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SUMMARY WITH CRITICAL APPRAISAL

Fluoroquinolones for Intra-Abdominal Infections: A Review of Clinical Effectiveness, Cost-Effectiveness, and Guidelines

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Abbreviations

AE	Adverse effects
AGREE II	Appraisal of Guidelines for Research and Evaluation
AMSTAR 2	A Measurement Tool to Assess Systematic Reviews
APACHE	Acute Physiology, Age, Chronic Health Evaluation
BW	Body weight
CA-IAI	Community acquired intra-abdominal infection
cIAI	Complicated intra-abdominal infection
CRD	Centre for Reviews and Dissemination
ECG	electrocardiography
FDA	Food and Drug Administration
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
ISPD	International Society for Peritoneal Disease
ITT	Intention to treat
IV	Intravenous
MedDRA	Medical Dictionary for Regulatory Activities
MXF	Moxifloxacin
PD	Peritoneal dialysis
PICO	Populations, Interventions, Comparators, Outcomes
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT	randomized controlled trial
RoB	Risk of bias
RR	Relative risk
SIS	Surgical Infection Society
EKMUD	Infectious Diseases and Clinical Microbiology Specialty Society of Turkey

Context and Policy Issues

Fluoroquinolones are a class of bactericidal antibiotics used to treat a variety of infections.[1] Several oral and injectable fluoroquinolones are available in Canada.[2] Approximately 3.1 million prescriptions are filled for fluoroquinolones each year in Canada, with 98% of them filled by adults.[2]

Intra-abdominal infections are an important cause of morbidity and mortality that require treatment with antibiotic agents.[3] This type of infection occurs following inflammation or disruption of the gastrointestinal tract, gynecologic tract, or urinary tract.[4] Organ infections considered as intra-abdominal infections include gastro duodenum, gallbladder, small and large intestine, appendix, liver, and spleen.[5] Intra-abdominal infections can be categorized as uncomplicated, defined as infections that extend into a normally sterile area of the abdomen, whereas complicated intra-abdominal infections are defined as infections that have "extended beyond the hollow organ into the peritoneal cavity, resulting in abscess or peritonitis."[5] (*p*308) According to Sartelli and colleagues, "early clinical diagnosis, adequate source control to stop ongoing contamination, appropriate antimicrobial therapy dictated by patient and infection risk factors, and prompt resuscitation in critically ill patients are the cornerstones in the management of intra-abdominal infections."[6] (*p*1)

Due to the development of resistance over time in some locations and the potential for severe adverse effects, decisions around the prescription of fluoroquinolones for the treatment of intra-abdominal infections and the choice of a fluoroquinolone regimen take into consideration local and regional susceptibility information,[1,7] whether infections are hospital-, intensive care unit-, or community—associated,[7] and the benefits and harms associated with their use.[1] Fluoroquinolone use has been associated with common adverse

effects, ranging from nausea and vomiting to memory impairment and disturbances in attention.[1] An FDA safety review of unclear methodology showed that systemic use of fluoroquinolones has been associated with more serious and potentially debilitating adverse events involving the tendons, muscles, joints, nerves and central nervous system.[8] Some fluoroquinolone drugs have been removed from the market in response to severe adverse events, such as fatal cardiovascular events, torsades de pointes, and liver failure.[1]

The objective of the current report is to summarize the evidence regarding the clinical effectiveness, cost-effectiveness, and evidence-based guidelines of fluoroquinolones for intra-abdominal infections.

Research Questions

1. What is the clinical effectiveness of fluoroquinolones for the treatment of intra-abdominal infections?
2. What is the cost-effectiveness of fluoroquinolones for the treatment of intra-abdominal infections?
3. What are the evidence-based guidelines regarding the use of fluoroquinolones for the treatment of intra-abdominal infections?

Key Findings

Evidence from one systematic review with meta-analysis, one meta-analysis without systematic review, and two randomized controlled trials (RCTs) suggested that fluoroquinolones did not differ from comparators with respect to effectiveness and safety for the treatment of adults with intra-abdominal infections. One pilot RCT also suggested similar effectiveness and safety for use in children, however statistical significance was not calculated. No evidence for the cost-effectiveness of fluoroquinolones for the treatment of intra-abdominal infections was identified. Two evidence-based guidelines were identified that provide recommendations regarding the use of fluoroquinolones for the treatment of intra-abdominal infections. Based on weak- to high-quality evidence, the guidelines provide weak- to strong-recommendations for the use of fluoroquinolones in adults and children under particular conditions and with some exceptions.

