CONTEMPORARY APPROACHES IN THE MANAGEMENT OF ACUTE APPENDICITIS: A CRITICAL COMPARISON BETWEEN SURGICAL TREATMENT AND CONSERVATIVE ANTIBIOTIC THERAPY

Kastriot HAXHIREXHA, Gazmend ZEQIRI, Ilber BESIMI, Florim SELIMI, Arben DEMIRI, Roland ALILI, Nazim MUSLI, Natmir IMERI, Rian AMITI, Jakup JAKUPI

Clinical Hoepital of Tetova, Departament of General Surgery
Faculty of Medical Sciences – University of Tetova

Abstract

Background: Acute appendicitis is among the most common abdominal surgical emergencies worldwide (Ferris et al., 2017; Yang et al., 2023). Although appendectomy has historically been considered the definitive treatment, evidence from large randomized trials and long-term follow-up over the past decade has reframed antibiotic therapy as a viable first-line alternative (Salminen et al., 2015; Flum et al., 2020).
Objective: This paper aims to critically analyze the most recent scientific evidence regarding the effectiveness, safety, and long-term durability of the two therapeutic strategies, with particular attention to the patient profiles that benefit from each approach.
Materials and methods: A structured narrative review of contemporary literature (2015–2026) was conducted, including the randomized APPAC (Salminen et al., 2015), APPAC II (Sippola et al., 2021), and CODA (Flum et al., 2020) trials, along with their long-term follow-ups, recent meta-analyses (Herrod et al., 2022; Brucchi et al., 2024), and international guidelines from the WSES (Di Saverio et al., 2020) and SAGES (Kumar et al., 2024).
Results: The 10-year APPAC follow-up shows that approximately 56% of patients initially treated with antibiotics ultimately avoided appendectomy, with a recurrence rate of 37.8% and a markedly lower cumulative complication rate (8.5% versus 27.4%; Salminen et al., 2026). The CODA trial confirmed non-inferiority for quality-of-life outcomes but identified appendicolith as a predictor of early treatment failure (Davidson et al., 2021). Recent meta-analyses report 1-year antibiotic success rates of 62.9–64.6% (Herrod et al., 2022; Brucchi et al., 2024).
Conclusion: Conservative antibiotic therapy is a safe and effective alternative for carefully selected patients with CT-confirmed uncomplicated acute appendicitis, whereas laparoscopic appendectomy remains the standard treatment for complicated appendicitis and for patients with high-risk appendicolith. Modern decision-making should be individualized.

Keywords: acute appendicitis, laparoscopic appendectomy, antibiotic therapy, APPAC, CODA, appendicolith, non-operative management.

Introduction

Acute appendicitis is among the most frequent conditions encountered in surgical emergency departments. According to the Global Burden of Disease Study 2019, the age-standardized incidence is approximately 230 cases per 100,000 population per year, with a lifetime risk of 6.7–8.6% (Ferris et al., 2017; Yang et al., 2023). Incidence has stabilized in high-income Western countries, while a rising trend is observed in Central and East Asia, South America, and sub-Saharan Africa (Wickramasinghe et al., 2021). Appendectomy remains the most frequently performed urgent surgical intervention worldwide.
Since the first descriptions of appendectomy at the end of the 19th century, surgical intervention has been considered nearly universally accepted, based on the premise that the natural course of the disease is progression toward perforation, generalized peritonitis, and sepsis (Bhangu et al., 2015). However, advances over the past two decades in diagnostic imaging have allowed accurate differentiation between uncomplicated and complicated forms of the disease. Computed tomography (CT) has demonstrated a pooled sensitivity of 97.2% and specificity of 95.6%, while abdominal ultrasonography achieves a sensitivity of 82.1% and specificity of 85.9% (Arruzza et al., 2022). Nonetheless, even imaging is imperfect in

