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2 days versus 5 days of postoperative antibiotics for complex appendicitis: a pragmatic, open-label, multicentre, non-inferiority randomised trial

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Summary

Background The appropriate duration of postoperative antibiotics for complex appendicitis is unclear. The increasing global threat of antimicrobial resistance warrants restrictive antibiotic use, which could also reduce side-effects, length of hospital stay, and costs.

Methods In this pragmatic, open-label, non-inferiority trial in 15 hospitals in the Netherlands, patients with complex appendicitis (aged ≥8 years) were randomly assigned (1:1) to receive 2 days or 5 days of intravenous antibiotics after appendicectomy. Randomisation was stratified by centre, and treating physicians and patients were not masked to treatment allocation. The primary endpoint was a composite endpoint of infectious complications and mortality within 90 days. The main outcome was the absolute risk difference (95% CI) in the primary endpoint, adjusted for age and severity of appendicitis, with a non-inferiority margin of 7·5%. Outcome assessment was based on electronic patient records and a telephone consultation 90 days after appendicectomy. Efficacy was analysed in the intention-to-treat and per-protocol populations. Safety outcomes were analysed in the intention-to-treat population. This trial was registered with the Netherlands Trial Register, NL5946.

Findings Between April 12, 2017, and June 3, 2021, 13 267 patients were screened and 1066 were randomly assigned, 533 to each group. 31 were excluded from intention-to-treat analysis of the 2-day group and 30 from the 5-day group owing to errors in recruitment or consent. Appendicectomy was done laparoscopically in 955 (95%) of 1005 patients. The telephone follow-up was completed in 664 (66%) of 1005 patients. The primary endpoint occurred in 51 (10%) of 502 patients analysed in the 2-day group and 41 (8%) of 503 patients analysed in the 5-day group (adjusted absolute risk difference 2·0%, 95% CI −1·6 to 5·6). Rates of complications and re-interventions were similar between trial groups. Fewer patients had adverse effects of antibiotics in the 2-day group (45 [9%] of 502 patients) than in the 5-day group (112 [22%] of 503 patients; odds ratio [OR] 0·344, 95% CI 0·237 to 0·498). Re-admission to hospital was more frequent in the 2-day group (58 [12%] of 502 patients) than in the 5-day group (29 [6%] of 503 patients; OR 2·135, 1·342 to 3·396). There were no treatment-related deaths.

Interpretation 2 days of postoperative intravenous antibiotics for complex appendicitis is non-inferior to 5 days in terms of infectious complications and mortality within 90 days, based on a non-inferiority margin of 7·5%. These findings apply to laparoscopic appendicectomy conducted in a well resourced health-care setting. Adopting this strategy will reduce adverse effects of antibiotics and length of hospital stay.

Funding The Netherlands Organization for Health Research and Development.

Introduction

With an incidence of 100–151 per 100 000 person-years in high-income countries, acute appendicitis is the most prevalent surgical emergency in both children and adults.[1] Approximately 30% of patients present with complex appendicitis, which is defined as appendicitis with necrosis, perforation, abscess, or purulent peritonitis.[2–5] The standard treatment for complex appendicitis is appendicectomy followed by antibiotics. The aim of postoperative antibiotics is to reduce infectious complications, which occur in up to 20% of patients.[6–10]

Antibiotics can have side-effects including diarrhoea, nausea, allergies, thrombophlebitis, and *Clostridioides difficile* infection. Restrictive use of antibiotics could reduce the length of hospital stay and health-care costs, whereas overuse is one of the main causes of antimicrobial resistance.[11] Antibiotic stewardship and standardisation of care is therefore warranted.[12] The STOPIT trial[10] showed that, after an adequate source-control procedure for a complicated intra-abdominal infection, 4 days of intravenous antibiotics is non-inferior to a longer regimen. The duration and route of administration of postoperative

Research in context

Evidence before this study

International guidelines recommend 3–5 days of postoperative antibiotics after an appendicectomy for complex acute appendicitis. A systematic review by our group, published in 2019, showed no association between the duration of antibiotics and the prevalence of infectious complications. Another systematic review of papers published until June, 2019, which included three randomised trials and four observational studies, reached similar conclusions. A systematic search of relevant studies published since June, 2019, found one randomised trial assessing a 3-day intravenous regimen in children younger than 14 years and five cohort studies evaluating the use of 3 days or fewer of postoperative antibiotics. None of these studies showed a benefit to extended antibiotic use. The validity of these reviews was limited by the poor methodological quality of the included studies. Therefore, no consensus exists regarding the optimum duration of antibiotics after appendicectomy for complex appendicitis, leading to great variation in clinical practice.

Added value of this study

The optimum duration of treatment has been a topic of debate, while the increasing global threat of antimicrobial resistance calls for antibiotic stewardship. To our knowledge, this is the first adequately powered level I randomised controlled trial that evaluates the safety and efficacy of postoperative antibiotics restricted to 2 days. This trial shows that a reduction in antibiotic use and length of hospital stay can be reached without compromising safety.

Implications of all the available evidence

This study indicates that more than 2 days of postoperative antibiotics for complex appendicitis is not needed after adequate source control. Adopting this strategy for most patients with complex appendicitis is expected to reduce the adverse effects of antibiotics and relieve pressure on hospital bed capacity. These recommendations are valid for laparoscopic appendicectomy in a well resourced health-care setting. After open appendicectomy, patients might benefit from an extended regimen of antibiotics. Whether 2 days of antibiotics is safe for patients who are immunocompromised or pregnant is unknown.

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See **Online** for appendix

antibiotics for complex appendicitis are highly variable.[13–15] Common practice is to administer intravenous antibiotics for 3–5 days, often followed by oral antibiotics at discharge.[6,10,16] One randomised trial (N=80)[17] and several observational studies[13,14,18] suggested that antibiotics could be restricted to 24–72 h after appendicectomy without increasing the risk of infectious complications.

The antibiotics following appendicectomy in complex appendicitis (APPIC) trial was designed to compare a 2-day regimen of intravenous postoperative antibiotics with a 5-day regimen. At the time of drafting the study protocol, 5 days of antibiotics was standard practice and this group was therefore defined as the control group of the study.[15,16,19,20] Cohort studies have suggested that 3 days or fewer might be sufficient.[7,21–26] Dutch guidelines advise a minimum of 3 days of antibiotics, which should be administered intravenously for at least 2 days. In addition, a 2-day antibiotic regimen was chosen for the experimental group because 2 days of antibiotics ensure sufficient tissue concentration and penetration to act against bacteria that are commonly isolated in patients with appendicitis (eg, *Escherichia coli*).[27,28] The hypothesis was that a 2-day regimen is non-inferior to a 5-day regimen in terms of infectious complications and mortality within 90 days after appendicectomy.