Methods

Literature Search Methods

A limited literature search was conducted on key resources including Medline via OVID, the Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2014 and March 27, 2019.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Patients with intra-abdominal infections (e.g., secondary peritonitis, cholecystitis, ascending cholangitis)
Intervention	Fluoroquinolones
Comparator	Q1-Q2: Any antibiotic comparator Q3: No comparator
Outcomes	Q1: Clinical effectiveness; harms (e.g., *Clostridioides difficile* infections) Q2: Cost-effectiveness Q3: Guidelines
Study Designs	Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, non-randomized studies, economic evaluations, guidelines

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published prior to 2014. Guidelines with unclear methodology or lacking methodological rigour were also excluded.

Critical Appraisal of Individual Studies

The included systematic reviews and meta-analyses were critically appraised by one reviewer using the AMSTAR 2 checklist,[9] randomized studies were critically appraised using the revised Cochrane risk of bias tool,[10] and guidelines were assessed with the AGREE II instrument.[11] Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations of each included study were described narratively.

Summary of Evidence

Quantity of Research Available

A total of 466 citations were identified in the literature search. Following screening of titles and abstracts, 449 citations were excluded and 17 potentially relevant reports from the electronic search were retrieved for full-text review. Five potentially relevant publications were retrieved from the grey literature search for full text review. Of these potentially relevant articles, 16 publications were excluded for various reasons, and six publications met the inclusion criteria and were included in this report. These comprised one systematic review with meta-analysis, one meta-analysis without systematic review, two RCTs, and two evidence-based guidelines. No relevant non-randomized studies or economic evaluations were identified. Appendix 1 presents the PRISMA[12] flowchart of the study selection.

Additional references of potential interest are provided in Appendix 5.

Summary of Study Characteristics

Details regarding the characteristics of included publications are provided in Appendix 2.

Study Design

One systematic review with meta-analysis,[13] one meta-analysis without systematic review,[14] two RCTs,[15,16] and two evidence-based guidelines[5,17] were included in this report. The systematic review was published in 2019,[13] the meta-analysis without systematic review was published in 2014,[14] the RCTs were published in 2018[15] and 2017,[16] and the guidelines were published in 2017[17] and 2016.[5]

Authors of the systematic review searched MEDLINE, Cochrane library, and clintrials.gov from inception to March 2018 and the meta-analyses included 7 multi-centre RCTs published between 1996 and 2009.[13] Authors assessed the methodological quality of the included studies using the Cochrane Risk of Bias tool (assessed selection bias, performance bias, detection bias, attrition bias, and other bias) and the Jadad scale (assessed randomization, random number generation, double-blinding procedure, withdrawals, and allocation concealment).[13]

Data in the meta-analysis without systematic review were pooled from four non-inferiority RCTs (three double-blind and one open label) published between 2006 and 2013.[14]

Among the two included RCTs, the first used a single-centre, open-label, parallel-arm study design[16] and the second used a multi-centre, double-blind, double-dummy, active-controlled parallel arm design.[15]

Two guidelines were included in this report. The revised Surgical Infection Society (SIS) guideline was conducted by a task force comprised of the standing SIS Therapeutics and Guidelines Committee and additional SIS members with subject matter expertise.[17] Medline was searched from 2000 to 2016 for eligible RCTs.[17] Where there were gaps in the literature, non-systematic searches for other study designs were conducted.[17] Recommendations were drafted via an iterative approach and finalized based on consensus.[17] The Infectious Diseases and Clinical Microbiology Specialty Society of Turkey (EKMUD) recommendations were developed by EKMUD members with expertise in intra-abdominal infections.[5] The Ulakbim Turkish Medicine Index, Turkey Citation Index, and Turkish Medline databases were searched for studies conducted in Turkey (dates not specified; eligibility criteria not specified).[5] Additionally, the pages of the European Congress of Clinical Microbiology and Infectious Diseases were searched from 2010 onwards.'[5] Citing a lack of high quality evidence from studies conducted in Turkey, recommendations were developed based on low quality evidence from Turkey (not described) and from existing international guidelines.[5] Recommendations were formulated in person over four face-to-face meetings and agreed to by consensus.[5] The methods for assigning strength of recommendations and assessing quality of underlying evidence are presented in Appendix 2, Table 4 for both guidelines.[5,17] The SIS guidelines[17] were assessed using the GRADE system and the EKMUD recommendations[5] were assessed using an unspecified system.

