**Region Västra Götaland, HTA-centrum**
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# Can the postoperative routine of intravenous/oral antibiotics after acute appendectomy in children with perforated appendicitis be shortened?

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# [Kan behandlingstiden med intravenös/oral antibiotika efter appendektomi hos barn som opererats på grund av perforerad appendicit förkortas?]

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# 1. Abstract


## Background

Acute appendicitis is one of the most common causes for surgery in children worldwide. In Region Västra Götaland, between 320 and 420 children (<18 years of age) are surgically treated every year and about 75 of these have a perforated appendix. In the latter subgroup, 8–20% experience complications, mostly because of intraabdominal abscess formation. To prevent complications, intravenous antibiotics are prescribed when a perforated appendix is suspected, requiring in-hospital administration postoperatively. In recent years, there is a trend to switch to oral antibiotics as soon as the child can eat after surgery, but recommendations in guidelines are not consistent. Length of postoperative intravenous/oral antibiotic treatment varies considerably between hospitals.

## Question at issue

For children undergoing acute appendectomy due to perforated appendicitis, is a shortened postoperative routine of intravenous/oral antibiotics non-inferior regarding the risk of intraabdominal abscess, and does it affect mortality, ileus, need for intensive care, sepsis, readmission, adverse drug reactions, wound infections, length of stay, and health-related quality of life?

## Methods

Two authors performed literature searches (October 2023) in Medline, Embase, the Cochrane Library, and Cinahl. They independently assessed the abstracts, and selected, in consensus, full-text articles to be sent to the other authors, who then decided in consensus on inclusion or exclusion. The included studies were critically appraised, and data were extracted. Studies without major risk of bias formed the basis for the conclusions. Meta-analyses were performed when applicable using random effects models. The non-inferiority margin for intraabdominal abscess was set beforehand, using the margin applied in a recent randomised controlled trial (RCT); the 95% confidence interval (CI) of the risk difference was not allowed to exceed 7.5 percentage points. Certainty of evidence was assessed according to GRADE. The study protocol was preregistered with PROSPERO (CRD42024501215).

## Results

Three RCTs including a total of 215 patients, and one before/after study including 288 patients, fulfilled the inclusion criteria. No study provided information regarding the need for intensive care, sepsis, or health-related quality of life.

**Intraabdominal abscess:** Three RCTs and one before/after study provided data. For the comparison between different routine treatment lengths of the entire course of intravenous and oral antibiotics, two RCTs (97 *vs.* 95 patients) reported no significant difference. These studies could not be pooled as a 5-day postoperative routine of antibiotic treatment was compared with a 7-day routine in one study and with a 2-day routine in the other. For the comparison between different routine treatment lengths of intravenous antibiotics alone (<5 days versus 5 days), two RCTs (92 vs. 97 patients; 16 vs. 15 events) could be pooled, resulting in a risk difference of 2.1 (-8.3 to 12.5) percentage points, with a corresponding risk ratio of 1.12 (95% CI 0.59 to 2.12). Thus, the upper 95% confidence limit of a 12.5 percentage point increase (one-sided: 10.8 percentage points) surpassed the predefined non-inferiority margin. There was serious imprecision, and some uncertainty regarding directness as well as some study limitations. ***Conclusion:*** The non-inferiority margin was not met and hence an increased risk of intraabdominal abscess by a shortened postoperative routine regarding the treatment length, by 2–3 fewer days for the entire intravenous/oral antibiotics course, and by using a <5-day routine of intravenous antibiotics alone, may not be excluded (GRADE ⊕⊕◯◯).

**Mortality, ileus, and surgical site infection:** One RCT (42 *vs.* 45 patients) provided data regarding these outcomes and compared a 2-day and a 5-day postoperative routine of intravenous antibiotics: 0 *vs.* 0 events regarding mortality, 1 *vs.* 4 events regarding ileus, and 1 *vs.* 0 events regarding surgical site infection. One RCT including 26 patients, comparing a 5-day and a 10-day postoperative routine of intravenous antibiotics, also provided information regarding ileus (0 *vs.* 0 events) and surgical site infection (1 *vs.* 1 event). The results had very serious imprecision and some uncertainty regarding directness as well as some study limitations. ***Conclusion:*** It is uncertain whether a shortened postoperative routine of intravenous antibiotics affects mortality within 90 days, or the risk of postoperative ileus or surgical site infections (GRADE ⊕◯◯◯).
**Readmission, complications to antibiotic treatment:** One RCT (42 *vs.* 45 patients) provided data regarding these outcomes and compared a 2-day and a 5-day postoperative routine of intravenous antibiotics. A total of 9 *vs.* 7 readmissions and 8 *vs.* 9 adverse drug reactions occurred. There was serious imprecision and some uncertainty regarding directness as well as some study limitations. ***Conclusion:*** A shortened postoperative routine of intravenous antibiotics (3 fewer days) may not affect the readmission rate or the risk of complications to antibiotic treatment (GRADE ⊕⊕◯◯).
**Length of stay:** For the comparison between different routine treatment lengths of intravenous antibiotics alone, two RCTs (97 *vs.* 97 patients), comparing <5 days and 5 days of postoperative antibiotics, reported statistically significant shorter length of stay in the intervention group. The mean difference was -2.2 days (95% CI: -2.94 to -1.46) in one RCT and unclear in the other. ***Conclusion:*** A shortened postoperative routine of intravenous antibiotics (total treatment length: <5 days) probably reduces the length of hospital stay (GRADE ⊕⊕⊕◯).

## Costs

The present evidence synthesis does not allow conclusions regarding critical outcomes, and cost analyses are therefore highly uncertain. Assuming that effectiveness and safety are similar for the comparison alternatives and that a shortened postoperative routine of antibiotic treatment would save two in-hospital days per patient (range: 1–3 days), the total cost reduction per patient could be translated to 34 kSEK (range: 17–51 kSEK). Assuming that the shortened routine would be applicable to 60 patients, the yearly resource savings in Region Västra Götaland could be translated to 2 MSEK (range: 1–3 MSEK).

## Ethical considerations

Regarding the patient benefit versus risk balance, this evidence synthesis reveals substantial uncertainties using a shortened postoperative routine of antibiotic treatment in children after surgery due to a perforated appendix. At the population level, a shortened routine is preferable from the perspective of antimicrobial resistance. Regarding equality, the needs and solidarity principle is relevant as a shortened postoperative routine of intravenous antibiotics would probably allow other children with conditions of higher degree of severity to take precedence for hospital care. Regarding the principle of cost-effectiveness, there are advantages with a shortened routine from a cost perspective, but there are uncertainties in the underlying evidence regarding effectiveness and safety. Finally, the principle of autonomy could be relevant as children do not make treatment decisions themselves.

## Conclusion

Non-inferiority regarding the risk of intraabdominal abscess was not shown for a shortened postoperative routine of antibiotic treatment, but a routine of intravenous antibiotics below 5 days, is unlikely to imply an increased risk that exceeds 12.5 percentage points. A shortened postoperative routine of intravenous antibiotics may not affect the risk of readmission and complications to antibiotic treatment, but it probably reduces the length of hospital stay. No

conclusions can be drawn regarding the critical and important outcomes mortality, ileus, and surgical site infection. Given the sparsity of evidence and the fact that the condition is not uncommon, further well-designed studies are considered highly warranted.

# 2. Populärvetenskaplig sammanfattning – Plain language summary in Swedish

### Fråga
Kan det förväntas att efterförloppet inte blir sämre om barn som opererats för brusten blindtarm behandlas kortare tid med antibiotika efter operationen?

### Konklusion
Denna systematiska översikt av befintliga vetenskapliga studier har inte kunnat säkerställa att kortare behandlingstid med antibiotika efter operation för brusten blindtarm inte ökar risken för ansamling av var i buken (abscess). Det är emellertid troligt att en eventuell ökad risk inte överstiger 12,5 procentenheter. Det är möjligt att kortare behandlingstid inte påverkar risken att barnet behöver läggas in på sjukhuset igen eller risken att få biverkningar av antibiotikabehandlingen. Eftersom studierna är små går det inte att dra några slutsatser avseende andra viktiga effekt- och säkerhetsmått. Kortare behandlingstid med antibiotika direkt in i blodet (intravenös behandling) ger dock troligen kortare vårdtider.

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### Bakgrund
I Västra Götalandsregionen opereras ungefär 400 barn varje år för blindtarmsinflammation. För ungefär 75 av dessa har blindtarmen brustit vilket innebär ökad risk för komplikationer i efterförloppet, till exempel bildning av abscess. Komplikationsrisken för patienter som opererats för brusten blindtarm är 8–20 procent. För att minska risken för allvarliga komplikationer ges förebyggande intravenös behandling med antibiotika efter operationen vilket i regel kräver sjukhusvård, och ibland även tablettbehandling efter utskrivning. Längden på behandlingstiden varierar avsevärt mellan olika sjukhus.

### Metod
Med hjälp av etablerade metoder identifierade vi de vetenskapliga artiklar som kunde bidra till att besvara den aktuella frågan. Vi granskade de enskilda studierna, summerade ihop deras resultat och bedömde hur säkra vi kunde vara på det sammanlagda resultatet.

### Resultat
Denna rapport baseras huvudsakligen på tre så kallade randomiserade kontrollerade studier, där patienterna slumpmässigt tilldelats antibiotikabehandling med varierande antal behandlingsdagar. Totalt 215 barn ingick i dessa studier. Materialet var för litet för att kunna säkert avgöra att förekomsten av abscess inte ökar med kortare antibiotikabehandlingstid. Det är dock troligt att en eventuell ökad risk inte överstiger 12,5 procentenheter. Det är möjligt att det inte gör någon skillnad om behandlingslängden med antibiotika kortas ner, vad gäller risken för återinläggning samt risken att få biverkningar av antibiotikabehandlingen. Avseende risken att avlida, att få tarmvred eller att få en sårinfektion var underlaget för litet för att dra några slutsatser – dessa händelser är ovanliga. Inga studier redovisade resultat avseende behov av intensivvård, förekomst av sepsis (”blodförgiftning”) eller livskvalitet. Med en kortare behandlingsrutin vad gäller intravenös antibiotika kommer troligen vårdtiden att minska.

### Kostnader
Tillgängliga studier medger inte slutsatser vad gäller viktiga effekt- och säkerhetsmått. Kostnadsberäkningar blir därför osäkra. Vid antagande om att metoderna är likvärdiga ur nytta- och risksynpunkt, och att vårdtiden minskar 2 dygn med kortare behandlingstid med intravenös

antibiotika, skulle resurser motsvarande totalt 34 tkr kunna frigöras per patient. Vid 1 eller 3 dygns kortare vårdtid skulle frigjorda resurser motsvara 17 respektive 51 tkr. Vid antagande att den kortare behandlingsrutinen skulle kunna användas för 60 patienter årligen skulle resurser motsvarande 2 Mkr per år kunna frigöras till annan prioriterad vård i Västra Götalandsregionen (spridning (1–3 Mkr).

### Etiska överväganden

Det finns betydande osäkerheter i det vetenskapliga underlaget avseende nytta/risk-balansen för kortare behandlingstid med antibiotika hos barn som opererats för brusten blindtarm. På samhällsnivå innebär kortare behandlingstid en fördel vad gäller antibiotikaresistensutveckling. Vad gäller rättviseaspekter är behovs- och solidaritetsprincipen aktuell. Med den troligen kortare vårdtid som behövs med kortare tids intravenös antibiotikabehandling kan platser frigöras för barn som är svårare sjuka. Vad gäller kostnadseffektivitetsprincipen innebär kortare vårdtid mindre kostnader, men på effektsidan är det vetenskapliga underlaget osäkert. Autonomiprincipen är aktuell eftersom barn inte själva tar beslut om sin behandling.

The HTA report was approved by the regional board for quality assurance of activity-based HTA. The English abstract is a concise summary of the HTA. The Swedish summary is written in plain language.

Ylva Carlsson, Associate professor, MD
Head of HTA-centrum of Region Västra Götaland, Sweden, 26 June 2024

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DDS Doctor of dental surgery
MD Medical doctor
PhD Doctor of Philosophy
OD Odontology doctor
PT Physiotherapist
RN Registered Nurse

# 3. Summary of findings

| Outcomes | Antibiotics | Studies (number of patients, I *vs.* C) Compared routine treatment lengths of antibiotics | Relative effect | Absolute effect | Certainty of evidence GRADE |
|---|---|---|---|---|---|
| Intraabdominal abscess | iv+po | 2 RCT (94 *vs.* 95)<br>2 *vs.* 5 days/5 *vs.* 7 days | RR NA | NA<br>(16 *vs.* 15 events, not poolable) | ⊕⊕◯◯[2] |
| | iv | 2 RCT (92 *vs.* 97)<br><5 *vs.* 5 days | RR: 1.12 (95% CI: 0.57 to 2.12) | 16 (17%) *vs.* 15 (15%) events<br>RD: 2.1 (95% CI: -8.3 to 12.5) percentage points | ⊕⊕◯◯[2] |
| Mortality | iv+po<br>iv | 1 RCT (42 *vs.* 45)<br>2 *vs.* 5 days | | 0 *vs.* 0 events | ⊕◯◯◯[1] |
| Ileus | iv+po | 1 RCT (42 *vs.* 45)<br>2 *vs.* 5 days | | 1 *vs.* 4 events | ⊕◯◯◯[1] |
| | iv | 2 RCT (58 *vs.* 55)<br>2 *vs.* 5 days/5 *vs.* 10 days | | NA<br>(1 *vs.* 4 events) | ⊕◯◯◯[1] |
| Intensive care | | 0 | | | - |
| Sepsis | | 0 | | | - |
| Readmission | iv+po<br>iv | 1 RCT (42 *vs.* 45)<br>2 *vs.* 5 days | RR: 1.38 (95% CI: 0.56 to 3.37 | 9 (21%) *vs.* 7 (16%) events<br>RD: 5.9 (95% CI: -10.4 to 22.2) percentage points | ⊕⊕◯◯[2] |
| Complication to antibiotic treatment | iv+po<br>iv | 1 RCT (42 *vs.* 45)<br>2 *vs.* 5 days | RR: 0.95 (95% CI: 0.41 to 2.24) | 8 (19%) *vs.* 9 (20%) events<br>RD: -1.0 (95% CI: -17.6 to 15.7) percentage points | ⊕⊕◯◯[2] |
| Surgical site infection | iv+po | 1 RCT (42 *vs.* 45)<br>2 *vs.* 5 days | | 1 *vs.* 0 events | ⊕◯◯◯[1] |
| | iv | 2 RCT (58 *vs.* 55)<br>2 *vs.* 5 days/5 *vs.* 10 days | | NA<br>(1 *vs.* 0 events) | ⊕◯◯◯[1] |
| Length of hospital stay | iv+po | 2 RCT (94 *vs.* 95)<br>2 *vs.* 5 days/5 *vs.* 7 days | | NA | |
| | iv | 2 RCT (92 *vs.* 97)<br><5 *vs.* 5 days | | P<0.05 in both studies, not poolable | ⊕⊕⊕◯[3] |
| Health-related quality of life | iv | 0 | | | - |

[1]Very serious imprecision, some uncertainty regarding directness, some study limitations
[2]Serious imprecision, some uncertainty regarding directness, some study limitations
[3]Some uncertainty regarding directness, some study limitations
C = comparison, CI = confidence interval, I = intervention, iv = intravenous antibiotic, NA = not applicable, po = oral antibiotic, RD = risk difference, RR = risk ratio

**Certainty of evidence**

| | |
|---|---|
| High certainty<br>⊕⊕⊕⊕ | We are very confident that the true effect lies close to that of the estimate of the effect. |
| Moderate certainty<br>⊕⊕⊕◯ | We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. |
| Low certainty<br>⊕⊕◯◯ | Confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect. |
| Very low certainty<br>⊕◯◯◯ | We have very little confidence in the effect estimate:<br>The true effect is likely to be substantially different from the estimate of effect |

# 4. Abbreviations/Acronyms

| | |
|---|---|
| CRP | C-reactive protein |
| HTA | Health technology assessment |
| RCT | Randomised controlled trial |

# 5. Background

### Disease/disorder of interest and its degree of severity

Acute appendicitis is one of the most common causes for surgery in children worldwide (Rentea et al., 2017). Surgical removal of the inflamed appendix is the most common treatment, the cure of the disease in most cases, and the length of stay in the hospital is usually short. However, approximately 15–20% of children undergoing surgery for acute appendicitis have a perforated appendix. In this group, the complication rate is 8–20%, mostly because of intraabdominal abscess formation but also, for instance, wound infections and adhesions causing intestinal obstruction (Frongia et al., 2016, Henry et al., 2007, Liu et al., 2020, Wang et al., 2019, van Wijck et al., 2010). These well-known complications can lead to a more complicated postoperative course necessitating prolonged antibiotic treatment to treat or prevent abscess formation. Some children even need surgical reintervention. Fatal outcome in children with acute perforated appendicitis is extremely rare (Almström et al., 2019). Untreated intraabdominal abscesses and postoperative inflammation due to acute perforated appendicitis, however, may lead to adhesions and intestinal obstruction (Rasmussen et al., 2018), but the number of children affected is not known.

