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Yaroslav Isaev

doctorisaev@gmail.com

Klinikum Saarbrücken

Arne Simon

Universitätsklinikum des Saarlandes

Marie-Claire Detemple

Klinikum Saarbrücken

Alexander Worm

Klinikum Saarbrücken

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Differentiated antibiotic approach based on the incidence of multidrug-resistant pathogens (MDRP) in complicated pediatric appendicitis

Yaroslav Isaev[1], Arne Simon[2], Marie Claire Detemple[1,3], Alexander Worm[1]

1 Pediatric Surgery, Center for Surgical and Conservative Pediatric and Adolescent Medicine, Children's Hospital, Saarbruecken, Germany
2 Pediatric Oncology and Hematology, Children's University Hospital Medical Center, Homburg/Saar, Germany
3 Center for Surgical and Conservative Pediatric and Adolescent Medicine, Children's Hospital, Saarbruecken, Germany

Corresponding author
Yaroslav Isaev
Pediatric Surgery, Center for Surgical and Conservative Pediatric and Adolescent Medicine, Children's Hospital, Winterberg 1, 66119, Saarbruecken, Germany
E-Mail doctorisaev@gmail.com

Abstract.
Background.
Antimicrobial resistance may compromise calculated antibiotic treatment in children with complicated appendicitis, although its clinical relevance may differ according to disease severity and the adequacy of surgical source control. This study evaluated the occurrence and clinical impact of multidrug-resistant pathogens (MDRP) across different phenotypes of complicated pediatric appendicitis.
Methods.
We retrospectively analyzed children aged ≤16 years treated for complicated acute appendicitis at a single pediatric surgical center between January 2020 and May 2026. Patients were stratified in 4 groups according to severity of intraoperative findings. Prevalence of MDRP, antimicrobial treatment, need for treatment escalation, and postoperative length of stay were analyzed adjusted to disease severity.
Results. A total of 136 patients were included. MDRP were detected in 13 patients (9.6%). Detection rates increased with disease severity, from 2.1% in localized peritonitis without perforation and 4.9% with perforation to 15.2% in patients with intra-abdominal abscess and 35.7% in those with diffuse peritonitis ($p<0.001$). All MDRP were detected from 2024 onward. Antibiotic therapy was escalated in nine of 13 patients because of an unsatisfactory clinical course and in vitro resistance to the calculated regimen. In four patients, adequate source control and favorable clinical improvement allowed continuation of the initial treatment despite detection of a MDRP.
Conclusion.
The clinical relevance of MDRP in complicated pediatric appendicitis appears to depend strongly on disease severity and surgical source control. Routine broad-spectrum escalation seems unwarranted in localized disease with adequate source control, whereas intra-abdominal abscess and particularly diffuse peritonitis may warrant an early (intra- or postoperative) switch to broad spectrum antibiotics.

Key words: Acute appendicitis · Antimicrobial resistance · Antimicrobial stewardship · Children · Complicated appendicitis · Drug-resistant pathogens

What is Known:
- Although complicated appendicitis in children comprises a heterogeneous spectrum of disease, this variability is rarely reflected in current treatment protocols, which mostly rely on a binary classification into complicated and uncomplicated diseases.
- Broadening empirical antimicrobial coverage has not consistently been shown to improve outcomes in unselected children with complicated appendicitis.

What is New:
- Detection of multidrug-resistant pathogens increased markedly with the severity of complicated appendicitis, reaching the highest prevalence in children with diffuse peritonitis.
- Detection of a resistant pathogen alone did not necessitate antibiotic escalation when adequate surgical source control was achieved, supporting a severity- and source-control-adapted rather than uniform broad-spectrum treatment strategy.

Introduction.

Acute appendicitis remains the most common pediatric surgical emergency worldwide. While uncomplicated appendicitis is usually associated with a favorable clinical course, complicated forms — particularly those accompanied by perforation, intra-abdominal abscess formation or diffuse

peritonitis — are associated with significantly higher rates of postoperative complications, readmission, repeated surgical interventions, prolonged length of stay (LOS), and increased healthcare costs (1-2).