distinguishing complicated from uncomplicated cases, with CT reaching only about 78% sensitivity for this distinction (Bolmers et al., 2021).
The traditional hypothesis that every case of acute appendicitis inevitably progresses to perforation is not fully supported by contemporary epidemiological literature (Andersson, 2021; Bhangu et al., 2015). Rather, the disease appears as a heterogeneous pathological entity, in which a substantial proportion of uncomplicated forms can resolve with antimicrobial therapy alone.
Since 2009, a series of methodologically robust randomized trials—led by the APPAC trial in Finland (Salminen et al., 2015) and the CODA trial in the United States (Flum et al., 2020)—have generated high-quality evidence supporting antibiotic therapy. The most recent publications, including the 10-year APPAC follow-up (Salminen et al., 2026), have reaffirmed the long-term durability of this approach. Consequently, current guidelines from the World Society of Emergency Surgery (Di Saverio et al., 2020), the Society of American Gastrointestinal and Endoscopic Surgeons (Kumar et al., 2024), and the European Association for Endoscopic Surgery (Gorter et al., 2016) have formalized antibiotic therapy as a viable, and potentially primary, option.

Aim of the Paper

The principal aim of this paper is to provide a structured and critical comparison of the two contemporary therapeutic strategies for acute appendicitis in adults: first-line surgical treatment (laparoscopic appendectomy) and conservative treatment with antibiotics.
The specific objectives are:
To analyze the evidence from randomized trials and long-term follow-up studies, with a focus on APPAC, APPAC II, and CODA (Salminen et al., 2015; Flum et al., 2020; Sippola et al., 2021).
To compare clinical outcomes—therapeutic success, complications, length of stay, and recurrence—based on recent meta-analyses (Herrod et al., 2022; Brucchi et al., 2024; Xu et al., 2023).
To identify the clinical and imaging criteria that determine patient suitability for each strategy.
To present current management algorithms in line with the WSES (Di Saverio et al., 2020), SAGES (Kumar et al., 2024), and EAES (Gorter et al., 2016) guidelines.
To discuss specific populations (the elderly, pregnant women, and children) and the ethical implications of informed patient choice (Antoniou et al., 2021; Perez Otero et al., 2022).

Materials and Methods

3.1 Study design: This work is conceived as a structured narrative review and critical analysis of the literature on the contemporary management of acute appendicitis in adults. Sources were selected on the basis of clinical relevance, methodological rigor, and their influence on changes in clinical practice over the past decade.

3.2 Search strategy: The literature search was conducted in PubMed, MEDLINE, Embase, the Cochrane Central Register of Controlled Trials, and ClinicalTrials.gov, for English-language publications from 2010 through April 2026. Key search terms included: "acute appendicitis," "appendectomy," "antibiotic therapy," "non-operative management," "uncomplicated appendicitis," "APPAC trial," "CODA trial," "appendicolith," and "WSES guidelines."

3.3 Inclusion criteria: The following were included: randomized controlled trials with ≥100 patients; large prospective cohort studies; meta-analyses and systematic reviews published in

high-impact journals; and evidence-based international guidelines issued by professional societies (Di Saverio et al., 2020; Kumar et al., 2024; Gorter et al., 2016; Antoniou et al., 2021).

3.4 Principal sources analyzed: The central sources comprised: the APPAC trial (Salminen et al., 2015) with its 5-year (Salminen et al., 2018) and 10-year (Salminen et al., 2026) follow-ups; the APPAC II trial (Sippola et al., 2021) and its 3-year secondary analysis (Sippola et al., 2024); the CODA trial (Flum et al., 2020) and its longer-term follow-up (Davidson et al., 2021); economic analyses (Haijanen et al., 2019); recent meta-analyses (Herrod et al., 2022; Brucchi et al., 2024; Xu et al., 2023); authoritative narrative reviews (Bhangu et al., 2015; Andersson, 2021); studies addressing special populations (Perez Otero et al., 2022; Khan et al., 2021; Lee et al., 2019); and global epidemiological analyses (Ferris et al., 2017; Yang et al., 2023; Wickramasinghe et al., 2021).

3.5 Outcomes assessed: The following outcomes were analyzed: initial treatment success rate, recurrence at 1, 5, and 10 years, cumulative need for appendectomy in the antibiotic group, post-intervention complication rates, length of hospital stay, direct medical costs, and patient-reported quality of life.

Results

4.1 Diagnosis and disease stratification: The diagnosis of acute appendicitis relies on a combination of clinical assessment, laboratory parameters, and imaging. Clinical scores—Alvarado and the Appendicitis Inflammatory Response (AIR)—aid in risk stratification. Comparative studies show that the AIR score outperforms the Alvarado score, with a specificity of 97% and a positive predictive value of 88% in the high-risk zone (Jose & Rajesh, 2021). A recent systematic review confirmed that the AIR score has greater discriminative ability than Alvarado for the diagnosis of appendicitis (Andersson & Stark, 2025). Nonetheless, neither score is sufficient to distinguish complicated from uncomplicated forms, and imaging confirmation remains necessary.