### Prevalence and incidence

In Sweden, between 2,000 and 2,500 children per year undergo appendectomy due to acute appendicitis. The incidence of acute appendicitis in children in Sweden is 1/1000 person-years (Almström et al., 2018).

### Present treatment

The algorithm for acute perforated appendicitis, used for children at the Sahlgrenska University Hospital, recommends 5–7 days of postoperative antibiotic treatment based on clinical parameters and C-reactive protein (CRP). Intravenous administration is recommended until CRP is below 50, often resulting in at least 5 days of intravenous treatment. In the algorithm, expected length of hospital stay is 7–10 days. A yet unpublished study from Region Västra Götaland, based on children undergoing surgery for acute perforated appendicitis, shows that the median duration of the entire course of intravenous and oral antibiotic treatment is 12.5 days at the Sahlgrenska University Hospital (range: 1–139; mean: 13.9), and 9.7 days in the county hospitals (range: 0–35; mean: 9.9). For intravenous antibiotics alone, the corresponding medians are 5.7 days (range: 1–54; mean: 6.6) and 2.7 days (range: 0.5–21; mean: 3.5), respectively.

### Normal pathway through the healthcare system and current wait time for medical assessment/treatment

Children with acute appendicitis are usually diagnosed in the emergency department. Clinical investigation together with laboratory findings, and in most cases imaging such as abdominal ultrasound or computer tomography scan, are used to confirm the diagnosis. After the decision for surgery, the child is admitted to the surgical department. Preoperative preparation takes place while waiting for surgery, including intravenous fluids and a single dose of intravenous antibiotic prophylaxis (trimethoprim/sulphametoxazol and metronidazole) to reduce the risk of wound infection. Based on the yet unpublished study mentioned under the previous heading, the median length of hospital stay is 6.8 days (range 2–62: days; mean: 8.1) in the Sahlgrenska University Hospital and 3.7 days (range: 0.5–36; mean: 4.6) in the county hospitals.

### Number of patients per year who undergo current treatment regimen

In Region Västra Götaland, between 320 and 420 children <18 years of age are surgically treated for acute appendicitis every year. Around 20% of these, i.e., about 75 patients, have a perforated

appendix. About half of these children are treated at Sahlgrenska University Hospital, and the remaining are equally distributed between the three general surgical units at the county hospitals.

### Present recommendations from medical societies or health authorities

The current postoperative treatment recommendations from the American Pediatric Surgical Association in children operated for acute perforated appendicitis is intravenous broad-spectrum antibiotics for 5 days postoperatively, with a total treatment length of 7 days and allowing an early switch to oral antibiotics if allowed by clinical criteria (Lee et al., 2010). Guidelines from the World Society of Emergency Surgery recommend a switch to oral antibiotics after 48 hours with a total treatment time of less than 7 days (Di Saverio et al., 2020). National guidelines concerning appendicitis were recently published by the Swedish Association of Local Authorities and Regions (SKR, 2024). They recommend starting treatment directly when a perforated appendix is suspected, to continue for 3−5 days, and to switch to oral treatment when allowed from a clinical perspective. Separate recommendations for children are not provided. Until now, many regions, including Region Västra Götaland, recommend a total treatment length of intravenous and oral antibiotics for 5-7 days, with a switch to oral antibiotics when the child can eat and drink.

# 6. Health technology at issue: Postoperative antibiotic treatment length

To prevent severe complications in children with acute perforated appendicitis, intravenous antibiotics have historically been prescribed up to 10 days after appendectomy or even longer, until laboratory values, such as white blood cell count and CRP, are normalised. In recent years, there is a trend towards a switch to oral antibiotics as soon as the child can eat after surgery, but there is no gold standard. Although several studies suggest that a shortened intravenous treatment routine can be safe, the total antibiotic treatment time is still long, often 7 days or more (Fraser et al., 2010, Slusher et al., 2014, Meier et al., 2003). Postoperative care varies greatly between hospitals, for instance regarding early oral feeding, use of catheters, and intravenous and total antibiotic treatment time (Gross et al., 2016). Such variation is also seen in hospitals in Region Västra Götaland, an aspect of importance for the length of stay and the healthcare costs (Pennell et al., 2020).

Regarding the antibiotics *per se*, piperacillin/tazobactam is a frequently prescribed intravenous antibiotic after appendectomy due to perforated appendicitis. Piperacillin is a broad-spectrum penicillin and tazobactam a beta-lactamase inhibitor. An alternative is cefotaxim, a broad-spectrum cephalosporin, combined with metronidazol, a drug specifically targeting anaerobic bacteria. Regarding subsequent oral antibiotics, amoxicillin/clavulanate is often used, a broad-spectrum penicillin and a beta-lactamase inhibitor. Other alternatives include a combination of ciprofloxacin and metronidazole, ciprofloxacin and clindamycin, or trimethoprim/sulphametoxazol and metronidazole, all representing broad-spectrum antibiotic treatment. The antibiotics used in the studies included in this HTA have been used for decades.

When the patient is eating, has normalised bowel movement, and is not vomiting, the bioavailability of oral metronidazole and trimethoprim/sulphametoxazol has been reported to be >90% compared with intravenous treatment, and the corresponding percentage for amoxicillin/clavulanate and ciprofloxacin is 50-90% (McCarthy and Avent, 2020). Consequently, the authors suggest a switch to oral antibiotics when all of the following apply: (i) clinical improvement, (ii) fever resolved or improving, (iii) no unexplained haemodynamic instability, (iv), tolerating oral intake with no concerns about malabsorption, and (v) a suitable oral antimicrobial with the same or similar spectrum, or an oral formulation of the same drug is available, with a suitable paediatric formulation (McCarthy and Avent, 2020).

# 7. Focused question

For children undergoing acute appendectomy due to perforated appendicitis, is a shortened postoperative routine of intravenous/oral antibiotics non-inferior regarding the risk of intraabdominal abscess, and does it affect mortality, ileus, need for intensive care, sepsis, readmission, adverse drug reactions, wound infections, length of stay, and health-related quality of life?

**PICO: P= Patients, I= Intervention, C= Comparison, O=Outcome**

**P** P1: Children (0-17 years of age) who have undergone acute appendectomy due to perforated appendicitis.
P2: Children (0-17 years of age) who have undergone acute appendectomy due to perforated appendicitis with localised peritonitis.
P3: Children (0-17 years of age) who have undergone acute appendectomy due to perforated appendicitis with diffused peritonitis.

**I** I1: Routine of postoperative intravenous and oral antibiotics equal to or below a defined number of days.
I2: Routine of postoperative intravenous antibiotics equal to or below a defined number of days.

**C** C1: Routine of postoperative intravenous and oral antibiotics above a defined number of days.
C2: Routine of postoperative intravenous antibiotics above a defined number of days.

**O**
<u>Critical for decision-making</u>

- Intraabdominal abscess
- Mortality
- Ileus
- Intensive care
- Sepsis

<u>Important for decision-making</u>

- Readmission
- Complication to antibiotics treatment (clostridium difficile, allergic reactions)
- Surgical site infection
- Length of hospital stay
- Health-related quality of life

Restricted to:

- Randomised controlled trials (RCT)
- Prospective controlled studies
- Studies written in English, Swedish, Danish or Norwegian

Subgroup analyses:

- Preoperative vomiting
- Symptom duration before surgery ≤48 hours
- Preoperative CRP >100

We did not involve a patient representative in the PICO definition.

# 8. Methods

The HTA was registered with PROSPERO (CRD42024501215).

### Systematic literature search (Appendix 1)

During October 2023 two authors (K.M., I.S.) performed systematic searches in Medline, Embase, the Cochrane Library and Cinahl. Websites of Scandinavian national and regional HTA-organisations were visited. Reference lists of relevant reports were also scrutinised for additional references. Search strategies, eligibility criteria, and a graphic presentation of the selection process are presented in Appendix 1. These two authors also independently screened the obtained abstracts, using the Rayyan tool (Ouzzani et al., 2016), to select full-text reports to be assessed for inclusion or exclusion by all authors. Any disagreements were resolved in consensus. The selected reports were sent to all authors. They were then independently assessed by the authors, after which a consensus meeting with all authors took place to decide on inclusion or exclusion according to PICO. For RCTs with mixed ages not reporting children separately, or focusing on complex appendicitis not reporting perforated appendicitis separately, we contacted the study investigators for additional details. For articles excluded in consensus, after full-text reading, reasons for exclusion are presented in Appendix 3.

### Critical appraisal and evidence synthesis

For included studies, data on design and methodology were extracted, as well as data regarding participant characteristics, the antibiotics regimen of the intervention and the control groups, and outcomes reported (Appendix 2). Number of events or measures of effect were also extracted. All data were independently extracted by at least two authors, with discrepancies resolved in consensus.

The included articles were independently appraised by the authors using checklists used by HTA-centrum, Sahlgrenska University Hospital, modified from checklists developed by the Swedish Agency for Health Technology Assessment and Assessment of Social Services. Consensus discussions were then conducted to decide on the domains directness, study limitations (risk of bias), and precision, in the categories: '+' (no or minor problems); '?' (some problems), and; '–' (major problems). The assessments regarding directness and study quality (risk of bias) are summarised in Appendix 5.

If two or more studies provided poolable data regarding the outcomes at issue, random effects meta-analyses were performed to obtain risk ratios (RR) and risk differences (RD), including 95% confidence intervals (CI), using Review Manager 5.4 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark). Before pooling, we determined if the studies were poolable with focus on the compared routine treatment lengths of antibiotics. Meta-analyses based on studies without major risk of bias were beforehand determined to be the primary basis for the conclusions. Beforehand, we also determined a non-inferiority margin of 7.5 percentage points based on the 95% confidence interval (CI) of the RD, as applied previously (de Wijkerslooth et al., 2023). As a sensitivity analysis, we also applied a one-sided confidence interval in the non-inferiority analysis; we considered it unlikely that a postoperative routine of longer intravenous/oral antibiotic treatment would increase the risk of intraabdominal abscess.

### Certainty of evidence

The certainty of evidence was assessed according to GRADE (Atkins et al., 2004), with reasons for downgrading described. Summary results per outcome and the associated certainty of evidence are presented in a Summary-of-findings table (page 10).

## Ongoing research

A search in Clinicaltrials.gov (21 Feb 2024) using the search terms *(appendicitis OR 17etronidazol OR appendix OR appendectomy OR appendectomies OR appendicectomy OR appendicectomies) AND (rupture OR ruptures OR ruptured OR perforation OR perforations OR perforated OR complicated OR complex) AND (surgery OR surgeries OR surgical OR surgically OR operative OR operatively OR operation OR operations OR operational OR operating OR postoperative OR postoperatively OR postoperation OR postoperational OR perioperative OR perioperatively OR perioperation OR perioperational OR 17etronidazole17 OR intraoperatively OR intraoperation OR intraoperational OR postsurgery OR postsurgeries OR postsurgical OR postsurgically OR perisurgery OR perisurgeries OR perisurgical OR perisurgically OR intrasurgery OR intrasurgeries OR intrasurgical OR intrasurgically OR appendectomy OR appendectomies OR appendectomized OR appendectomised OR appendicectomy OR appendicectomies OR appendicectomized OR appendicectomised OR laparoscopy OR laparoscopies laparoscopic OR laparoscopical OR laparoscopically OR postlaparoscopy OR laparoscopies OR postpostlaparoscopic OR postlaparoscopical OR postlaparoscopically OR perilaparoscopy OR perilaparoscopies OR perilaparoscopic OR perilaparoscopical OR perilaparoscopically OR intralaparoscopy OR intralaparoscopies OR intralaparoscopic OR intralaparoscopical OR intralaparoscopically) AND (child OR childs OR children OR childrens OR adolescent OR adolescents OR teen OR teens OR preteen OR preteens OR juvenile OR juveniles OR youth OR youths OR preschool OR preschools OR school OR schools OR kindergarten OR kindergartens OR kinder-garten OR kinder-gartens OR kid OR kids OR infant OR infants OR newborn OR newborns OR new-born OR new-borns OR neonate OR neonates OR neonatal OR neonatals OR neo-nate OR neo-nates OR neo-natal OR neo-natals OR baby OR babies OR toddler OR toddlers OR minor OR minors OR pediatric OR pediatrics OR paediatric OR paediatrics OR immature OR immatures OR immaturity OR immatureness OR immaturely OR preterm OR preterms OR pre-term OR pre-terms) AND (antibiotic OR antibiotics OR anti-biotic OR anti-biotic OR antimicrobial OR antimicrobials OR antimicrobic OR antimicrobics OR antimicrobe OR anti-microbial OR anti-microbials OR anti-microbic OR anti-microbics OR anti-microbe OR antibacterial OR antibacterials OR anti-bacterial OR anti-bacterials OR antimycobacterial OR antimycobacterial OR anti-mycobacterial OR anti-mycobacterial OR antimyco-bacterial OR antimyco-bacterial OR anti-myco-bacterial OR anti-myco-bacterial OR bacteriocidal OR bacteriocide OR bacteriocides OR bacterio-cidal OR bacterio-cide OR bacterio-cides)* identified 48 trials.

