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Optimal initial antibiotic regimen for the treatment of acute appendicitis: a systematic review and network meta-analysis with surgical intervention as the common comparator

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Background: The optimal antibiotic regimen for the medical management of acute appendicitis remains unknown due to a lack of head-to-head comparisons between different antibiotic regimens.

Methods: We systematically searched the PubMed, EMBASE, Scopus and Cochrane Central Register of Controlled Trials databases from their inception through to August 2020. We selected randomized controlled trials (RCTs) or observational studies comparing antibiotic therapy and appendectomy as the initial treatment for adult or paediatric patients with acute appendicitis. We performed a Bayesian network meta-analysis (NMA) to obtain the indirect comparison results between different antibiotic regimens by employing the group managed by surgery as a common comparator. Antibiotic regimens were classified into three categories: those including a carbapenem; those including a cephalosporin; and those including a β-lactam/β-lactamase inhibitor combination.

Results: A total of 9 RCTs (adults, $n=8$; paediatrics, $n=1$) and 12 observational studies (adults, $n=3$; paediatrics, $n=9$) were included in the NMA, with a total of 4551 patients. The most commonly administered regimen was a β-lactam/β-lactamase inhibitor combination (9/21; 43%), followed by a cephalosporin (7/21; 33%) or a carbapenem (5/21; 24%). The NMA indicated that surgery significantly increased 1 year treatment success, compared with cephalosporins [OR: 16.79; 95% credible interval: 3.8–127.64] or β-lactam/β-lactamase inhibitor combinations (OR: 19.99; 95% credible interval: 4.87–187.57), but not carbapenems (OR: 3.50, 95% credible interval: 0.55–38.63). In contrast, carbapenems were associated with fewer treatment-related complications compared with surgery (OR: 0.12; 95% credible interval: 0.01–0.85).

Conclusions: Carbapenems might be recommended as the initial antibiotic regimen for the non-operative management of adult patients with acute appendicitis. Nevertheless, due to the imprecise estimates in our NMA, additional RCTs are needed to corroborate these findings, especially for paediatric patients.

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Introduction

Acute appendicitis is the most common cause of abdominal surgery, accounting for about 11%–23% of patients presenting to emergency departments with acute abdominal pain.[1] The recommended treatment for acute appendicitis has been emergency appendectomy for more than a century.[2] Current guidelines[3] recommend laparoscopic appendectomy as the first choice when laparoscopic equipment and skilled surgeons are available, even for complicated appendicitis.[4]

Although emergency appendectomy is well tolerated by most patients, in the NOTA study Di Saverio *et al*.[5] indicated that during 2 years of follow-up less than 14% of patients with appendicitis who were treated non-operatively experienced recurrence, suggesting appendicitis might be safely and effectively treated with antibiotics. Nevertheless, the meta-analysis by Podda *et al*.[6] found that with respect to both initial and 1 year treatment success rate, medical management with antibiotics was inferior to appendectomy, with the 1 year rate of recurrence of appendicitis reaching as high as 30%–40%.

However, emergency appendectomy carries its own set of risks. Post-operative complications occur in about 2%–23% of patients.[7,8] Approximately 3% of patients undergoing appendectomy were hospitalized for intestinal obstruction caused by post-operative adhesions over a 10 year follow-up period.[9,10] Given this risk–benefit profile, in patients whose diagnosis is clinically or radiologically equivocal and who express a strong objection to an operation or have concomitant comorbidities, guidelines suggest that it may be justified to proceed with antibiotic treatment first, allowing for appendectomy to serve as the rescue therapy.[3]

Current guidelines do not recommend a specific antibiotic regimen for acute appendicitis.[3] Hence, variations in the comparator antibiotics in previous studies comparing medical management with emergency appendectomy[6] have led to substantial between-study heterogeneity in treatment efficacy. We attempted to reduce this heterogeneity by using a network meta-analysis (NMA) framework in order to identify the optimal antibiotic regimen for the medical management of acute appendicitis in both adult and paediatric populations.

Materials and methods

The current systematic review and NMA were performed in accordance with the PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of healthcare interventions[11] and was registered in PROSPERO (CRD42020210602).

Data sources and search strategy

Two investigators (C.-C.Y. and C.-H.W.) independently searched PubMed, EMBASE, Scopus and the Cochrane Central Register of Controlled Trials (CENTRAL) databases from inception (PubMed, 1997; EMBASE, 1947; Scopus, 1966; and CENTRAL, 1996) until August 2020 to identify relevant studies. The search strings were constructed using the following terms: (a) patient: acute appendicitis; (b) intervention: antimicrobial, antibiotic, anti-infective, conservative, non-operative or antibacterial; and (c) comparator: appendectomy, appendicectomy, operation, surgery, operative, surgical or non-conservative. For detailed search strings see Table S1, available as Supplementary data at *JAC* Online. No restrictions were set on publication year or language. To ensure completeness, we screened relevant review articles and meta-analyses for references not captured by our search strategy.