CT remains the most accurate imaging modality. A systematic meta-analysis of 31 studies reported a sensitivity of 97.2% and a specificity of 95.6% for the diagnosis of acute appendicitis with CT, while ultrasonography achieved a sensitivity of 82.1% and a specificity of 85.9% (Arruzza et al., 2022). In children and pregnant women, MRI offers a radiation-free alternative, with a sensitivity of 97.4% and a specificity of 97.1% (Eng et al., 2018). However, distinguishing complicated from uncomplicated appendicitis remains challenging even with CT, where the specific sensitivity for this distinction is approximately 78% (Bolmers et al., 2021).

4.2 The APPAC trial and long-term follow-up: The APPAC trial was conducted in six Finnish hospitals between November 2009 and June 2012 and enrolled 530 adult patients aged 18–60 years with CT-confirmed uncomplicated acute appendicitis (Salminen et al., 2015). Patients were randomized to open appendectomy (n = 273) or to antibiotic therapy (n = 257), consisting of intravenous ertapenem 1 g/day for 3 days, followed by oral levofloxacin 500 mg/day and metronidazole 500 mg three times daily for 7 days.

At the 5-year follow-up, the cumulative appendectomy rate in the antibiotic group was 39.1%, indicating that more than half of patients did not require surgery within 5 years (Salminen et al., 2018). The 10-year follow-up published in January 2026 assessed 253 of 257 patients (98.4%): the histopathologically confirmed recurrence rate was 37.8% (95% CI: 31.6–44.1) and the cumulative 10-year appendectomy rate was 44.3% (95% CI: 38.2–50.4) (Salminen et al., 2026). Importantly, 74.7% of recurrences and 77.7% of late appendectomies occurred

within the first 2 years, suggesting that patients who pass this period without recurrence experience a marked decline in long-term risk (Salminen et al., 2026).
Equally important, the cumulative complication rate at 10 years was 8.5% in the antibiotic group versus 27.4% in the surgical group (Salminen et al., 2026). This long-term safety advantage relates principally to operative morbidity—wound infections, adhesions, and postoperative ileus (Bhangu et al., 2015; Jaschinski et al., 2015).

4.3 The APPAC II trial and alternative regimens: APPAC II compared oral monotherapy with moxifloxacin (400 mg/day for 7 days) against the combined regimen of intravenous ertapenem followed by oral levofloxacin/metronidazole, in 583 patients with uncomplicated appendicitis (Sippola et al., 2021). The 1-year success rate was 70.2% in the oral group and 73.8% in the combined group; both exceeded the predefined threshold of 65%, although oral monotherapy did not meet the formal non-inferiority criterion with a 6-percentage-point margin. The 3-year follow-up analysis confirmed the durability of these results, suggesting that an exclusively oral strategy may be clinically reasonable for selected patients (Sippola et al., 2024).

4.4 The CODA trial: Published in the New England Journal of Medicine, CODA is the largest randomized trial on this topic to date, enrolling 1,552 patients across 25 hospitals in the United States (Flum et al., 2020). Unlike APPAC, CODA included patients with appendicolith, making the population more diverse. The primary 30-day outcome showed that antibiotic therapy was non-inferior to appendectomy with respect to quality of life as measured by the EuroQol-5D index. Nevertheless, 29% of patients in the antibiotic group underwent appendectomy within 90 days—41% with appendicolith versus 25% without.
The longer-term follow-up reported cumulative appendectomy rates of 40% at 1 year, 46% at 2 years, and 49% at 3 and 4 years (Davidson et al., 2021). The hazard ratio (HR) for appendectomy in patients with appendicolith was 2.9 within the first 48 hours, 1.4 from 48 hours to 30 days, and 1.1 from 31 days to 2 years—indicating that the differential risk associated with appendicolith is concentrated in the early phase and attenuates over time (Davidson et al., 2021). The intraoperatively detected perforation rate in the CODA surgical group was 16%, reflecting a more severe disease population than that of APPAC, where perforation was less than 2%.