Beside appropriate surgical focus control, calculated antibiotic therapy plays a critical role in the early postoperative management of pediatric patients with complicated appendicitis. Current protocols often rely on a binary classification into uncomplicated and complicated appendicitis; however, this framework fails to capture the heterogenous clinical spectrum of complicated disease. In particular, perforated appendicitis with diffuse peritonitis represents the most severe form of complicated appendicitis, in which complete local source control may be difficult to achieve leading to an increased risk of infectious complications (3-4).

While prolonged postoperative antibiotic therapy (e.g. intravenously or continued as oral antibiotic therapy after discharge) has not been shown to be of any proven benefit in complicated appendicitis, the administration of an adequate ABT in the first 3 to 4 days after surgery may have a significant impact on the clinical course (5-7).

Given the rising global prevalence of multidrug-resistant pathogens (MDRP), their clinical role in pediatric patients with severe complicated appendicitis warrants further investigation, particularly with respect to disease severity and clinical outcomes (8-9). A calculated ABT with a broader spectrum of activity against *P. aeruginosa* and MDRP has not been shown to reduce the rates of organ space infection and resource utilization concerning all patients with complicated appendicitis, but broader spectrum antibiotics may be beneficial in patients with most severe clinical manifestation (10-11).

One principle of antimicrobial stewardship is “listen to your hospital” concerning the in vitro sensitivity of pathogens, which have been isolated intraoperatively in most severe cases; this retrospective single center study aimes to explore temporal changes in MDRP detection rates among pediatric patients with complicated appendicitis, and to evaluate the adequacy of established calculated antibiotic regimens.

Methods.

A retrospective analysis of medical records was conducted in pediatric patients (≤ 16 years of age) treated for complicated acute appendicitis at our institution between Jan’ 2020 and May 2026. Inclusion criteria comprised a diagnosis of acute appendicitis which was defined according to intraoperative and histopathological findings as acute appendicitis with either a gangrenous inflamed appendix with or without perforation, intra-abdominal abscess, peri-appendicular contained phlegmon or purulent free fluid as proposed by EAES consensus (12).

The following data were extracted and analyzed: demographic characteristics, operative reports, microbiological and histopathological findings, antibiotic treatment regimens, postoperative complications, and length of hospital stay.

To address clinical heterogeneity, patients were stratified into four distinct groups based on intraoperative and histological findings:

Group 1: Acute appendicitis with localized peritonitis or peri-appendicular phlegmon without perforation

Group 2: Acute appendicitis with localized peritonitis and appendiceal perforation

Group 3: Appendicitis complicated by intra-abdominal abscess

Group 4: Appendicitis with diffuse purulent or fecal peritonitis

Outcome measures were analyzed in relation to the clinical form of complicated appendicitis and the presence of drug-resistant pathogens. In addition, temporal trends in the incidence of drug-resistant pathogens over the study period were assessed. MDRP were defined as bacterial isolates exhibiting antimicrobial resistance against the first line Betalactam-antibiotics (such as ceftriaxone or cefotaxime). That compromised the effectiveness of the established antibiotic regimens used at our institution.

Statistics

Comparisons of length of hospital stay between groups were performed using the Mann–Whitney U test. Differences in the frequency of drug-resistant organisms and inadequate empirical antimicrobial coverage across clinical severity groups were assessed using the chi-square test or Fisher's exact test, as appropriate. The Cochran-Armitage test for trend was used to assess whether DRPS detection rates increased across ordered categories of disease severity. Pairwise A p-value < 0.05 was considered statistically significant. Due to sample size limitations no multivariable adjustment was performed.

Ethical approval

This study used retrospective data derived from clinical records. After data sampling with the case report form, these data were anonymized for final analysis. The Ethics Committee of the Saarland Medical Association has confirmed that, in this case, no informed consent is required from the patients' legal guardians or the patients themselves for the data analysis and publication.

Results.

Basic demographic data and stratification

A total of 136 pediatric patients with complicated acute appendicitis were included in the study. The cohort comprised 86 boys and 50 girls (male-to-female ratio 1.76:1). Baseline demographic characteristics are summarized in tab. 1.

