EDITORIAL

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Treating Appendicitis Without Surgery

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In 1886, Fitz[1] assembled a large amount of autopsy data and reviewed the literature trying to understand what caused typhlitis and pelvic infections, disorders that were highly lethal at the time. He noted a range of pathologies, including mucosal inflammation, transmural inflammation, gangrene, and perforation of the appendix. Piecing it all together, Fitz concluded that appendicitis progressed from mild, mucosal disease to a transmural process that then caused the appendix to become gangrenous. Eventually, the appendix would perforate resulting in pelvic abscesses. Shortly after Fitz published his observations, appendectomy was shown to prevent pelvic abscess.[2] The assumed progression of appendicitis from mild disease to perforation with appendectomy as the only means for preventing serious infection became established in medical thought and continues to guide appendicitis management.

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Lost in history was Fitz's observation that one-third of autopsy examinations showed evidence of spontaneous resolution of previous episodes of appendicitis,[1] a fact Fitz used to support his contention that the appendix was responsible for typhlitis. Also lost in history was a report by Coldrey[3] of a large series of patients treated with antibiotics and not surgery in the 1950s. So powerful is the perceived evidence of the benefits of appendectomy for appendicitis that surgical treatment for appendicitis remains unquestioned with seemingly little interest in studying the problem.

However, appendicitis management has changed even if appendectomy remains the end result. Computed tomographic (CT) imaging establishes the diagnosis with almost perfect diagnostic accuracy. New antibiotics providing broad-spectrum coverage for organisms that cause serious complications associated with appendicitis are changing the disease's natural history. Indeed, several trials have suggested that many cases of appendicitis can be treated without surgery.

In this issue of *JAMA*, Salminen et al[4] report the results of the Appendicitis Acuta (APPAC) trial, a randomized clinical trial examining the effect of antibiotics for treating CT-confirmed uncomplicated appendicitis instead of surgery. The trial overcame limitations of prior studies by enrolling a large number of patients (n = 530), confirmed the diagnosis of uncomplicated appendicitis by CT in all enrolled patients, and excluded patients whose CT scans showed appendicoliths, perforation, or abscess, findings that the majority of experts believe require surgery. Ertapenem was used as the antibiotic to ensure that most of the bacteria associated with appendicitis-related infection were adequately covered.

In the APPAC trial, among 273 patients in the surgical group, 272 patients underwent successful appendectomy (ie, a success rate of 99.6% [95% CI, 98.0% to 100.0%]). Among 256 patients in the antibiotic group available for 1-year follow-up, 70 patients (27.3%; 95% CI, 22.0% to 33.2%) underwent surgical intervention within 1 year of initial presentation for appendicitis, and 186 of 256 patients (72.7%; 95% CI, 66.8% to 78.0%) available for follow-up did not require surgery. In the intention-to-treat analysis, the between group difference in success rates was −27.0% (95% CI, −31.6% to ∞; P = .89), which failed to meet criteria for noninferiority based on the prespecified margin of 24%. Although technically a negative trial because the noninferiority boundary for antibiotic treatment was not met relative to surgery, many aspects of the trial justify new approaches for treating appendicitis.

The majority (73%) of the 257 patients initially treated with antibiotics did not require surgery during the 1-year follow-up period. Of those who did undergo surgery, none had major complications attributable to receiving antibiotics before surgery—dispelling the notion that appendectomy is necessarily an emergency. These findings suggest that for CT-diagnosed uncomplicated appendicitis, an initial trial of antibiotics is reasonable followed by elective appendectomy for patients who do not improve with antibiotics or present with recurrent appendicitis.

As with any study, it is important to understand the patients for whom these findings do not apply. Patients with complicated appendicitis, children, and pregnant women were excluded from this study so the results do not apply to these groups. Because appendicoliths are associated with treatment failure when appendicitis is managed with antibiotics,[5] Salminen et al[4] excluded patients whose CT scans showed an appendicolith to be present. Thus, the report by Salminen et al[4] does provide good evidence that antibiotics may be a reasonable alternative to appendectomy for patients with acute, CT-verified uncomplicated appendicitis.