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# 9. Results

### Search results and study selection (Appendix 1)

After removal of duplicates, the literature search identified 2,421 records. Two authors excluded 2,342 records at the abstract level and 79 reports were sought for retrieval. One report could not be retrieved, and 50 reports were excluded after full-text reading. The remaining 28 reports were sent to all authors, and three fulfilled the PICO. Another three RCTs reported relevant results for a mixed population of children/adults and complex/perforated appendicitis combined. In these cases, the corresponding author was contacted to obtain data for children with perforated appendicitis alone. From one of these, data were obtained and the RCT was included (de Wijkerslooth et al., 2023). The 74 excluded reports, with reasons for exclusion noted, are presented in Appendix 3.

### Included studies

The PICO of this HTA was fulfilled in three RCTs including a total of 215 patients, and in one before/after study including 288 patients. The studies were performed in the United States (n=3) and in the Netherlands (n=1) (Appendix 2). None of the included publications analysed patients with localised (P2) and diffused (P3) peritonitis separately. In one of the RCTs and the before/after study, all children underwent a laparoscopic appendectomy, and in another RCT, 95% of the surgeries were laparoscopic. In the oldest RCT, all appendectomies were performed with open technique.

The compared routine treatment lengths of the entire course of intravenous and oral antibiotics ranged between two and five days in the intervention group, and between five and ten days in the control group. Regarding intravenous antibiotics alone, the routine treatment lengths ranged between two to five days in the intervention group, and between up to tolerating diet and ten days in the control group. In two RCTs, as well as in the before/after study, cephalosporin and metronidazole were used for the intravenous part of the antibiotic treatment, followed by oral amoxicillin/clavulanate in two studies. The oldest RCT used a triple combination of ampicillin, gentamicin, and clindamycin, with a subsequent oral regimen of amoxicillin/clavulanate. No RCT had major risk of bias (Appendix 5), and the conclusions in this HTA were primarily based on these RCTs.

### Results per outcome

#### Outcomes, critical for decision-making

### Intraabdominal abscess (Appendix 4.1)

Data on intraabdominal abscess were available from three RCTs and one before/after study. For the comparison between different routine treatment lengths of the entire course of intravenous and oral antibiotics, two RCTs including 189 patients provided data. These studies could not be pooled as a 5-day postoperative routine of intravenous/oral antibiotic treatment was compared with a 7-day routine in one study and with a 2-day routine in the other (Figure 1). The third RCT did not provide data as a total of 10 days of intravenous/oral antibiotic treatment was applied in both comparison groups.

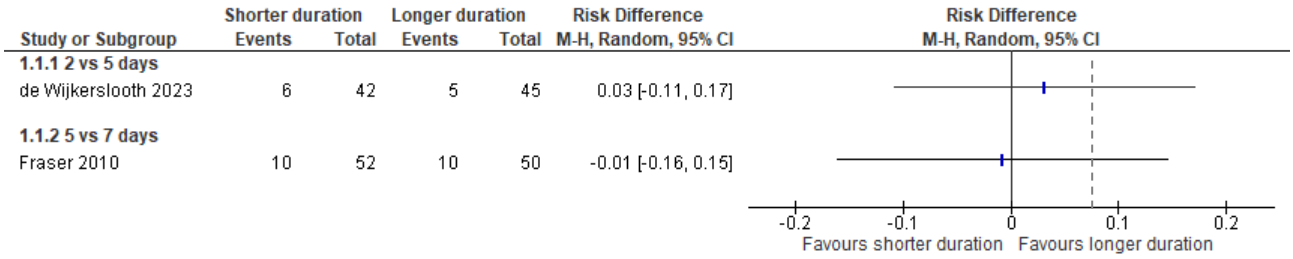



**Figure 1** Forest plot of risk differences in the two RCTs comparing two routine treatment lengths of postoperative antibiotics (intravenous plus oral) regarding intraabdominal abscess. The non-inferiority margin in presented with a dashed line.

For the comparison between different routine treatment lengths of intravenous antibiotics alone, the two RCTs including 189 patients could be pooled. One study compared a 2-day routine with a 5-day routine, and the other a <5-day with a 5-day routine. A total of 16 versus 15 events occurred in the randomisation groups, resulting in an RD of 2.1 (-8.3 to 12.5) percentage points, with a corresponding RR of 1.12 (95% CI: 0.59 to 2.12) (Figure 2). In the sensitivity analysis where a one-sided CI was applied, the upper confidence limit was 10.8 percentage points.

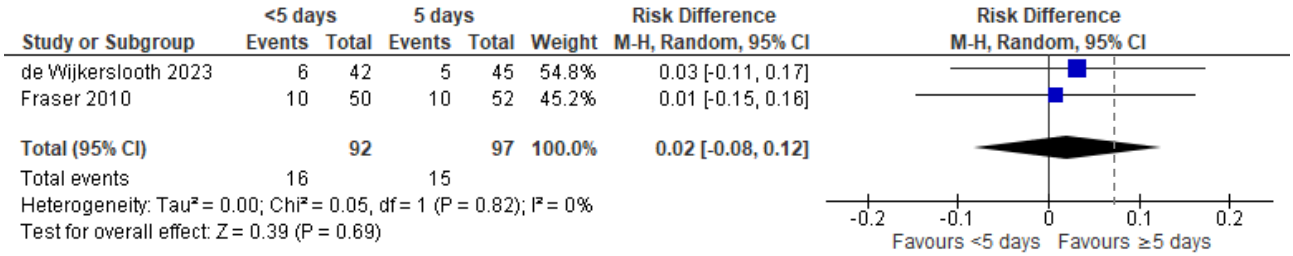



**Figure 2** Forest plot and meta-analysis of RCTs comparing two routine treatment lengths of postoperative intravenous antibiotics regarding intraabdominal abscess. The non-inferiority margin in presented with a dashed line.

In the GRADE process, we downgraded one step because of serious imprecision; there were few patients and events in the studies, and the 95% CI of the pooled estimate surpassed the predefined non-inferiority margin. We also downgraded one step because of a combination of some uncertainty regarding directness and some study limitations. Underlying reasons are elaborated upon in Appendix 5.

> *Conclusion:* The non-inferiority margin was not met and hence an increased risk of intraabdominal abscess by a shortened postoperative routine regarding the treatment length, by 2–3 fewer days for the entire intravenous/oral antibiotics course, and by using a <5-day routine of intravenous antibiotics alone, may not be excluded (GRADE ⊕⊕◯◯).

### Mortality (Appendix 4.2)

Data on mortality were available from one RCT that included 87 children undergoing acute appendectomy due to perforated appendicitis. The routine antibiotic treatment lengths were two days in the intervention group and five days in the control group. The entire treatment course was restricted to intravenous antibiotics. No deaths occurred within 90 days.

In the GRADE process, we downgraded two steps because of very serious imprecision; the study contained no events. We also downgraded one step because of a combination of some uncertainty

regarding directness and some study limitations. Underlying reasons are elaborated upon in Appendix 5.

> *Conclusion:* It is uncertain whether a shortened postoperative routine of intravenous antibiotics, in children who have undergone acute appendectomy due to perforated appendicitis, affects mortality within 90 days (GRADE ⊕◯◯◯).

### Ileus (Appendix 4.3)

Data on ileus were available from two RCTs. Regarding different routine treatment lengths of the entire postoperative antibiotics course, one RCT including 87 children compared a 2-day and a 5-day routine of intravenous antibiotics. A total of one versus four events occurred in the comparison groups. For the comparison between different routines of intravenous treatment alone, another RCT, including 26 patients, also provided data but no events occurred.

In the GRADE process, we downgraded two steps because of very serious imprecision; the studies contained few events. We also downgraded one step because of a combination of some uncertainty regarding directness and some study limitations. Underlying reasons are elaborated upon in Appendix 5.

> *Conclusion:* It is uncertain whether a shortened postoperative routine of intravenous antibiotics, in children who have undergone acute appendectomy due to perforated appendicitis, affects the risk of postoperative ileus (GRADE ⊕◯◯◯).

### Intensive care and sepsis

No studies reported results regarding the outcomes intensive care or sepsis.

## Outcomes, important for decision-making

### Readmission (Appendix 4.4)

Data on readmission were available from one RCT. It included 87 children undergoing acute appendectomy due to perforated appendicitis and compared a 2-day and a 5-day postoperative routine of intravenous antibiotics. Nine versus seven events occurred in the comparison groups resulting in an RR of 1.38 (95% CI: 0.56; 3.37) and an RD of 5.9 (95% CI: -10.4 to 22.2) percentage points.

In the GRADE process, we downgraded one step because of serious imprecision, and one step because of a combination of some uncertainty regarding directness and some study limitations. Underlying reasons are elaborated upon in Appendix 5.

> *Conclusion:* In children who have undergone acute appendectomy due to perforated appendicitis, a shortened postoperative routine of intravenous antibiotics (3 fewer days) may not affect the readmission rate (GRADE ⊕⊕◯◯).

### Complications to antibiotic treatment (Appendix 4.5)

Data on complications to antibiotic treatment were available from one RCT including 87 children undergoing acute appendectomy due to perforated appendicitis, and compared a 2-day and a 5-day postoperative routine of intravenous antibiotics. Eight versus nine adverse events occurred in the comparison groups, resulting in an RR of 0.95 (95% CI: 0.41; 2.24) and an RD of -1.0 (95% CI: -17.6 to 15.7) percentage points.

In the GRADE process, we downgraded one step because of serious imprecision, and one step because of a combination of some uncertainty regarding directness and some study limitations. Underlying reasons are elaborated upon in Appendix 5.

> *Conclusion:* In children who have undergone acute appendectomy due to perforated appendicitis, a shortened postoperative routine of intravenous antibiotics (3 fewer days) may not affect the risk of complications to antibiotic treatment (GRADE ⊕⊕◯◯).

### Surgical site infection (Appendix 4.6)

Data on surgical site infection were available from two RCTs. Regarding different routine treatment lengths of the entire antibiotics course, one RCT including 87 children compared a 2-day and a 5-day postoperative routine of intravenous antibiotics. A total of 1 versus 0 events occurred in the comparison groups. For the comparison between different routine treatment lengths of intravenous treatment alone, another RCT, including 26 patients, also provided data, with 1 event in each comparison group. As the 5-day postoperative routine of antibiotic treatment was represented in the control group of one RCT, and in the intervention group in the other, pooling was not relevant.

In the GRADE process, we downgraded two steps because of very serious imprecision, and one step because of a combination of some uncertainty regarding directness and some study limitations. Underlying reasons are elaborated upon in Appendix 5.

> *Conclusion:* It is uncertain whether a shortened postoperative routine of intravenous antibiotics, in children who have undergone acute appendectomy due to perforated appendicitis, affects the risk of surgical site infection (GRADE ⊕◯◯◯).

### Length of stay (Appendix 4.7)

Data on length of stay were available from two RCTs. Regarding different routine treatment lengths of the entire antibiotics course, two RCTs including 189 patients provided data. These studies could not be pooled as a 5-day postoperative routine of intravenous/oral antibiotic treatment was compared with a 7-day routine in one study and with a 2-day routine in the other.

For the comparison between different routine treatment lengths of intravenous treatment alone, the two RCTs including 189 patients could be pooled, comparing <5 days and 5 days of postoperative antibiotics. Both studies reported statistically significant shorter length of stay in the intervention group. In one of the RCTs, the mean difference was -2.2 (95% CI: -2.94 to -1.46) days. In the other, the difference could not be estimated based on reported figures.

In the GRADE process, we downgraded one step because of the combination of some uncertainty regarding directness and some study limitations. There was no inconsistency and no imprecision as both studies showed similar and statistically significant results.

> *Conclusion:* In children who have undergone acute appendectomy due to perforated appendicitis, a shortened postoperative routine of intravenous antibiotics (total treatment length: <5 days) probably reduces the length of hospital stay (GRADE ⊕⊕⊕◯).

### Health-related quality of life

No studies reported health-related quality of life data.

# 10. Organisational aspects

### Time frame for the putative introduction of the new health technology

After the completion of this HTA, a new regional treatment algorithm will be produced, planned to be completed at the end of 2024.

### Present use of the technology in other hospitals in Region Västra Götaland

The county hospitals in Region Västra Götaland treat children who have undergone surgery for acute perforated appendicitis in the same way they treat adults, i.e., post-operative antibiotics for a minimum of 72 hours.

### Consequences of the new health technology for personnel

A shortened postoperative routine of antibiotic treatment combined with a new meticulous treatment algorithm for this group of patients can be expected to facilitate patient care for nurses and physicians. The need for thorough education at children's hospitals will be extensive as it is difficult to change a routine that has been used for a long time. This applies for all personnel categories.

### Consequences for other clinics or supporting functions at the hospital or in the Region Västra Götaland

If a shortened postoperative routine of antibiotic treatment would be applied, and the actual treatment length would be guided by clinical parameters and laboratory tests, such a routine may increase the number of tests, mainly CRP and white blood cell counts.

# 11. Economic aspects

The present evidence synthesis does not allow conclusions regarding critical outcomes, and cost analyses are therefore highly uncertain. The cost calculations are performed from a healthcare perspective, i.e. societal costs, including indirect costs for parents taking care of their children in hospital or at home, are not considered.

### Present costs of currently used technologies

In Region Västra Götaland, the mean length of hospital stay associated with appendectomy for perforated appendicitis in children is 8.1 days in Sahlgrenska University Hospital and 4.6 days in the county hospital. The total number of patients is estimated at 75 per year, equally distributed between the university and the county hospitals. Assuming that the cost of the first day of in-hospital care, including the surgery, is 63 kSEK, that the following days cost 17 kSEK per day, and that the mean length of stay is 6.4 days, the total costs for 75 patients with the condition at issue are estimated at 12 MSEK in Region Västra Götaland.

### Expected costs of the new health technology

Assuming that effectiveness and safety are similar for the comparison alternatives and that a shortened postoperative routine of antibiotic treatment would save two in-hospital days per patient (range: 1–3 days), the total cost reduction per patient could be translated to 34 kSEK (range: 17–51 kSEK).

### Total change in costs

Assuming that a shortened postoperative routine of antibiotic treatment would result in a reduction of two in-hospital days per patient, and that such a routine would be applicable for 60 patients per year, the yearly resource savings in Region Västra Götaland could be estimated at 2 MSEK. With assumptions of reductions of 1 or 3 in-hospital days per patient, the resource savings could be translated to 1 MSEK and 3 MSEK, respectively. Thus, these resources could be redistributed to the care of other children with more severe conditions.

### Possibility to adopt and use the new technology within the present budget

From a budget perspective, a shortened postoperative routine of intravenous antibiotic treatment would probably reduce the costs due to a shorter hospital stay. Thus, not considering the uncertainties in patient outcomes, the budget impact would be beneficial.

## 12. Ethical aspects

Regarding the benefit-risk balance at the individual level, the current evidence synthesis does not show non-inferiority regarding a shortened postoperative routine of antibiotic treatment. Furthermore, there are substantial uncertainties in the underlying evidence and for some critical outcomes, no conclusions can be drawn. At the population level, a shortened postoperative routine of antibiotic treatment would be beneficial from the perspective of antimicrobial resistance. This aspect may also be of particular importance for the patients at issue in this HTA. As they are children, their need of healthcare interventions requiring effective antibiotics will to a considerable extent occur many years ahead.

