humans. Mouse models are being increasingly used to study CDIs because of improved ease of inducing infection and more widespread availability of mouse-specific reagents for performing tissue analyses.⁴ Nonetheless, despite the ability to induce histopathologic and immune responses that mimic those in humans, the applicability of animal studies to humans must always be questioned. Only 33% of findings in animal studies progress to clinical trials, and 10% of interventions are eventually approved for human use.⁵

Kulaylat et al should be commended for validating findings from an animal model in humans. Although there are inherent limitations to using administrative datasets for research, they were able to identify easily available, inexpensive, and clinically relevant variables that were associated with outcome after CDI. Furthermore, they validated the

results from their training cohort on a separate dataset from another institution. The model had a >90% accuracy among patients with a predicted probability of mortality exceeding 20%. However, as with all prediction rules, the true test of its clinical utility is whether or not outcomes can be improved by interventions based on patients' risk stratification.

In conclusion, admission eosinopenia may be a novel and inexpensive prognosticator for guiding management of CDIs. Moreover, there is data to suggest that resolution of eosinopenia may be a marker for response to antimicrobial therapy in infections.⁶ Ultimately, interventions to block the TLR2 dependent pathway or to restore eosinophil counts may have therapeutic potential in CDIs.

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