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follow-up (mean [SD] change from baseline, 1.8 [0.8]; from 1 year, -0.003 [0.6]). Adjusted mean between-group difference in change from baseline was -0.03 (95% CI, -0.25 to 0.19;  $P = .79$ ) and from 1 year was -0.03 (95% CI, -0.23 to 0.17;  $P = .76$ ). No between-group differences were found in the secondary outcomes (Table 2).

**Discussion** | To our knowledge, this is the first randomized trial to evaluate long-term outcomes of CTS surgery. After a mean follow-up of 12.8 years after CTS surgery, there were no significant differences between open and endoscopic carpal tunnel release. The large symptom and functional improvements and high level of patient satisfaction achieved with surgery were durable and few patients had undergone further surgery.

Study limitations include a single institution in Sweden and unknown generalizability. Our long-term follow-up was limited to patient-reported outcomes, which are central in CTS and were consistent across several measures with established reliability and validity. The results should help clinicians and patients in making treatment decisions.

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**Author Contributions:** Dr Atroshi had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

**Study concept and design:** Atroshi.

**Acquisition, analysis, or interpretation of data:** All authors.

**Drafting of the manuscript:** Atroshi.

**Critical revision of the manuscript for important intellectual content:** All authors.

**Statistical analysis:** Atroshi, Ranstam.

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**Administrative, technical, or material support:** Atroshi, Hofer, Larsson.

**Study supervision:** Atroshi.

**Conflict of Interest Disclosures:** The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.

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**Role of the Funder/Sponsor:** Region Skåne had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

**Trial Registration:** clinicaltrials.gov Identifier: NCT01887145

**Additional Information:** The trial protocol is available upon request from the authors.

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## COMMENT & RESPONSE

### Treatment of Uncomplicated Acute Appendicitis

**To the Editor** The use of a noninferiority design in the Appendicitis Acuta (APPAC) trial allowed for the assessment of primary outcomes specific to each treatment.<sup>1</sup> However, we believe that the chosen outcomes were not equally patient-centric, leading to the erroneous conclusion that antibiotics did not meet the prespecified criterion for noninferiority compared with appendectomy.<sup>1</sup>

The primary end point in the antibiotic-treated group of “discharge from the hospital without the need for surgery and no recurrent appendicitis during a 1-year follow-up period” was patient-centric and answers the patient’s question: “If I choose to be treated with antibiotics, what is the chance that I will eventually need an appendectomy?” However, the primary end point for the surgical group of “successful completion of an appendectomy” is irrelevant to patients who rightfully assume that an appendectomy will successfully remove the appendix.<sup>1</sup> Patients undergoing an appendectomy are typically concerned with the risk of postoperative complications and the extent of postoperative disability.

Therefore, a more patient-centric end point would have been development of a postoperative complication, which answers the patient’s question: “If I choose to be treated with an appendectomy, what is the chance I will have a complication from surgery?” When applying this outcome, antibiotics were within the predetermined noninferiority margin (24%) because there was a 20% complication rate in the appendectomy group and a 27% failure rate in the antibiotic group. In addition, consistent with previous randomized clinical trials, the APPAC trial confirmed the safety of nonoperative management by demonstrating no difference in rates of complicated or perforated appendicitis between the 2 groups.<sup>2</sup>

Applying the results of the APPAC trial in the United States will be difficult because the surgical group underwent open appendectomies and the antibiotic group received 3 days of intravenous antibiotics. The standard of care in the United States for patients with uncomplicated appendicitis is to undergo a laparoscopic appendectomy with either same-day discharge or discharge on the first postoperative day. Early results from a US study in children demonstrated the feasibility of nonoperative management of uncomplicated appendicitis using 24 hours of intravenous antibiotics with improved quality of life and fewer disability days compared with laparoscopic appendectomy.<sup>3</sup>

Results from trials of nonoperative management suggest that 3 of 4 patients with uncomplicated appendicitis treated with antibiotics can avoid surgery.<sup>1,2</sup> Because patient preferences will differ based on which outcomes are most important to them, future studies investigating nonoperative management should incorporate relevant patient-centric outcomes, such as disability, quality of life, and costs associated with health care, to better inform decision making.