From the perspective of equality, a national routine regarding postoperative antibiotic treatment length would be preferable. Furthermore, as a shortened postoperative routine of intravenous antibiotics would probably reduce the length of hospital stay, the needs and solidarity principle could be relevant. Indeed, a shorter in-hospital stay would allow children with conditions of higher degree of severity to take precedence for hospital care, over children merely requiring a hospital bed for the administration of antibiotics. Regarding the principle of cost-effectiveness, there are advantages from a cost perspective with a shortened postoperative routine of antibiotic treatment. As there are uncertainties in the underlying evidence regarding effectiveness, this principle, however, was not possible to assess.

Finally, the principle of autonomy could be relevant as the children do not make treatment decisions themselves.

As the current evidence base does not indicate evident patient risks, there are no ethical obstacles for further research on shortened postoperative routines of antibiotic treatment for children undergoing acute appendectomy due to perforated appendicitis.

# 13. Discussion

### Summary of main results

Evaluating a shortened postoperative routine of antibiotic treatment in children undergoing acute appendectomy due to perforated appendicitis, this HTA shows that the pre-defined non-inferiority margin regarding the risk of intraabdominal abscess was not met. However, the results show that a potential increase in the rate of abdominal abscesses using a treatment length of intravenous antibiotics below 5 days is unlikely to exceed 12.5 percentage points. Consequently, the worst-case scenario implies that one extra event of an abdominal abscess could occur per eight children exposed to a shortened postoperative routine of intravenous antibiotics. This condition, however, is clinically manageable by antibiotic treatment and/or drainage, and has been described to lead to minor morbidity (de Wijkerslooth et al., 2023). Furthermore, this HTA shows that the risk of readmission and complications to antibiotic treatment may not be affected by a shortened postoperative routine of intravenous antibiotics, while no conclusions can be drawn regarding the critical and important outcomes mortality, ileus, and surgical site infection. However, a shortened postoperative routine of intravenous antibiotics probably reduces the length of hospital stay.

### Overall completeness and applicability of evidence

Postoperative intraabdominal abscess is a complication after appendectomy due to perforated appendicitis, and with an incidence of 8–20% (Frongia et al., 2016, Henry et al., 2007, Liu et al., 2020, Wang et al., 2019, van Wijck et al., 2010), this unwanted course of events is not uncommon. Although the non-inferiority margin applied in the present HTA was not met, the data suggested no apparent risks. On the other hand, the non-inferiority margin allowed quite large differences. In the RCT from which this margin was taken (de Wijkerslooth et al., 2023), the authors considered the level justified under the assumption that infectious complications after appendicectomy for complex appendicitis would lead to minor morbidity. In this context, the length of hospital stay and antimicrobial resistance also need to be considered.

As postoperative care of children who have been treated with appendectomy due to perforated appendicitis constitutes a non-negligible share of patients in a children's surgical ward, the findings of the HTA are encouraging. If the routine of postoperative intravenous antibiotic treatment can be shortened, the length of hospital stay can probably be reduced. This may be preferable both for the patients and their families. Furthermore, the resource savings could allow other children with conditions of higher degree of severity to take precedence for hospital care. Several recent studies suggest algorithms for postoperative antibiotic treatment in children (and adults) with acute perforated appendicitis based on clinical criteria, including ability to eat, normalisation of white blood cell count, and tolerable stomach pain (Bonasso et al., 2019, Gerard et al., 2018, Meier et al., 2003, Pennel et al., 2020, Slusher et al., 2014). Such guidance could be helpful if a shortened routine would be considered; the treatment length in two RCTs in the current HTA was adjusted according to the status of the child (Fraser et al., 2010, Rice et al., 2001).

Our systematic search of evidence, comparing different length of postoperative antibiotic treatment routines after surgery for acute perforated appendicitis in children, revealed surprisingly few studies. Indeed, only two RCTs, published in 2001 and 2010 and including 128 children, provided data regarding our PICO within the actual publication. Furthermore, they lacked information regarding most of our outcomes. Upon request though, the first author of the third RCT prepared data for our question at issue, i.e., the subgroup of study participants that were children and had a perforated appendix. These data contributed to conclusions on several outcomes. However, as 27% of eligible patients in that study were excluded for unclear reasons and only 8% of the participants were children, it can be speculated that some of the most critically ill patients were not included.

Nonetheless, the sparsity of available data did not allow analyses for patients with localised (P2) and diffused peritonitis (P3), or for the predefined subgroups of interest.

### Other guidelines and systematic reviews

During the process of this HTA, the authors assessed two guidelines (Lee et al., 2010, Di Saverio et al., 2020) according the third (rigour of development) and sixth (editorial independence) domains of the Appraisal of Guidelines for REsearch & Evaluation (AGREE) II (Brouwers et al., 2016). The second guideline (Di Saverio et al., 2020) was considered largely acceptable, whereas the first one was not (Lee et al., 2010). We also assessed two systematic reviews (Wang et al., 2019, van den Boom et al., 2020) according to Quickstar, an assessment tool issued by the Swedish Agency for Health Technology Assessment and Assessment of Social Services (SBU, 2023). None of the systematic reviews passed all steps required to be considered fully useful. Regarding the first one, the first step of the assessment was not passed as the literature search could not be reproduced with the information provided (Wang et al., 2019). For the second one, there were uncertainties regarding the third step including the risk of bias assessments (van den Boom et al., 2020).

### Implications for research

Although only low or very low certainty evidence was available for patient outcomes, there were no apparent increased risks. Given the sparsity of evidence and the fact that the condition is not uncommon, further well-designed studies are considered highly warranted.

# 14. Future perspectives

### Scientific knowledge gaps

Given that there was only low certainty evidence regarding the outcomes intraabdominal abscess, readmissions, and adverse drug reaction, including  a wide confidence interval regarding intraabdominal abscess that did not meet the pre-defined non-inferiority margin,  and very low certainty evidence regarding the critical outcomes mortality, ileus, intensive care, and sepsis, there are evident knowledge gaps regarding patient-relevant effects of a shortened postoperative routine of antibiotics for children undergoing acute appendectomy due to perforated appendicitis.

### Ongoing research

The search in Clinicaltrials.gov resulted in 48 records. One of these represented an RCT already included in this HTA (Fraser et al., 2010). No additional studies fulfilled our PICO.

# 15. Participants in the project

### The question was nominated by
Cathrine Gatzinsky, head, Department of Paediatric Surgery, Sahlgrenska University Hospital

### Participating healthcare professionals
Elias Berge, MD, resident in paediatric surgery. Department of Paediatric Surgery, Sahlgrenska University Hospital
Pia Löfgren, MD, consultant in paediatric surgery. Department of Paediatric Surgery, Sahlgrenska University Hospital
Sofia Sjöström, MD, consultant in paediatric surgery; PhD, associate professor. Department of Paediatric Surgery, Sahlgrenska University Hospital

### Participants from HTA-centrum
Lennart Jivegård, MD, consultant vascular surgeon; PhD, associate professor
Jahangir Khan, professor of health economics
Susanna M Wallerstedt, MD, consultant physician specialised in clinical pharmacology; PhD, professor of pharmacotherapy

### Participants from the Medical Library
Kajsa Magnusson, librarian
Ida Stadig, librarian

### External reviewers
Magnus Axelsson, MD, consultant clinical chemist, PhD
Daniel Bremell, MD, consultant infectious diseases; PhD, associate professor

### Declaration of interests
The authors report that they have no conflicts of interest related to the content of this HTA.

### Project time
The HTA was accomplished during the period of 4 October 2023 – 26 June 2024.
Literature searches were made on 23 October 2023.

**Appendix 1: PICO, study selection, search strategies, and references**

**Question(s) at issue:** For children undergoing acute appendectomy due to perforated appendicitis, is a shortened postoperative routine of intravenous/oral antibiotics non-inferior regarding the risk of intraabdominal abscess, and does it affect mortality, ileus, need for intensive care, sepsis, readmission, adverse drug reactions, wound infections, length of stay, and health-related quality of life?

**PICO:** (*P=Patient I=Intervention C=Comparison O=Outcome*)

**P** P1: Children (0-17 years of age) who have undergone acute appendectomy due to perforated appendicitis.
P2: Children (0-17 years of age) who have undergone acute appendectomy due to perforated appendicitis with localised peritonitis.
P3: Children (0-17 years of age) who have undergone acute appendectomy due to perforated appendicitis with diffused peritonitis.

**I** I1: Routine of postoperative intravenous and oral antibiotics equal to or below a defined number of days.
I2: Routine of postoperative intravenous antibiotics equal to or below a defined number of days.

**C** C1: Routine of postoperative intravenous and oral antibiotics above a defined number of days.
C2: Routine of postoperative intravenous antibiotics above a defined number of days.

**O** <u>Critical for decision-making</u>

- Intraabdominal abscess
- Mortality
- Ileus
- Intensive care
- Sepsis

<u>Important for decision-making</u>

- Readmission
- Complication to antibiotics treatment (clostridium difficile, allergic reactions)
- Surgical site infection
- Length of hospital stay
- Health-related quality of life

**<u>Eligibility criteria</u>**

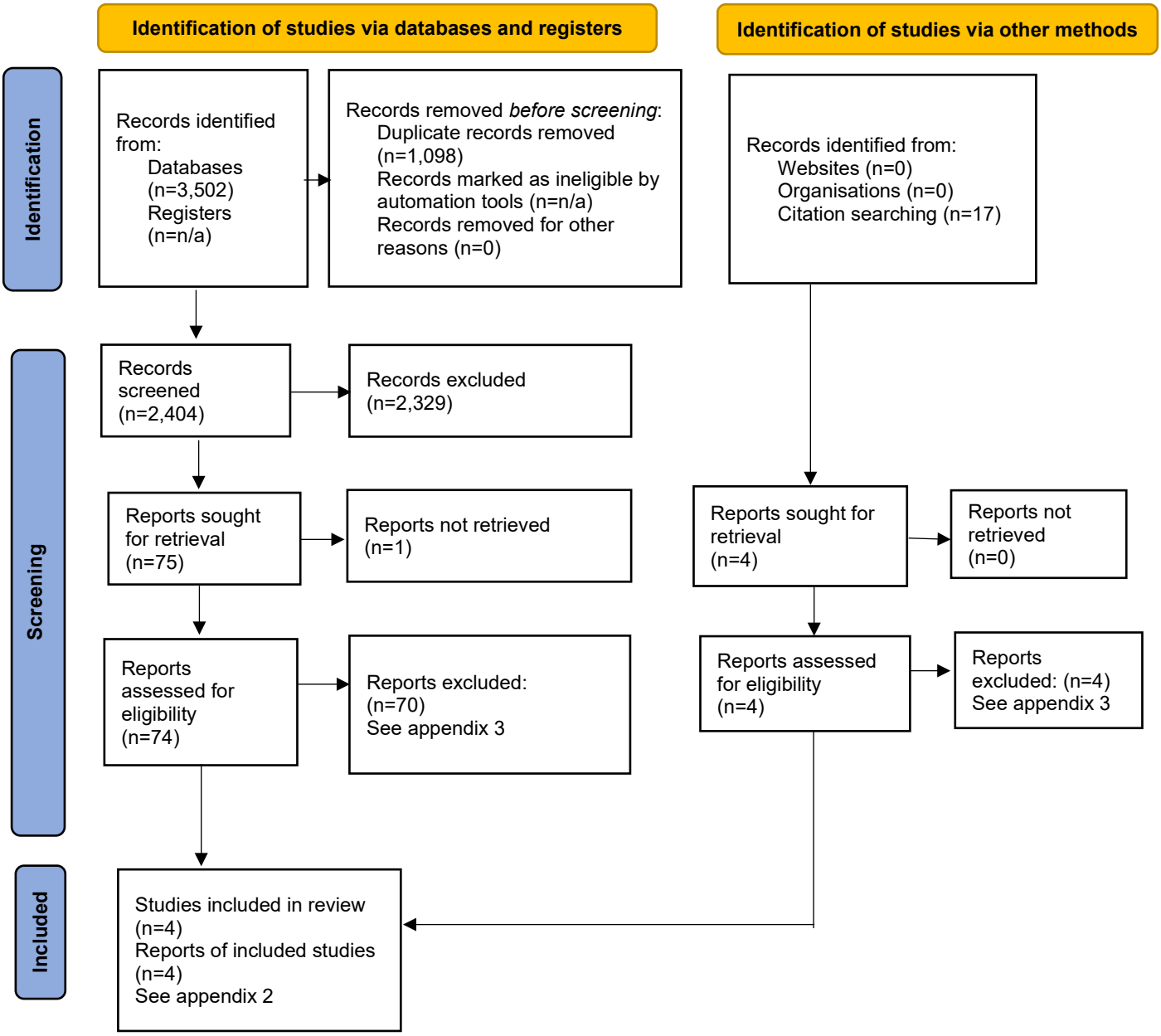
**Study design:**
Randomised controlled trials (RCT)
Prospective controlled studies

**Language:**
English, Swedish, Danish, Norwegian

**Publication date:**
No restrictions

## Selection process – flow diagram

**PRISMA 2020 flow diagram for new systematic reviews which included searches of databases, registers and other sources**




*From:* Page et al., 2021

## Search strategies

**Database:** Ovid MEDLINE(R) ALL
**Date:** 23 Oct 2023
**No. of results:** 1,114

| # | Searches | Results |
|---|---|---|
| 1 | exp Appendicitis/ | 21258 |
| 2 | exp Appendectomy/ | 12695 |
| 3 | ((appendicit* or appendix* or appendectom* or appendicectom*) adj3 (ruptur* or perforat* or complicated or complex)).ab,kf,ti. | 4944 |
| 4 | (surg* or operat* or postoperat* or perioperat* or intraoperative* or postsurg* or perisurg* or intrasurg* or appendectom* or appendicectom* or laparoscopic* or postlaparoscopic* or perilaparoscopic* or intralaparoscopic*).ab,kf,ti. | 3542572 |
| 5 | 3 and 4 | 3746 |
| 6 | 1 or 2 or 5 | 27205 |
| 7 | exp Child/ | 2165176 |
| 8 | exp Adolescent/ | 2223262 |
| 9 | exp Infant/ | 1257320 |
| 10 | exp Pediatrics/ | 63145 |
| 11 | (child* or adolesc* or teen* or preteen* or pre-teen* or juvenil* or youth* or preschool* or school* or kindergarten* or kinder-garten* or kid or kids or infant* or newborn* or new-born* or neonat* or neo-nat* or baby or babies or toddler* or minor or minors or pediat* or paediat* or immatur* or preterm* or pre-term*).ab,kf,ti. | 3315131 |
| 12 | 7 or 8 or 9 or 10 or 11 | 5270828 |
| 13 | exp Anti-Bacterial Agents/ | 821368 |
| 14 | exp beta-Lactams/ | 139978 |
| 15 | exp Aminoglycosides/ | 170799 |
| 16 | exp Lincomycin/ | 8064 |
| 17 | exp Nitroimidazoles/ | 20049 |
| 18 | exp Sulfonamides/ | 133424 |
| 19 | exp Trimethoprim/ | 12894 |
| 20 | (antibiot* or anti-biot* or antimicrob* or anti-microb* or antibact* or anti-bact* or antimycobact* or anti-mycobact* or antimyco-bact* or anti-myco-bact* or bacteriocid* or bacterio-cid*).ab,kf,ti. | 670318 |
| 21 | 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 | 1363793 |
| 22 | 6 and 12 and 21 | 1435 |
| 23 | animals/ not (animals/ and humans/) | 5126813 |
| 24 | (animal or animals or rat or rats or mouse or mice or rodent or rodents or dog or dogs or cat or cats or hamster or hamsters or rabbit or rabbits or swine or murine or porcine or horses or horse).ti. | 2117903 |
| 25 | 23 or 24 | 5545689 |
| 26 | 22 not 25 | 1433 |
| 27 | (comment or editorial or letter).pt. | 2198253 |
| 28 | 26 not 27 | 1391 |
| **29** | **limit 28 to (danish or english or norwegian or swedish)** | **1114** |

