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Letters to the Editor

Fecal Lactoferrin Screening Assay for Inflammatory Bacterial Diarrhea

A recent report by Choi et al. (1) concluded that a test for detection of fecal lactoferrin (Leukotest; Techlab, Blacksburg, Va.) is useful and cost-effective for screening stool samples submitted to the laboratory for routine stool culture. If only samples with positive results (titer, >1:50) were cultured for enteric pathogens, the authors estimate a savings to the laboratory of $800 per positive culture.

I would like to respectfully disagree with the authors' conclusions that this or any other screening test, such as that for detection of fecal leukocytes (fWBCs), offers clinicians or laboratorians a useful, cost-effective method. Guerrant and colleagues have published numerous papers proposing that markers for "inflammatory" diarrhea such as the two tests above should be used in a clinical algorithm to distinguish inflammatory from noninflammatory diarrhea (Fig. 2 in the Choi et al. paper). With those patients positive for fWBCs or lactoferrin, cultures should be performed and patients considered for antimicrobial therapy. I recently reviewed and summarized numerous studies that examined fWBCs in bacterial diarrheal disease (3). The sensitivity of fWBC analysis averages 50% for *Campylobacter* (range, 25 to 80%) and *Salmonella* (range, 11 to 82%), and about 75% for *Shigella* (range, 49 to 100%) spp. (3). Thus, such tests are not sensitive enough to be used as screening tests for these pathogens. Second, I am unaware of any study that shows that patients with "inflammatory" diarrhea caused by *Campylobacter*, *Salmonella*, or *Shigella* spp. benefit any more from antimicrobial therapy than those patients without the presence of inflammatory markers. Without such clinical evidence, the use of these tests by clinicians will be very misleading and perhaps increase cost by directing physicians to look for other etiologies. The final comment by the authors that a recent study by Manabe et al. (2) concluded that the Leukotest provided the best predictor for *Clostridium difficile* is very misleading. On the basis of data published by Manabe et al., I calculated the sensitivity and specificity of the Leukotest to be 60.5 and 69.3%, respectively, with a positive and negative predictive value of 27.4 and 90.2%, respectively. Although in the logistic regression model Leukotest results may have been more predictive than those of other tests, the performance characteristics of the test are far from those of an acceptable screening or diagnostic procedure.

I agree with the authors that developing a cost-effective strategy for use with stool microbiology is extremely important in these days of cost containment. According to a recent College of American Pathology Q-Probe survey, however, few laboratories have any criteria for the number of samples submitted or limit routine cultures to outpatients or patients hospitalized for less than 3 days (5), guidelines that we first proposed several years ago (4). Putting such guidelines in place will have a significant impact of the cost-effectiveness of stool microbiology practices and markedly increase the yield of enteric pathogens.

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Authors' Reply

We greatly appreciate the important points raised by Dr. Nachamkin, which enable us to clarify a couple of points and to concur in the need for further clinical studies as well as multiple approaches toward the optimal utilization of the clinical microbiology laboratory.

First, we agree that fecal leukocyte tests are relatively insensitive and as with any test should be overridden by clinical concerns. Indeed, we are among those who have raised and documented the viability of concerns that many tests using fecal specimens (especially swab or diaper specimens) are relatively insensitive for fecal leukocytes, which are otherwise usually found when fecal specimens are promptly examined by an expert microscopist in culture-documented shigellosis (3). Reported evidence to date from several different laboratories indeed suggests that tests for fecal lactoferrin (lactoferrin latex agglutination [LFLA]) are, however, considerably more sensitive for inflammatory diarrhea caused by pathogens recognized to be invasive or inflammatory (i.e., *Shigella* and *Salmonella* spp., *Campylobacter jejuni*, and toxigenic *C. difficile*) (1, 5, 8, 7) (Table 1).

In addition, an analysis of the summary receiver operating characteristic (SROC) curves constructed from 25 published studies by Huicho et al. further shows that fecal leukocyte tests showed the lowest level of performance (as assessed by area under the curve) and those with occult blood intermediate and fecal lactoferrin were best at predicting inflammatory diarrhea as defined as stool culture being positive for *Salmonella*, *Shigella*, or *Campylobacter* spp., enteroinvasive *Escherichia coli*, enteropathogenic *E. coli*, or cytotoxigenic *C. difficile* (2).

Regarding Dr. Nachamkin's second concern about whether patients with inflammatory diarrhea with *Campylobacter*, *Salmonella*, or *Shigella* spp. may benefit more from antimicrobial therapy than those without fecal lactoferrin or leukocytes, we fully agree that, while this is a reasonable hypothesis, it certainly warrants further testing in a carefully done prospective study.

Regarding the performance of the Leukotest as the "best predictor of *C. difficile* toxin positivity" in the Johns Hopkins Hospital study reported by Manabe et al. (4), we would agree that a negative Leukotest should be overridden by clinical concerns, as we stated in our paper and above. It does, however, offer a simple, inexpensive, prompt initial assessment of the degree of intestinal inflammation present.

We concur with Dr. Nachamkin's additional suggestions to

TABLE 1. Comparison of LFLA and fWBC with invasive diarrhea

Patient population (reference)	% Positive	
	LFLA	WBC
Travelers with *Salmonella* or *Shigella* spp. or *C. jejuni* (5)	94	69
Patients positive for *C. difficile* toxin at MGH[a] (8)	75	40
Patients showing correlation with invasive pathogens or *C. difficile* toxin (Utah) (1)	45	21
U.S. troops with *Shigella* spp. in Restore Hope, Somalia (7)	88[b]	63

[a] MGH, Massachusetts General Hospital, Boston, Mass.
[b] Also 33% of 21 specimens positive by LFLA and negative by culture were PCR positive for *Shigella* spp.

limit excessive and unnecessary cultures when the yield is low. In this era of cost containment, all potential means to improve our use of laboratory tests should be considered to improve cost-effective care of our patients. However, this must be done in full consideration of patient history, epidemiologic setting, and special considerations such as those we have attempted to include in our algorithm. Our goals are to try to improve our assessment of inflammatory enteritis, and the findings with fecal lactoferrin now in several laboratories suggest that it may help in the diagnostic assessment of inflammatory diarrhea. Clearly its use in any treatment algorithm requires documentation from further study.

Finally, as we were preparing this letter, the paper by Silletti et al. (6) was published. This paper reports that the negative predictive value of the Leukotest is 99.4% when it is used to screen 416 stool specimens for those from which enteric pathogens would likely be recovered when cultured. They further report that neither fecal leukocytes nor fecal occult blood was reliable for screening and that pathogen culture or *C. difficile* toxin testing was useful when the Leukotest was positive, at or less than or at greater than 3 days' hospitalization, respectively. Thus Silletti et al. nicely demonstrate the potential value of combining the points raised by Dr. Nachamkin and by us.

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