Markers of Intestinal Inflammation for the Diagnosis of Infectious Gastroenteritis

Mark D. Gonzalez, PhD[a,1], Craig B. Wilen, MD, PhD[b,1], Carey-Ann D. Burnham, PhD[b,*]

KEYWORDS

• Biomarker • C-reactive protein • Erythrocyte sedimentation reaction • IL-6 • IL-8 • IFN-γ • TNF-α • Fecal leukocyte

KEY POINTS

- It can be difficult to differentiate infectious versus noninfectious causes of diarrhea using clinical information.
- One approach to include or exclude an infectious cause of diarrhea is to measure a serum or fecal biomarker that is designed to detect the host's response to infection.
- An ideal biomarker would be inexpensive, rapid, and easy to perform, with high sensitivity and specificity.
- Systemic biomarkers, such as C-reactive protein, erythrocyte sedimentation rate, and serum cytokines, cannot be reliably used to include or exclude an infectious cause of diarrhea.
- Fecal biomarkers, such as fecal lactoferrin, fecal calprotectin, and fecal occult blood, cannot be reliably used to include or exclude an infectious cause of diarrhea.
- At this time, biomarker analysis cannot supplant diagnostic methods that specifically detect pathogens associated with infectious gastroenteritis, such as culture, nucleic acid detection, or antigen detection methods.

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[a] Division of Laboratory and Genomic Medicine, Department of Pathology and Immunology, Washington University School of Medicine, Washington University in St. Louis, 660 South Euclid Avenue, St Louis, MO 63110, USA; [b] Department of Pathology and Immunology, Washington University School of Medicine, Washington University in St. Louis, 660 South Euclid Avenue, St. Louis, MO 63110, USA

[1] These authors contributed equally to this work.

* Corresponding author. Washington University School of Medicine, Washington University in St. Louis, 660 South Euclid Avenue, Campus Box 8118, St. Louis, MO 63110.

E-mail address: cburnham@path.wustl.edu

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INTRODUCTION

Infectious diarrhea is a major cause of morbidity; globally, gastrointestinal infections result in an estimated 2200 pediatric deaths each day, predominantly in the developing world.[1] In the United States, it is estimated that there are 178.8 million gastrointestinal infections per year, resulting in at least 474,000 hospitalizations and more than 5000 deaths annually.[2] Numerous types of microorganisms can cause gastrointestinal infections, including parasites, viruses, and bacteria. These organisms can be acquired through contaminated food and/or water sources and person-person or environmental transmission or may cause disease as a consequence of dysbiosis secondary to antibiotic therapy.

The identification of an etiologic agent causing infectious gastroenteritis can be labor intensive and expensive, and many commonly used methodologies have suboptimal analytical sensitivity. Traditionally, bacterial pathogens have been routinely identified using culture-based techniques, nucleic acid detection, or antigen detection. Viral pathogens are typically identified by nucleic acid detection or antigen detection methods, while parasites are identified by antigen detection methods combined with microscopic examination and special staining methods. Although some of these testing methods can be completed within a few hours, others require days, can be costly, and can require considerable laboratory resources and expertise. Newer US Food and Drug Administration–approved multiplexed nucleic acid detection assays are now available and allow for the simultaneous identification of a panel of bacterial, viral, and parasitic pathogens.[3–7]

The most appropriate course of therapy for a patient with diarrhea can be a significant clinical conundrum. Numerous noninfectious diseases, such as inflammatory bowel disease (IBD; eg, ulcerative colitis and Crohn disease), gastrointestinal malignancy, irritable bowel syndrome (IBS), and food allergies/intolerances, may present very similarly to infectious gastroenteritis. A biomarker that could rapidly differentiate between infectious and noninfectious causes of gastroenteritis with a very high negative predictive value for infection would be clinically useful in the triage of these patients. In addition, the ideal biomarker could rapidly differentiate between bacterial, viral, and parasitic causes. Based on these results, and before the identification of the etiologic agent, clinicians could identify which patients might require hospitalization, order the appropriate testing for pathogen identification, initiate the optimal therapy or supportive measures, and/or invoke appropriate infection prevention precautions. Such biomarkers would facilitate appropriate testing of patients with active infections (and thereby reduce potential false positives due to asymptomatic colonization), would reduce hospital costs by eliminating unnecessary testing, and could prevent patient morbidity and mortality related to more invasive procedures.

This article summarizes the data regarding the analytical performance characteristics of many of the common biomarkers that have been examined for the identification of gastrointestinal infections. An overview of the methods discussed can be found in **Table 1**.

SYSTEMIC MARKERS

C-Reactive Protein

C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) were 2 of the first markers of systemic inflammation to be described. Although both inflammatory markers are widely available, easy to perform, and well-described, they lack specificity, limiting their use as markers for infectious gastroenteritis.