Age	Group 1 m/f	Group 2 m/f	Group 3 m/f	Group 4 m/f	Total m/f
2 – 4 y.o.	4 / 1	0 / 1	1 / 2	0 / 1	**10**
5 – 10 y.o.	13 / 7	8 / 5	12 / 6	1 / 1	**53**
11 – 15 y.o.	15 / 8	15 / 12	9 / 3	8 / 3	**73**
Total	**48**	**41**	**33**	**14**	**136**

Tab 1. Demographic data, age and sex distribution in different forms of acute complicated appendicitis (m – male, f – female)

Based on intraoperative findings, 48 patients had localized peritonitis without perforation (Group 1), 40 had localized peritonitis with perforation (Group 2), 33 presented with an intra-abdominal abscess (Group 3), and 14 presented with diffuse purulent or fecal peritonitis (Group 4). The distribution of clinical forms according to age and sex is presented in tab. 1.

Antimicrobial treatment

The decision to initiate systemic antibiotic therapy and the choice of the empirical regimen were made at the discretion of the attending pediatric surgeon. The in-house consent for calculated antibiotic treatment comprised the use of a 3rd generation cephalosporin with metronidazole. Antibiotic selection exhibited substantial variability between 2020 and 2024. Following the implementation of a institutional standard protocol for complicated appendicitis in 2024, the combination of cefotaxime and metronidazole became the predominant regimen (n = 50, 46.7%). Other regimens administered during the study period included cefuroxime plus metronidazole (n = 27, 25.2%), piperacillin/tazobactam (n = 26, 24.3%), and ampicillin/sulbactam (n = 4, 3.8%).

Intraoperative microbiological findings

Multidrug-resistant organisms were detected in 13 patients (9.6%). Among these, *P. aeruginosa* was identified in eight cases (61.5%), while five cases (38,5%) involved drug-resistant Escherichia coli.

All MDRP were detected from 2024 onward. While zero cases were detected between 2020 and 2023, 13 cases emerged thereafter. MDRP detection rates increased progressively with disease severity, from 2.1% in localized peritonitis without perforation and 4.9% in localized peritonitis with perforation to 15.2% in patients with intra-abdominal abscesses and 35.7% in those with diffuse peritonitis (Cochran–Armitage test for trend, $p < 0.001$). When the analysis was restricted to patients treated from 2024 onward, the corresponding detection rates were 4.5%, 10.5%, 33.3%, and 41.7%, respectively, and the trend remained significant ($p = 0.002$) (tab.2).

	Group 1 vs Group 2	Group 1 vs Group 3	Group 1 vs Group 4
2020-2026	p = 1,000	p = 0,085	**p = 0,0032**

2024-2026	p = 0,588	**p = 0,031**	**p = 0,014**
	Group 2 vs Group 3	Group 2 vs Group 4	Group 3 vs Group 4
2020-2026	p = 0,111	**p = 0,004**	p = 0,137
2024-2026	p = 0,199	p = 0,078	p = 0,706

Tab. 2. MDRP Prevelence in Groups 1-4, compared with Exact Fisher's test

In nine of the 13 cases, antibiotic therapy was escalated because of an unsatisfactory clinical course and microbiological evidence of resistance, most commonly from cefotaxime combined with metronidazole or from piperacillin–tazobactam to meropenem. In the remaining four cases, detection of drug-resistant pathogens alone did not prompt escalation because adequate surgical source control had been achieved and the subsequent clinical course was uneventful

These cases included three patients with localized peritonitis and one patient with an intra-abdominal abscess.