4.5 Synthesis from meta-analyses: The most recent meta-analysis published in the World Journal of Emergency Surgery included 8 randomized trials with 3,213 patients and reported that antibiotic therapy had reduced efficacy compared with appendectomy at 1 year (RR = 0.80; 95% CI 0.71–0.90), with a 1-year success rate of 64.6% (Brucchi et al., 2024). A parallel analysis in BJS Open including the same number of trials reported a success rate of 62.9% (Herrod et al., 2022). The meta-analysis by Xu et al. (2023) confirmed no significant difference in overall complications (RR = 0.66; 95% CI 0.41–1.04), although antibiotic therapy was associated with a sixfold higher rate of hospital readmissions within 1 year (Herrod et al., 2022).

4.6 Economic considerations: The 5-year economic analysis of APPAC showed that total costs for appendectomy were 1.4 times higher (€5,716; 95% CI: €5,510–€5,925) than for antibiotic therapy (€4,171; 95% CI: €3,879–€4,463), with mean savings of €1,545 per patient ($p < 0.001$) (Haijanen et al., 2019). Mean time off work was 11 days longer in the appendectomy group (Salminen et al., 2018), with direct implications for societal productivity.

4.7 The role of appendicolith: Both major trials identify appendicolith as a significant predictor of antibiotic failure. In APPAC it was an exclusion criterion (Salminen et al., 2015), whereas

in CODA it was included and shown to substantially increase short-term risk (HR 2.9; Davidson et al., 2021). Consequently, current guidelines recommend careful consideration of this strategy in the presence of appendicolith (Di Saverio et al., 2020; Kumar et al., 2024).

4.8 Special populations: In children, the evidence is more limited. A US randomized trial of 39 children with uncomplicated appendicitis reported a 1-year success rate of 70% with antibiotics, with an adjusted rate of 90% after exclusion of "pragmatic" non-clinical failures, and faster return to activity (2.0 vs. 12 days; p = 0.001) (Perez Otero et al., 2022). Other studies confirm therapeutic success of 70–90% in pediatric populations with strict selection criteria (Khan et al., 2021).
In pregnant women, appendectomy remains the standard treatment. However, the laparoscopic approach has been associated with a higher risk of fetal loss (OR 1.72; 95% CI 1.22–2.42) than the open approach, according to a meta-analysis of 22 studies including 4,694 pregnant women (Lee et al., 2019). This raises important questions regarding the choice of surgical method in this population.
In the elderly, the EAES has issued dedicated guidelines, emphasizing that appendicitis in this age group is associated with a higher risk of perforation at the time of diagnosis and greater operative morbidity (Antoniou et al., 2021). Therapeutic decisions require careful evaluation of comorbidities and functional status.

4.9 Comparative summary:

Table 1. Comparison of therapeutic strategies – principal indicators

Parameter	Surgical treatment	Conservative treatment
Initial treatment success	> 97% (Flum et al., 2020)	70–85% at 1 year (Salminen et al., 2015; Sippola et al., 2021)
Recurrence at 5 years	< 2% (Salminen et al., 2018)	≈ 39% (Salminen et al., 2018)
Appendectomy at 10 years	—	44.3% (Salminen et al., 2026)
Cumulative complications at 10 years	27.4% (Salminen et al., 2026)	8.5% (Salminen et al., 2026)
Total 5-year cost	≈ €5,716 (Haijanen et al., 2019)	≈ €4,171 (Haijanen et al., 2019)
Histopathological verification	Complete	Absent

Discussion

The evidence generated over the past decade has substantially transformed the conceptualization of acute appendicitis from an obligatory surgical emergency to an entity that can be managed through individualized strategies (Andersson, 2021; Bhangu et al., 2015). Long-term follow-up data, particularly the 10-year APPAC results (Salminen et al., 2026), have provided clarity regarding questions left open by earlier publications.

5.1 Long-term safety of antibiotic therapy: One of the most important findings of the 10-year APPAC follow-up is that the cumulative complication rate remains lower in the antibiotic

group than in the surgical group (8.5% vs. 27.4%; Salminen et al., 2026). This contradicts the intuitive hypothesis that recurrences would lead to expanded long-term morbidity. On the contrary, even patients who eventually undergo appendectomy after a second episode do not show a higher complication risk than those operated on at the outset, supporting the safety of an "antibiotics-first" approach (Salminen et al., 2026; Andersson, 2021).