Study selection

Two investigators (C.-C.Y. and C.-H.W.) independently reviewed the titles and abstracts of all identified articles and selected those pertinent to this review. The following inclusion criteria were applied: (a) adult or paediatric patients with acute appendicitis; (b) comparisons made between antibiotic therapy and appendectomy as the initial treatment; (c) explicit specification of antibiotic regimen; and (d) outcomes of interest including treatment success or treatment-related complications. Studies focusing specifically on complicated appendicitis or using multiple antibiotic regimens without offering their corresponding proportions were excluded. After retrieving the full reports of potentially relevant studies, the same two investigators independently assessed each study's eligibility based on the inclusion and exclusion criteria. Differences of opinion regarding study eligibility were settled by consultation with a third investigator (C.-C.L.).

Data extraction and quality assessment

Four investigators (C.-C.Y., C.-H.W., W.-T.H. and H.-P.W.) independently extracted qualitative and quantitative data and a third investigator (C.-C.L.) adjudicated discordant assessments. We extracted data based on ITT analysis, including study characteristics (e.g. study design, area and period), patient characteristics (e.g. age and sex), diagnostic criteria of appendicitis, details of interventions (e.g. initial antibiotic regimen, administration method and period), methods of appendectomy and definitions of patient outcomes. For assessing risk of bias in included studies, we adopted the Cochrane risk-of-bias tool[12] for evaluating randomized controlled trials (RCTs) and the 'risk of bias in non-randomized studies' tool (ROBINS-I)[13] for evaluating non-randomized studies, respectively.

Outcome measures

In the current analysis, 1 year treatment success was specified as the primary outcome, whereas initial treatment success and treatment-related complications were specified as secondary outcomes. Each outcome was defined as follows: (a) 1 year treatment success: clinical resolution of appendicitis without recurrence or need for operation at 1 year follow-up; (b) initial treatment success: success of the initial treatment with an uncomplicated course (no post-operative complications, adverse events or treatment failure) during the index hospitalization; (c) treatment-related complications: any adverse event during the index hospitalization, including post-operative abscesses, surgical site infections, incisional hernias, obstructive symptoms and other general complications, such as adverse reaction to antibiotics, anaesthesiology complications and cardiovascular and pulmonary adverse events.

Statistical analysis

We performed an NMA by combining information from different studies that compared antibiotics versus surgical treatments but used different initial antibiotic regimens. In the main analysis, the antibiotic regimens were classified into three categories: (1) those including a β-lactam/β-lactamase inhibitor combination; (2) those including a carbapenem; and (3) those including a cephalosporin, according to the Guidelines by the Surgical Infection Society and IDSA for intra-abdominal infection.[14] We used a random-effects model within a Bayesian framework. For binary outcomes, the model corresponds to a generalized linear model with a logit link. A random-effects model was used to allow for a different but related treatment effect for each individual study. We used non-informative prior distributions given that the relative effectiveness of different antibiotic regimens is uncertain. A network geometry plot was created to confirm whether a multiple treatment comparison analysis could be performed.

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Inconsistency assumption, defined as the statistical disagreement between results obtained from direct and indirect comparison in a closed loop, was assessed locally using a loop-specific approach and globally using a design-by-treatment interaction model.[15] However, the paucity of head-to-head trials for different antibiotic regimens precluded planned evaluations of consistency using loop-specific approaches.

A random-effects Bayesian hierarchical model assuming common heterogeneity was implemented across all comparisons and ORs with their associated 95% credible intervals were calculated. The rank order of a comparator is presented as a 'surface under the cumulative ranking' (SUCRA) probability.[16] The SUCRA is a numerical presentation of the overall ranking, which assigns a single number to each treatment. SUCRA values range from 0% to 100%, with treatments having higher values (closer to 100%) deemed as more likely to be effective and those with lower SUCRA values (closer to 0%) deemed as more likely to be ineffective. Publication bias was assessed by visual inspection of a comparison-adjusted funnel plot.