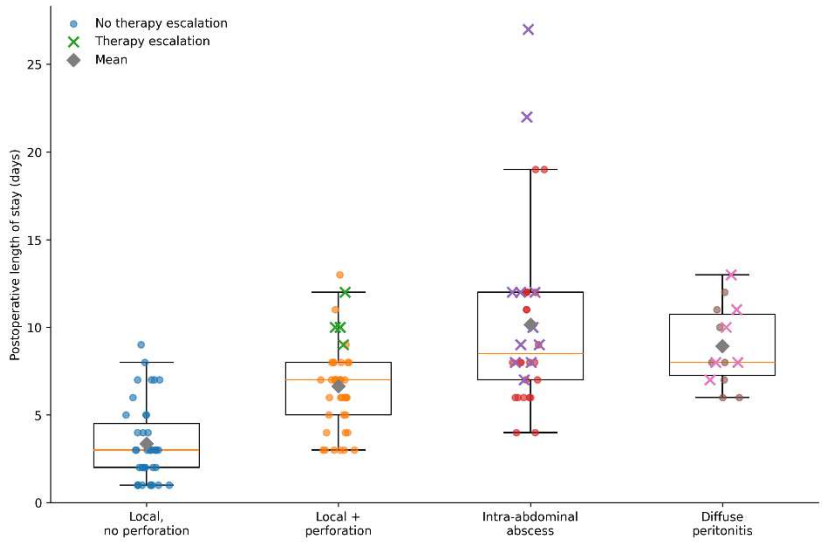


Fig.1. Postoperative LOS according to disease severity and antibiotic therapy escalation.

Length of Hospital Stay.

Postoperative LOS correlated with the severity of intra-abdominal infection (fig.1). Escalation of antibiotic therapy was associated with a prolonged LOS across all clinical subgroups. This association reached statistical significance in patients with localized peritonitis and appendiceal perforation (Group 2; 6.43 ± 2.29 vs. 10.25 ± 1.09 days, p = 0.0041). In groups 3 and 4 escalation of antibiotic therapy was associated with a longer LOS; however, this difference did not reach statistical significance (group 3: 9.19 ± 4.18 vs. 12.00 ± 5.94 days, p = 0.09; group 4: 8.93 ± 2.23 vs. 9.50 ± 2.26 days, p = 0.3086), despite a clear numerical trend.

Discussion

The present retrospective single center evaluation of 136 pediatric complex acute appendicitis cases demonstrates a marked association between the clinical severity of complicated appendicitis and the detection of multidrug-resistant pathogens. Two findings appear particularly relevant. First, MDRP detection increased progressively across the clinical severity spectrum, and this association was statistically significant. This finding is consistent with previous reports demonstrating an association between disease severity and the likelihood of isolating resistant pathogens (8, 9, 13).

Second, and perhaps more importantly, microbiological resistance did not uniformly translate into failure of calculated antimicrobial therapy. The clinical relevance of resistance appeared to depend strongly on disease severity and the adequacy of surgical source control.

The detection of a resistant organism alone did not necessarily indicate a subsequent clinical failure of the initial antimicrobial regimen. In four patients, antimicrobial escalation was not required despite microbiological detection of an MDRP after adequate surgical source control.. This was particularly evident in patients with localized disease. In contrast, antimicrobial escalation was required in the majority of patients with resistant pathogens and intra-abdominal abscesses and in all affected patients with diffuse peritonitis. These observations suggest that the clinical relevance of antimicrobial resistance is determined not only by in vitro susceptibility but also by the underlying disease phenotype and the effectiveness of surgical source control.

This distinction could have direct implications for calculated antimicrobial selection. In localized complicated appendicitis, adequate source control may permit successful treatment despite microbiological resistance to components of the initial regimen, and routine broad-spectrum escalation therefore appears questionable. Conversely, patients with more complicated disease represent a substantially different clinical setting. In these patients, incomplete or less predictable source control, greater bacterial burden, and a higher prevalence of resistant pathogens may increase the potential consequences of inadequate initial antimicrobial coverage.

In our cohort, all patients requiring antimicrobial escalation showed clinical improvement following conversion to meropenem as part of their subsequent management. Carbapenems are generally reserved for severe intra-abdominal infections with suspected or confirmed resistant organisms. Although there are isolated reports, we do not consider carbapenems should as first-line calculated therapy in all patients with complicated appendicitis (14-17). Of course, our observation cannot establish the superiority of a specific antimicrobial regimen, it raises the question whether the threshold for broader initial antimicrobial coverage should be lower in selected high-risk patients, particularly those presenting with diffuse peritonitis, when local surveillance demonstrates a substantial probability of resistance to established empirical regimens. In such circumstances, empirical meropenem may represent a reasonable option, provided that treatment is reassessed promptly after 48 hours, when the results of the intraoperative sampling are available. These results may guide a de-escalation from meropenem to antibiotics with a smaller spectrum of activity, as

definite (targeted) treatment. This approach advocates for a severity- and resistance-adapted antimicrobial therapy.