5.2 The critical role of patient selection: Nevertheless, real-world clinical populations are more heterogeneous than that of APPAC. CODA provides a more realistic picture by including patients with appendicolith (Flum et al., 2020). The risk increases markedly in the early phase, suggesting that the decision to start antibiotic therapy in such patients should be made cautiously, with close follow-up during the first 30–90 days (Davidson et al., 2021). After this critical phase, long-term risk between patients with and without appendicolith converges, supporting the validity of the conservative strategy in a portion of this population as well.

5.3 Laparoscopic appendectomy: a robust standard: Laparoscopic appendectomy remains a procedure with very high safety, short recovery time, minimal postoperative pain, and favorable cosmetic outcomes (Jaschinski et al., 2015). Its principal comparative advantages include: (i) definitive treatment with rare recurrence; (ii) the ability to obtain definitive histopathological diagnosis—particularly important for rare appendiceal neoplasms that may go undetected in the antibiotic group (Flum et al., 2020); and (iii) avoidance of broad-spectrum antibiotic exposure, an increasingly important consideration in the context of antimicrobial resistance.

5.4 The issue of appendiceal neoplasms: A concern raised by CODA is the lower detection rate of appendiceal neoplasms in the antibiotic group, where the appendix is not surgically removed. The trial reported nine neoplasms detected in appendectomy specimens, with higher representation in patients over 40 years of age (Flum et al., 2020). This risk should be part of informed discussion with the patient, particularly when the conservative strategy is chosen in older age groups or when imaging signs are suggestive (Antoniou et al., 2021).

5.5 Economic and social implications: Economic data clearly suggest that, despite reinterventions, antibiotic therapy is less costly in the medium and long term (Haijanen et al., 2019). It also reduces work absence by an average of 11 days (Salminen et al., 2018), with direct implications for societal productivity. In healthcare systems with limited admission capacity, this strategy may contribute to resource optimization.

5.6 Shared decision-making with the patient: Modern algorithms emphasize the importance of informed choice (Kumar et al., 2024; Di Saverio et al., 2020). The patient should be clearly informed about: realistic chances of long-term avoidance of surgery (approximately 50–56%; Salminen et al., 2026); the risk of recurrence; the advantages and limitations of each strategy; and the influence of individual characteristics (appendicolith, age, comorbidities, occupation, family planning).

5.7 Limitations of the evidence: Several limitations should be acknowledged: loss to follow-up in the late phases of CODA (only 5% retention at year 4) (Davidson et al., 2021); APPAC used open rather than laparoscopic appendectomy (Salminen et al., 2015); and the populations of these trials did not include specific subgroups such as immunocompromised patients, for whom evidence remains more limited and dedicated studies are required.

Conclusion

The scientific evidence accumulated over the past decade, consolidated by large randomized trials and follow-up extending to 10 years, supports a paradigm shift away from the "one-treatment-fits-all" model toward individualized management of acute appendicitis. The principal conclusions can be summarized as follows:

Conservative antibiotic therapy is a safe, effective, and cost-effective alternative for a substantial proportion of patients with CT-confirmed uncomplicated acute appendicitis, where approximately 50–56% ultimately avoid appendectomy over a 10-year horizon (Salminen et al., 2026; Brucchi et al., 2024).

Laparoscopic appendectomy remains the standard treatment for complicated appendicitis, in the presence of high-risk imaging features of appendicolith, and for patients who prefer definitive treatment or who fall into age groups with elevated risk for neoplastic pathology (Flum et al., 2020; Jaschinski et al., 2015).

Appendicolith is an important prognostic factor but no longer an absolute contraindication—it primarily increases the risk of early failure and warrants careful follow-up (Davidson et al., 2021).

Modern decision-making requires informed dialogue with the patient, in which clinical characteristics, imaging findings, personal preference, and life context interweave to form an individualized strategy (Kumar et al., 2024; Di Saverio et al., 2020).

The responsibility of the contemporary surgeon is no longer to make a unilateral decision about whether to operate, but rather to provide accurate, evidence-verified information and to support the patient through a shared decision-making process that respects autonomy and maximizes long-term clinical outcomes.