Country of Origin

The systematic review was published by an author in the US,[13] the meta-analysis without systematic review was published by an author in Belgium,[14] and the two RCTs were published by authors in the Germany[15] and China.[16] The guidelines were published for audiences in the US[17] and Turkey.[5]

Patient Population

The systematic review included data from 4,125 adult patients aged ≥18 years (included study sample sizes ranged from 364 to 804) being treated for various complicated intra-abdominal infections as defined by study authors and adhering to the general definition by the SIS. Patients with secondary peritonitis resulting from infected peritoneal dialysis catheters were excluded "due to the differences in pathophysiology and management."[13] (*p*7) The meta-analysis without systematic review pooled data from 1,229 adult (≥18 years) patients with complicated intra-abdominal infection (i.e., acute peritonitis).[14] All patients required surgery and supportive management for their infection.[14] The two RCTs also included patients with complicated intra-abdominal infection.[15,16] The most recently published of the two examined 451 pediatric patients, aged 3 months to 17 years (median age 13 years) with various types of infections[15] and the second study examined data from 80 adult patients aged >18 years (mean age 47.6 years) with peritoneal dialysis related peritonitis.[14] All patients in the pediatric study had been treated by surgical or interventional radiological procedure at baseline.[15]

The two sets of guidelines included in this report were intended to offer guidance to clinicians regarding the treatment of intra-abdominal infections.[5,17] The EKMUD recommendations were specifically developed to offer guidance to physicians in Turkey.[5]

Interventions and Comparators

Studies included in the systematic review treated participants with Fluoroquinolone-based regimens.[13] Participants in the comparator conditions were treated with Beta lactam-based regiments.[13] Intervention and comparator treatments were initiated intravenously, with the possibility to switch to oral treatment once the patient became stable.[13] Additional information about duration of treatments, doses, or frequency was not available.

Moxifloxacin-based interventions were examined in the meta-analysis without systematic review and in each of the two RCTs.[14-16] Doses in the pediatric RCT were scaled by age- and body weight according to an adult dose of 400 milligrams.[15] In the other RCT and in the meta-analysis without systematic review, adult intervention group patients were treated with 400 milligrams of moxifloxacin per day.[15,16] In the meta-analysis, adults assigned to the comparator group in one of the four pooled studies were treated with one of: i) piperacillin-tazobactam followed by amoxicillin/clavulanic acid; ii) ceftriaxone plus metronidazole, followed by amoxicillin clavulanic acid; iii) ceftriaxone plus metronidazole; or iv) ertapenem.[14] Pediatric patients randomized to the comparator group in one RCT were treated with intravenous ertapenem followed by oral amoxicillin and clavulanate according to the dosage on the label (dosage not further described).[15] Finally, adult patients randomized to the comparator group in the second RCT received 1 gram of intraperitoneal ceftazidime daily.[16]

The guidelines presented recommendations specific to moxifloxacin monotherapy,[5] ciprofloxacin plus metronidazole,[5] levofloxacin plus metronidazole,[5] adjunctive fluoroquinolones to beta lactams,[17] fluoroquinolone-based regimens,[17] and oral quinolones plus amoxicillin clavulanic acid.[5]

Outcomes

Data from the systematic review on clinical effectiveness (i.e., treatment success defined as resolution of infection or improvement in symptoms without surgical site infection requiring systemic antimicrobial treatment) and adverse effects (as defined in each study) associated with fluoroquinolone-based regimens compared with beta lactam-based regimens were assessed at the test of cure visit (follow up period not reported).