Although our results primarily reflect a regional microbiological profile, similar patterns have been reported by other centers. (15,17).

Patients requiring antimicrobial escalation in our cohort had longer hospital stays. However, this association should not be interpreted as evidence that escalation itself prolongs hospitalization, since escalation may be a surrogate for higher clinical severity and inadequate initial antimicrobial coverage.

Our findings therefore support a differentiated rather than binary approach to antimicrobial management in complicated appendicitis. Escalating treatment appears unnecessary for most patients with localized disease and adequate source control, but patients with intra-abdominal abscesses and particularly those with diffuse peritonitis may benefit from an antimicrobial strategy adapted to disease severity and the local resistance profile.

Interestingly, our data indicate that the clinical efficacy of piperacillin–tazobactam has dropped to levels comparable with third-generation cephalosporins combined with metronidazole. This shift is likely driven by the rising prevalence of resistant *Pseudomonas* species, which diminishes the expected advantages of piperacillin–tazobactam. These observations highlight the importance of continuous local surveillance for MDRP and regular reassessment of antimicrobial strategies in pediatric intra-abdominal infections.

Several limitations should be acknowledged. The retrospective single-center design limits causal inference and generalizability, and the number of resistant isolates was small, particularly within individual severity subgroups. The temporal analysis may additionally have been influenced by the COVID-19 pandemic, during which changes in presentation patterns and disease severity have been reported (18). Furthermore, the association between antimicrobial escalation and length of stay is susceptible to confounding by disease severity. Finally, the present analysis primarily reflects the local microbiological ecology and should therefore not be interpreted as establishing a universally applicable empirical antibiotic regimen.

Despite these limitations, the study provides a clinically relevant severity-stratified analysis of antimicrobial resistance in pediatric complicated appendicitis. Rather than considering complicated appendicitis as a uniform entity, our findings suggest that disease phenotype, adequacy of source control, local resistance patterns, and the probability of adequate empirical antimicrobial coverage should jointly inform postoperative antimicrobial management.

Conclusion.

In this retrospective single-center study, the prevalence of drug-resistant organisms increased over the later study period and was strongly associated with disease severity in pediatric complicated appendicitis. Multidrug-resistant pathogens were predominantly identified in patients with intra-

abdominal abscesses and diffuse peritonitis and frequently necessitated escalation of antimicrobial therapy, which was associated with prolonged hospital stay. While established empirical regimens remained sufficient in localized disease, their effectiveness appeared reduced in severe cases. These findings underscore the importance of severity-adapted empirical antibiotic strategies, continuous local microbiological surveillance, and careful consideration of early escalation with subsequent de-escalation in high-risk pediatric patients