Subgroup analyses were planned *a priori* for subgroups of adult or paediatric studies. Sensitivity analyses were also performed to investigate the influence of study design (RCTs versus observational studies), classification methods of antibiotic regimens (classification by guidelines versus by antibacterial mechanism versus by antibacterial spectrum) and different assumptions for prior distributions (using the results of the meta-analysis by Podda *et al.*[6] to construct informative prior distributions, i.e. 1 year treatment success rates for surgery and antibiotics: 82.3% versus 67.2%, respectively). A two-tailed *P* value <0.05 was considered statistically significant. All analyses were performed using the gemtc package (version 0.8-6) in R 3.3.1 software (R Foundation for Statistical Computing, Vienna, Austria), which fits a generalized linear model.[17]

Results

Twenty-one studies,[18–38] including 9 RCTs and 12 observational studies, were included in the NMA, with a total of 4551 patients (Figure 1, Table 1). Eleven studies were exclusive to adults and 10 were exclusive to children. In the antibiotic group, the most

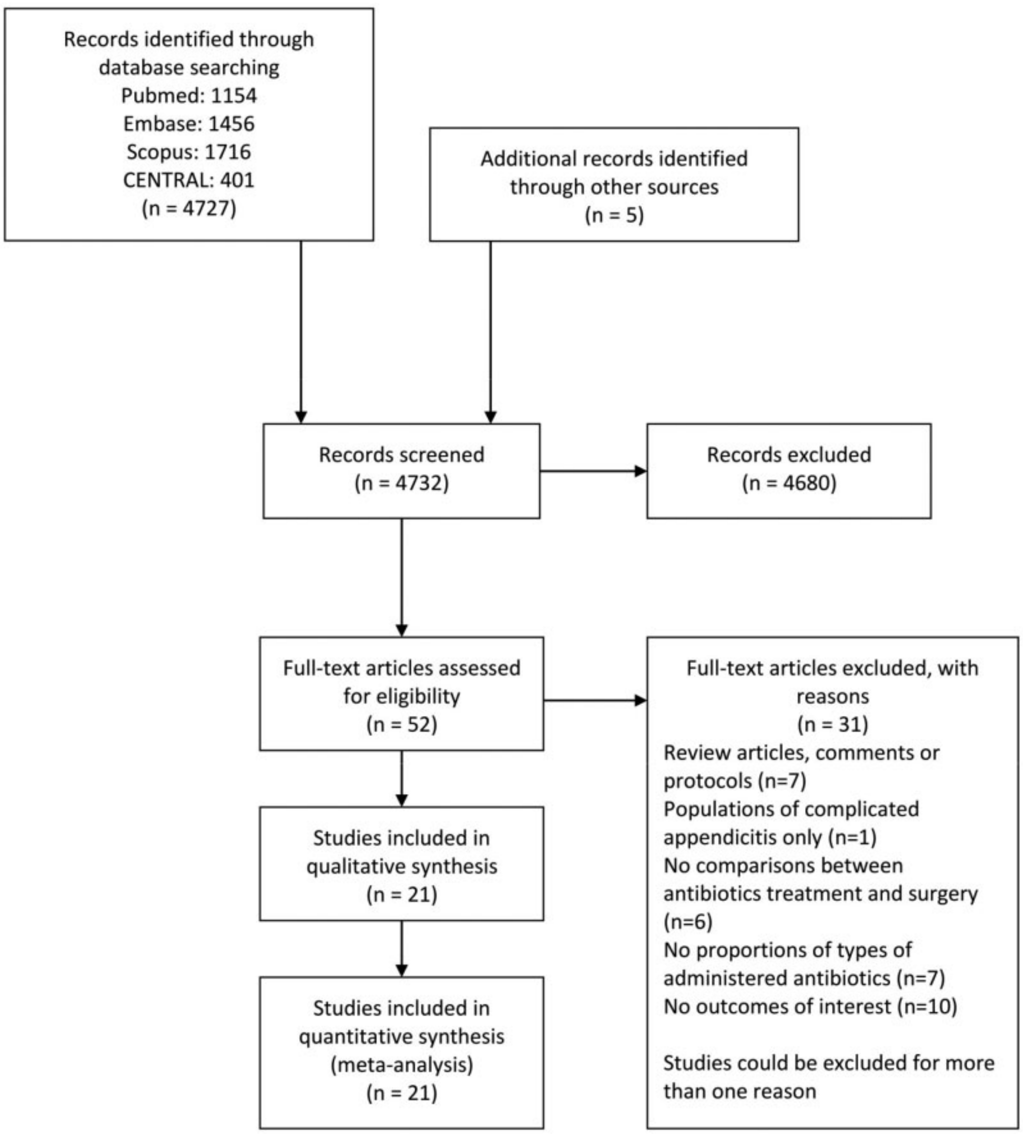

Figure 1. Literature search flowchart.