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**Conflict of Interest Disclosures:** The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.

1. Salminen P, Paajanen H, Rautio T, et al. Antibiotic therapy vs appendectomy for treatment of uncomplicated acute appendicitis: the APPAC randomized clinical trial. *JAMA*. 2015;313(23):2340-2348.
2. Varadhan KK, Neal KR, Lobo DN. Safety and efficacy of antibiotics compared with appendectomy for treatment of uncomplicated acute appendicitis: meta-analysis of randomised controlled trials. *BMJ*. 2012;344:e2156.
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**To the Editor** The APPAC trial<sup>1</sup> successfully recruited and randomized a large number of patients with uncomplicated appendicitis into surgical or antibiotic treatment groups. Even though the results support antibiotic treatment as a viable alternative to surgery for uncomplicated appendicitis, such a change in practice needs to be viewed in the context of the global increase in antimicrobial resistance.<sup>2</sup>

Can the authors provide any information on the ecology of antimicrobial susceptibility within the study population, such as from microbiological analysis of infected appendices removed in the surgical group of the study? Were ertapenem and levofloxacin chosen with this in mind, or would antibiotics with narrower spectrums have been an alternative? "Last-line" broad-spectrum carbapenem antibiotics are often reserved for the most vulnerable patients, such as those with neutropenic sepsis, and the increase in carbapenem resistance<sup>2</sup> puts an onus on clinicians to minimize selective pressure for resistance to emerge by limiting their use to patients with the greatest need.<sup>3</sup>

The duration of antibiotic therapy in the APPAC trial (median of 10 days) is also relatively long. The Study to Optimize Peritoneal Infection Therapy<sup>4</sup> demonstrated that, following effective source control, a short course of antibiotics (median of 4 days) was adequate. In our opinion, source control remains a key component of both individual patient care and broader antimicrobial stewardship.

The majority of appendectomies in the APPAC trial were open procedures with only 5.5% being performed laparoscopically. Increased use of laparoscopic appendectomies

may concurrently reduce complication rates and restrict antibiotic use.<sup>5</sup> Antimicrobials are a powerful but precious resource, and stewardship of their use needs to be considered on a wider scale and remains a cornerstone of the global battle against antimicrobial resistance.

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**Conflict of Interest Disclosures:** The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.

1. Salminen P, Paajanen H, Rautio T, et al. Antibiotic therapy vs appendectomy for treatment of uncomplicated acute appendicitis: the APPAC randomized clinical trial. *JAMA*. 2015;313(23):2340-2348.
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**To the Editor** We believe the results of the APPAC trial<sup>1</sup> should be interpreted and used with caution despite it being a randomized trial. First, there is concern over the increasing global problem of antibiotic resistance<sup>2</sup>; triple therapy, including broad-spectrum carbapenem antibiotics, such as ertapenem, for appendicitis seems like overtreatment. Use of carbapenem antibiotics (once reserved for patients in the intensive care unit setting against multiresistant gram-negative bacteria) have produced resistant *Enterobacteriaceae*.

Second, the use of low-dose computed tomographic (CT) scanning for the diagnosis of uncomplicated appendicitis is still radiation to the patient that can be avoided. In the United Kingdom, routine imaging to diagnose appendicitis is not advocated. The use of CT scanning is limited to diagnostic dilemmas, atypical histories, or patients in an age group in which colonic malignancy needs to be excluded.

Third, most middle- and high-income countries perform laparoscopic appendectomies rather than open ones. Faiz et al<sup>3</sup> reported in a UK study that the 1-year mortality rates were higher with open appendectomies compared with laparoscopic appendectomies (0.64% vs 0.29%, respectively;  $P < .001$ ) over a 10-year period. Therefore, using open appendectomy as the surgical standard is flawed. The authors stated that the open approach was chosen for global generalization of the study, but such generalization is not possible because low-income countries would not be able to afford the costly antibiotic regime, hospital admission, and loss of earnings.