Methods

Study design

The APPIC trial was a pragmatic, open-label, randomised controlled trial powered for non-inferiority. The trial design was published in May, 2018,[29] and the full protocol, including the statistical analysis plan, is available in the appendix (p 27). The trial was approved by the institutional review board of Erasmus MC (reference number MEC2016719) and the ethics committee at each trial site. The trial was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. This Article was prepared in concordance with the Consolidated Standards of Reporting Trials (CONSORT) checklist and its extensions applicable to the trial design.[30]

Patients

Patients with acute appendicitis were eligible for inclusion if they were aged 8 years or older, had an American Society of Anesthesiologists (ASA) classification of I–III, and had a diagnosis of complex appendicitis (defined as the presence of necrosis, perforation, or abscess, as assessed intraoperatively).[2–5] Patients were excluded if they were pregnant, immunocompromised, or had a contraindication to the trial drugs (eg, allergy), or if adequate source control could not be reached during surgery. Other exclusion criteria are provided in the full protocol (appendix p 48). Eligible patients were approached for participation in the study before or after surgery in one academic centre and 14 teaching hospitals in the Netherlands, a well resourced health-care setting. All participants gave written informed consent. In June, 2019, an informational video was developed to support the informed consent process.

For the **informational video** see https://youtu.be/LhGM6JHs7QQ

Randomisation and masking

Surgeons and surgical residents recruited and randomly assigned eligible patients online to one of two groups

within 24 h after appendicectomy. Computerised block randomisation (random sized blocks, size range 4 to 8), stratified for centre, was used to allocate patients in a 1:1 ratio to receive 2 days or 5 days of intravenous antibiotics after appendicectomy. Treating physicians and patients were not blinded to treatment allocation because of feasibility concerns.

Procedures

Participants were randomised to 2 days or 5 days of postoperative antibiotics after appendicectomy. The antibiotics administered were either intravenous cefuroxime (1500 mg three times daily) or ceftriaxone (2000 mg once daily), plus metronidazole (500 mg three times daily). The first dose was to be administered within 8 h after appendicectomy. In children (aged 8–17 years), the dose was adjusted according to weight. A daily single dose of intravenous gentamycin was allowed as a co-intervention, according to local hospital protocol (ie, in case of sepsis). After 2 days or 5 days, antibiotics were stopped. A deviation in trial regimen was allowed only in one of three situations: intraoperative culture results necessitated a change to a different antibiotic agent, an extension of antibiotic treatment, or both; adverse effects to antibiotics (eg, allergic reaction or thrombophlebitis) or repeated failure of intravenous administration required early discontinuation; or a postoperative infectious complication (supported by laboratory and imaging studies) warranted a restart or extension of antibiotic treatment, or a change to a different antibiotic agent. A change to oral formula was not allowed owing to concerns regarding compliance with the study protocol and possible inferior tissue penetration of the oral antibiotics (amoxicillin–clavulanate) that are most frequently used in practice in the Netherlands.[27]

Diagnostic tests, preoperative antibiotic prophylaxis, and surgical approach followed local hospital standards. In each centre, the surgical staff was trained in trial procedures (ie, knowledge of inclusion and exclusion criteria, diagnosis of complex appendicitis, informed consent procedure, and study medication regimen).

Postoperative laboratory tests, imaging studies, and blood cultures were done upon clinical indication, according to local protocol. Discharge criteria were absence of fever for 24 h, ability to tolerate oral intake, ability to mobilise, and adequate pain control with oral analgesics. Final discharge and the type (visit or telephone consultation) and timing of follow-up were at the discretion of the treating physician. 4 weeks after appendicectomy, patients received a Productivity Cost Questionnaire by mail. Follow-up ended 90 days after appendicectomy, at which time the central trial coordinator attempted to contact patients for a telephone consultation.

Outcomes

The primary endpoint was a composite endpoint of infectious complications and mortality within 90 days after appendicectomy. Infectious complications were intra-abdominal abscess and surgical-site infection, according to the US Centers for Disease Control and Prevention definitions of these conditions.[31] Secondary endpoints were the duration of postoperative antibiotics; the rates of intra-abdominal abscess, surgical-site infection, all postoperative complications (classified according to Clavien-Dindo[32]), adverse effects to antibiotics, restart of antibiotics, re-admission to hospital, and surgical or radiological re-interventions; the length of hospital stay (initial admission and any subsequent stay), the type and number of postoperative imaging studies, and costs. Data on costs will be made available in a separate cost-effectiveness analysis. The trial protocol also listed time to reach discharge criteria as a secondary endpoint; however, for most patients, data on discharge criteria were unavailable or incomplete, so this endpoint is not reported. Primary and secondary outcomes were obtained from the electronic patient files. No routine laboratory or imaging tests were done to detect complications. A structured telephone interview at 90 day follow-up was conducted to complement the information in the electronic patient records regarding complications, including signs of surgical-site infection, and unplanned visits to medical facilities.

All data were registered in a secure online ALEA database in a pseudonymised manner by a member of the research team who was unmasked to patient allocation. The ALEA database system was tested and validated by the International Society for Pharmaceutical Engineering GAMP 5 Good Practice Guide.

We conducted two interim safety analyses, after complete follow-up of the 266th patient and the 666th patient, which were reviewed by the data safety and monitoring board. Safety endpoints were mortality and complications classified as Clavien-Dindo class 3 or higher.[32]

Statistical analysis

Cohort studies in the Netherlands have reported infectious complications in 14–19% of patients with complex appendicitis.[21,33,34] In other studies, infectious complications were reported in 14–24% of patients.[2,35–37] On the basis of these data, the primary endpoint for the control group was estimated to be 15%. Sawyer and colleagues[10] defined a margin of 10% to assess non-inferiority for infectious complications after source control for complicated intra-abdominal infections. We set the non-inferiority margin at 7·5%, assuming that infectious complications after appendicectomy for complex appendicitis would lead to minor morbidity and the anticipated advantageous effects of a 2-day antibiotic regimen would be realised.

We did a power analysis using simulation, based on a one-sided 97·5% confidence interval for the effect (absolute risk difference in primary endpoint, adjusted for severity of disease and age) of the trial group. To obtain a power of 90% to establish non-inferiority under the assumptions listed above, 960 patients were needed

(480 per trial arm). To account for possible effects of dropout and missing data in 10% of patients, 1066 patients needed to be included.

We conducted intention-to-treat and per-protocol analyses. In the 2-day group, adherence to the protocol was defined as six doses (within one dose) after appendicectomy. In the 5-day group, adherence to the protocol was defined as 15 doses (within two doses) after appendicectomy. Non-adherence excluded patients from the per-protocol analysis, although exceptions were made for patients who deviated from the regimen because of intraoperative culture results, adverse events to antibiotics, or postoperative complications.

For the primary endpoint, we assessed non-inferiority of the 2-day course using a one-sided 97·5% CI for the effect of the study group (absolute risk difference). This CI was adjusted for the effects of severity of disease (absence *vs* presence of perforation or abscess) and age (age below *vs* above the median age of the trial population) as one categorical covariate, with the method proposed by Klingenberg for the Mantel-Haenszel common risk difference.[38,39] A forest plot was created to show the absolute risk difference and adjusted CIs broken down by age, severity of appendicitis, and surgical approach.[21] In addition, we did logistic regression analysis to identify predictors of the primary endpoint. We used a generalised estimating equations model with an exchangeable working correlation matrix to account for centre effects.[40] The following (prespecified) independent variables were included: treatment allocation, sex, age, ASA classification, surgical approach (laparoscopy *vs* open procedure), and severity of appendicitis (absence *vs* presence of perforation or abscess). Interaction effects between treatment allocation and other predictors were tested and included in the final regression model if significant ($p<0·05$).