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Table 1. Characteristics of the studies included in the NMA

Year, first author	Study region, type, period	Age group, age (years); male (%)[a]	WBC (10^9/L); CRP (mg/L)[a]	Initial IV antibiotic regimen	Antibiotic classification[b]	Comparator	1 year treatment success events/patients (%)		Initial treatment success events/patients (%)		Treatment-related complications events/ patients (%)	
							antibiotics	surgery	antibiotics	surgery	antibiotics	surgery
1995 Eriksson et al.[18]	Sweden RCT 1992–94	Adults 31; 68	13.9; 41	CTX + TNZ	C/3gC/GNB + GPC	LA	13/20 (65)	20/20 (100)	13/20 (65)	18/20 (90)	NA	2/20 (10)
2006 Styrud et al.[19]	Sweden RCT 1996–99	Adults NA; 100	12.5; 55	CTX + TNZ	C/3gC/GNB + GPC	OA or LA	97/128 (76)	120/124 (97)	93/128 (73)	107/124 (86)	4/128 (3)	17/124 (14)
2009 Hansson et al.[20]	Sweden RCT 2006–07	Adults 38; 54	13.1; 54.4	CTX + MTZ	C/3gC/GNB + GPC	OA or LA	93/119 (78)	223/250 (89)	57/119 (48)	143/250 (57)	36/119 (30)	80/250 (32)
2009 Turhan et al.[21]	Turkey RCT 2005–06	Adults 28; 66	NA; NA	AMP + GEN + MTZ	BB/AP/ESBL + PsA	OA or LA	87/107 (81)	183/183 (100)	82/107 (77)	175/183 (96)	5/107 (5)	8/183 (4)
2011 Vons et al.[22]	France RCT 2004–07	Adults 33; 60	13.3; NA	AMC	BB/AP/GNB + GPC	OA or LA	75/119 (63)	119/120 (98)	63/120 (53)	114/119 (96)	12/120 (10)	3/119 (3)
2014 Park et al.[23]	Korea PCS 2010–11	Adults 38; 51	11.8; 44.1	2gC + MTZ	C/2gC/GNB	OA or LA	96/119 (81)	152/159 (96)	95/119 (80)	136/159 (86)	1/119 (1)	16/159 (10)
2015 Salminen et al.[24]	Finland RCT 2009–12	Adults 34; 62	11.9; 33	ETP	Carb/Carb/ ESBL	OA or LA	186/257 (72)	254/273 (93)	180/257 (70)	209/273 (77)	6/257 (2)	43/273 (16)
2015 Svensson et al.[25]	Sweden RCT 2012	Children 12; 52	14.3; 28.7	MEM + MTZ	Carb/Carb/ESBL + PsA	LA	18/24 (75)	26/26 (100)	18/24 (75)	26/26 (100)	0/24 (0)	0/26 (0)
2015 Tanaka et al.[26]	Japan PCS 2007–13	Children 10; 69	15; 54.3	CMZ	C/2gC/GNB	LA	55/78 (71)	86/86 (100)	55/78 (71)	84/86 (98)	NA	NA
2016 Hartwich et al.[27]	USA PCS 2012–14	Children 12; 59	15.3; NA	TZP	BB/UP/PsA	NA	17/24 (71)	50/50 (100)	17/24 (71)	50/50 (100)	NA	NA
2016, Mahida et al.[28]	USA PCS 2014–15	Children 12; 43	14.1; NA	TZP	BB/UP/PsA	OA or LA	2/5 (40)	9/9 (100)	2/5 (40)	9/9 (100)	NA	NA
2016 Minneci et al.[29]	USA PCS 2012–13	Children 12; 68	12.9; NA	TZP	BB/UP/PsA	LA	28/37 (76)	61/65 (94)	28/37 (76)	56/65 (86)	NA	5/65 (8)
2017 Allievi et al.[30]	Italy PCS 2011–15	Adults 38; 49	13.2; 56.3	ETP	Carb/Carb/ ESBL	OA or LA	232/284 (82)	78/109 (72)	232/284 (82)	89/109 (82)	NA	20/109 (18)
2017 Lee et al.[31]	USA PCS 2015–16	Children 10; 57	14.4; NA	CRO + MTZ	C/3gC/GNB + GPC	LA	26/51 (51)	31/32 (97)	17/51 (33)	25/32 (78)	9/51 (18)	6/32 (19)