**Database: Embase** 1974 to 2023 October 20 (OvidSP)
**Date:** 23 Oct 2023
**No. of results:** 1,903

| # | Searches | Results |
|---|---|---|
| 1 | exp acute appendicitis/ | 11363 |
| 2 | exp appendectomy/ | 26576 |
| 3 | ((appendicit* or appendix* or appendectom* or appendicectom*) adj3 (ruptur* or perforat* or complicated or complex)).ab,kf,ti. | 6114 |
| 4 | (surg* or operat* or postoperat* or perioperat* or intraoperative* or postsurg* or perisurg* or intrasurg* or appendectom* or appendicectom* or laparoscopic* or postlaparoscopic* or perilaparoscopic* or intralaparoscopic*).ab,kf,ti. | 4580084 |
| 5 | 3 and 4 | 5019 |
| 6 | 1 or 2 or 5 | 33178 |
| 7 | juvenile/ | 55743 |
| 8 | exp adolescent/ | 1785852 |
| 9 | exp child/ | 3109923 |
| 10 | exp pediatrics/ | 128111 |
| 11 | (child* or adolesc* or teen* or preteen* or pre-teen* or juvenil* or youth* or preschool* or school* or kindergarten* or kinder-garten* or kid or kids or infant* or newborn* or new-born* or neonat* or neo-nat* or baby or babies or toddler* or minor or minors or pediat* or paediat* or immatur* or preterm* or pre-term*).ab,kf,ti. | 4104856 |
| 12 | 7 or 8 or 9 or 10 or 11 | 5565538 |
| 13 | exp antibiotic agent/ | 1787631 |
| 14 | exp sulfonamide/ | 404765 |
| 15 | (antibiot* or anti-biot* or antimicrob* or anti-microb* or antibact* or anti-bact* or antimycobact* or anti-mycobact* or antimyco-bact* or anti-myco-bact* or bacteriocid* or bacterio-cid*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word] | 1202847 |
| 16 | 13 or 14 or 15 | 2447508 |
| 17 | 6 and 12 and 16 | 2471 |
| 18 | animal/ not (animal/ and human/) | 1201231 |
| 19 | (animal or animals or rat or rats or mouse or mice or rodent or rodents or dog or dogs or cat or cats or hamster or hamsters or rabbit or rabbits or swine or murine or porcine or horses or horse).ti. | 2281306 |
| 20 | 18 or 19 | 3205600 |
| 21 | 17 not 20 | 2468 |
| 22 | limit 21 to (article or article in press or conference paper or "review") | 2058 |
| **23** | **limit 22 to (danish or english or norwegian or swedish)** | **1903** |

**Database:** The Cochrane Library
**Date:** 23 Oct 2023
**No of results:** 250 ref
*Cochrane reviews: 2*
*Cochrane protocols: 0*
*Trials: 248*
*Editorials: 0*
*Special collections: 0*
*Clinical answers: 0*

| ID | Search | Hits |
|---|---|---|
| #1 | MeSH descriptor: [Appendicitis] explode all trees | 803 |
| #2 | MeSH descriptor: [Appendectomy] explode all trees | 719 |
| #3 | ((appendicit* OR appendix* OR appendectom* OR appendicectom*) NEAR/2 (ruptur* OR perforat* OR complicated OR complex)):ti,ab,kw (Word variations have been searched) | 525 |
| #4 | (surg* OR operat* OR postoperat* OR perioperat* OR intraoperative* OR postsurg* OR perisurg* OR intrasurg* OR appendectom* OR appendicectom* OR laparoscopic* OR postlaparoscopic* OR perilaparoscopic* OR intralaparoscopic*):ti,ab,kw (Word variations have been searched) | 384300 |
| #5 | #3 AND #4 | 486 |
| #6 | #1 OR #2 OR #5 | 1303 |
| #7 | MeSH descriptor: [Child] explode all trees | 78615 |
| #8 | MeSH descriptor: [Adolescent] explode all trees | 125922 |
| #9 | MeSH descriptor: [Infant] explode all trees | 42054 |
| #10 | MeSH descriptor: [Pediatrics] explode all trees | 1179 |
| #11 | (child* OR adolesc* OR teen* OR preteen* OR (pre NEXT teen*) OR juvenil* OR youth* OR preschool* OR school* OR kindergarten* OR (kinder NEXT garten*) OR kid OR kids OR infant* OR newborn* OR (new NEXT born*) OR neonat* OR (neo NEXT nat*) OR baby OR babies OR toddler* OR minor OR minors OR pediat* OR paediat* OR immatur* OR preterm* OR (pre NEXT term*)):ti,ab,kw (Word variations have been searched) | 387925 |
| #12 | #7 OR #8 OR #9 OR #10 OR #11 | 387937 |
| #13 | MeSH descriptor: [Anti-Bacterial Agents] explode all trees | 15279 |
| #14 | MeSH descriptor: [beta-Lactams] explode all trees | 10565 |
| #15 | MeSH descriptor: [Aminoglycosides] explode all trees | 10011 |
| #16 | MeSH descriptor: [Lincomycin] explode all trees | 1013 |
| #17 | MeSH descriptor: [Nitroimidazoles] explode all trees | 3043 |
| #18 | MeSH descriptor: [Sulfonamides] explode all trees | 15475 |
| #19 | MeSH descriptor: [Trimethoprim] explode all trees | 1390 |
| #20 | (antibiot* OR (anti NEXT biot*) OR antimicrob* OR (anti NEXT microb*) OR antibact* OR (anti NEXT bact*) OR antimycobact* OR (anti NEXT mycobact*) OR (antimyco NEXT bact*) OR (anti NEXT myco NEXT bact*) OR bacteriocid* OR (bacterio NEXT cid*)):ti,ab,kw (Word variations have been searched) | 49874 |
| #21 | #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 | 77018 |
| #22 | #6 AND #12 AND #21 | 307 |
| #23 | (clinicaltrials OR trialsearch):so | 483266 |
| #24 | (conference proceeding):pt | 226743 |
| #25 | #23 OR #24 | 710009 |
| **#26** | **#22 NOT #25** | **250** |

**Database:** CINAHL (EBSCOhost)
**Date:** 23 Oct 2023
**No. of results:** 235

| # | Query | Results |
|---|---|---|
| **S22** | **S17 NOT S20**<br>**Limiters - Language: Danish, English, Norwegian, Swedish** | **235** |
| S21 | S17 NOT S20 | 238 |
| S20 | S18 OR S19 | 190,427 |
| S19 | TI (animal OR animals OR rat OR rats OR mouse OR mice OR rodent OR rodents OR dog OR dogs OR cat OR cats OR hamster OR hamsters OR rabbit OR rabbits OR swine OR murine OR porcine OR horses or horse) | 122,433 |
| S18 | (MH "animals") NOT ( (MH "animals") AND (MH "human")) | 88,841 |
| S17 | S6 AND S10 AND S16 | 238 |
| S16 | S11 OR S12 OR S13 OR S14 OR S15 | 146,455 |
| S15 | TI ( antibiot* OR anti-biot* OR antimicrob* OR anti-microb* OR antibact* OR anti-bact* OR antimycobact* OR anti-mycobact* OR antimyco-bact* OR anti-myco-bact* OR bacteriocid* OR bacterio-cid* ) OR AB ( antibiot* OR anti-biot* OR antimicrob* OR anti-microb* OR antibact* OR anti-bact* OR antimycobact* OR anti-mycobact* OR antimyco-bact* OR anti-myco-bact* OR bacteriocid* OR bacterio-cid* ) | 85,603 |
| S14 | (MH "Trimethoprim+") | 1,599 |
| S13 | (MH "Sulfonamides+") | 9,744 |
| S12 | (MH "Metronidazole") | 2,202 |
| S11 | (MH "Antibiotics+") | 89,695 |
| S10 | S7 OR S8 OR S9 | 1,537,926 |
| S9 | TI ( child* OR adolesc* OR teen* OR preteen* OR pre-teen* OR juvenil* OR youth* OR preschool* OR school* OR kindergarten* OR kinder-garten* OR kid OR kids OR infant* OR newborn* OR new-born* OR neonat* OR neo-nat* OR baby OR babies OR toddler* OR minor OR minors OR pediat* OR paediat* OR immatur* OR preterm* OR pre-term* ) OR AB ( child* OR adolesc* OR teen* OR preteen* OR pre-teen* OR juvenil* OR youth* OR preschool* OR school* OR kindergarten* OR kinder-garten* OR kid OR kids OR infant* OR newborn* OR new-born* OR neonat* OR neo-nat* OR baby OR babies OR toddler* OR minor OR minors OR pediat* OR paediat* OR immatur* OR preterm* OR pre-term* ) | 1,109,934 |
| S8 | (MH "Adolescence+") | 604,463 |
| S7 | (MH "Child+") | 755,271 |
| S6 | S1 OR S2 OR S5 | 5,109 |
| S5 | S3 AND S4 | 754 |
| S4 | TI ( surg* OR operat* OR postoperat* OR perioperat* OR intraoperative* OR postsurg* OR perisurg* OR intrasurg* OR appendectom* OR appendicectom* OR laparoscopic* OR postlaparoscopic* OR perilaparoscopic* OR intralaparoscopic* ) OR AB ( surg* OR operat* OR postoperat* OR perioperat* OR intraoperative* OR postsurg* OR perisurg* OR intrasurg* OR appendectom* OR appendicectom* OR laparoscopic* OR postlaparoscopic* OR perilaparoscopic* OR intralaparoscopic* ) | 709,646 |
| S3 | TI ( (appendicit* OR appendix* OR appendectom* OR appendicectom*) N2 (ruptur* OR perforat* OR complicated OR complex) ) OR AB ( (appendicit* OR appendix* OR appendectom* OR appendicectom*) N2 (ruptur* OR perforat* OR complicated OR complex) ) | 1,011 |
| S2 | (MH "Appendectomy") | 2,560 |
| S1 | (MH "Appendicitis") | 4,040 |

The websites of **Statens beredning för medicinsk och social utvärdering (SBU)** , **Folkehelseinstituttet, a number of regional HTA units, International HTA Database** and **Nationellt kliniskt kunskapsstöd** were visited
23 Oct 2023
Nothing relevant to the question at issue was found

| Source | Search terms / Browsing | No. of results | No. of relevant results |
|---|---|---|---|
| **SBU**<br>www.sbu.se<br>"Visa även träffar äldre än 5 år" | Blindtarm<br>Blindtarmsbihang<br>Blindtarmsinflammation<br>Appendix<br>Appendicit<br>Appendektomi<br>blindtarmsoperation | 0<br>0<br>0<br>10<br>1<br>1<br>2 | 0<br>0<br>0<br>0<br>0<br>0<br>0 |
| **Folkehelseinstituttet (Norge)**<br>https://www.fhi.no/ku/metodevurdering/ | blindtarm<br>Blindtarmsvedhenget<br>blindtarmbetennelse<br>appendix<br>appendisitt<br>appendektomi<br>Blindtarmsoperasjon | 1<br>0<br>0<br>0<br>0<br>0<br>0 | 0<br>0<br>0<br>0<br>0<br>0<br>0 |
| **CAMTÖ**<br>https://www.regionorebrolan.se/sv/forskning/kontakt-och-organisation/hta-enheten-camto/ | Browsat | | 0 |
| **HTA Region Stockholm**<br>https://www.chis.regionstockholm.se/hta/rapporter/ | Browsat | | 0 |
| **Regional samverkansgrupp HTA (tidigare Metodrådet) i Sydöstra sjukvårdsregionen**<br>https://sydostrasjukvardsregionen.se/samverkansgrupper/hta/genomforda-bedomningar/ | Browsat | | 0 |
| **HTA Syd**<br>https://vardgivare.skane.se/kompetens-utveckling/sakkunniggrupper/hta-skane/#110365 | Browsat | | 0 |
| **Medicinska rådet, Region Dalarna**<br>https://www.regiondalarna.se/plus/vard/ovriq-halso--och-sjukvard/medicinska-radet/ | Browsat | | 0 |
| **International HTA Database**<br>https://database.inahta.org/ | (appendicitis or appendectomy or appendectomies or appendicectomy or appendicectomies)<br><br>Year: 2013 - 2023 | 7 | 0 |
| **Nationellt kliniskt kunskapsstöd**<br>https://nationelltklinisktkunskapsstod.se | Blindtarm<br>blindtarmsbihang<br>blindtarmsinflammation<br>appendix<br>appendicit<br>appendektomi<br>blindtarmsoperation | 0<br>0<br>0<br>11<br>10<br>0<br>0 | 0<br>0<br>0<br>0<br>0<br>0<br>0 |

**Reference lists**
A comprehensive review of reference lists brought 17 new records.

## Reference lists

### Included reports:

de Wijkerslooth EML, Boerma EJG, van Rossem CC, van Rosmalen J, Baeten CIM, Beverdam FH, et al. 2 days versus 5 days of postoperative antibiotics for complex appendicitis: a pragmatic, open-label, multicentre, non-inferiority randomised trial. The Lancet. 2023;401:366-76. doi: doi:https://dx.doi.org/10.1016/S0140-6736%2822%2902588-0.

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(6):912-4. doi: doi:https://dx.doi.org/10.1016/j.jpedsurg.2015.03.006.

Fraser JD, Aguayo P, Leys CM, Keckler SJ, Newland JG, Sharp SW, 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(6):1198-202. doi: doi:https://dx.doi.org/10.1016/j.jpedsurg.2010.02.090.

Rice HE, Brown RL, Gollin G, Caty MG, Gilbert J, Skinner MA, et al. Results of a pilot trial comparing prolonged intravenous antibiotics with sequential intravenous/oral antibiotics for children with perforated appendicitis. Arch Surg. 2001;136(12):1391-5.

### Systematic reviews and guidelines, only commented on:

Di Saverio S, Podda M, De Simone B, Ceresoli M, Augustin G, Gori A, et al. Diagnosis and treatment of acute appendicitis: 2020 update of the WSES Jerusalem guidelines. World J Emerg Surg. 2020;15(1):27. doi: 10.1186/s13017-020-00306-3.

Lee SL, Islam S, Cassidy LD, Abdullah F, Arca MJ; 2010 American Pediatric Surgical Association Outcomes and Clinical Trials Committee. Antibiotics and appendicitis in the pediatric population: an American Pediatric Surgical Association Outcomes and Clinical Trials Committee systematic review. J Pediatr Surg. 2010;45(11):2181-5. doi: 10.1016/j.jpedsurg.2010.06.038.