Secondary endpoints were compared between trial groups in univariable analysis. We used the χ^2 test for categorical variables and the Mann-Whitney test for continuous variables. A two-sided $p<0·05$ was considered significant. Secondary endpoints were also compared between trial groups in an exploratory subgroup analysis of patients who had open appendicectomy, given the results of the regression analysis on the primary endpoint.

For interim safety analyses, we compared safety endpoints (90-day mortality and overall complications classified as Clavien-Dindo class 3) among the intention-to-treat population using a χ^2 test, with a significance level based on the alpha spending approach of O'Brien and Fleming.[41] Prespecified trial stopping rules were $p<0·000014$ at the first interim analysis and $p<0·009130$ at the second interim analysis. The safety analyses were conducted by the trial statistician (JvR). The results were included in interim reports prepared by the central trial coordinator for review by the data safety and monitoring board; the board was unmasked to treatment allocation. Local collaborators did not have access to interim data. No interim analysis of efficacy (the primary endpoint) was conducted, therefore we did not adjust for bias in the primary endpoint analysis.

In the absence of missing data in the primary outcome and predictors in multivariable analyses, imputation of missing data was not necessary. No allowance was made for multiplicity. Data were analysed with SPSS (version 25) and R statistical software (version 3.5.0).

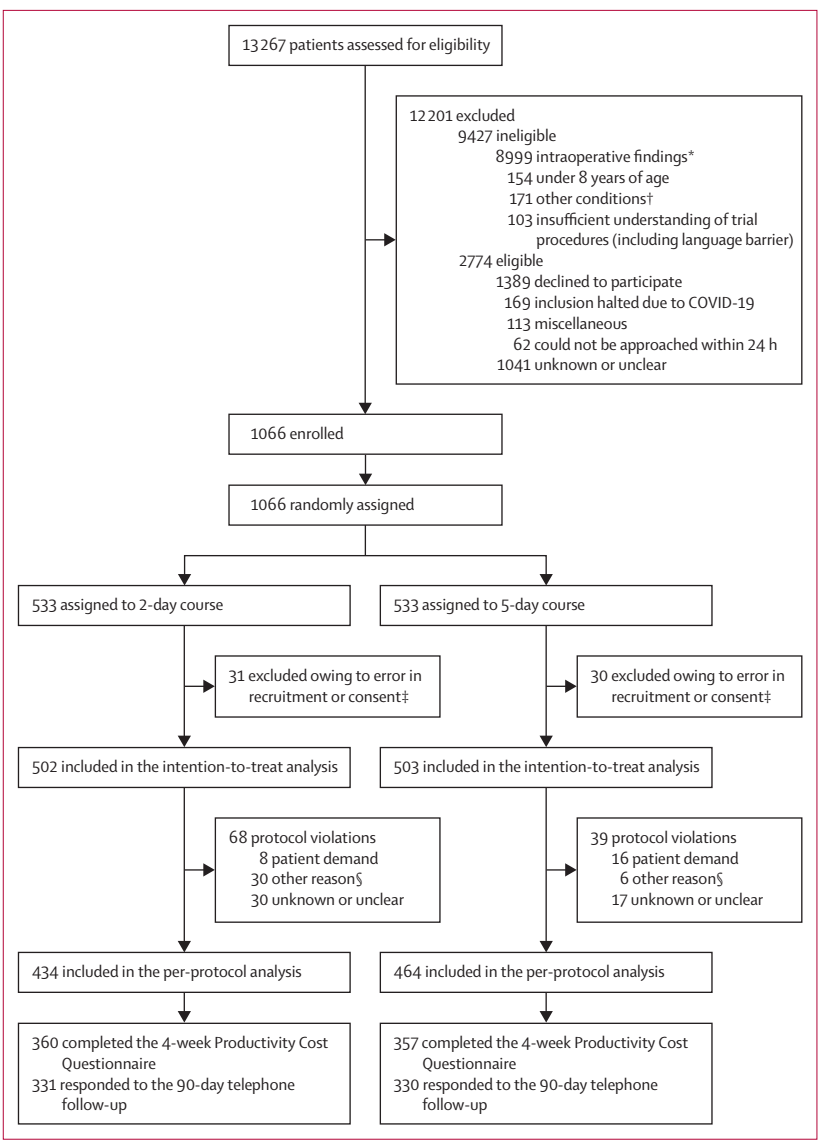

Figure 1: **Trial profile**
*8696 simple appendicitis, 170 complex findings present but not considered indication for postoperative antibiotics, 92 normal appendix, 41 other. †40 immune-compromised, 39 pregnant, 31 contraindication for trial medication, 24 other indication for postoperative antibiotics, 22 signs of severe sepsis, 15 American Society of Anestheologists (ASA) class IV. ‡14 patients were excluded because of a missed exclusion criterion (11 patients who were immunocompromised, two patients classified into ASA class IV, and one with a concurrent other indication for postoperative antibiotics), 39 because of incomplete or unsaved written consent, and eight because of patient withdrawal shortly after randomisation. §Three patients (two in the 2-day group and one in the 5-day group) were given an off-protocol antibiotic agent and seven patients (six in the 2-day group and one in the 5-day group) were prescribed an insufficient dose of cefuroxime. In 26 patients (22 in the 2-day group and four in the 5-day group), antibiotic use was extended in response to clinical signs such as increased body temperature or a single measurement of increased serum C-reactive protein without additional laboratory or imaging studies that detected an infectious focus.

This trial was registered with the Netherlands Trial Register, NL5946.

Role of the funding source

The funder of the study had no role in trial design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between April 12, 2017, and June 3, 2021, 13 267 patients were screened for participation, of whom 9427 (71%) were ineligible for inclusion (figure 1). 1066 patients were randomly assigned: 533 were allocated to the 2-day group and 533 were allocated to the 5-day group. After exclusions due to errors in recruitment or consent, 502 patients in the 2-day group and 503 patients in the 5-day group were included in the intention-to-treat analysis. Follow-up ended on Sept 1, 2021. No important changes in design or methods were made after the start of the trial. Because of the COVID-19 pandemic, trial inclusion was temporarily halted in ten centres for periods ranging from 23 days to 105 days. Evaluation of interim safety reports at the prespecified intervals led the data safety and monitoring board to recommend continuation of the trial (appendix pp 17–18, 25–26). Demographic and clinical characteristics of the intention-to-treat population (n=1005) are shown in table 1. Protocol adherence was 86% (434 of 502 patients) in the 2-day group and 92% (464 of 503 patients) in the 5-day group (table 2). Baseline characteristics of the per-protocol population (n=898) are shown in the appendix (pp 2–4). In 84 (19%) of 434 patients in the 2-day group and 66 (14%) of 464 patients in the 5-day group who adhered to the protocol, a deviation in antibiotic regimen was recorded. The duration of antibiotics was reduced in 12 patients because of adverse reactions to antibiotics, and extended in 47 patients because of perioperative culture results or a postoperative complication (details available in appendix p 3). In 88 patients (58 [13%] of 434 patients in the 2-day group and 30 [6%] of 464 patients in the 5-day group), antibiotics were restarted because of postoperative complications.