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Table 1. *Continued*

Year, first author	Study region, type, period	Age group, age (years); male (%)[a]	WBC (10^9/L); CRP (mg/L)[a]	Initial IV antibiotic regimen	Antibiotic classification[b]	Comparator	1 year treatment success events/patients (%)		Initial treatment success events/patients (%)		Treatment-related complications events/patients (%)	
							antibiotics	surgery	antibiotics	surgery	antibiotics	surgery
2017 Mudri *et al.*[32]	UK RCS 2012–15	Children 12; 48	NA; NA	CRO + MTZ	C/3gC/GNB + GPC	LA	17/26 (65)	25/26 (96)	17/26 (65)	21/26 (81)	NA	4/26 (15)
2017 Poillucci *et al.*[33]	Italy, RCS 2014–16	Adults 35; 43.6	NA; NA	TZP	BB/UP/PsA	OA or LA	87/162 (54)	159/184 (86)	128/162 (79)	159/184 (86)	4/162 (2)	25/184 (14)
2017 Talan *et al.*[34]	USA RCT 2015	Adults 33; 60	15; 44.1	ETP	Carb/Carb/ESBL	OA or LA	14/16 (88)	14/14 (100)	13/16 (81)	12/14 (86)	1/16 (6)	2/14 (14)
2018 Gorter *et al.*[35]	Netherlands PCS 2012–14	Children 14; 66	12; 33	AMC + GEN	BB/AP/ESBL + PsA	OA or LA	21/25 (84)	19/19 (100)	9/25 (36)	8/19 (42)	12/25 (48)	11/19 (58)
2019 Ceresoli *et al.*[36]	Italy RCT 2011–14	Adults 35; 51	13.9; 44	ETP	Carb/Carb/ ESBL	LA	15/16 (94)	17/22 (77)	16/19 (84)	19/22 (86)	0/19 (0)	3/22 (14)
2019 Miyano *et al.*[37]	Japan PCS 2014–16	Children 8.5; NA	NA; NA	TZP	BB/UP/PsA	LA	NA	NA	27/58 (47)	34/34 (100)	5/58 (9)	0/34 (0)
2020 Minneci *et al.*[38]	USA PCS 2015–19	Children 12.4; 62	12.4; NA	TZP	BB/UP/PsA	LA	261/370 (70.5)	646/698 (93)	324/370 (88)	686/698 (98)	30/370 (8)	80/698 (11)

2gC, second-generation cephalosporin; 3gC, third-generation cephalosporin; AMC, amoxicillin/clavulanate; AMP, ampicillin; AP, aminopenicillin; BB, β-lactam/β-lactamase inhibitor combination; C, cephalosporin; Carb, carbapenem; CMZ, cefmetazole; CRO, ceftriaxone; CRP, C-reactive protein; CTX, cefotaxime; ETP, ertapenem; GNB, Gram-negative bacteria; GPC, Gram-positive cocci; LA, laparoscopic appendectomy; MEM, meropenem; MTZ, metronidazole; NA, not available; OA, open appendectomy; PCS, prospective cohort study; PsA, *P. aeruginosa*; RCS, retrospective cohort study; TNZ, tinidazole; TZP, piperacillin/tazobactam; UP, ureidopenicillin.

[a]Age, WBC count and CRP level were given as mean values in some studies and median values in other studies.

[b]The content is presented in the order of antibiotic classification by guidelines/antibacterial mechanism/antibacterial spectrum.

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commonly administered regimen was a β-lactam/β-lactamase inhibitor combination (9/21; 43%), followed by a cephalosporin (7/21; 33%) and a carbapenem (5/21; 24%). In the surgical group, 11 studies (52%) included patients receiving open or laparoscopic appendectomy while 9 studies (43%) exclusively included patients undergoing laparoscopic appendectomy.

Because of the nature of surgical intervention, blinding of patients could not be achieved in all included RCTs,[18–22,24,25,34,36] resulting in a high risk of potential bias (Table S2). Most observational studies were assessed to have moderate degrees of bias according to the ROBINS-I tool (Table S3).

For the primary outcome, a star-shaped network geometry without any closed loops is presented in Figure 2, which suggested that only indirect comparisons could be obtained with the surgical group as the common comparator. As shown in Figure 3, the NMA indicated that surgery remained the best treatment for appendicitis (SUCRA: 97.2%). Surgery was significantly better than using a cephalosporin (OR: 16.79; 95% credible interval: 3.8–127.64) or a β-lactam/β-lactamase inhibitor combination (OR: 19.99; 95% credible interval: 4.87–187.57) for achieving 1 year treatment success but was not significantly better than using a carbapenem (OR: 3.5; 95% credible interval: 0.55–38.63). The results were consistent when examining subgroups of adult or paediatric patients.

In the sensitivity analyses (Figure 4), the comparison results were similar if only RCTs were included in the NMA. When the antibiotic regimens were reclassified by antibacterial mechanism or spectrum, the NMA results indicated that surgery was superior to all antibiotic regimens, except for carbapenems. The use of informative prior distributions did not change the results of the main analysis.

For the secondary outcomes (Table S4), surgery was ranked as the best treatment with respect to initial treatment success (SUCRA: 94.8%), while carbapenems were ranked as the best treatment (SUCRA: 92.7%) with respect to treatment-related complications. Carbapenems were significantly associated with fewer complications compared with surgery (OR: 0.12; 95% credible interval: 0.01–0.85).

A visual inspection of the criterion of symmetry showed no evidence of publication bias for carbapenems versus surgery while asymmetric distribution was noted for β-lactam/β-lactamase inhibitor combinations or cephalosporins (Figure S1).