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(2):101-10. doi: 10.1159/000497482.

Wang C, Li Y, Ji Y. Intravenous versus intravenous/oral antibiotics for perforated appendicitis in pediatric patients: a systematic review and meta-analysis. BMC Pediatrics. 2019;19(1):407. doi:https://dx.doi.org/10.1186/s12887-019-1799-6.

### Excluded reports:

Abdulkareem A, Wosornu L, Al-Arfaj A, Grant C, Shawan S. Comparative evaluation of solo augmentin with cephradine and metronidazole combined for prophylaxis of post-appendicectomy wound infection. Surg Res Commun. 1992;12:337-41.

Anderson KT, Bartz-Kurycki MA, Kawaguchi AL, Austin MT, Holzmann-Pazgal G, Kao LS, et al. Home Antibiotics at Discharge for Pediatric Complicated Appendicitis: Friend or Foe? J Am Coll Surg. 2018;227(2):247-54. doi: doi:https://dx.doi.org/10.1016/j.jamcollsurg.2018.04.004.

Anonymous. A Danish multicenter study: cefoxitin versus ampicillin + metronidazole in perforated appendicitis. Br J Surg. 1984;71(2):144-6.

Anonymous. Choosing antibiotics for ruptured appendixes. Emergency Medicine (00136654). 1992;24(1):200-3.

Basoli A, Chirletti P, Cirino E, D'Ovidio NG, Doglietto GB, Giglio D, et al. A prospective, double-blind, multicenter, randomized trial comparing ertapenem 3 vs >or=5 days in community-acquired intraabdominal infection. J Gastrointest Surg. 2008;12(3):592-600. doi: 10.1007/s11605-007-0277-x.

Berne TV, Yellin AE, Appleman MD, Heseltine PN, Gill MA. A clinical comparison of cefepime and metronidazole versus gentamicin and clindamycin in the antibiotic management of surgically treated advanced appendicitis. Surg Gynecol Obstet. 1993;177:18-22; discussion 35-40.

Bueno-Rodríguez JC, Hernández-Moore E, Aguilar-Atanay D, Castelló-González M, Castro-Guevara JE, Piovet-Dorta Y. Sequential antibiotic therapy in complicated acute appendicitis. Cir Cir. 2012;80(3):233-8.

Bufo AJ, Chen MK, Lobe TE, Laird D, Burman G, Hixson DS, et al. Pilot assessment of interval laparoscopic appendectomy for treatment of perforated appendicitis in children. Pediatric Endosurgery and Innovative Techniques. 1997;1:127-30. doi: doi:http://dx.doi.org/10.1089/pei.1997.1.127.

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;27:142-6. doi: 10.1016/j.ijsu.2016.01.069.

Cunningham ME, Zhu H, Hoch CT, DeMello AS, Gusman ND, Fallon SC, et al. Effectiveness of a clinical pathway for pediatric complex appendicitis based on antibiotic stewardship principles. J Pediatr Surg. 2020;55(6):1026-31. doi: doi:https://dx.doi.org/10.1016/j.jpedsurg.2020.02.045.

Di Benedetto V, Bagnara V, Caccamo F, Aleo G, Di Cottonaro G, Cottonaro G, et al. Our management of acute complicated appendicitis in children. J Chemother. 1989;1(4):814-5.

el-Mufti M, Rakas F, Glessa A, Sanallah B, Abusidra A. A single prophylactic antibiotic for emergency appendicectomy? Chemotherapy. 1989;35(5):383-8.

Evbuomwan I, Onwanyin ON. Management of peritonitis in perforated appendicitis in children. East Afr Med J. 1994;71(5):279-81.

Fink BJ, Jepsen OB, Knudsen JB. Cephaloridine or penicillin-streptomycin in the treatment of severe acute appendicitis. A sequential analysis. Ugeskr Laeger. 1979;141(6):366-8.

Fishman SJ, Pelosi L, Klavon SL, O'Rourke EJ. Perforated appendicitis: prospective outcome analysis for 150 children. J Pediatr Surg. 2000;35(6):923-6.

Flannigan GM, Clifford RP, Carver RA, Yule AG, Madden NP. Antibiotic prophylaxis in acute appendicitis. Surg Gynecol Obstet. 1983;156(2):209-11.

Gollin G, Abarbanell A, Moores D. Oral antibiotics in the management of perforated appendicitis in children. Am Surg. 2002;68(12):1072-4.

Gottrup F, Sorensen I. Infection after appendectomy. Effect of preventive metronidazole therapy. Ugeskr Laeger. 1979;141(34):2293-6.

Higginbotham P, Gottlieb A. Protocols in practice. Improving care with a pediatric appendicitis pathway. Nurs Case Manag. 1998;3(1):26-35.

Höllwarth M, Graf D, Kurz R, Sauer H. Antibiotic treatment of perforated appendicitis in childhood--a prospective study. Zeitschrift fur Kinderchirurgie[Surgery in infancy and childhood]. 1986;41(1):14-8. doi: doi:10.1055/s-2008-1043299.

Irfan Farooqi M, Baqir W, Haider W, Mahmood A. Role of One Versus Three Doses of Antibiotics Given Prophylactically in Patients Undergoing Appendicectomy to Prevent Surgical Site Infections. Pakistan Journal of Medical and Health Sciences. 2021;15:1248-50.

Jewett TC, Jr., Allen JE, Tan SS. The use of sulfadiazene in acute perforated appendicitis in children. J Pediatr Surg. 1971;6(2):121-3.

Kekomaki M, Louhimo I. Perforated appendix and antibiotics. Z Kinderchir. 1981;32(4):310-4.

Khan S, Siow VS, Lewis A, Butler G, Narr M, Srinivasan S, et al. An Evidence-Based Care Protocol Improves Outcomes and Decreases Cost in Pediatric Appendicitis. J Surg Res. 2020;256:390-6. doi: doi:https://dx.doi.org/10.1016/j.jss.2020.05.067.

Kling PA, Holmlund D, Burman LG. Prevention of post-operative infection in appendicectomy by single dose intravenous metronidazole. An open prospective randomised study. Acta Chir Scand. 1985;151(1):73-6.

Kooi GH, Pit S. Ceftazidime/metronidazole versus netilmicin/metronidazole in the treatment of perforated appendicitis in children. Clin Ther. 1990;12(1):54-60.

Lansdale N, Fryer S, Stockdale M, Bancroft J, Orr J, Corbett H, et al. Prospective evaluation of a clinical response directed pathway for complicated appendicitis. J Pediatr Surg. 2019;54(2):272-5. doi: doi:https://dx.doi.org/10.1016/j.jpedsurg.2018.10.082.

Lindahl F. Acute perforative appendicitis and periappendicular abscess. Treatment with colistin and rolitetracycline. Ugeskr Laeger. 1969;131(39):1637-40.

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(9):778-83. doi: doi:https://dx.doi.org/10.1089/sur.2019.293.

Lose G, Holm B, Bauer T, Graversen P, Kristensen ES, Larsen E, et al. Three days cefoxitin in perforated appendicitis. Ann Chir Gynaecol. 1986;75(5):270-3.

Maltezou HC, Nikolaidis P, Lebesii E, Dimitriou L, Androulakakis E, Kafetzis DA. Piperacillin/Tazobactam versus cefotaxime plus metronidazole for treatment of children with intra-abdominal infections requiring surgery. Eur J Clin Microbiol Infect Dis. 2001;20(9):643-6.

Mazuski JE, Tessier JM, May AK, Sawyer RG, Nadler EP, Rosengart MR, et al. The Surgical Infection Society Revised Guidelines on the Management of Intra-Abdominal Infection. Surg Infect (Larchmt). 2017;18(1):1-76. doi: 10.1089/sur.2016.261.

Meller JL, Reyes HM, Loeff DS, Federer L, Hall JR. One-drug versus two-drug antibiotic therapy in pediatric perforated appendicitis: a prospective randomized study. Surgery. 1991;110(4):764-7; discussion 7-8.

Miholic J, Riezinger F, Wurnig P. Metronidazole plus cefazolin versus cefazolin in gangrenous and perforated appendicitis in childhood--a prospective randomised trial. Z Kinderchir. 1983;38(3):159-62.

Naess K. Appendicitis and the use of antibiotics. The danger of serious complications. Tidsskr Nor Laegeforen. 1968;88(4):284-5.

Ong CP, Chan TK, Chui CH, Jacobsen AS. Antibiotics and postoperative abscesses in complicated appendicitis: is there any association? Singapore Med J. 2008;49(8):615-8.

Perez V, Saenz D, Madriz J, Harhay M, Feoli J, Castro M, et al. A double-blind study of the efficacy and safety of multiple daily doses of amikacin versus one daily dose for children with perforated appendicitis in Costa Rica. Int J Infect Dis. 2011;15(8):e569-75. doi: doi:https://dx.doi.org/10.1016/j.ijid.2011.04.012.

Pinto DJ, Sanderson PJ. Rational use of antibiotic therapy after appendicectomy. Br Med J. 1980;280(6210):275-7.

Pogorelic Z, Silov N, Jukic M, Elezovic Baloevic S, Poklepovic Pericic T, Jeroncic A. Ertapenem Monotherapy versus Gentamicin Plus Metronidazole for Perforated Appendicitis in Pediatric Patients. Surg Infect (Larchmt). 2019;20(8):625-30. doi: doi:https://dx.doi.org/10.1089/sur.2019.025.

Pokorny WJ, Kaplan SL, Mason EO, Jr. A preliminary report of ticarcillin and clavulanate versus triple antibiotic therapy in children with ruptured appendicitis. Surg Gynecol Obstet. 1991;172:54-6.

Puri P, Rangecroft L, Zervos G, Guiney EJ, O'Donnell B. Perforated appendicitis in children: use of metronidazole for the reduction of septic complications. Z Kinderchir. 1981;32(2):111-5.

Raahave D, Friis-Moller A, Bjerre-Jepsen K, Thiis-Knudsen J, Rasmussen LB. The infective dose of aerobic and anaerobic bacteria in postoperative wound sepsis. Arch Surg. 1986;121(8):924-9.

Raahave D, Poulsen PE. Perforated appendicitis and antibiotics. A survey and a controlled clinical trial. Acta Chir Scand. 1970;136(8):715-23.

Raffensperger JG, Metzger W. Antibiotic therapy for perforated appendicitis in children. Chic Med Sch Q. 1969;28(4):179-83.

Rangel SJ, Anderson BR, Srivastava R, Shah SS, Ishimine P, Srinivasan M, et al. Intravenous Versus Oral Antibiotics for the Prevention of Treatment Failure in Children With Complicated Appendicitis: Has the Abandonment of Peripherally Inserted Catheters Been Justified? Ann Surg. 2017;266(2):361-8. doi: doi:https://dx.doi.org/10.1097/SLA.0000000000001923.

Robinson JR, Avritscher EBC, Gay JC, Willis ZI, Putnam LR, Anglemyer A, et al. Measuring the Value of a Clinical Practice Guideline for Children With Perforated Appendicitis. Ann Surg. 2017;266(1):195-200. doi: doi:https://dx.doi.org/10.1097/SLA.0000000000001946.

Russell KW, Skarda DE, Jones TW, Barnhart DC, Short SS. Cessation of Antibiotics for Complicated Appendicitis at Discharge Does Not Increase Risk of Post-operative Infection. J Pediatr Surg. 2023;26:26. doi: doi:https://dx.doi.org/10.1016/j.jpedsurg.2023.09.023.

Samelson SL, Reyes HM. Management of perforated appendicitis in children--revisited. Arch Surg. 1987;122(6):691-6.

Sawyer RG, Claridge JA, Nathens AB, Rotstein OD, Duane TM, Evans HL, et al. Trial of short-course antimicrobial therapy for intraabdominal infection. N Engl J Med. 2015;372(21):1996-2005. doi: doi:https://dx.doi.org/10.1056/NEJMoa1411162.

Schmitt M, Bondonny JM, Delmas P, Galifer RB, Revillon Y, Robert M. Antibiotic therapy of perforated appendicitis in children: comparison between the amoxicillin-clavulanic acid and the benzylpenicillin-netilmicin-metronidazole combinations. Pediatrie. 1993;48(9):633-7.

Schmitt M, Bondonny JM, Delmas P, Galifer RB, Revillon Y, Robert M, et al. Antibiotic therapy of perforated appendicitis in children: a comparison of amoxycillin/clavulanate with a combination of benzylpenicillin, netilmicin and metronidazole. J Antimicrob Chemother. 1989;24:157-63.

Schultz A, Frederiksen W. Antibiotics in perforated appendicitis. A controlled prospective comparison of penicillin and streptomycin with minocyclin. Ugeskr Laeger. 1979;141(6):363-5.

Shandling B, Ein SH, Simpson JS, Stephens CA, Bandi SK. Perforating appendicitis and antibiotics. J Pediatr Surg. 1974;9(1):79-83.

Shbat L, Emil S, Elkady S, Baird R, Laberge JM, Puligandla P, et al. Benefits of an abridged antibiotic protocol for treatment of gangrenous appendicitis. J Pediatr Surg. 2014;49(12):1723-5. doi: doi:https://dx.doi.org/10.1016/j.jpedsurg.2014.09.039.

Sirinek KR, Levine BA. Antimicrobial management of surgically treated gangrenous or perforated appendicitis: comparison of cefoxitin and clindamycin-gentamicin. Clin Ther. 1987;9(4):420-8.

Sirinek KR, Levine BA. A randomized trial of ticarcillin and clavulanate versus gentamicin and clindamycin in patients with complicated appendicitis. Surg Gynecol Obstet. 1991;172:30-5.

Skarda DE, Schall K, Rollins M, Andrews S, Olson J, Greene T, et al. Response-based therapy for ruptured appendicitis reduces resource utilization. J Pediatr Surg. 2014;49(12):1726-9. doi: doi:https://dx.doi.org/10.1016/j.jpedsurg.2014.09.012.

Slusher J, Bates CA, Johnson C, Williams C, Dasgupta R, von Allmen D. Standardization and improvement of care for pediatric patients with perforated appendicitis. J Pediatr Surg. 2014;49(6):1020-4; discussion 4-5. doi: doi:https://dx.doi.org/10.1016/j.jpedsurg.2014.01.045.

Solomkin JS, Yellin AE, Rotstein OD, Christou NV, Dellinger EP, Tellado JM, et al. Ertapenem versus piperacillin/tazobactam in the treatment of complicated intraabdominal infections: results of a double-blind, randomized comparative phase III trial. Ann Surg. 2003;237(2):235-45.

Sorooshian P, Ward R, Sandison A. A simple intervention to improve the use of postoperative antibiotics and intra-abdominal drains in appendicectomy patients. Ann R Coll Surg Engl. 2022;104(3):210-5. doi: doi:https://dx.doi.org/10.1308/rcsann.2021.0185.

St Peter SD, Tsao K, Spilde TL, Holcomb GW, 3rd, Sharp SW, Murphy JP, et al. Single daily dosing ceftriaxone and metronidazole vs standard triple antibiotic regimen for perforated appendicitis in children: a prospective randomized trial. J Pediatr Surg. 2008;43(6):981-5. doi: doi:https://dx.doi.org/10.1016/j.jpedsurg.2008.02.018.