The primary endpoint occurred in 51 (10%) of 502 patients in the 2-day group and 41 (8%) of 503 patients in the 5-day group (table 2). No data were missing for the primary endpoint or for covariates used in multivariable analyses. The absolute risk difference, adjusted for age and severity of appendicitis, was 2·0% (95% CI −1·6 to 5·6). By not exceeding the prespecified non-inferiority margin of 7·5%, this finding was consistent with non-inferiority of the 2-day course to the 5-day course. In the logistic regression analysis, an interaction effect was found between treatment allocation and surgical approach (p=0·046). This interaction effect was included in the final regression model. Estimates of the effect of treatment allocation are stratified by the type of surgery. Treatment allocation was not an independent predictor of the primary endpoint (adjusted odds ratio [OR] 1·128 [95% CI 0·719–1·769]; p=0·599) in patients who had laparoscopic appendicectomy. For patients who had open appendicectomy, the adjusted OR of treatment allocation was 10·825 (1·231–95·201; p=0·032) to the disadvantage of the 2-day group. A forest plot of the adjusted absolute risk difference in primary endpoint between the 2-day group and the 5-day group, broken down by age, severity of appendicitis, and surgical approach, is shown in figure 2 for the intention-to-treat population. Per-protocol analyses of the primary endpoint showed similar results (table 2).

Intra-abdominal abscess was observed in 43 (9%) of 502 patients in the 2-day group and 36 (7%) of 503 patients in the 5-day group (table 2); of these patients, 22 (4%) in the 2-day group and 14 (3%) in the 5-day group required

	2-day group (n=502)	5-day group (n=503)
Age (years)	51 (31–62)	52 (30–64)
Age distribution		
8–17 years	49 (10%)	62 (12%)
18–64 years	346 (69%)	320 (64%)
≥65 years	107 (21%)	121 (24%)
Sex		
Male	285 (57%)	286 (57%)
Female	217 (43%)	217 (43%)
ASA score*		
ASA I	235 (47%)	235 (47%)
ASA II	216 (43%)	217 (43%)
ASA III	51 (10%)	51 (10%)
BMI (kg/m²)	26 (23–29)	25 (23–29)
Missing	97 (19%)	109 (22%)
Duration of symptoms (days)	2·0 (1·0–3·0)	2·0 (1·0–2·8)
Missing	9 (2%)	11 (2%)
Body temperature (°C)	37·5 (37·0–38·2)	37·6 (37·0–38·2)
Missing	6 (1%)	6 (1%)
Pulse (bpm)	90 (78–102)	90 (79–104)
Missing	30 (6%)	21 (4%)
White blood cell count (×10⁹ cells per L)	15·1 (12·0–18·1)	15·0 (12·2–18·7)
Missing	..	2 (<1%)
C-reactive protein concentration (mg/L)	100 (44–175)	99 (48–167)
Missing	..	1 (<1%)
Imaging test		
Ultrasonography	397 (79%)	389 (77%)
CT	238 (47%)	228 (45%)
Multiple imaging tests	153 (30%)	139 (28%)
Faecolith on imaging	170 (34%)	151 (30%)
Intravenous antibiotics in the emergency department or ward	150 (30%)	151 (30%)
Antibiotic prophylaxis in the operating room	418 (83%)	405 (81%)
Missing	..	3 (<1%)

(Table 1 continues on next page)

invasive treatment (percutaneous drainage or re-operation). Surgical-site infection occurred in ten (2%) of 502 patients in the 2-day group and five (1%) of 503 patients in the 5-day group (table 2), requiring invasive treatment in only two (<1%) patients in the 2-day group. One patient (in the 2-day group) died on postoperative day 84 of metastasised oesophageal cancer. No significant difference was observed in rates of re-interventions (table 3). The difference in median postoperative length of hospital stay was −2·0 days (95% CI −2·0 to −2·0) in favour of the 2-day group (table 3). Adverse effects of antibiotics (mostly nausea or vomiting and diarrhoea) were observed in more patients in the 5-day group than in the 2-day group (table 3). Visits to the emergency department and hospital re-admission were more frequent in the 2-day group than in the 5-day group (table 3). 94 hospital re-admissions were recorded for 87 (9%) of 1005 patients. Infectious complications were the cause of 49 (52%) of the 94 re-admissions; other reasons are listed in the appendix (p 5). Median time between discharge and re-admission was 5·2 days (IQR 1·3 to 8·8) in the 2-day group and 8·8 days (4·6 to 11·2) in the 5-day group (difference in median −3·2 days, 95% CI −5·3 to −1·0). 20 (35%) of 58 re-admissions in the 2-day group occurred within 5 days after appendicectomy. Results for secondary endpoints were similar in the per-protocol analysis, as shown in the appendix (p 4).

Appendicitis with a perforation or periappendiceal abscess was reported in 775 (77%) of 1005 trial patients, 388 allocated to the 2-day group and 387 to the 5-day group. Outcomes for these patients were similar to outcomes for the total study population. The primary endpoint occurred in 42 (11%) of 388 patients in the 2-day group and 36 (9%) of 387 patients in the 5-day group (adjusted risk difference of 1·5% [95% CI −2·7 to 5·7]; figure 2). Complications required re-admission to hospital in 50 (13%) of 388 patients in the 2-day group and 26 (7%) of 387 patients in the 5-day group (unadjusted OR 2·054 [95% CI 1·250 to 3·375]). 27 (7%) of 388 patients in the 2-day group and 17 (4%) of 387 patients in the 5-day group had radiological or surgical re-intervention (unadjusted OR 1·628 [0·872 to 3·038]).

50 (5%) of 1005 patients had an open appendicectomy, including 28 patients for whom a laparoscopy was converted to an open procedure during surgery. In the 2-day group, six (27%) of 22 patients had an infectious complication (four intra-abdominal abscesses and two surgical-site infections). In the 5-day group, one (4%) of 28 patients had an infectious complication. Details of patients who had an open appendicectomy are shown in the appendix (pp 6–7).

	2-day group (n=502)	5-day group (n=503)
(Continued from previous page)		
Laparoscopic procedure	480 (96%)	475 (94%)
Operating time (min)	47 (36–59)	46 (36–58)
Missing	3 (<1%)	11 (2%)
Classification of appendicitis†		
Gangrenous	264 (53%)	283 (56%)
Perforated	365 (73%)	365 (73%)
Periappendiceal abscess	75 (15%)	61 (12%)
Pus or peritonitis present	421 (84%)	440 (87%)
Diffuse peritonitis	51 (10%)	45 (9%)
Drain placement	8 (2%)	13 (3%)
Histopathological examination‡		
Appendicitis	485 (97%)	491 (98%)
Malignant or premalignant lesion	12 (2%)	8 (2%)
Missing	4 (1%)	5 (1%)

Data are n (%) or median (IQR). Percentages might not total 100 because of rounding. The distribution of patient allocation stratified by centre is shown in the appendix (p 8). ASA=American Society of Anesthesiologists. bpm=beats per min. *For 57 patients in the 2-day group and 51 in the 5-day group, ASA classification was not registered in the electronic patient files but was retrospectively assigned by the researchers on the basis of information in the patient files. †For 23 patients in the 2-day group and 17 in the 5-day group, the type of appendicitis was judged as complex, without explicit description of necrosis, perforation, or abscess in the surgical report; for another three patients the surgical report was missing or incomplete, but notes in the electronic patient dossier confirmed complex findings. ‡For seven patients in the 2-day group and 13 patients in the 5-day group, the histopathology report showed findings of appendicitis alongside findings of benign, malignant, or premalignant lesion; for one patient in the 2-day group and three patients in the 5-day group, benign pathology was found without signs of appendicitis.