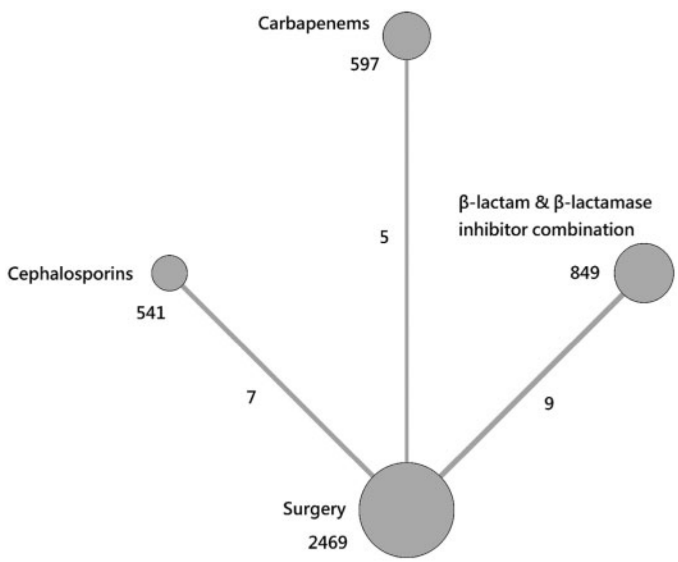

Figure 2. Network geometry for 1 year treatment success.

Discussion

Main findings

Our NMA indicated that emergency appendectomy was superior to all antibiotic regimens with regard to 1 year and initial treatment success while incurring more treatment-related complications. The probability analysis ranked carbapenems as the best antibiotic

(a) All studies

Surgery (SUCRA: 97.2%)			
3.5 (0.55–38.63)	Carbapenems (SUCRA: 63.5%)		
16.79 (3.8–127.64)	4.81 (0.33–67.21)	Cephalosporins (SUCRA: 22.3%)	
19.99 (4.87–187.57)	5.68 (0.45–93.6)	1.19 (0.12–15.48)	β-Lactam/β-lactamase inhibitors combination (SUCRA: 17.0 %)

(b) Subgroup of adults-only studies

Surgery (SUCRA: 91.2%)			
1.95 (0.24–23.17)	Carbapenems (SUCRA: 67.0%)		
7.75 (1.15–100.54)	4.01 (0.18–112.38)	Cephalosporins (SUCRA: 29.1%)	
16.04 (1.82–334.95)	8.25 (0.33–318.21)	2.06 (0.08–63.17)	β-Lactam/β-lactamase inhibitors combination (SUCRA: 12.7%)

(c) Subgroup of paediatrics-only studies

Surgery (SUCRA: 99.6%)		
22.17 (3.37–1359.37)	β-Lactam/β-lactamase inhibitor combinations (SUCRA: 36.6%)	
70.89 (3.69–3930.46)	3.32 (0.02–160.81)	Cephalosporins (SUCRA: 13.9%)

Figure 3. League table presenting NMA comparisons of 1 year treatment success between different treatments for all studies (a) and studies of age-defined subgroups (b and c). The unlabelled data in the boxes are ORs and 95% credible intervals. An OR of >1 suggests that the upper left intervention is associated with higher odds for 1 year treatment success compared with the corresponding lower right intervention. The order of intervention from upper left to lower right is ranked by SUCRA. Bold-type characters are used to indicate a statistically significant difference.

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(a) RCTs

Surgery (SUCRA: 96.7%)			
8.28 (0.62–40.60)	Carbapenems (SUCRA: 45.0%)		
8.33 (0.76–217.21)	1.01 (0.01–54.38)	Cephalosporins (SUCRA: 44.9%)	
44.88 (1.49–9414.57)	5.4 (0.03–1519.39)	5.32 (0.05–1546.72)	β-Lactam/β-lactamase inhibitor combinations (SUCRA: 13.4%)

(b) Classification by antibacterial mechanism

Surgery (SUCRA: 97.2%)					
3.93 (0.46–64.55)	Carbapenems (SUCRA: 68.8%)				
9.53 (1.47–93.93)	2.41 (0.09–53.55)	3gC (SUCRA: 50.5%)			
14.83 (1.92–248.72)	3.75 (0.14–116.97)	1.56 (0.08–44.17)	Ureidopenicillins (SUCRA: 40.5%)		
32.24 (1.15–2856.9)	8.21 (0.11–979.98)	3.42 (0.06–381.8)	2.19 (0.03–240.09)	2gC (SUCRA: 28.0%)	
70.8 (3.73–7120.16)	18.06 (0.37–2397.53)	7.42 (0.2–946.2)	4.76 (0.1–562.08)	2.2 (0.01–557.61)	Aminopenicillin (SUCRA: 15.1%)