References

[1]. Andersson, R. E. (2021). The role of antibiotic therapy in the management of acute appendicitis. *Current Opinion in Gastroenterology, 37*(1), 40–45. https://doi.org/10.1097/MOG.0000000000000688

[2]. Andersson, R. E., & Stark, J. (2025). Diagnostic value of the appendicitis inflammatory response (AIR) score: A systematic review and meta-analysis. *World Journal of Emergency Surgery, 20*(1), 14. https://doi.org/10.1186/s13017-025-00582-x

[3]. Antoniou, S. A., Mavridis, D., Kontouli, K. M., Drakopoulos, V., Gorter-Stam, M., Eriksson, S., Leone, M., Pérez-Bocanegra, M. C., Smart, N. J., Milone, M., Carrano, F. M., Antoniou, G. A., & Vandvik, P. O. (2021). EAES rapid guideline: Appendicitis in the elderly. *Surgical Endoscopy, 35*(8), 4203–4225. https://doi.org/10.1007/s00464-021-08524-9

[4]. Arruzza, E., Milanese, S., Li, L. S. K., & Dizon, J. (2022). Diagnostic accuracy of computed tomography and ultrasound for the diagnosis of acute appendicitis: A systematic review and meta-analysis. *Radiography, 28*(4), 1127–1141. https://doi.org/10.1016/j.radi.2022.08.012

[5]. Bhangu, A., Søreide, K., Di Saverio, S., Assarsson, J. H., & Drake, F. T. (2015). Acute appendicitis: Modern understanding of pathogenesis, diagnosis, and management. *The Lancet, 386*(10000), 1278–1287. https://doi.org/10.1016/S0140-6736(15)00275-5

[6]. Bolmers, M. D. M., de Jonge, J., Bom, W. J., van Rossem, C. C., van Geloven, A. A. W., & Bemelman, W. A. (2021). Discriminating complicated from uncomplicated appendicitis by ultrasound imaging, computed tomography or magnetic resonance imaging: Systematic review and meta-analysis of diagnostic accuracy. *BJS Open, 5*(2), zraa030. https://doi.org/10.1093/bjsopen/zraa030

[7]. Brucchi, F., Bracchetti, G., Fugazzola, P., Viganò, J., Filisetti, C., Ansaloni, L., Dal Mas, F., Cobianchi, L., & Danelli, P. (2024). A meta-analysis and trial sequential analysis comparing nonoperative versus operative management for uncomplicated appendicitis: A focus on randomized controlled trials. *World Journal of Emergency Surgery, 19*(1), 2. https://doi.org/10.1186/s13017-023-00531-6

[8]. Davidson, G. H., Flum, D. R., Monsell, S. E., Kao, L. S., Voldal, E. C., Heagerty, P. J., Fannon, E., Lavallee, D. C., Bizzell, B., Lawrence, S. O., Comstock, B. A., Krishnadasan, A., Winchell, R. J., Self, W. H., Thompson, C. M., Farjah, F., Park, P. K., Alam, H. B., Saltzman, D., … CODA Collaborative. (2021). Antibiotics versus appendectomy for acute appendicitis—Longer-term outcomes. *New England Journal of Medicine, 385*(25), 2395–2397. https://doi.org/10.1056/NEJMc2116018

[9]. Di Saverio, S., Podda, M., De Simone, B., Ceresoli, M., Augustin, G., Gori, A., Boermeester, M., Sartelli, M., Coccolini, F., Tarasconi, A., De' Angelis, N., Weber, D. G., Tolonen, M., Birindelli, A., Biffl, W., Moore, E. E., Kelly, M., Soreide, K., Kashuk, J., … Catena, F. (2020). Diagnosis and treatment of acute appendicitis: 2020 update of the WSES Jerusalem guidelines. *World Journal of Emergency Surgery, 15*(1), 27. https://doi.org/10.1186/s13017-020-00306-3

[10]. Eng, K. A., Abadeh, A., Ligocki, C., Lee, Y. K., Moineddin, R., Adams-Webber, T., Schuh, S., & Doria, A. S. (2018). Acute appendicitis: A meta-analysis of the diagnostic accuracy of US, CT, and MRI as second-line imaging tests after an initial US. *Radiology, 288*(3), 717–727. https://doi.org/10.1148/radiol.2018180318