Table 1: **Baseline characteristics of the intention-to-treat population**

Discussion

This pragmatic, randomised controlled trial on the duration of postoperative antibiotics in patients with complex appendicitis showed that 2 days of intravenous antibiotics was non-inferior to 5 days. The absolute risk difference in infectious complications and mortality—corrected for age and severity of appendicitis—was 2·0% in favour of the 5-day group. Patients in the 5-day group had fewer Clavien-Dindo class 2 complications, visits to the emergency department, and hospital re-admissions than patients in the 2-day group. Patients in the 2-day group had fewer adverse effects from antibiotics than those in the 5-day group, and their overall hospital stay was shorter, even when including re-admissions.

This study supports the idea that extended antibiotic prophylaxis for intra-abdominal infections is not indicated after adequate source control.[10,18,42] 2 days of antibiotics did not result in a significant increase in postoperative complications or re-interventions. However, the higher rate of Clavien-Dindo class 2 complications in the 2-day group than in the 5-day group deserves attention. In approximately half of patients in the 2-day group with these complications, an infectious focus (intra-abdominal infection, surgical-site infection, pneumonia, urinary tract infection, or other) was diagnosed and treated with antibiotics. In about a quarter of these patients, antibiotics were restarted because of fever, abdominal pain, increased inflammation parameters, or ileus, without confirmation of an infection in imaging studies or cultures. These symptoms could be considered as a manifestation of ongoing postoperative

	2-day group	5-day group	Risk difference (95% CI)		Odds ratio (95% CI)	
			Univariable	Multivariable*	Univariable	Multivariable†
Intention-to-treat						
Intra-abdominal abscess, surgical-site infection, or mortality	51 (10%)	41 (8%)	2·0% (–1·6 to 5·6)	2·0% (–1·6 to 5·6)	1·274 (0·828 to 1·961)	1·128 (0·719 to 1·769)
Intra-abdominal abscess	43 (9%)	36 (7%)	1·4% (–1·9 to 4·8)	..	1·215 (0·766 to 1·927)	..
Surgical-site infection	10 (2%)	5 (1%)	1·0% (–0·6 to 2·6)	..	2·024 (0·687 to 5·965)	..
Mortality	1 (<1%)	..	0·2% (–0·5 to 0·9)	..	..	..
Total	n=502	n=503	..	..	..	..
Per-protocol						
Intra-abdominal abscess, surgical-site infection, or mortality	45 (10%)	39 (8%)	2·0% (–1·9 to 5·8)	2·1% (–1·8 to 5·9)	1·261 (0·804 to 1·978)	1·132 (0·710 to 1·805)*
Intra-abdominal abscess	38 (9%)	34 (7%)	1·4% (–2·2 to 5·0)	..	1·214 (0·749 to 1·966)	..
Surgical-site infection	8 (2%)	5 (1%)	0·8% (–0·9 to 2·5)	..	1·724 (0·560 to 5·311)	..
Mortality	1 (<1%)	..	0·2% (–0·5 to 1·0)	..	..	..
Total	n=434	n=464	..	..	..	..

*Adjusted for age (below *vs* above median age) and severity of appendicitis (absence *vs* presence of perforation or abscess). †Adjusted for the following independent variables: treatment allocation, centre, sex, age, American Society of Anesthesiologists classification, surgical approach (laparoscopy *vs* open procedure), and severity of appendicitis (absence *vs* presence of perforation or abscess) and for the interaction effect between treatment allocation and surgical approach. Given values apply to patients who had a laparoscopic appendicectomy. For patients who had an open appendicectomy, the adjusted odds ratio of treatment allocation was 10·825 (95% CI 1·231–95·201; p=0·032) in the intention-to-treat population and 11·038 (1·115–109·242; p=0·040) in the per-protocol population.

***Table 2*: Primary endpoint analysis**

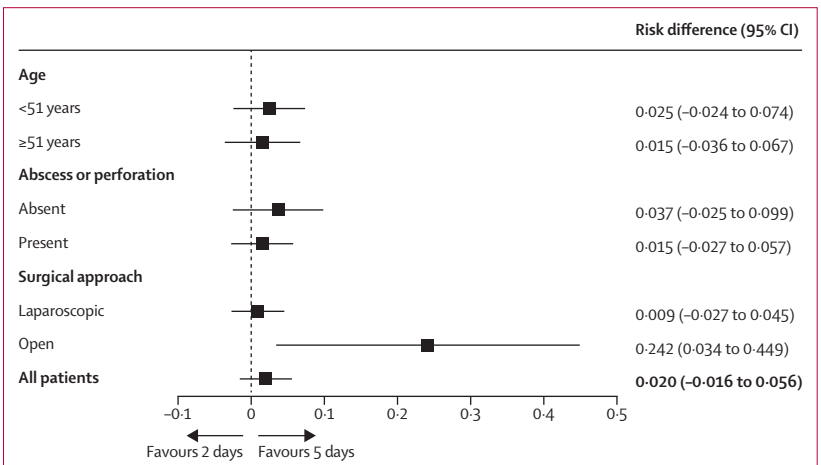

***Figure 2*: Forest plot of primary endpoint by age, severity of appendicitis, and surgical approach**
Risk differences and 95% CIs are based on the Klingenberg method for the Mantel-Haenszel common risk difference.[38,39]

systemic inflammatory response, and a restart of antibiotics might have been avoided.

The higher rate of hospital re-admissions in the 2-day group than in the 5-day group could be attributed to infectious complications in 53% of these patients. Other indications for re-admission were mostly postoperative ileus and pain or fever without an infectious focus. A third of hospital re-admissions in the 2-day group occurred within 5 days after appendicectomy. Patients in the 5-day group could have had similar symptoms while in hospital. Despite the higher rate of re-admission, the total length of hospital stay within 90 days (including re-admission) was still significantly shorter in the 2-day group than in the 5-day group. It can be concluded that the benefit of reduced antibiotic use and shorter hospital stay outweighs an increased risk of re-admission or complications that do not need surgical or radiological interventions. Physicians could have had a low threshold for re-admitting patients and restarting antibiotics for patients in the 2-day group, as this was experimental when the study started. Implementation of a 2-day course of postoperative antibiotics in clinical practice might increase familiarity with this regimen and result in fewer re-admissions to hospital and a reduction in the restarting of antibiotics in the absence of an infectious focus.