(c) Classification by antibacterial spectrum

Surgery (SUCRA: 93.9%)				
1.91 (0.29–16.44)	Anti-ESBL (SUCRA: 75.1%)			
8.29 (2.25–44.35)	4.32 (0.38–56.48)	Anti-GNB+GPC (SUCRA: 37.9%)		
11.73 (2.43–107.44)	6.12 (0.48–116.18)	1.42 (0.15–17.24)	Anti-PsA (SUCRA: 28.1%)	
24.1 (1.86–747.86)	12.65 (0.48–627.14)	2.91 (0.14–104.46)	2.05 (0.07–74.06)	Anti-GNB (SUCRA: 15.1%)

(d) Assumption with informative prior distributions

Surgery (SUCRA: 97.0%)			
3.50 (0.53–37.60)	Carbapenems (SUCRA: 63.5%)		
16.89 (3.84–128.89)	4.85 (0.34–72.40)	Cephalosporins (SUCRA: 22.4%)	
19.98 (4.91–177.57)	5.71 (0.47–95.16)	1.19 (0.121-4.33)	β-Lactam/β-lactamase inhibitor combinations (SUCRA: 17.1%)

Figure 4. League table presenting NMA comparisons of 1 year treatment success between different treatments in sensitivity analysis for RCTs (a), different classification methods of antibiotics (b and c) and different meta-analytic methods (d). 2gC, second-generation cephalosporin; 3gC, third-generation cephalosporin; GNB, Gram-negative bacteria; GPC, Gram-positive cocci; PsA, *P. aeruginosa*. The unlabelled data in the boxes are ORs and 95% credible intervals. An OR of >1 suggests that the upper left intervention is associated with higher odds for 1 year treatment success compared with the corresponding lower right intervention. The order of intervention from upper left to lower right is ranked by SUCRA. Bold-type characters are used to indicate a statistically significant difference.

regimen for 1 year and initial treatment success as well as the fewest treatment-related complications. The comparisons were not sensitive to the study types analysed or classification methods of antibiotic regimens.

Comparison with previous studies

A recent meta-analysis by Podda *et al.*[6] compared treatment effects between antibiotic treatments and surgery by pooling RCTs and observational studies, indicating that antibiotic treatment was associated with a lower 1 year treatment success rate, compared with surgery (72.6% versus 93.1%; OR: 0.12; 95% confidence interval: 0.06–0.24). However, the heterogeneity of this pooled effect estimate was as high as 81%, which was only partly explained by the age group; in the subgroup analysis, heterogeneity decreased to 0% in the paediatric subgroup whereas in the adult subgroup heterogeneity was still as high as 88%. One of the potential causes leading to this substantial heterogeneity was the various regimens that were included in the antibiotic arm. Because of ethical issues, head-to-head comparisons between different antibiotic regimens may not be feasible for RCTs, which we aimed to address indirectly in the framework of an NMA and using the surgery group as a common comparator.

Another recent NMA by Poprom *et al.*[39] pooled RCTs comparing antibiotics with surgery for appendicitis and indicated that piperacillin/tazobactam was the best regimen among antibiotic groups

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regarding initial treatment success. However, the only RCT[40] included to support the use of piperacillin/tazobactam was actually not an RCT but an observational study, which may undermine the Poprom *et al.*[39] conclusion. There is growing interest in using real-world evidence from non-randomized studies in order to corroborate findings from RCTs and further evidence-based medicine.[41] Therefore, we performed this current NMA incorporating both RCTs and observational studies, which suggested that carbapenems might be the optimal antibiotic regimen in treating appendicitis non-operatively.

Interpretation of current study

As shown in Figure 3, surgery remained the best treatment for appendicitis with respect to 1 year treatment success and was significantly better than all antibiotic regimens except carbapenems, which might explain the substantial heterogeneity noted in the Podda *et al.*[6] meta-analysis. In the Poprom *et al.*[39] NMA, if the non-RCTs[40] were not pooled in the analysis, ertapenem would have been the best regimen. In our NMA, among the five studies classified as using carbapenems,[24,25,30,34,36] four adult studies used ertapenem,[24,30,34,36] while only one paediatric study used meropenem with metronidazole.[25] Therefore, in the subgroup analysis for paediatric studies, carbapenems were not pooled in the NMA because of the limited study number. The advantage observed in the carbapenem group is then mostly attributable to the adult studies. Hence, our results may not be generalizable to paediatric patients, necessitating more evidence of carbapenem use in paediatric appendicitis.

In the main analysis, we categorized antibiotic regimens by guideline recommendations.[14] In order to broaden and identify potentially effective antibiotic regimens, we classified antibiotics according to their antibacterial mechanisms or spectrums in the sensitivity analysis. The ranking by SUCRA analysis indicated that not only carbapenems but also antibiotics targeted against ESBL-producing bacteria may be effective in treating appendicitis. In the main analysis and sensitivity analysis, carbapenems or antibiotics possessing anti-ESBL capability were ranked as second-best, second only to surgery, and there were no significant pairwise differences between different antibiotic regimens. In the face of the huge amount of data presented in an NMA, even with the assistance of SUCRA analysis, this ranking should be interpreted cautiously.[42] In the calculation process, SUCRA does not account for the magnitude of treatment differences. Nevertheless, because of the lack of an RCT with head-to-head comparison of different antibiotics, it may be justified to use the rankings by SUCRA to guide clinicians in selecting the optimal antibiotic regimen.