References

1. Anandalwar SP, Cameron DB, Graham DA, Melvin P, Dunlap JL, Kashtan M, Hall M, Saito JM, Barnhart DC, Kenney BD, Rangel SJ. Association of intraoperative findings with outcomes and resource use in children with complicated appendicitis. JAMA Surg. 2018;153(11):1021–1027.
2. Walędziak M, Lasek A, Wysocki M, Su M, Bobowicz M, Myśliwiec P, et al. Risk factors for serious morbidity, prolonged length of stay and hospital readmission after laparoscopic appendectomy – results from the Pol-LA multicenter large cohort study. Sci Rep. 2019;9(1):14793.
3. Kerri A. McKee, Donne A. Graham, Shanon L. Gramm et al. Population-Based Intraoperative Disease Severity Criteria for Appendicitis in Children. JAMA Surg. 2024 Sep 1;159(9):1041-1050.
4. Seema P Anandalwar, Danielle B Cameron, Dionne A Graham et al. Association of Intraoperative Findings With Outcomes and Resource Use in Children With Complicated Appendicitis. JAMA Surg. 2018 Nov 1;153(11):1021-1027.
5. Javier Arredondo Montero, María Rico-Jiménez.Post-discharge oral home antibiotic use in complicated pediatric appendicitis: a systematic review and meta-Analysis. World J Pediatr. 2026 Jan;22(1):104-128.
6. Pia Löfgren, Elias Berge, Elisabeth M L de Wijkerslooth et al.Effectiveness and Safety of Shortened Postoperative Antibiotic Regimens in Children with Perforated Appendicitis: A Systematic Review and Meta-Analysis. Eur J Pediatr Surg. 2026 Jun;36(3):210-216.
7. Loes van den Boom, Elisabeth M L de Wijkerslooth, Bas P L Wijnhoven.Systematic Review and Meta-Analysis of Postoperative Antibiotics for Patients with a Complex Appendicitis. Dig Surg. 2020;37(2):101-110.
8. Rimma Melamed, Doreen Ozalvo, Orli Sagi et al. Rising Multidrug-Resistant Pathogens in Pediatric Appendicitis: A Decade-Long Study from Southern Israel. Observational Study Eur J Pediatr Surg. 2025 Oct;35(5):375-381.
9. Faruk Koca, Sara Fatima Faqar-Uz-Zaman, Claudia Reinheimer et al. A Prospective Analysis of the Burden of Multi-Drug-Resistant Pathogens in Acute Appendicitis and Their Implication for Clinical Management. Antibiotics (Basel). 2025 Apr 4;14(4):378.
10. Rana F Hamdy, Lori K Handy, Evangelos Spyridakis et al.Comparative Effectiveness of Ceftriaxone plus Metronidazole versus Anti-Pseudomonal Antibiotics for Perforated Appendicitis in Children. Surg Infect (Larchmt). 2019 Jul;20(5):399-405.
11. Mark A Kashtan, Dionne A Graham, Patrice Melvin et al.Ceftriaxone with Metronidazole versus Piperacillin/Tazobactam in the management of complicated appendicitis in children: Results from a multicenter pediatric NSQIP analysis. J Pediatr Surg. 2022 Oct;57(10):365-372.
12. Ramon R Gorter, Hasan H Eker, Marguerite A W Gorter-Stam.Diagnosis and management of acute appendicitis. EAES Consensus development conference 2015. Surg Endosc. 2016 Nov;30(11):4668-4690.
13. Andrés García-Marín, Mercedes Pérez-López, Elena Martínez-Guerrero. Microbiologic Analysis of Complicated and Uncomplicated Acute Appendicitis. Surg Infect (Larchmt). 2018 Jan;19(1):83-86.

14. Orlando Bunces-Orellana, Eduardo Arevalo-Vidal, Karla Bustos-Galarza et al. Carbapenems versus ciprofloxacin/metronidazole for decreasing complications and hospital stay following complicated acute appendicitis surgery: A prospective cohort in an Ecuadorian population. Cir Cir. 2020;88(3):297-305.
15. Tsubasa Aiyoshi, Kouji Masumoto, Nao Tanaka et al. Optimal First-Line Antibiotic Treatment for Pediatric Complicated Appendicitis Based on Peritoneal Fluid Culture. Pediatr Gastroenterol Hepatol Nutr. 2021 Nov;24(6):510-517.
16. Quanwei Wang, Xiao Xu, Weiwei Ma et al. Bacteriological Profile and Antimicrobial Resistance in Intraoperative Purulent Samples From Acute Appendicitis: A 3-Year Retrospective Analysis ANZ J Surg. 2026 Apr;96(4):989-998.
17. Zenon Pogorelić , Nikica Silov, Miro Jukić et al. Ertapenem Monotherapy versus Gentamicin Plus Metronidazole for Perforated Appendicitis in Pediatric Patients. 2019 Dec;20(8):625-630.
18. Simeon Barth, Markus Hufnagel, Lennard Forßmann et al. Bacterial Pathogens and Antibiotic Resistance Patterns in Pediatric Appendicitis: Implications for Antibiotic Choice. Pediatric Infect Dis J . 2026 Feb 24.
19. Zenon Pogorelić, Sachit Anand, Tomislav Žuvela et al. Incidence of Complicated Appendicitis during the COVID-19 Pandemic versus the Pre-Pandemic Period: A Systematic Review and Meta-Analysis of 2782 Pediatric Appendectomies. Diagnostics (Basel). 2022 Jan 6;12(1):127.