The findings of this study are valid for laparoscopic appendicectomy. In a small subgroup of patients who had open appendicectomy (N=50), allocation to the 2-day group was an independent predictor of infectious complications. Approximately half of the open procedures were laparoscopies that were converted to open procedures during surgery. Patients in this group possibly had more severe intra-abdominal contamination, which could therefore represent suboptimal source control with an increased risk of infectious complications. 5 days of antibiotics could be indicated after open appendicectomy for complex appendicitis, but this needs further investigation.

Overuse of antibiotics is a risk factor for antimicrobial resistance.[11,43] This increasing worldwide threat calls for

	2-day group (n=502)	5-day group (n=503)	Effect size* (95% CI)
Protocol adherence	434 (86%)	464 (92%)	0·536 (0·354 to 0·812)
Administered medication†			
Number of days	2·0 (2·0 to 2·3)	5·0 (4·7 to 5·0)	−2·7 (−3·0 to −2·7)
Number of doses	6 (6 to 7)	15 (14 to 15)	−8·0 (−9·0 to −8·0)
Missing	20 (4%)	13 (3%)	..
Complications			
Any complication	125 (25%)	104 (21%)	1·272 (0·946 to 1·710)
Clavien-Dindo class 1	36 (7%)	53 (11%)	0·656 (0·421 to 1·021)
Clavien-Dindo class 2	72 (14%)	51 (10%)	1·484 (1·013 to 2·175)
Clavien-Dindo class 3a	19 (4%)	11 (2%)	1·759 (0·829 to 3·736)
Clavien-Dindo class 3b	14 (3%)	12 (2%)	1·174 (0·537 to 2·564)
Clavien-Dindo class 4a	1 (<1%)	0	..
Comprehensive complication index‡	20·9 (20·9 to 26·2)	20·9 (8·6 to 29·4)	0·0 (0·0 to 3·2)
Re-interventions			
Any re-intervention	32 (6%)	21 (4%)	1·563 (0·888 to 2·749)
Percutaneous drainage	18 (4%)	13 (3%)	1·402 (0·679 to 2·892)
Reoperation	15 (3%)	10 (2%)	1·518 (0·676 to 3·413)
Adverse effects of antibiotics§	45 (9%)	112 (22%)	0·344 (0·237 to 0·498)
Postoperative length of stay (h)	69 (61 to 94)	126 (118 to 139)	−56 (−58 to −53)
Missing	1 (<1%)	2 (<1%)	..
Postoperative length of stay (days)	3·0 (2·0 to 4·0)	5·0 (5·0 to 6·0)	-2·0 (-2·0 to 2·0)
Missing	..	1 (<1%)	..
Unplanned medical visits			
Emergency department visits	76 (15%)	39 (8%)	2·118 (1·409 to 3·185)
Outpatient clinic visits	59 (12%)	49 (10%)	1·231 (0·825 to 1·838)
General practitioner visits	56 (17%)	47 (14%)	1·248 (0·819 to 1·902)
Missing	172 (34%)	169 (34%)	..
Hospital re-admission	58 (12%)	29 (6%)	2·135 (1·342 to 3·396)
Total length of stay (days)¶	3·0 (3·0 to 5·0)	5·0 (5·0 to 6·0)	−2·0 (−2·0 to −2·0)
Missing	..	1 (<1%)	..

Data are n (%) or median (IQR), unless otherwise stated. Between-group differences in medians were estimated using the Hodges-Lehmnann estimator. CIs for between-group differences in proportions were calculated using the Agresti-Caffo interval. *Effect size is shown as odds ratio (95% CI) for categorical outcomes and absolute difference in median (95% CI) for continuous outcomes. †Postoperative administration of cefuroxime (1500 mg three times a day) or ceftriaxone (2000 mg once a day), combined with metronidazole (500 mg three times a day). In the 2-day group, 16 (3%) of 502 patients were prescribed follow-up oral antibiotics, which was classed as a protocol violation in five (1%) patients. In the 5-day group, 28 (6%) of 503 patients were prescribed follow-up oral antibiotics, which was classed as a protocol violation in 13 (3%) patients. Two (<1%) patients in the 2-day group and six (1%) patients in the 5-day group received gentamycin as a co-intervention. ‡The comprehensive complication index (CCI) result is a median of CCI scores of 125 patients in the 2-day group and 104 patients in the 5-day group who had a postoperative complication. §The reported adverse effects were nausea or vomiting (n=96), diarrhoea (n=83), allergic reaction (n=4), *Clostridioides difficile* infection (n=3), and thrombophlebitis (N=2). For 31 patients, two adverse effects were reported. ¶Total length of hospital stay is the sum of the original hospital admission and any re-admissions.

Table 3: **Univariable comparison of secondary outcomes in the intention-to-treat population**

critical review of standard antibiotic courses. As approximately 15% of prescribed antibiotics are related to perioperative care, this setting can be a major driver of emerging infections (eg, *C difficile*) and antimicrobial resistance.[12] Standard courses of antibiotics have been reduced in length after studies showed no benefit of extended courses.[42] The STOPIT trial showed similar rates (22%) of infectious complications and mortality after a fixed 4-day course of antibiotics to those after a longer, variable course (median 8 days), in patients with intra-abdominal infections and adequate source control.[10] 73 of 518 patients in that trial had complex appendicitis. Therefore, no definite conclusion on the safety and efficacy of a short course of antibiotics after complex appendicectomy could be made.

Two randomised studies on postoperative antibiotics for complex appendicitis have been published within the past 4 years. Liu and colleagues[6] found similar rates of infectious complications in children with a fixed 72 h intravenous course of antibiotics (N=350) and with a

prolonged intravenous course of antibiotics (minimum of 5 days intravenous antibiotics followed by oral antibiotics to complete 10 days; N=336). 9% of patients in the 72 h group still received additional oral antibiotics at discharge. Saar and colleagues[17] compared 24 h of intravenous antibiotics to an extended course on the basis of clinical signs. Approximately 20% of patients had infectious complications in both groups. The small sample size (N=80) and the short follow-up of 1 month limit the internal validity of this study. The rate of infectious complications in our trial was lower than expected. We anticipated a rate of 15% based on pre-existing cohort studies,[2,21,33–37] including a large Dutch cohort of 1901 patients with appendicitis.[21] A potential explanation is that the rate of open surgery (or surgery that was converted to open from laparoscopic) in the present population was lower than in the study of the large Dutch cohort (5% *vs* 8%) and the median age in our study was higher (51 years *vs* 44 years).[21] Few paediatric patients (111 patients, aged 8–17 years) were included in our trial. Younger age is associated with an increased risk of intra-abdominal abscess after appendicectomy.[33,44,45] The rate of surgical-site infection in the study by Liu and colleagues[6] (7%) was almost five times that in our study (1·5%). Their follow-up was longer (6 months); however, all infectious complications in the present study were diagnosed within 34 days after operation. To minimise the risk of bias in data collection by an unmasked research team, an independent trial agency monitored trial conduct at regular intervals. The monitors also reviewed primary endpoint assessment in a random selection of trial patients. Another measure taken to prevent under-reported complications was the telephone consultation at 90 days follow-up. 664 (66%) of 1005 patients responded to the follow-up call. None of these patients reported a complication that was not already present in the electronic patient files. However, surgical-site infection could still be under-reported. A study showed a high risk of under-reported surgical-site infection when no physical examination was conducted.[46]

The 7·5% non-inferiority margin might seem large given the low rate of infectious complications, but the risk difference observed between groups was small. Logistic regression analysis also showed no significant association between treatment allocation and infectious complications for laparoscopic appendicectomy. The risk difference of 2·0% translates to a number needed to treat of 50; that is, for each 50 patients that would be treated with the experimental 2-day course, one additional patient will have an infectious complication. The upper limit of 95% CI for the risk difference, 5·6%, would translate to a number needed to treat of 18. Given the mild to moderate morbidity associated with infectious complications, and the shorter hospital stay and reduced adverse events related to antibiotics that are associated with a shorter course, the 7·5% non-inferiority margin is still adequate.