The study by Salminen et al has several limitations and more research is needed. When future trials are designed of surgery compared with antibiotic treatment of appendicitis, careful consideration of the study design and definition of what represents a clinically important difference needs to be carefully considered. Salminen et al designed their trial as a noninferiority study. Because appendectomy is the commonly accepted treatment for appendicitis, the investigators needed to show that an alternative treatment not involving surgery would not be worse than the currently accepted treatments by some margin. This margin, the minimal clinically important difference,

was established somewhat arbitrarily by Salminen et al because little clinical information was available to provide a better estimate for it.

Future studies should be carefully designed with a strong justification for the minimal clinically important difference. Antibiotics with broad enough coverage to treat appendicitis may cause the development of resistant organisms or *Clostridium difficile* infections. Given the balance between potential complications of antibiotic treatment or appendectomy for appendicitis, is 10% of patients with appendicitis not experiencing successful treatment with antibiotics clinically important? 30%? 50%? Investigators will need to determine and fully justify how much worse than appendectomy antibiotic treatment of appendicitis must be before the notion of replacing appendectomy with antibiotic treatment is rejected.

Because appendectomy is performed to prevent major pelvic infection, the strongest design would be one showing that antibiotics could prevent pelvic abscesses as effectively as surgery. However, because pelvic abscess is infrequent, a trial using this outcome would need to enroll a very large number of patients.

The time has come to consider abandoning routine appendectomy for patients with uncomplicated appendicitis. The operation served patients well for more than 100 years. With development of more precise diagnostic capabilities like CT and effective broad-spectrum antibiotics, appendectomy may be unnecessary for uncomplicated appendicitis, which now occurs in the majority of acute appendicitis cases.

ARTICLE INFORMATION

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Development Assistance for Health
Potential Contribution to the Post-2015 Agenda

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Despite economic growth in low-income countries, the internal resources available to some governments will be inadequate to support the delivery of health care to their populations for years to come.[1] Approximately 150 million people worldwide experience catastrophic expenditure annually to cover out-of-pocket payments for health.[1] Despite substantial progress, 6.6 million children who were younger than 5 years died in 2012 and a quarter of all children younger than 5 years were stunted (having an inadequate height or length for age).[2] Almost 300 000 women died in 2013 of causes related to pregnancy and childbirth.[2] Against this background, the study by Dieleman and colleagues[3] in this issue of *JAMA* makes a substantial contribution to the current understanding of the flow of development assistance for health (DAH) and how these resources can contribute to the achievement of international health goals.

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The authors made helpful distinctions between the primary sources of funding, the channels through which funding flows and the implementing institutions, as well as distinguishing between "commitments," which may not be implemented, and actual disbursements that reflect the real transfer of resources. Their report clearly demonstrated how, following a substantial increase in yearly funding between 2000-2010 from approximately $7 billion to $35 billion, DAH has essentially plateaued since 2010 as a result of constraints in government spending in many donor countries. The authors also documented changes in funding between health priorities (such as increased support of newborn and child health in recent years) and showed the importance of US government funding (especially for human immunodeficiency virus [HIV]/AIDS). Private sources and the UK government constitute the second and third most important sources of DAH as a whole. The importance of funding from the Bill and Melinda Gates Foundation is highlighted by the estimate that, since 1999, when it began providing DAH, the Gates Foundation has provided 5.6% of the total DAH.

The study is particularly timely because the United Nations' (UN's) millennium development goals (MDGs), which have shaped the international development agenda over the past 15 years, are due to be achieved this year. Progress by countries and across different goals has been highly variable.[2] The post-2015 development agenda is currently the subject of intergovernmental negotiations and the UN's sustainable development goals (SDGs) to be adopted at the forthcoming