A clinical trial and another clinical practice bites the dust, or should there not be an appendix?

There are clinical directives that I recall reiterated in multiple settings from medical school onwards. On medical school pediatric rotations, general surgery rotations, and during my time in the emergency ward as a resident and attending physician, the patient with potential acute appendicitis was evaluated by a surgeon and, without an alternative explanation for the symptoms and physical examination findings, the patient was admitted to the surgical service with the expectation of going to the operating room (OR). The dictum was that some patients without appendicitis need to go to the OR to avoid "missing" the opportunity to appropriately surgically treat every patient with acute appendicitis. Perhaps from naivete, it never really struck me to question the general underpinnings of this practice. Yet over the past 2 decades, several studies have assessed an alternative approach to acute appendicitis: treatment with systemic antibiotics and observation.

In this issue of the *Journal*, DeRoss and Fathalizadeh¹ offer a commentary with their perspective on the clinical practice implications of the Comparison of Outcomes of Antibiotic Drugs and Appendectomy (CODA) trial,² which demonstrated short-term noninferiority of antibiotic therapy vs surgical therapy for patients diagnosed with acute appendicitis.

Several challenges confront the prospective evaluation of surgical and other physical interventions. There can be significant placebo and "nocebo" effects that can only be teased out with the use of sham procedural interventions, and sometimes only incompletely. These are particularly troublesome when using subjective outcome measures like pain. For instance, there may be a 40% to 50% pain-relief response to intra-articular saline (placebo) injection into the knees of patients with osteoarthritis. This makes it extremely difficult to ascribe great benefit to the intra-articular injection of hyaluronate or corticosteroid when compared with the saline control. But in patients with acute appendicitis, unless there is a marked nocebo response associated with surgery that could muddle the interpretation, this seems not to be an issue with analysis of data from the current study.

Another challenge interpreting surgical studies like CODA is the difficulty of selecting for analysis small subsets of patients who may behave differently from the study mean and derive benefit from early surgical intervention—and detriment from an alternative approach. There have been several randomized clinical trial (RCT) evaluations of (previously) well-accepted, frequently performed surgical procedures over the past few years. These have included arthroscopic intervention for degenerative knee arthritis with or without a "torn" meniscus,³ vertebroplasty for painful vertebral fractures,⁴ and surgical decompression with or without fusion in patients with degenerative lumbar spondylolisthesis.⁵ A common reaction from surgeons to the results of these trials, which indicated little if any benefit of the studied procedures, was that patient selection and the clinical acumen and skill of the surgeon truly make a difference. Hence, it is argued that the procedures can still be of benefit in appropriately selected patients. It is tempting to dismiss this as professional hubris, but there is undoubtedly some truth in their critique of the trials.

As internists, we can espouse that we practice based on trial data and evidence-based guidelines, but population practice metrics do not bear this out. And we frequently hark to the limitations of guidelines and RCTs when it comes to individual patient treatment decisions, citing the limited external validity of the clinical trial data when applied to the very specific patient in front of us.

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There is no reason to believe that the same premise would not apply for surgical interventions. And I would offer that surgeons in particular "have a lot of skin in the game" when taking a patient to the OR—ie, they are uniquely and individually associated with the surgical outcome. Their assessment requires more than cursory assessment of imaging, physical examination, and clinical history. Recognition of this supports the argument for publicizing outcome data for individual surgeons.

The CODA trial was reasonably sized and, unlike several earlier studies, was broadly inclusive of a diverse patient population, respresentative of general practice. Nonetheless, it was not powered to perform discrete subset analysis. The short-term (30-day) results indicating noninferiority of antibiotics vs surgery jibe with older observations and suggest that the fear of imminent appendix perforation, sepsis, and possibly death for the "missed" case of acute appendicitis may have been overblown.

DeRoss and Fathalizadeh discuss details of the CODA trial and the impact they feel it should have on practice. To me, a striking part of the study—an appendix, if you will—is presented in the long-term CODA follow-up,⁶ which showed that more patients in the antibiotic-treatment group subsequently visited the emergency room, and nearly 50% of patients in this group ultimately underwent appendectomy, 30% within 90 days.

I wonder if there will ultimately be a way—other than a particularly skilled surgeon's hand and clinical gestalt—that those 50% could be recognized early on.

But again, trial data cannot yet completely replace clinical judgment.

Bran Marcher

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