Treatment success was also assessed in the meta-analysis without systematic review and the two RCTs that examined moxifloxacin versus comparators.[14-16] Clinical effectiveness included clinical and bacteriologic efficacy at test of cure conducted between 28 and 42 days after end of treatment in one RCT.[15] It was assessed as complete cure, primary treatment failure, secondary treatment failure; relapse, recurrent, or repeat peritonitis; and peritonitis related death at 1, 3, 5, 7, 10, 14, and 21 days following the initiation of treatment in the second RCT.[16] In the meta-analysis without systematic review, clinical effectiveness was assessed as treatment success (i.e., resolution or improvement of clinical signs and symptoms of infection not requiring antibiotics without surgical site infection requiring antimicrobial treatment) at test of cure conducted between 10 and 45 days after antibiotic therapy.[14]

Adverse effects were assessed in the meta-analysis without systematic review and in one RCT, both defined according to the Medical Dictionary for Regulatory Activities (MedDRA).[14,15] In the RCT, adverse effects were cardiac specific effects measured by electrocardiography (ECG) and musculoskeletal effects assessed by physical examination and parent-reported medical history questionnaire (measurement properties not provided), assessed at treatment day one, three to five, day of switch from IV to oral therapy, and at test of cure (28 to 42 days after end of treatment).[15] Patients with musculoskeletal adverse effects were further followed up to one year and until resolution or for five years.[15] In the meta-analysis without systematic review, adverse effects were broader, and included all adverse effects and subcategories, assessed at test of cure.[14]

Summary of Critical Appraisal

Meta-Analyses with or without Systematic Review

Reporting of the systematic review with meta-analysis included clearly specified research questions and inclusion criteria, and authors suggested use of an a priori established protocol, comprehensive literature search strategy, inclusion of predominately high quality RCTs, and adequate investigation of publication bias and assessment of other types of potential bias.[13] Despite these strengths, it remains unclear if or how the study authors managed their reported conflicts of interest.[13] It is also unclear if or how risk of bias and the observed statistical heterogeneity may have affected the results of the review as these were not discussed.[13]

There were a few strengths and several limitations identified with respect to the meta-analysis without systematic review.[14] Strengths included a clearly described research question, included studies were described in adequate detail, statistical methods used to combine studies were reported, and pooled studies were homogenous.[14] Key limitations were the absence of reporting regarding the methods for searching for included studies and the lack of a comprehensive literature search strategy, which reduces confidence in the reported results. The risk that other studies may have reported contradictory findings that would change the direction of the results cannot be ruled out. Bias may also have been introduced due to missing outcome data.[14] Data were calculated using an intention-to-treat approach that did not include all randomized participants. Rather, only those who took at least one treatment dose and had follow-up data for at least one time point were included in the analysis; those who did not can be considered as missing. A large amount of missing data among those who received the first dose of medication would call into question whether participants withdrew due to outcomes associated with the assigned intervention. It is not possible to assess without knowledge of the number assigned or the reasons missing.

Randomized Controlled Trials

The quality of evidence associated with the included RCTs was assessed using the revised Cochrane risk of bias tool.[10] Following from this, it was determined that included studies presented a low-risk of bias resulting from the randomization process.[15,16] Each study reported using a random allocation sequence,[15,16] and although no studies specified a strategy for allocation concealment, baseline characteristics were similar between intervention and comparator groups in both studies.[15,16]

Next, there was a moderate risk that bias was introduced due to the potential for deviations from the intended interventions in one of the included RCTs.[16] The study by Xu et al. [16] was not blinded, reducing certainty that participants or investigators did not behave in a way that would influence the result, whether intentional or unintentional. Bias may have been introduced due to missing outcome data. While outcome data were available for all patients in the adult RCT,[16] and data were available for nearly all (91.9%) participants randomized in the pediatric RCT,[15] the reasons for missing data in that study are likely to be due to the treatment group and the outcome of interest (i.e., adverse effects). Twenty six patients (8.5%) in the intervention group and four patients (2.4%) in the comparator group did not complete study medication and reasons in the intervention group were largely due to the outcome of interest (15 patients or 4.9% of the intervention group withdrew due to experiencing an adverse effect versus 2 patients or 1.3% of the comparator group). The impact of this on the overall findings is not known.