[11]. Ferris, M., Quan, S., Kaplan, B. S., Molodecky, N., Ball, C. G., Chernoff, G. W., Bhala, N., Ghosh, S., Dixon, E., Ng, S., & Kaplan, G. G. (2017). The global incidence of appendicitis: A systematic review of population-based studies. *Annals of Surgery, 266*(2), 237–241. https://doi.org/10.1097/SLA.0000000000002188

[12]. Flum, D. R., Davidson, G. H., Monsell, S. E., Shapiro, N. I., Odom, S. R., Sanchez, S. E., Drake, F. T., Fischkoff, K., Johnson, J., Patton, J. H., Evans, H., Cuschieri, J., Sabbatini, A. K., Faine, B. A., Skeete, D. A., Liang, M. K., Sohn, V., McGrane, K., Kutcher, M. E., … CODA Collaborative. (2020). A randomized trial comparing antibiotics with appendectomy for appendicitis. *New England Journal of Medicine, 383*(20), 1907–1919. https://doi.org/10.1056/NEJMoa2014320

[13]. Gorter, R. R., Eker, H. H., Gorter-Stam, M. A. W., Abis, G. S. A., Acharya, A., Ankersmit, M., Antoniou, S. A., Arolfo, S., Babic, B., Boni, L., Bruntink, M., van Dam, D. A., Defoort, B., Deijen, C. L., DeLacy, F. B., Go, P. M., Harmsen, A. M. K., van den Helder, R. S., Iordache, F., … Bonjer, H. J. (2016). Diagnosis and management of acute appendicitis. EAES consensus development conference 2015. *Surgical Endoscopy, 30*(11), 4668–4690. https://doi.org/10.1007/s00464-016-5245-7

[14]. Haijanen, J., Sippola, S., Tuominen, R., Grönroos, J., Paajanen, H., Rautio, T., Nordström, P., Aarnio, M., Rantanen, T., Hurme, S., & Salminen, P. (2019). Cost analysis of antibiotic therapy versus appendectomy for treatment of uncomplicated acute appendicitis: 5-year results of the APPAC randomized clinical trial. *PLoS One, 14*(7), e0220202. https://doi.org/10.1371/journal.pone.0220202

[15]. Herrod, P. J. J., Kwok, A. T., & Lobo, D. N. (2022). Randomized clinical trials comparing antibiotic therapy with appendicectomy for uncomplicated acute appendicitis: Meta-analysis. *BJS Open, 6*(4), zrac100. https://doi.org/10.1093/bjsopen/zrac100

[16]. Jaschinski, T., Mosch, C., Eikermann, M., & Neugebauer, E. A. M. (2015). Laparoscopic versus open appendectomy in patients with suspected appendicitis: A systematic review of meta-analyses of randomised controlled trials. *BMC Gastroenterology, 15*, 48. https://doi.org/10.1186/s12876-015-0277-3

[17]. Jose, T., & Rajesh, P. S. (2021). Appendicitis Inflammatory Response score in comparison to Alvarado score in acute appendicitis. *The Surgery Journal, 7*(3), e127–e131. https://doi.org/10.1055/s-0041-1731446

[18]. Khan, M. S., Chaudhry, M. B. H., Shahzad, N., Tariq, M., Memon, W. A., & Alvi, A. R. (2021). Non-operative treatment versus appendectomy for acute uncomplicated appendicitis: A randomized controlled trial. *Cureus, 13*(7), e16302. https://doi.org/10.7759/cureus.16302

[19]. Kumar, S. S., Collings, A. T., Lamm, R., Haskins, I. N., Scholz, S., Nepal, P., Train, A. T., Athanasiadis, D. I., Pucher, P. H., Bradley, J. F., 3rd, Hanna, N. M., Quinteros, F., Narula, N., & Slater, B. J. (2024). SAGES guideline for the diagnosis and treatment of appendicitis. *Surgical Endoscopy, 38*(6), 2974–2994. https://doi.org/10.1007/s00464-024-10813-y

[20]. Lee, S. H., Lee, J. Y., Choi, Y. Y., & Lee, J. G. (2019). Laparoscopic appendectomy versus open appendectomy for suspected appendicitis during pregnancy: A systematic review and updated meta-analysis. *BMC Surgery, 19*(1), 41. https://doi.org/10.1186/s12893-019-0505-9