Stone HH. Perforated appendix in children. Am Fam Physician. 1971;4(6):60-8.

Stovroff MC, Totten M, Glick PL. PIC lines save money and hasten discharge in the care of children with ruptured appendicitis. J Pediatr Surg. 1994;29(2):245-7.

Svensson J. Antibiotic treatment of appendicitis. J Pediatr. 2016;176:221-4. doi: doi:https://dx.doi.org/10.1016/j.jpeds.2016.06.074.

Talei A, Banani SA. Does oral metronidazole reduce complications in acute appendicitis? Iranian Journal of Medical Sciences. 1994;19:95-100.

Taylor E, Berjis A, Bosch T, Hoehne F, Ozaeta M. The efficacy of postoperative oral antibiotics in appendicitis: a randomized prospective double-blinded study. Am Surg. 2004;70(10):858-62.

Teppler H, Meibohm AR, Woods GL. Management of complicated appendicitis and comparison of outcome with other primary sites of intra-abdominal infection: results of a trial comparing ertapenem and piperacillin-tazobactam. J Chemother. 2004;16(1):62-9.

Theodorou CM, Lee SY, Lawrence Y, Saadai P, Hirose S, Brown EG. The Utility of Discharge Antibiotics in Pediatric Perforated Appendicitis Without Leukocytosis. J Surg Res. 2022;275:48-55. doi: doi:https://dx.doi.org/10.1016/j.jss.2022.01.024.

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(2):101-10. doi: 10.1159/000497482.

van Rossem CC, Schreinemacher MH, van Geloven AA, Bemelman WA. Antibiotic Duration After Laparoscopic Appendectomy for Acute Complicated Appendicitis. JAMA Surgery. 2016;151(4):323-9. doi: doi:https://dx.doi.org/10.1001/jamasurg.2015.4236.

Vennits BP, Bauer T, Hahn-Pedersen J, Galatius H, Lysen D, Holm B, et al. Factors determining the development of wound infection after appendectomy. Danish. Ugeskr Laeger. 1990;152:157-60.

Wang C, Li Y, Ji Y. Intravenous versus intravenous/oral antibiotics for perforated appendicitis in pediatric patients: a systematic review and meta-analysis. BMC Pediatr. 2019;19(1):407. doi: doi:https://dx.doi.org/10.1186/s12887-019-1799-6.

Willis ZI, Duggan EM, Gillon J, Blakely ML, Di Pentima MC. Improvements in Antimicrobial Prescribing and Outcomes in Pediatric Complicated Appendicitis. Pediatr Infect Dis J. 2018;37(5):429-35. doi: doi:https://dx.doi.org/10.1097/INF.0000000000001816.

Yu TC, Hamill JK, Evans SM, Price NR, Morreau PN, Upadhyay VA, et al. Duration of postoperative intravenous antibiotics in childhood complicated appendicitis: a propensity score-matched comparison study. Eur J Pediatr Surg. 2014;24(4):341-9. doi: doi:https://dx.doi.org/10.1055/s-0033-1349055.

## Other references:

Almström M, Svensson JF, Svenningsson A, Hagel E, Wester T. Population-based cohort study of the correlation between provision of care and the risk for complications after appendectomy in children. J Pediatr Surg. 2019;54(11):2279-2284. doi: 10.1016/j.jpedsurg.2019.03.013.

Almström M, Svensson JF, Svenningsson A, Hagel E, Wester T. Population-based cohort study on the epidemiology of acute appendicitis in children in Sweden in 1987-2013. BJS Open. 2018;2(3):142-150. doi: 10.1002/bjs5.52.

Atkins D, Best D, Briss PA, Eccles M, Falck-Ytter Y, Flottorp S, et al. GRADE Working Group. Grading quality of evidence and strength of recommendations. BMJ. 2004;328(7454):1490-4. doi: 10.1136/bmj.328.7454.1490.

Bonasso PC, Dassinger MS, Wyrick DL, Smith SD, Burford JM. Evaluation of white blood cell count at time of discharge is associated with limited oral antibiotic therapy in children with complicated appendicitis. Am J Surg. 2019;217(6):1099-101.

Brouwers MC, Kerkvliet K, Spithoff K; AGREE Next Steps Consortium. The AGREE Reporting Checklist: a tool to improve reporting of clinical practice guidelines. BMJ. 2016;352:i1152. doi: 10.1136/bmj.i1152.

[Checklist from SBU regarding non-randomized controlled studies. (Modified) Version 2021]. [Internet]. [cited 2024 Jan 17]. Available from: https://mellanarkiv-

offentlig.vgregion.se/alfresco/s/archive/stream/public/v1/source/available/sofia/su4372-1728378332-652/native

[Checklist from SBU regarding randomized controlled trials]. (Modified) Version 2021]. [Internet]. [cited 2024 Jan 17]. Available from: https://web.archive.org/web/20220725142002/https://mellanarkiv-offentlig.vgregion.se:443/alfresco/s/archive/stream/public/v1/source/available/sofia/su4372-1728378332-412/native/Granskningsmall%20%20RCT_2021-05-19.doc

Di Saverio S, Podda M, De Simone B, Ceresoli M, Augustin G, Gori A, et al. Diagnosis and treatment of acute appendicitis: 2020 update of the WSES Jerusalem guidelines. World J Emerg Surg. 2020;15(1):27. doi: 10.1186/s13017-020-00306-3.

Fraser JD, Aguayo P, Leys CM, Keckler SJ, Newland JG, Sharp SW, 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(6):1198-202. doi: 10.1016/j.jpedsurg.2010.02.090.

Frongia G, Mehrabi A, Ziebell L, Schenk JP, Günther P. Predicting Postoperative Complications After Pediatric Perforated Appendicitis. J Invest Surg. 2016;29(4):185-94. doi: 10.3109/08941939.2015.1114690.

Gerard RR, Kielhorn BA, Petersen B, Mullard AJ, McCahill LE. Post-operative management of perforated appendicitis: Can clinical pathways improve outcomes? Am J Surg. 2018;215(4):593-8.

GRADE Working Group. [Internet]. [Place unknown]: GRADE Working Group, c2004-2021 [cited 2021 Feb 13]. Available from: http://www.gradeworkinggroup.org

Gross TS, McCracken C, Heiss KF, Wulkan ML, Raval MV. The contribution of practice variation to length of stay for children with perforated appendicitis. J Pediatr Surg. 2016;51(8):1292-7. doi: 10.1016/j.jpedsurg.2016.01.016.

Guyatt GH, Oxman AD, Kunz R, Vist GE, Falck-Ytter Y, Schunemann HJ. What is "quality of evidence" and why is it important to clinicians? BMJ. 2008;336(7651):995-8. doi: 10.1136/bmj.39490.551019.BE.

Henry MC, Walker A, Silverman BL, Gollin G, Islam S, Sylvester K, 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(3):236-41; discussion 241. doi: 10.1001/archsurg.142.3.236.

Lee SL, Islam S, Cassidy LD, Abdullah F, Arca MJ; 2010 American Pediatric Surgical Association Outcomes and Clinical Trials Committee. Antibiotics and appendicitis in the pediatric population: an American Pediatric Surgical Association Outcomes and Clinical Trials Committee systematic review. J Pediatr Surg. 2010;45(11):2181-5. doi: 10.1016/j.jpedsurg.2010.06.038.

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. Surgical Infections. 2020;21(9):778-83. doi:https://dx.doi.org/10.1089/sur.2019.293.

McCarthy K, Avent M. Oral or intravenous antibiotics? Aust Prescr. 2020;43(2):45-48. doi: 10.18773/austprescr.2020.008.

Meier DE, Guzzetta PC, Barber RG, Hynan LS, Seetharamaiah R. Perforated appendicitis in children: is there a best treatment? J Pediatr Surg. 2003;38(10):1520-4. doi: 10.1016/s0022-3468(03)00549-9.

Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan-a web and mobile app for systematic reviews. Syst Rev. 2016;5(1):210.

Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. Bmj. 2021;372:n71.

Pennell C, Meckmongkol T, Arthur LG, Ciullo S, Prasad R, Lindholm E, et al. A Standardized Protocol for the Management of Appendicitis in Children Reduces Resource Utilization. Pediatr Qual Saf. 2020;5(6):e357. doi: 10.1097/pq9.0000000000000357.

Rasmussen T, Fonnes S, Rosenberg J. Long-Term Complications of Appendectomy: A Systematic Review. Scand J Surg. 2018;107(3):189-196. doi: 10.1177/1457496918772379.

Rentea RM, Peter SDS, Snyder CL. Pediatric appendicitis: state of the art review. Pediatr Surg Int. 2017;33(3):269-83. doi: 10.1007/s00383-016-3990-2.

Slusher J, Bates CA, Johnson C, Williams C, Dasgupta R, von Allmen D. Standardization and improvement of care for pediatric patients with perforated appendicitis. J Pediatr Surg. 2014;49(6):1020-4; discussion 1024-5. doi: 10.1016/j.jpedsurg.2014.01.045.

Statens beredning för medicinsk och social utvärdering (SBU). Utvärdering av insatser i hälso- och sjukvården och socialtjänsten: En metodbok [internet]. Stockholm: Statens beredning för medicinsk och social utvärdering (SBU); 2023. Chapter 10.1, Möjliga användningsområden för systematiska översikter; p. 130-1. [cited 2024 May 3]. Available from: https://www.sbu.se/metodbok

Sveriges kommuner och regioner (SKR). Nationellt vårdprogram för akut appendicit hos vuxna och barn: Nationellt programområde mag- och tarmsjukdomar[internet]. Stockholm: Sveriges kommuner och regioner (SKR); 2024. [cited 2024 May 3]. Available from: https://www.nationelltklinisktkunskapsstod.se/globalassets/nkk/nationell/media/dokument/kunskapsstod/vardprogram/nationellt-vardprogram-for-akut-appendicit2.pdf

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(12):3049-53.

Wang C, Li Y, Ji Y. Intravenous versus intravenous/oral antibiotics for perforated appendicitis in pediatric patients: a systematic review and meta-analysis. BMC Pediatr. 2019;19(1):407.

**Project: Postoperative routine of antibiotic treatment**
**Appendix 2** Included articles

| First author Year Country | Study Design Surgery | Patients (n) | Age, years (Mean± SD) | Female sex (%) | Subgroups* | Intervention | Comparison | Outcome variables |
|---|---|---|---|---|---|---|---|---|
| de Wijkerslooth et al. 2023** NL (15 hospitals) | RCT<br><br>Laparo-scopic surgery: 95% | I: 42<br>C: 45 | I1/I2: 12.7±3.1<br>C1/C2: 13.1±3.0 | I1/I2: 29%<br>C1/C2: 29% | Preoperative vomiting NR<br><br>Symptom duration before surgery ≤48 hours<br>I1/I2: 57%<br>C1/C2: 87%<br>(P=0.002)<br><br>Preoperative serum CRP >100<br>I1/I2: 40%<br>C1/C2: 38% | I1/I2:<br>IV: cefuroxine (1500 mg x3) or ceftriazone (2000 mg x1) + metronidazole (500 mg x3)<br>**2 days** | C1/C2:<br>IV: cefuroxine (1500 mg x3) or ceftriazone (2000 mg x1) + metronidazole (500 mg x3)<br>**5 days** | Mortality<br>Intraabdominal abscess<br>Ileus<br>Readmission<br>Complication to antibiotic treatment<br>Surgical site infection<br>Length of hospital stay |
| Desai et al., 2015<br>USA | Cohort (Before/ after)<br><br>Laparo-scopic surgery: 100% | I: 152<br>C: 136 | NR | NR | NR | I1:<br>IV: ceftriaxone (50 mg/kg) + metronidazole (30 mg/kg)<br><5 days<br>If normal WBC count: No oral antibiotic;<br>**total: <5 days** of antibiotic treatment<br><br>(If elevated WBC count; amoxicillin-clavulanate ≥2 days, total: 7 days of antibiotic treatment) | C1:<br>IV: ceftriaxone (dose NR) + metronidazole (dose NR) <5 days<br>Oral: amoxicillin-clavulanate ≥2 days,<br>**total: 7 days** of antibiotic treatment | Intraabdominal abscess |
| Fraser et al., 2010<br>USA | RCT<br><br>Laparo-scopic surgery: 100% | I1/C2: 52<br>C1/I2: 50 | I1/C2: 9.7±4.2<br>C1/I2: 10.1±4 | I1/C2: 40%<br>C1/I2: 40% | NR | I1:<br>IV: ceftriaxone + metronidazole (dose NR) 5 days<br>If normal WBC count: No oral antibiotic; | C1:<br>IV: ceftriaxone + metronidazole (dose NR) until tolerating diet<br>If <5 days: ≥2 days with oral amoxicillin-clavulanate (dose NR), | Intraabdominal abscess<br>Length of hospital stay |

**Project: Postoperative routine of antibiotic treatment**
**Appendix 2** Included articles

| First author Year Country | Study Design Surgery | Patients (n) | Age, years (Mean± SD) | Female sex (%) | Subgroups* | Intervention | Comparison | Outcome variables |
|---|---|---|---|---|---|---|---|---|
| | | | | | | **total: 5 days** of antibiotic treatment<br><br>(If elevated WBC count: prolonged IV antibiotics ≥2 days) | **total: 7 days** of antibiotic treatment | |
| | | | | | | I2 (=C1 above):<br>IV: ceftriaxone + metronidazole (dose NR) **until tolerating diet**<br>If <5 days: ≥2 days with oral amoxicillin-clavulanate (dose NR), total: 7 days of antibiotic treatment | C2 (=I1 above):<br>IV: ceftriaxone + metronidazole (dose NR) **5 days**<br>If normal WBC count: No oral antibiotic<br><br>(If elevated WBC count: prolonged IV antibiotics ≥2 days) | |
| Rice et al., 2001<br>USA | RCT<br><br>Open surgery: 100% | I: 16<br>C: 10 | I: 11.9±3.9<br>C: 12.5±3.7 | I: 5<br>C: 4 | NR | I2:<br>IV: ampicillin (400 mg/kg x4) + gentamicin (6.5 mg/kg x3) + clindamycin (40 mg/kg x3); until return of GI function; **maximum 5 days**<br><br>(PO: amoxicillin-clavulanate (40 mg/kg x3) + metronidazole (40 mg/kg x3)<br>Total antibiotic duration: 10 days) | C2:<br>IV: ampicillin (400 mg/kg x4) + gentamicin (6.5 mg/kg x3) + clindamycin (40 mg/kg x3); **10 days** | Intraabdominal abscess<br>Surgical site infection |

C = comparison, GI = gastrointestinal, I = intervention, IV = intravenous, NA = not applicable, NL = the Netherlands, NR = not reported, RCT = randomised controlled trial, SD = standard deviation, USA = United Stated of America, WBC = white blood cell
*Predefined subgroups were with/without preoperative vomiting, symptom duration before surgery ≤/48 hours, and preoperative CRP >100
**Data obtained from authors

