Are the permanent sequelae of Crohn’s disease a failure to treat the gastrointestinal microbiota?

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ABSTRACT

Using parallel knowledge derived from gynecological infections, the thesis is advanced that late sequelae in Crohn’s disease are the consequence of the failure to treat or the undertreating of the co-functioning infection by the gastrointestinal microbiota.

Advances in medicine often demand that they deviate from the established evidence-based standard of care. Evidence-based data is largely the product of double-blind, placebo controlled studies. Funding of studies evidence-based comparative studies that are large enough to achieve statistical significance is rarely funded by the federal agencies. The primary reliance on evidence-based data to allow medicine to advance has come at the cost of undermining deductive thinking and clinical observations derived from smaller scale experimental designs or observations in nature.

Crohn’s disease is a chronic infection of the gastrointestinal tract that continues its global epidemic expansion. The longer an individual is afflicted with Crohn’s disease, the greater is the probability that the ensuing clinical course of disease will be complicated by the development of small bowel strictures, loop-to-loop fistulae, and perianal fistulae.

The current standard of care is framed around the invalidated paradigm of autoimmunity. The demonstration that disruption of the individual’s pro-inflammatory immune response had the potential to arrest the signs and symptoms of disease became the foundation for an unsustainable conjecture that autoimmunity was the cause of Crohn’s disease [1–3]. For almost two decades, therapy for Crohn’s disease has been framed by comparative studies of steroids and biologics. Very few industry-funded comparative studies cited among the 2018 The American College of Gastroenterology Clinical Guideline’s 375 references incorporated any form of concomitant antibiotic therapy. In its segment on Future Directives, the American College of Gastroenterology apparently defends the status quo by stating that advances in therapy will reside in “expanding the discipline’s treatment war chest and uncover effective biologics with different mechanisms of action” [4].

The ability of steroids, immunomodulatory, or biologics to, more often not, arrest symptomology without concomitant antibiotic administration undermined established knowledge as to what happens when mucosal integrity is lost and a polymicrobial flora gains sustained access to the underlying tissue layers. By necessity, eighty percent of host immunity resides within the gastrointestinal tract. A reasonable bacterial challenge within well vascularized tissues can be eradicated by local and systemic host immunity, but at a price. Key to achieving this objective is re-establishment of mucosal integrity. Once anaerobic infection becomes well established within poorly vascularized tissues, bowel penetration will more likely than not, occur. Inflammatory adherence to adjacent bowel creates the conduit for loop-to-loop fistulae. Not properly interpreting the significance of concomitant infection resulted in the under treatment or, more frequently than not, the non-treatment with antibiotics. Even before the prevailing pathogenesis of Crohn’s disease became delineated [5], deductive reasoning based upon established knowledge of comparable infectious disease entities should have identified the very real probability that the permanent sequelae of Crohn’s disease, strictures, loop-to-loop fistula, fistula, abscess formation, and bowel penetration were the consequences of infection and not a dysfunctional immune-mediated process [5,6].

The pathogenesis of gonococcal infections and understanding of the anaerobic progression constituted a didactic base for the understanding of the process by which permanent alterations of anatomical structure are achieved in individuals afflicted by Crohn’s disease [7–14]. By virtue of healing by fibrosis, untreated gonococcal infection in males produces urethral strictures by superinfecting Enterobacteriaceae. The Enterobacteriaceae function as facultative anaerobes and do not persist when the microbiological environment is more conducive for obligatory anaerobic bacteria. In women, the same pathogen, Neisseria gonorrhoeae, initiates changes in the local microbiological environment that allows constituents of the vaginal bacterial flora to assume a role in what is termed the anaerobic progression. Healing by fibrosis can result in secondary infertility and ectopic pregnancies. Once the more obligatory anaerobic bacteria gain dominance within the anaerobic progression, intraluminal and extra-mural tubo-ovarian abscesses are created. A ruptured tubo-ovarian abscess, loop-to-loop fistula, perianal fistula, and bowel perforation are the hallmark of transmural penetration by obligatory anaerobic bacteria. Understanding the transference of pathogenicity between bacteria within the anaerobic progression, the Centers for Disease Control and Prevention (CDC) radically transformed its recommendations with respect to antibiotic selection for women with pelvic inflammatory disease [15]. The decision by the CDC to recommend specific antibiotic regimens that spanned a defined bacterial spectrum for gonococcal disease in women, but not in men, was based upon deductive reasoning and the evidence derived from relatively forward diseased studies of the respective diseases.
Given the importance of the gastrointestinal microbiota to health and disease, the natural presumption is that the subspecialty of gastroenterology would be at the forefront of knowledge concerning the infectious disease processes that directly impact on their area of clinical practice. Historically, that has not been the case. For decades “peptic ulcer disease” was one of the pillars of a gastroenterologist’s clinical practice until peptic ulcer disease was proven to be an infectious disease curable by antibiotic therapy.

Based upon deductive reasoning and established knowledge of comparable infectious diseases, the postulate is advanced that the late sequelae, strictures, loop-to-loop fistulae, perianal fistulae and bowel perforation, are causally related to physician failure to early incorporate comprehensive antibiotic coverage into the prevailing therapeutic regimen.

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Conflict of interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.mehy.2018.11.008.

References


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