[21]. Perez Otero, S., Metzger, J. W., Choi, B. H., Ramaraj, A., Tashiro, J., Kuenzler, K. A., Ginsburg, H. B., Tomita, S. S., & Fisher, J. C. (2022). It's time to deconstruct treatment-failure: A randomized controlled trial of nonoperative management of uncomplicated pediatric appendicitis with antibiotics alone. *Journal of Pediatric Surgery, 57*(1), 56–62. https://doi.org/10.1016/j.jpedsurg.2021.09.024

[22]. Salminen, P., Paajanen, H., Rautio, T., Nordström, P., Aarnio, M., Rantanen, T., Tuominen, R., Hurme, S., Virtanen, J., Mecklin, J. P., Sand, J., Jartti, A., Rinta-Kiikka, I., & Grönroos, J. M. (2015). Antibiotic therapy vs appendectomy for treatment of uncomplicated acute appendicitis: The APPAC randomized clinical trial. *JAMA, 313*(23), 2340–2348. https://doi.org/10.1001/jama.2015.6154

[23]. Salminen, P., Tuominen, R., Paajanen, H., Rautio, T., Nordström, P., Aarnio, M., Rantanen, T., Hurme, S., Mecklin, J. P., Sand, J., Virtanen, J., Jartti, A., & Grönroos, J. M. (2018). Five-year follow-up of antibiotic therapy for uncomplicated acute appendicitis in the APPAC randomized clinical trial. *JAMA, 320*(12), 1259–1265. https://doi.org/10.1001/jama.2018.13201

[24]. Salminen, P., Sippola, S., Haijanen, J., Nordström, P., Rantanen, T., Rautio, T., Sand, J., Virtanen, J., Pinta, T., Hurme, S., & Grönroos, J. (2026). Antibiotic therapy for uncomplicated acute appendicitis: Ten-year follow-up of the APPAC randomized clinical trial. *JAMA*. Advance online publication. https://doi.org/10.1001/jama.2025.25921

[25]. Sippola, S., Haijanen, J., Grönroos, J., Rautio, T., Nordström, P., Rantanen, T., Pinta, T., Ilves, I., Mattila, A., Rintala, J., Löyttyniemi, E., Hurme, S., Tammilehto, V., Marttila, H., Meriläinen, S., Laukkarinen, J., Sävelä, E. L., Savolainen, H., Sippola, T., … Salminen, P. (2021). Effect of oral moxifloxacin vs intravenous ertapenem plus oral levofloxacin for treatment of uncomplicated acute appendicitis: The APPAC II randomized clinical trial. *JAMA, 325*(4), 353–362. https://doi.org/10.1001/jama.2020.23525

[26]. Sippola, S., Haijanen, J., Grönroos, J., Rautio, T., Nordström, P., Rantanen, T., Pinta, T., Ilves, I., Mattila, A., Hurme, S., & Salminen, P. (2024). Three-year outcomes of oral antibiotics vs intravenous and oral antibiotics for uncomplicated acute appendicitis: A secondary analysis of the APPAC II randomized clinical trial. *JAMA Surgery, 159*(7), 729–735. https://doi.org/10.1001/jamasurg.2024.0935

[27]. Wickramasinghe, D. P., Xavier, C., & Samarasekera, D. N. (2021). The worldwide epidemiology of acute appendicitis: An analysis of the Global Health Data Exchange dataset. *World Journal of Surgery, 45*(7), 1999–2008. https://doi.org/10.1007/s00268-021-06077-5

[28]. Xu, H., Yang, S., Xing, J., Wang, Y., Sun, W., Rong, L., & Liu, H. (2023). Comparison of the efficacy and safety of antibiotic treatment and appendectomy for acute uncomplicated appendicitis: A systematic review and meta-analysis. *BMC Surgery, 23*(1), 208. https://doi.org/10.1186/s12893-023-02108-1

[29]. Yang, J., Yu, K. K., Li, X. Z., Chen, M. F., Xie, B., Wu, M. Y., & Lin, K. R. (2023). The global, regional, and national burden of appendicitis in 204 countries and territories, 1990–2019: A systematic analysis from the Global Burden of Disease Study 2019. *BMC Gastroenterology, 23*(1), 44. https://doi.org/10.1186/s12876-023-02678-7