Fourth, the cost of the conservative method (summing up the antibiotics, CT scanning, hospital stay, and follow-up based on the UK National Health Service) would be approximately \$2300, given the national average bed cost of \$470,<sup>4</sup> without including the potential cost of patients requiring surgery within 1 year. The cost of care in the United Kingdom for a laparoscopic appendectomy is approximately \$3100 with a stay of less than 2 days.<sup>4,5</sup> Therefore, treating uncomplicated appendicitis with antibiotics may not be cost-effective and should be selective based on risks and patient choice.

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**Conflict of Interest Disclosures:** The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.

1. Salminen P, Paajanen H, Rautio T, et al. Antibiotic therapy vs appendectomy for treatment of uncomplicated acute appendicitis: the APPAC randomized clinical trial. *JAMA*. 2015;313(23):2340-2348.
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**In Reply** The APPAC trial tested the hypothesis that uncomplicated acute appendicitis can be successfully treated with antibiotics by comparing antibiotic therapy with emergency open appendectomy. There is an intrinsic difficulty in defining a common primary outcome for these dissimilar treatments. Although Drs Minneci and Deans advocate for more patient-centric outcomes, we aimed to identify a clear and concise definition of efficacy (ie, resolution of acute appendicitis) that would apply to both treatments.

Open or laparoscopic appendectomy cures appendicitis. To enable a fair comparison, we aimed to standardize both treatment procedures for efficacy as much as possible. To succeed, the antibiotic must provide broad-spectrum coverage for all the pathogens that might cause appendicitis. The most common organism in acute appendicitis is *Escherichia coli*, and the selection of antibiotics should cover both aerobic and anaerobic bacteria. The selection of antibiotics presented a limitation in the trial by Vons et al<sup>1</sup> because amoxicillin-clavulanic acid was used to treat appendicitis despite its limited coverage for *E coli*.

To answer Drs Pollara and Marks and Dr Alfa-Wali and colleagues, we used ertapenem in our study because it effec-

tively treats serious intra-abdominal infections, provides broad-spectrum coverage, and only requires a single, daily dose.<sup>2</sup> The total duration of the antibiotic therapy in our trial was 10 days, including 3-day intravenous ertapenem, resulting in a longer hospital stay in the antibiotic group. This was predefined in the protocol for monitoring of the antibiotic group to ensure patient safety in the trial.

However, shortening the hospital stay may be feasible with the use of narrower-spectrum antibiotics and a shorter duration of antibiotic therapy. The majority (73%) of patients with uncomplicated acute appendicitis were successfully treated with antibiotics and none of the patients treated initially with antibiotics and later with appendectomy had major complications.

We agree that future studies of antibiotic treatment for appendicitis should seek efficacy while using antibiotics with a more-restricted antibacterial spectrum and shorter treatment duration, which will also affect the health economics. We are performing a cost analysis of the APPAC trial, but the final cost-effectiveness comparison between antibiotic therapy and appendectomy needs to incorporate both optimized antibiotic treatment and optimized surgery (ie, laparoscopic appendectomy) as noted in all the letters.

Alfa-Wali and colleagues are also concerned about the use of CT for diagnosis. The diagnostic accuracy of CT imaging for acute appendicitis is almost perfect. Use of CT reduces the negative appendectomy rate, improving patient care by avoiding unnecessary surgery, and resulting in more efficient use of hospital resources.<sup>3</sup> In the Netherlands, a guideline for imaging for suspected appendicitis was implemented in 2010, resulting in both a reduced negative appendectomy rate (23% vs 6%) and a decrease in average cost per patient by \$650.<sup>4</sup> Concerns regarding radiation exposure may be minimized by use of low-dose CT.<sup>5</sup>

The optimal use of antibiotic therapy regarding both spectrum and duration of the treatment in patients with uncomplicated acute appendicitis needs to be prospectively evaluated in a large patient series including assessment of relevant patient-centric outcomes. Spontaneous resolution of appendicitis presents a possible bias for antibiotic treatment for acute appendicitis and a double-blind, placebo-controlled randomized clinical trial is needed to differentiate these effects.