**Project: Postoperative routine of antibiotic treatment**
**Appendix 3.**
Excluded articles

| Author, year | Reason for exclusion |
|---|---|
| Abdulkareem 1992 | Wrong population (non-perforated) |
| Anderson 2018 | Wrong study design (retrospective) |
| Anonymous 1992 | Wrong comparison (different drugs) |
| Anonymous 1984 | Mixed population (ages). Wrong comparison (different drugs) |
| Bafu 1997 | Wrong intervention/comparison (acute appendectomy vs antibiotics and delayed appendectomy) |
| Basoli 2008 | Wrong population (adults) |
| Berne 1993 | Wrong population (adults) |
| Bueno-Rodriguez 2012 | Wrong language (Spanish) |
| Cho 2016 | Mixed population (ages). Non-RCT |
| Cunningham 2020 | Wrong intervention (pathway of antibiotic regimen, number of days not specified) |
| Di Benedetto 1989 | Wrong study design (case series) |
| el-Mufti 1989 | Mixed population (ages). Wrong I/C (ceftriaxone versus metronidazole/gentamicin/ampicillin) |
| Evbuomwan 1994 | Wrong focus (clinical classification, no comparison of antibiotic duration) |
| Fink 1979 | Mixed population (ages). Wrong I/C (cefaloridin vs penicillin/streptomycin) |
| Fishman 2000 | Wrong comparison (hospital vs at home) |
| Flannigan 1983 | Wrong intervention (no postoperative intravenous antibiotics) |
| Gollin 2002 | Wrong study design (case series) |
| Gottrup 1979 | Wrong comparison (different drugs) |
| Higginbotham 1998 | Wrong focus (development and implementation of pathway, control unclear) |
| Höggwarth 1986 | Wrong language (German) |
| Irfan Farooqi 2021 | Mixed population (ages). Wrong I (only preoperative antibiotics) |
| Jewett 1971 | Wrong comparison (sulfadiazine as add on vs no sulfadiazine, duration unclear in control group) |
| Kekomaki 1981 | Wrong comparison (different drugs) |
| Khan 2020 | Wrong comparison (before vs after protocol) |
| Kling 1985 | Wrong comparison (different drugs) |
| Kooi 1990 | Wrong comparison (different drugs) |
| Lansdale 2019 | Wrong population (complicated appendicitis including gangrenous appendicitis). Non-RCT |
| Lindahl 1969 | Mixed population (ages). Non-RCT |
| Liu 2020 | Wrong population (including gangrenous appendicitis). Data matching the PICO requested but not obtained. |
| Lose 1986 | Mixed population (ages). Non-RCT |
| Maltezou 2001 | Wrong comparison (different drugs) |
| Mazuski 2017 | Wrong design (guidelines) |
| Meller 1991 | Wrong comparison (different drugs) |
| Miholic 1983 | Wrong comparison (different drugs and administrations) |
| Naess 1968 | Wrong publication type (summary) |

**Project: Postoperative routine of antibiotic treatment**
**Appendix 3.**
Excluded articles

| Author, year | Reason for exclusion |
|---|---|
| Ong 2008 | Wrong study design (retrospective) |
| Perez 2011 | Wrong comparison (different doses) |
| Pinto 1980 | Mixed population (ages). Wrong I/C (metronidazol vs ampicillin/no antibiotic) |
| Pogorelic 2019 | Wrong comparison (different drugs) |
| Pokorny 1991 | Wrong comparison (different drugs) |
| Puri 1981 | Wrong comparison (different drugs) |
| Raahave 1986 | Wrong comparison (different drugs) |
| Raahave 1970 | Wrong comparison (part 1: no comparison, part two: placebo) |
| Raffensperger 1969 | Wrong comparison (different drugs) |
| Rangel 2017 | Wrong study design (retrospective) |
| Robinson 2017 | Wrong comparison (before vs after guideline implementation) |
| Russel 2023 | Wrong intervention (number of days with intravenous antibiotics not specified) |
| Samelson 1987 | Wrong intervention (protocol, no comparison of duration of antibiotics between groups) |
| Sawyer 2015 | Wrong P (intraabdominal infection). Wrong I/C (total number of days not specified) |
| Schmitt 1993 | Wrong language (French) |
| Schmitt 1989 | Wrong comparison (different drugs) |
| Schultz 1979 | Mixed population (ages). Wrong I/C (minocyclin vs penicillin/streptomycin) |
| Shandling 1974 | Wrong study design (retrospective) |
| Shbat 2014 | Wrong population (non-perforated) |
| Sirinek 1987 | Mixed population (ages). Wrong I/C (cefoxitin vs clindamycin/gentamicin) |
| Sirinek 1991 | Wrong comparison (different drugs) |
| Skarda 2014 | Wrong intervention (number of days with intravenous antibiotics not specified) |
| Slusher 2014 | Wrong intervention/comparison (different surgical strategies) |
| Solomkin 2003 | Wrong population (adults) |
| Sorooshian 2022 | Wrong study design (retrospective) |
| St Peter 2008 | Wrong comparison (different drugs) |
| Stone 1971 | Wrong study design (case series) |
| Stovroff 1994 | Wrong intervention/comparison (with vs without peripheral inserted central line) |
| Svensson 2016 | Wrong publication type (comment) |
| Talei 1994 | Mixed population (ages). Wrong I/C (metronidazol versus penicillin/chloramphenicol/gentamicin) |
| Taylor 2004 | Mixed population (ages). Wrong I/C (total number of days not specified) |
| Teppler 2004 | Wrong population (adults) |
| Theodorou 2022 | Wrong study design (retrospective) |
| van den Boom 2020 | Wrong design (systematic review) |
| van Rossem 2016 | Mixed population (ages). Non-RCT |

**Project: Postoperative routine of antibiotic treatment**
**Appendix 3.**
Excluded articles

| Author, year | Reason for exclusion |
|---|---|
| Vennits 1990 | Mixed population (ages, diagnosis). Data matching the PICO requested but not obtained. |
| Wang 2019 | Wrong design (systematic review) |
| Willis 2018 | Wrong intervention (antimicrobial stewardship, practice guideline) |
| Yu 2013 | Wrong population (including gangrenous appendicitis). Non-RCT |

**Project: Postoperative routine of antibiotic treatment**
**Appendix 4.1**
**Outcome variable:** Intraabdominal abscess

* + No or minor problems
? Some problems
- Major problems

| Author Year Country | Study design | Patients | Withdrawals - dropouts | Results | | Comments | Directness * | Study limitations * | Precision * |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Intervention | Comparison | | | | |
| de Wijkerslooth et al., 2023 NL | RCT | I: 42<br>C: 45 | 0 | I1/I2:<br>6/42 (15%)<br><br>*Symptom duration before surgery ≤48 hours:* 3/24 (13%)<br><br>*Preoperative serum CRP >100:* 5/17 (29%) | C1/C2:<br>5/45 (11%)<br><br>*Symptom duration before surgery ≤48 hours:* 4/39 (10%)<br><br>*Preoperative serum CRP >100:* 4/17 (24%) | | ? | ? | + |
| Desai et al., 2015 USA | Cohort (Before/after) | I: 152<br>C: 136 | 0 | I1:<br>12/152 (7.9%) | C1:<br>6/136 (4.4%) | Excluding 17 patients in I with elevated WBC: 11/135 (8.1%) | + | ?/- | - |
| Fraser et al., 2010 USA | RCT | I1/C2: 52<br>C1/I2: 50 | 0 | I1:<br>10/52 (19%)<br><br>I2:<br>10/50 (20%) | C1:<br>10/50 (20%)<br><br>C2:<br>10/52 (19%) | Preterminated<br>Number of patients in I without oral antibiotic NR | ? | ? | - |
| Rice et al., 2001 USA | RCT | I: 16<br>C: 10 | 0 | I2:<br>0/16 | C2:<br>0/10 | | - | ? | - |

C = comparison, CRP = C-reactive peptide, I = intervention, NL = the Netherlands, NR = not reported, RCT = randomised controlled trial, USA = United States of America, WBC = white blood cell

**Project: Postoperative routine of antibiotic treatment**
**Appendix 4.2**
**Outcome variable:** Mortality

* + No or minor problems
? Some problems
- Major problems

| Author Year Country | Study design | Patients | Withdrawals - dropouts | Results | | Comments | Directness * | Study limitations * | Precision * |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Intervention | Comparison | | | | |
| de Wijkerslooth et al., 2023 NL | RCT | I: 42<br>C: 45 | 0 | I1/I2:<br>0 | C1/C2:<br>0 | Within 90 days | ? | ? | + |

C = comparison, I = intervention, NL = the Netherlands, RCT = randomised controlled trial

**Project: Postoperative routine of antibiotic treatment**
**Appendix 4.3**
**Outcome variable:** Ileus

* + No or minor problems
? Some problems
- Major problems

| Author Year Country | Study design | Patients | Withdrawals - dropouts | Results | | Comments | Directness * | Study limitations * | Precision * |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Intervention | Comparison | | | | |
| de Wijkerslooth et al., 2023 NL | RCT | I: 42<br>C: 45 | 0 | I1/I2:<br>1/42 | C1/C2:<br>4/45 | | ? | ? | + |
| Rice et al., 2001 USA | RCT | I: 16<br>C: 10 | 0 | I2:<br>0/16 | C2:<br>0/10 | No surgical reinterventions, interpreted as no events of ileus | - | ? | - |

C = comparison, I = intervention, NL = the Netherlands, RCT = randomised controlled trial, USA = United States of America

**Project: Postoperative routine of antibiotic treatment**
**Appendix 4.4**
**Outcome variable:** Readmission

* + No or minor problems
? Some problems
- Major problems

| Author Year Country | Study design | Patients | Withdrawals - dropouts | Results | | Comments | Directness * | Study limitations * | Precision * |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Intervention | Comparison | | | | |
| de Wijkerslooth et al., 2023 NL | RCT | I: 42<br>C: 45 | 0 | I1/I2:<br>9/42 | C1/C2:<br>7/45 | Within 90 days | ? | ? | + |

C = comparison, I = intervention, NL = the Netherlands, RCT = randomised controlled trial

**Project: Postoperative routine of antibiotic treatment**
**Appendix 4.5**
**Outcome variable:** Complication to antibiotic treatment

* + No or minor problems
? Some problems
- Major problems

| Author Year Country | Study design | Patients | Withdrawals - dropouts | Results | | Comments | Directness * | Study limitations * | Precision * |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Intervention | Comparison | | | | |
| de Wijkerslooth et al., 2023 NL | RCT | I: 42<br>C: 45 | 0 | I1/I2:<br>8/42 | C1/C2:<br>9/45 | Adverse effects reported | + | ? | + |

C = comparison, I = intervention, NL = the Netherlands, RCT = randomised controlled trial

**Project: Postoperative routine of antibiotic treatment**
**Appendix 4.6**
**Outcome variable:** Surgical site infection

* + No or minor problems
? Some problems
- Major problems

| Author Year Country | Study design | Patients | Withdrawals - dropouts | Results | | Comments | Directness * | Study limitations * | Precision * |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Intervention | Comparison | | | | |
| de Wijkerslooth et al., 2023 NL | RCT | I: 42<br>C: 45 | 0 | I1/I2:<br>1/42 | C1/C2:<br>0/45 | | + | ? | + |
| Rice et al., 2001 USA | RCT | I: 16<br>C: 10 | 0 | I2:<br>1/16 | C2:<br>1/10 | Pilot study | - | ? | - |

C = comparison, I = intervention, NL = the Netherlands, RCT = randomised controlled trial, USA = United States of America

**Project: Postoperative routine of antibiotic treatment**
**Appendix 4.7**
**Outcome variable:** Length of hospital stay

* + No or minor problems
? Some problems
- Major problems

| Author Year Country | Study design | Patients | Withdrawals - dropouts | Results | | Comments | Directness * | Study limitations * | Precision * |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Intervention | Comparison | | | | |
| de Wijkerslooth et al., 2023 NL | RCT | I: 42<br>C: 45 | 0 | I1/I2:<br>3.4±1.6 | C1/C2:<br>5.6+1.9 | Days, mean+SD | ? | ? | + |
| Fraser et al., 2010 USA | RCT | I1/C2: 52<br>C1/I2: 50 | 0 | I1:<br>6:06±2:00<br>I1 *vs.* C1: P=0.01<br><br>I2:<br>4:48±2:36 (SIC)<br>I2 *vs.* C2: P=0.01 | C1:<br>4:48±2:36 (SIC)<br><br>C2:<br>6:06±2:00 | Days:hours, mean+SD<br>Number of patients in I without oral antibiotic NR | ? | ? | - |

C = comparison, I = intervention, NL = the Netherlands, RCT = randomised controlled trial, SD = standard deviation, SIC = sic erat scriptum, thus it was written

**Project: Postoperative routine of antibiotic treatment**

**Appendix 5** Aspects regarding directness and study limitations identified during the assessment process contributing to the study being categorised as having no/minor (+), some (?) or major (-) problems. These assessments applied to all outcomes if not explicitly stated otherwise.

| Author<br>Year<br>Country | Study design | Problems contributing to downgrading the study in the assessment | | | | | |
|---|---|---|---|---|---|---|---|
| | | Directness | | Study limitations | | Precision | |
| de Wijkerslooth et al.<br>2023<br>NL | RCT | ? | Children <8 years of age not included. In the entire study, not restricted to age, 27% of eligible patients (1,041/3,880) were excluded for unclear reasons. | ? | Not blinded assessments. Symptom duration before surgery was more often ≤48 hours in the control group (87% *vs.* 57%). Protocol violation not evenly distributed between randomisation groups. | + | |
| Desai et al.<br>2015<br>USA | Before/after | + | | ?/- | Confounding factors sparsely reported (e.g. not duration of symptoms and CRP). Adherence to protocol NR. Not blinded assessments. | - | Power calculations NR. Non-significant results interpreted as non-inferiority. |
| Fraser et al.<br>2010<br>USA | RCT | ? | Participant flowchart NR | ? | Adherence to protocol NR. Not blinded assessments. | - | Power calculation performed, study preterminated before calculated sample size was recruited despite non-significant results in interim analysis. |
| Rice et al.<br>2001<br>USA | RCT | - | Children <5 years not included. Reasons for declined participation NR. Length of antibiotic treatment in C out of date (10 days). Open surgery. | ? | Length of intravenous treatment not clearly predefined in I and C. Not blinded assessments. | - | Power calculation NR, pilot study. Non-significant results interpreted as non-inferiority. |

C = comparison, NL = the Netherlands, RCT = randomised controlled trial, USA = United States of America

## Innehållsdeklaration

Denna HTA-rapport är baserad på följande moment:

- ☑ Metodbeskrivning
- ☑ PICO
- ☑ Uttömmande litteratursökning
- ☑ Flödesschema
- ☑ Urval relevans
- ☑ Kvalitetsgranskning
- ☑ Tabelldata
- ☑ Sammanvägning av resultat
- ☑ Metaanalys
- ☑ Evidensgradering enligt GRADE
- ☑ Sammanfattning
- ☑ Ekonomi
- ☑ Organisation
- ☑ Etik
- ☑ Pågående studier
- ☑ Exkluderade artiklar
- ☑ Expertgrupp deltar
- ☑ Extern granskning
- ☑ Kunskapsluckor identifierade
- ☑ Jävsdeklaration inhämtad från projektdeltagarna