As for the secondary outcomes, carbapenems were ranked as the best type of antibiotic regimen in achieving initial treatment success. In the between-antibiotic comparisons, initial treatment success, instead of 1 year treatment success, may be more representative of the treatment efficacy of antibiotics, since long-term recurrence may be related to other factors, such as the presence of an appendicolith,[43] instead of the choice of initial antibiotics. Regarding treatment-related complications, carbapenems were ranked as the best type of antibiotic regimen, with the fewest complications occurring during the index hospitalization. In contrast, surgery was ranked as the least favourable treatment with regard to treatment-related complications. This finding was consistent with the Podda *et al.*[6] meta-analysis, which indicated lower rates of post-intervention complications associated with antibiotic treatment, compared with appendectomy (7.1% versus 14.5%).

Clinical applications

Recently, there has been increased interest in the non-operative management of acute appendicitis[44] because of evolving understanding of acute appendicitis.[45] After accounting for both treatment success and treatment-related complications, we conclude that carbapenems (particularly ertapenem) seem to provide the greatest net clinical benefit. In the study by Song *et al.*,[46] among the 1678 patients undergoing appendectomy, 694 (41.4%) patients had positive culture results, which were dominated by *Escherichia coli* (448/694, 64.6%). Of note, 13.2% of *E. coli* were identified to be ESBL-producing. This bacteriology might explain why carbapenems were superior to other antibiotics in this NMA. In the practice guidelines published by the Surgical Infection Society and IDSA,[14] ertapenem and ticarcillin/clavulanate were the only two single agents recommended for both adult and paediatric patients with community-acquired intra-abdominal infection, including appendicitis. Our results may further lend support to existing guidelines recommending ertapenem as the first-line regimen for appendicitis.[14] At the same time, *Pseudomonas aeruginosa* was identified to be the second most common organism in the Song *et al.*[46] study (114/694, 16.4%), which was resistant to ertapenem. The cause of this inexplicably high incidence of *P. aeruginosa* infection associated with community-acquired appendicitis needs further studies to elucidate; before this, antibiotics such as ertapenem may still be preferable to regimens with substantial antipseudomonal activity.[14] In addition, during the era of the COVID-19 pandemic, non-operative treatment with ertapenem may limit operating-room utilization and avoid prolonged hospital stays.[47,48] In a global online survey, conservative management of complicated and uncomplicated appendicitis was used by 6.6% and 2.4% of sites, respectively, before the pandemic but 23.7% and 5.3%, respectively, during the pandemic,[49] further highlighting the importance of identifying the optimal antibiotics for acute appendicitis. Nevertheless, non-operative management may not be suitable for all patients with appendicitis. As indicated by the CODA trial,[50] patients with an appendicolith suffered from higher risks and complications of appendectomy than those without an appendicolith and emergency appendectomy may still be the optimal management for these patients.

Study limitations

First, because of the nature of surgical interventions, all RCTs suffered from a high risk of bias associated with failure in the blinding procedure. Also, due to the limited number of eligible RCTs, our NMA also included observational studies, which have their own limitations including selection bias. However, there has been growing interest in applying real-world evidence provided by observational studies,[41] which may increase precision and further corroborate findings from RCTs. In our NMA, the rankings by SUCRA were similar between the main analysis and sensitivity analysis for RCTs, suggesting that the conclusions may not be sensitive to the study designs that were included. Second, there were no uniform classification methods for antibiotics. This classification method

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could probably lead to unstable meta-analytic models because of the limited number of studies in some groups. Accordingly, several methods were tested to identify the optimal regimen. Finally, among paediatric studies there was only one RCT, with 50 patients, the remaining studies being observational in design, indicating the lack of high-quality evidence in the paediatric population. In consideration of the logistically and ethically challenging nature of conducting such an RCT among paediatric patients, the current NMA may serve as the best evidence available for this group of patients.

Conclusions

In the current NMA, surgery and carbapenems were identified as the best and second-best method for achieving 1 year or initial treatment success. In contrast, surgery and carbapenems were ranked as the treatment associated with the most and fewest complications, respectively. Therefore, carbapenems might be recommended as the initial antibiotic regimen for the non-operative management of adult patients with acute appendicitis. For paediatric patients, a lack of high-quality evidence precluded the possibility of making further recommendations.

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Transparency declarations

None to declare.

Supplementary data

Tables S1 to S4 and Figure S1 are available as Supplementary data at *JAC* Online.

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