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**Conflict of Interest Disclosures:** The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Salminen reported receiving personal fees for lectures from Merck and Roche. No other disclosures were reported.

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### Failure to Report Financial Disclosure Information

**To the Editor** This is in reference to my Viewpoint article in *JAMA*<sup>1</sup> and my letter in response to Drs Lee and Macdonald.<sup>2</sup> Due to my misinterpretation of the requirements for reporting of potential conflicts of interest, I neglected to cite the following disclosures.

I have received research funding from Amarin Pharmaceuticals, consulting fees from Amgen and Sanofi, and speaker's honoraria from Janssen and Merck.

I regret this oversight and have now completed and submitted revised ICMJE forms. Both articles have been corrected online.

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- Ganda OP. Deciphering cholesterol treatment guidelines: a clinician's perspective. *JAMA*. 2015;313(10):1009-1010.
- Lee TC, McDonald EG. Clinician understanding of cholesterol treatment guidelines. *JAMA*. 2015;313(23):2381-2382.

### CORRECTION

**Omitted Financial Disclosures:** In the Viewpoint "Deciphering Cholesterol Treatment Guidelines: A Clinician's Perspective" published in the March 10, 2015, issue of *JAMA*,<sup>1</sup> and in the subsequent reply letter entitled "Clinician Understanding of Cholesterol Treatment Guidelines" published in the June 16, 2015, issue of *JAMA*,<sup>2</sup>

the author neglected to cite conflict of interest disclosures. Dr Ganda reports receiving research funding from Amarin Pharmaceuticals, consulting fees from Amgen and Sanofi, and speaker's honoraria from Janssen and Merck. These articles were corrected online.

- Ganda OP. Deciphering cholesterol treatment guidelines: a clinician's perspective. *JAMA*. 2015;313(10):1009-1010.
- Ganda OP. Clinician understanding of cholesterol treatment guidelines. *JAMA*. 2015;313(23):2381-2382.

**Incorrect Title for Table:** In the Review article entitled "Septic Shock: Advances in Diagnosis and Treatment" published in the August 18, 2015, issue of *JAMA*,<sup>1</sup> the title of a table was incorrectly printed. The title, which read "Table 1. Major Advances in the Diagnosis and Treatment of Traumatic and Septic Shock" should be "Table 1. Major Advances in the Diagnosis and Treatment of Septic Shock." This article was corrected online.

- Seymour CW, Rosengart MR. Septic shock: advances in diagnosis and treatment. *JAMA*. 2015;314(7):708-717.

### Guidelines for Letters

Letters discussing a recent *JAMA* article should be submitted within 4 weeks of the article's publication in print. Letters received after 4 weeks will rarely be considered. Letters should not exceed 400 words of text and 5 references and may have no more than 3 authors. Letters reporting original research should not exceed 600 words of text and 6 references and may have no more than 7 authors. They may include up to 2 tables or figures but online supplementary material is not allowed. All letters should include a word count. Letters must not duplicate other material published or submitted for publication. Letters not meeting these specifications are generally not considered. Letters being considered for publication ordinarily will be sent to the authors of the *JAMA* article, who will be given the opportunity to reply. Letters will be published at the discretion of the editors and are subject to abridgement and editing. Further instructions can be found at <http://jama.com/public/InstructionsForAuthors.aspx>. A signed statement for authorship criteria and responsibility, financial disclosure, copyright transfer, and acknowledgment and the ICMJE Form for Disclosure of Potential Conflicts of Interest are required before publication. Letters should be submitted via the *JAMA* online submission and review system at <http://manuscripts.jama.com>. For technical assistance, please contact [jama-letters@jamanetwork.org](mailto:jama-letters@jamanetwork.org).

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