This study has limitations. Only 28% of eligible patients agreed to participate in our study. Our screening log revealed that for 27% of eligible patients the reason for non-participation was unclear. This lack of knowledge about non-participation could have introduced some degree of selection bias. Upon completion of data collection for the cohort-eligible non-participants, comparison with the trial population will address this concern. As few children participated in the trial and patients who were pregnant or immunocompromised were excluded from participation, whether a 2-day course of antibiotics is safe in these patients remains unclear. Non-adherence to the study protocol was 14% in the 2-day group and 8% in the 5-day group. Incomplete adherence potentially creates bias in the intention-to-treat analysis towards the hypothesis of non-inferiority of the experimental intervention. The per-protocol analysis produced nearly identical results, which alleviates this concern. This was a pragmatic trial, in which clinicians and researchers were not masked to treatment allocation. Masking could have reduced the risk of outcome assessment bias; however, the choice of a non-masked design was made because of feasibility concerns. Having the experimental group remain in hospital for additional days of intravenous saline fluid administration would have increased the pressure on hospital bed capacity compared with general practice. We anticipated that this would discourage hospitals from participating, which in turn would have jeopardised completion of the trial within an acceptable timeframe. Unnecessary hospital stays would also put patients at risk of nosocomial infections. We were unable to reach 34% of patients for the telephone follow-up after 90 days. However, the response rate was similar in both groups, which limits the concern of bias due to potentially under-reported outcomes. As it is nearly impossible to conceal shorter and longer intravenous treatment (and hospital stay) from the electronic patient dossier, outcome assessment was not masked. Of interest is the ongoing ABAP study, which will clarify whether 24 h of intravenous antibiotics can be considered non-inferior to 3 days in a placebo-controlled design.[3] The Danish PIPA trial, a cluster-randomised study of 3 days of postoperative oral versus intravenous antibiotics, might also support reduced use of intravenous antibiotics for complex appendicitis in the future.[47]

In conclusion, after laparoscopic appendicectomy for complex appendicitis, 2 days of intravenous antibiotics is non-inferior to 5 days in the prevention of infectious complications, as measured against our prespecified non-inferiority margin of 7·5%. Restricting postoperative antibiotics to 2 days is expected to lead to a clinically relevant reduction in antibiotic use and hospital stay. Special consideration should be given to patients who have open surgery, who could benefit from an extended regimen of postoperative antibiotics. Further analysis, considering direct hospital costs and societal costs, will

show whether the restrictive 2-day course was also cost-effective.

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Contributors

All authors were involved in the design of the study. ALvdB and BPLW were the lead investigators. EMLdW was the central trial coordinator. All Study Group members were involved with the recruitment of patients. EMLdW collected the data, with support from the Study Group members. The central trial team had access to the full dataset, local investigators had access to the dataset for patients from their centre. JvR and EMLdW did the statistical analyses. EMLdW drafted the manuscript, and all authors critically revised, read, and approved the final manuscript. EMLdW, ALvdB, JvR, and BPLW had full access to all data in the trial. All authors had final responsibility for the decision to submit for publication and vouch for the completeness and accuracy of the data, as well as the fidelity of the trial to the protocol.

Declaration of interests

We declare no competing interests.

Data sharing

The study protocol, including the statistical analysis plan, is provided in the appendix (p 27). After publication of primary and secondary trial results, deidentified patient-level data will be made available upon request (b.wijnhoven@erasmusmc.nl); access criteria will be defined after receipt of a research proposal.

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References

1 Ferris M, Quan S, Kaplan BS, et al. The global incidence of appendicitis: a systematic review of population-based studies. *Ann Surg* 2017; **266:** 237–41.

2 Bhangu A, Søreide K, Di Saverio S, Assarsson JH, Drake FT. Acute appendicitis: modern understanding of pathogenesis, diagnosis, and management. *Lancet* 2015; **386:** 1278–87.

3 Sabbagh C, Siembida N, Dupont H, et al. The value of post-operative antibiotic therapy after laparoscopic appendectomy for complicated acute appendicitis: a prospective, randomized, double-blinded, placebo-controlled phase III study (ABAP study). *Trials* 2020; **21:** 451.

4 Sartelli M, Baiocchi GL, Di Saverio S, et al. Prospective observational study on acute appendicitis worldwide (POSAW). *World J Emerg Surg* 2018; **13:** 19.

5 Cameron DB, Anandalwar SP, Graham DA, et al. Development and implications of an evidence-based and public health-relevant definition of complicated appendicitis in children. *Ann Surg* 2020; **271:** 962–68.

6 Liu Q, Hao F, Chen B, Li L, Liu Q, Guo C. Multi-center prospective study of restrictive post-operative antibiotic treatment of children with complicated appendicitis. *Surg Infect (Larchmt)* 2020; **21:** 778–83.

7 van Rossem CC, Schreinemacher MH, Treskes K, van Hogezand RM, van Geloven AA. Duration of antibiotic treatment after appendicectomy for acute complicated appendicitis. *Br J Surg* 2014; **101:** 715–19.

8 Mazuski JE, Tessier JM, May AK, et al. The Surgical Infection Society revised guidelines on the management of intra-abdominal infection. *Surg Infect (Larchmt)* 2017; **18:** 1–76.

9 Di Saverio S, Podda M, De Simone B, et al. Diagnosis and treatment of acute appendicitis: 2020 update of the WSES Jerusalem guidelines. *World J Emerg Surg* 2020; **15:** 27.

10 Sawyer RG, Claridge JA, Nathens AB, et al. Trial of short-course antimicrobial therapy for intraabdominal infection. *N Engl J Med* 2015; **372:** 1996–2005.

11 Iskandar K, Murugaiyan J, Hammoudi Halat D, et al. Antibiotic discovery and resistance: the chase and the race. *Antibiotics (Basel)* 2022; **11:** 182.

12 Sartelli M, Duane TM, Catena F, et al. Antimicrobial stewardship: a call to action for surgeons. *Surg Infect (Larchmt)* 2016; **17:** 625–31.

13 Ramson DM, Gao H, Penny-Dimri JC, et al. Duration of post-operative antibiotic treatment in acute complicated appendicitis: systematic review and meta-analysis. *ANZ J Surg* 2021; **91:** 1397–404.

14 van den Boom AL, de Wijkerslooth EML, Wijnhoven BPL. Systematic review and meta-analysis of postoperative antibiotics for patients with a complex appendicitis. *Dig Surg* 2020; **37:** 101–10.

