Nonoperative treatment of appendicitis may have unknown long-term risks and costs

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It is too early to change the standard treatment of appendicitis in U.S. adults to initial antibiotic therapy only, rather than surgical removal of the appendix, or appendectomy, authors of a new systematic review study conclude. Conducted by surgeons and emergency medicine physicians, the review article appears online as an 'article in press' on the *Journal of the American College of Surgeons* website in advance of print publication early next year.

Prompt appendectomy has been the standard treatment of appendicitis for more than 120 years. It is the most frequently performed urgent abdominal operation in the U.S.,[1]where an estimated 300,000 cases of appendicitis are diagnosed each year.[2]

However, in the past 20 years, some research studies from Europe, including one this year,[3] have concluded that some patients with acute uncomplicated appendicitis—meaning the appendix has not ruptured—can cure their appendicitis by taking antibiotics alone. That study found that the one in four patients who later needed removal of their appendix did not have a higher rate of postoperative complications or a greater risk of a ruptured appendix.[3]

"Despite the generally low rate of complications after appendectomy, some U.S. physicians and the public are questioning whether we should change to nonoperative treatment of appendicitis, as many surgeons in Europe already have done," said the study's lead investigator, Anne P. Ehlers, MD, a research fellow in the Department of Surgery at the

University of Washington, Seattle.

"What we found in our review," Dr. Ehlers said, "is that antibiotics-first treatment of appendicitis is probably safe for adults and successful in 3 out of 4 patients. However, there are many unanswered questions about outcomes of antibiotics-first treatment that patients have told us are important to them. These include their quality of life, long term residual symptoms, time to return to work and school and other financial considerations."

Important differences exist between the U.S. and European health care systems and surgical approaches, and the European studies potentially had limitations that might prevent their findings from being applied in general surgical practice, the authors wrote in their article. Therefore, they conducted a systematic review to summarize the best available research studies published on this topic, identify the studies' limitations and the current gaps in knowledge about the new treatment approach, and guide physicians who may want to adopt an antibiotics-first strategy.

Their analysis, according to Dr. Ehlers, is the most up-to-date review of the best available evidence comparing results of antibiotics-first treatment and appendectomy for patients with uncomplicated appendicitis.

The researchers evaluated six randomized controlled clinical trials[4]—widely considered the highest quality of scientific evidence—that compared antibiotics-first with appendectomy for treatment of acute appendicitis.

Results of the clinical trials were published between 1995 and 2015. All six studies were conducted in Europe in adults aged younger than 75, with one study also including children and one study excluding women, the investigators reported. According to their analysis, the number of

patients totaled 1,724.

In all but one of these studies, 24 to 35 percent of the patients randomly assigned to the antibiotics-first group later required appendectomy because the medications did not cure the appendicitis, or due to recurrent disease or symptoms. Most studies reportedly had a follow-up period of one year.

A one-year follow-up, according to Dr. Ehlers, may be too short to detect the rate that appendicitis recurs in patients who kept their appendix. In addition, she said one year after nonoperative treatment is likely not long enough to identify rare outcomes such as cancers of the appendix. This rare cancer, whose cause remains unknown, is likely found in less than 2 percent of all appendectomy specimens analyzed under a microscope, Dr. Ehlers said.

Major differences existed between the European studies' measured outcomes and U.S. standards of care, according to Dr. Ehlers and her collaborators.

Typically, the nonoperative approach involves a 10-day course of antibiotics, initially given intravenously in the hospital and followed at home by oral treatment. Among the six studies combined, the reported average length of hospital stay was approximately three days in both the surgically treated group and the antibiotics-first group.

"Three days in the hospital after a routine appendectomy is far longer than our practice in the United States," said Dr. Ehlers. "Most patients here are discharged within 24 hours."

Another difference in the U.S. is that the most common type of appendectomy is minimally invasive laparoscopy. Most of the European studies included in the review used open appendectomy, which usually

requires a longer hospital stay and recovery and generally has more complications compared with laparoscopic appendectomy. Therefore, Dr. Ehlers said the difference in complication rates between appendectomy and antibiotics-first treatment (on average, 27 percent versus 9 percent in the studies) might not be as great if these two treatments were compared in the U.S.

A final problem with all the studies is they did not track several patient-centered outcomes that Dr. Ehlers said would help patients with appendicitis decide which treatment to receive. These outcomes include quality of life, such as time needed away from work, pain severity and long term symptoms, and fear of getting appendicitis again; the chances of regretting their decision; and whether out of pocket costs will be higher if they need appendectomy later compared with undergoing the operation right away.

Until future research answers these questions, Dr. Ehlers said it's likely some surgeons will offer patients with appendicitis the option of antibiotics-first therapy. This may only be a good idea if patients are aware of all the unknown elements and ideally this approach should only be part of a clinical trial or as part of a registry such as the Antibiotics-First Registry (available at http://www.becertain.org/appyregistry).

A new multicenter clinical trial called Comparing Outcomes of Drugs and Appendectomy (CODA) will investigate patient-reported outcomes of antibiotics-first treatment, to help patients make a more informed decision about which treatment is best for them. Funded by the Patient-Centered Outcomes Research Institute, the five-year study is expected to start recruiting patients in Washington State and California early next year, Dr. Ehlers said.

More information: Anne P. Ehlers et al. Evidence for an Antibiotics-First Strategy for Uncomplicated Appendicitis in Adults: A Systematic

Review and Gap Analysis, *Journal of the American College of Surgeons* (2015). DOI: 10.1016/j.jamcollsurg.2015.11.009

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3 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 Jun;313(23):2340-2348.

4 References 11 to 16 in the article by Dr. Ehlers and colleagues.

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