

Oral Antibiotics for Uncomplicated Acute Appendicitis: The Role of Extended-Spectrum Beta-Lactamase Risk Factor Stratification

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The World Society of Emergency Surgery 2020 guidelines recommend antibiotics as an effective and safe alternative to appendectomy for managing patients with computed tomography-confirmed uncomplicated acute appendicitis without appendicolith [1]. The safe avoidance of hospitalization for surgical patients is an important task during the coronavirus disease 2019 (COVID-19) pandemic, therefore this recommendation was also acknowledged by the American College of Surgeons (COVID-19 Guideline for Triage of Emergency General Surgery Patients) [2]. However, up to now, the optimum antibiotic regimen for the non-operative management of uncomplicated acute appendicitis has not been defined [1]. The results of the Appendicitis Acute (APPAC) II randomized controlled trial, comparing 7 days of oral moxifloxacin with 2 days of intravenous ertapenem followed by 5 days of oral levofloxacin and metronidazole, have been recently published [3]. This study showed that antibiotic therapy resulted in success rates at 1 year greater than 65% in both groups (70.2% for patients treated with oral antibiotics and 73.8% for patients treated with intravenous followed by oral antibiotics), but failed to demonstrate noninferiority ($P = 0.26$) of the only oral moxifloxacin regimen as compared to sequential intravenous to oral antibiotic treatment.

Moxifloxacin has the advantage of once daily administration exerting an excellent oral bioavailability of 86% [4], and was selected as a broad-spectrum antibiotic that could overwhelm antibiotic resistance issues. However, the two study arms present important differences in the antibiotics' antimicrobial spectrum. According to the Study for Monitoring Antimicrobial Resistance Trends (SMART), the resistance rates of *Escherichia coli* isolates from intraabdominal infections in Europe in the period 2008 - 2009, when the APPAC II study

started, were 23.6% for ciprofloxacin and 21% for levofloxacin, whereas only 0.2% for ertapenem [5]. The difference in resistance rates was more profound in *Escherichia coli* isolates with production of extended-spectrum beta-lactamases (ESBLs), which were highly resistant to quinolones (73.9% resistance rate to ciprofloxacin and 69.9% to levofloxacin), whereas resistance to ertapenem was only 0.3% [5]. The prevalence of ESBL-producing pathogens for the corresponding period in Europe was 11% and since then is steadily increasing. These epidemiological data if extrapolated in the patient population of the APPAC II study may reflect an incidence of about 8% of inappropriate antibiotic treatment, owing to quinolone resistance, in the oral moxifloxacin arm. ESBL-producing bacteria are typically associated with co-resistance to quinolones, aminoglycosides and trimethoprim-sulfamethoxazole, because multiple resistance genes often reside on the same plasmid [5]. Despite most patients with acute appendicitis in the APPAC II study were young (median age (IQR), 34 (26 - 45) years), a minority might possess risk factor(s) for infection with ESBL-producing Enterobacteriaceae, like recent exposure to antibiotics, recent hospitalization, or comorbidities. By excluding those patients from the study's results analysis, the positive outcome of the oral therapy with moxifloxacin would be reasonably increased potentially rendering this option noninferior to sequential intravenous to oral therapy. In addition, considering the problem of increasing resistance to carbapenems worldwide, the use of this class of antibiotics is not recommended for treatment of community-acquired infections without ESBL risk factors [1].

Therefore, careful stratification of patients according to their individual risk for infection with resistant microorganisms is the key for appropriate antibiotic selection. In clinically stable patients with uncomplicated acute appendicitis who do not present ESBL risk factors per oral antibiotic monotherapy with moxifloxacin seems appropriate. In patients with ESBL risk factors, treatment with ertapenem seems to be appropriate, either as initial intravenous therapy followed by per oral antibiotics or as outpatient parenteral antibiotic therapy (OPAT) to avoid hospitalization.

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Author Contributions

SFA: conception and design, and writing of the manuscript. IM, CT and MM: critical revision of the manuscript for important intellectual content. All authors read and gave final approval of the manuscript.

Data Availability

The authors declare that data supporting the findings of this study are available within the article.

Abbreviations

APPAC: Appendicitis Acute; SMART: Study for Monitoring Antimicrobial Resistance Trends; ESBL: extended-spectrum

beta-lactamases; OPAT: outpatient parenteral antibiotic therapy

References

1. Di Saverio S, Podda M, De Simone B, Ceresoli M, Augustin G, Gori A, Boermeester M, et al. Diagnosis and treatment of acute appendicitis: 2020 update of the WSES Jerusalem guidelines. *World J Emerg Surg.* 2020;15(1):27.
2. COVID 19: elective case triage guidelines for surgical care. American College of Surgeons. 2020. Updated December 8, 2020. <https://www.facs.org/covid-19/clinical-guidance/elective-case/emergency-surgery> [Assessed November 25th, 2021].
3. Sippola S, Haijanen J, Gronroos J, Rautio T, Nordstrom P, Rantanen T, Pinta T, et al. Effect of oral moxifloxacin vs intravenous ertapenem plus oral levofloxacin for treatment of uncomplicated acute appendicitis: the APPAC II randomized clinical trial. *JAMA.* 2021;325(4):353-362.
4. Stass H, Kubitzka D. Pharmacokinetics and elimination of moxifloxacin after oral and intravenous administration in man. *J Antimicrob Chemother.* 1999;43(Suppl B):83-90.
5. Hawser SP, Bouchillon SK, Lascols C, Hackel M, Hoban DJ, Badal RE, Canton R. Susceptibility of European *Escherichia coli* clinical isolates from intra-abdominal infections, extended-spectrum beta-lactamase occurrence, resistance distribution, and molecular characterization of ertapenem-resistant isolates (SMART 2008-2009). *Clin Microbiol Infect.* 2012;18(3):253-259.