15 de Wijkerslooth EML, van den Boom AL, Wijnhoven BPL. Variation in classification and postoperative management of complex appendicitis: a European survey. *World J Surg* 2019; **43:** 439–46.

16 van den Boom AL, de Wijkerslooth EML, Mauff KAL, et al. Interobserver variability in the classification of appendicitis during laparoscopy. *Br J Surg* 2018; **105:** 1014–19.

17 Saar S, Mihnovitš V, Lustenberger T, et al. Twenty-four hour versus extended antibiotic administration after surgery in complicated appendicitis: a randomized controlled trial. *J Trauma Acute Care Surg* 2019; **86:** 36–42.

18 Surat G, Meyer-Sautter P, Rüsch J, Braun-Feldweg J, Germer CT, Lock JF. Retrospective cohort analysis of the effect of antimicrobial stewardship on postoperative antibiotic therapy in complicated intra-abdominal infections: short-course therapy does not compromise patients' safety. *Antibiotics (Basel)* 2022; **11:** 120.

19 Daskalakis K, Juhlin C, Påhlman L. The use of pre- or postoperative antibiotics in surgery for appendicitis: a systematic review. *Scand J Surg* 2014; **103:** 14–20.

20 Desai AA, Alemayehu H, Holcomb GW 3rd, St Peter SD. Safety of a new protocol decreasing antibiotic utilization after laparoscopic appendectomy for perforated appendicitis in children: a prospective observational study. *J Pediatr Surg* 2015; **50:** 912–14.

21 van Rossem CC, Schreinemacher MH, van Geloven AA, Bemelman WA. Antibiotic duration after laparoscopic appendectomy for acute complicated appendicitis. *JAMA Surg* 2016; **151:** 323–29.

22 Henry MCW, Walker A, Silverman BL, et al. Risk factors for the development of abdominal abscess following operation for perforated appendicitis in children: a multicenter case-control study. *Arch Surg* 2007; **142:** 236–41.

23 Skarda DE, Schall K, Rollins M, et al. Response-based therapy for ruptured appendicitis reduces resource utilization. *J Pediatr Surg* 2014; **49:** 1726–29.

24 Kim DY, Nassiri N, Saltzman DJ, et al. Postoperative antibiotics are not associated with decreased wound complications among patients undergoing appendectomy for complicated appendicitis. *Am J Surg* 2015; **210:** 983–87.

25 Kimbrell AR, Novosel TJ, Collins JN, et al. Do postoperative antibiotics prevent abscess formation in complicated appendicitis? *Am Surg* 2014; **80:** 878–83.

26 Cho J, Park I, Lee D, Sung K, Baek J, Lee J. Antimicrobial treatment after laparoscopic appendectomy for preventing a post-operative intraabdominal abscess: a prospective cohort study of 1817 patients. *Int J Surg* 2016; **27:** 142–46.

27 de Velde F, de Winter BC, Koch BC, van Gelder T, Mouton JW. Non-linear absorption pharmacokinetics of amoxicillin: consequences for dosing regimens and clinical breakpoints. *J Antimicrob Chemother* 2016; **71:** 2909–17.

28 Wenzel RP, Edmond MB. Antibiotics for abdominal sepsis. *N Engl J Med* 2015; **372:** 2062–63.

29 van den Boom AL, de Wijkerslooth EML, van Rosmalen J, et al. Two versus five days of antibiotics after appendectomy for complex acute appendicitis (APPIC): study protocol for a randomized controlled trial. *Trials* 2018; **19:** 263.

30 Piaggio G, Elbourne DR, Pocock SJ, Evans SJ, Altman DG, CONSORT Group. Reporting of non-inferiority and equivalence randomized trials: extension of the CONSORT 2010 statement. *JAMA* 2012; **308:** 2594–604.

31 Horan TC, Andrus M, Dudeck MA. CDC/NHSN surveillance definition of health care-associated infection and criteria for specific types of infections in the acute care setting. *Am J Infect Control* 2008; **36:** 309–32.

32 Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg* 2004; **240:** 205–13.

33 van Wijck K, de Jong JR, van Heurn LW, van der Zee DC. Prolonged antibiotic treatment does not prevent intra-abdominal abscesses in perforated appendicitis. *World J Surg* 2010; **34:** 3049–53.

34 Giesen LJ, van den Boom AL, van Rossem CC, den Hoed PT, Wijnhoven BP. Retrospective multicenter study on risk factors for surgical site infections after appendectomy for acute appendicitis. *Dig Surg* 2017; **34:** 103–07.

35 St Peter SD, Sharp SW, Holcomb GW 3rd, Ostlie DJ. An evidence-based definition for perforated appendicitis derived from a prospective randomized trial. *J Pediatr Surg* 2008; **43:** 2242–45.

36 Fallon SC, Hassan SF, Larimer EL, et al. Modification of an evidence-based protocol for advanced appendicitis in children. *J Surg Res* 2013; **185:** 273–77.

37 McGillen PK, Drake FT, Vallejo A, Brahmbhatt TS, Sanchez SE. Retrospective analysis of post-operative antibiotics in complicated appendicitis. *Surg Infect (Larchmt)* 2019; **20:** 359–66.

38 Klingenberg B. A new and improved confidence interval for the Mantel-Haenszel risk difference. *Stat Med* 2014; **33:** 2968–83.

39 Mohamed K, Embleton A, Cuffe RL. Adjusting for covariates in non-inferiority studies with margins defined as risk differences. *Pharm Stat* 2011; **10:** 461–66.

40 Kahan BC. Accounting for centre-effects in multicentre trials with a binary outcome—when, why, and how? *BMC Med Res Methodol* 2014; **14:** 20.

41 O'Brien PC, Fleming TR. A multiple testing procedure for clinical trials. *Biometrics* 1979; **35:** 549–56.

42 Spellberg B. The new antibiotic mantra—"shorter is better". *JAMA Intern Med* 2016; **176:** 1254–55.

43 Malik B, Bhattacharyya S. Antibiotic drug-resistance as a complex system driven by socio-economic growth and antibiotic misuse. *Sci Rep* 2019; **9:** 9788.

44 Fraser JD, Aguayo P, Leys CM, et al. A complete course of intravenous antibiotics vs a combination of intravenous and oral antibiotics for perforated appendicitis in children: a prospective, randomized trial. *J Pediatr Surg* 2010; **45:** 1198–202.

45 Emil S, Elkady S, Shbat L, et al. Determinants of postoperative abscess occurrence and percutaneous drainage in children with perforated appendicitis. *Pediatr Surg Int* 2014; **30:** 1265–71.

46 Ali-Mucheru MN, Seville MT, Miller V, Sampathkumar P, Etzioni DA. Postoperative surgical site infections: understanding the discordance between surveillance systems. *Ann Surg* 2020; **271:** 94–99.

47 Mohamud AA, Kleif J, Gögenur I. Peroral versus intravenous post-operative antibiotics after surgery for complicated appendicitis: protocol for a cluster-randomised cluster-crossover non-inferiority study. *Dan Med J* 2021; **68:** A12200917.