One potentially important source of bias is related to management of conflicts of interest. A pharmaceutical company funded and participated in the development of one RCT, and did not include a statement indicating that the views of the company did not influence the reported result, which introduces a high potential for bias.[15]

The measurement of study outcomes was judged to present a low risk of bias. Measurement methods were not reported in one RCT and outcome assessors were not blinded,[16] however it is not likely measurement differed between groups and assessment of the outcomes was not likely to have differed based on knowledge of the intervention received, given the objective nature of the outcomes. It was also determined that there was a low risk of bias associated with the selection of the reported results. The RCT authors did not indicate that a pre-specified analysis plan was used, however it was determined to be unlikely that this was not likely to have introduced bias.

Evidence-Based Guidelines

Additional details regarding the strengths and limitations of included publications are provided in Appendix 3.

Strengths and weaknesses of evidence-based guidelines[5,17] were assessed using the AGREE II instrument.[11] Common strengths include a clearly reported scope and purpose, target users, and recommendations, inclusion of individuals from all relevant professional groups on the guideline development group, and consideration of the health benefits, side effects, and risks in the formulation of recommendations.[5,17] Common weaknesses include an absence of the views and preferences of the target population at any point in the development process and a lack of monitoring or auditing criteria.[5,17] Notwithstanding these few limitations, the guidelines developed by the SIS used rigorous methodology, provide supports for implementation, and were generally well done.[17] In contrast, there were a number of additional important limitations associated with the development of the EKMUD guidelines that are of concern. Specifically, the EKMUD development group conducted a

systematic search for Turkish RCTs for the purpose of limiting generalizability to the Turkish population, which limits generalizability outside of that country. Finding none, the guideline development committee selected recommendations from existing guidelines to incorporate. It is unclear how guidelines were identified or specific recommendations chosen, although it was reported that guidelines were only considered if they used a common recommendation strength and evidence quality rating system pre-selected by the development committee. Finally, non-randomized studies conducted in Turkey informed the development of the recommendations but the methods for identifying these studies or incorporating them into the recommendations in unknown.

Summary of Findings

Appendix 4 presents a table of the main study findings and authors' conclusions.

Clinical Effectiveness of Fluoroquinolones

Effectiveness

Clinical effectiveness was assessed in one systematic review with meta-analysis,[13] one meta-analysis without systematic review,[14] and two RCTs.[15,16]

In the systematic review, fluoroquinolone-based regimens did not significantly differ from beta-lactam based regimens for the treatment of complicated intra-abdominal infections.[13]

In the meta-analysis without systematic review, authors concluded that moxifloxacin had similar efficacy compared with four previously approved antibiotic regimens for the treatment of complicated intra-abdominal infections.[14]

In the pediatric RCT of patients being treated for complicated intra-abdominal infection, the moxifloxacin group experienced greater treatment success and clinical cure at time of cure compared with ertapenem followed by amoxicillin and clavulanate, although statistical significance was not assessed.[15] The moxifloxacin group also had a higher percentage of patients with any clinical failure, infectious failure, and wound infection versus comparator, and no apparent differences between reoperation or administration of other microbials and again, statistical significance was not assessed.[15]

There were no statistically significant differences in complete cure, primary treatment failure, secondary treatment failure, peritonitis-related death, successive episodes of peritonitis up to three months follow-up, successive episodes of peritonitis, transfer to hemodialysis, or maintenance of peritoneal dialysis between fluoroquinolones and comparators in the RCT that examined adult patients.[14,16] Authors concluded that moxifloxacin had similar efficacy compared with ceftazidime for the treatment of peritonitis secondary to ambulatory peritoneal dialysis compared with ceftazidime.[16]

Adverse Effects

Adverse effects were assessed in one systematic review,[13] one meta-analysis without systematic review,[14] and one RCT.[15]

In the systematic review, fluoroquinolone-based regimens did not significantly differ from beta-lactam based regimens with regard to all-cause mortality, overall treatment related-adverse effects, or withdrawal from the study due to adverse effects in patients with complicated intra-abdominal infections.[13]

In the meta-analysis without systematic review that examined moxifloxacin for the treatment of complicated intra-abdominal infections, authors determined the rates of adverse effects were similar to comparator groups for adverse effects overall, for drug-related adverse effects occurring in more than five patients in either group, for serious adverse effects, drug-related adverse effects, premature discontinuations due to adverse effects, and deaths.[14]

In the pediatric RCT, authors determined the rates of adverse events were similar to the comparator group for all adverse effects, with the exception of QT prolongation.[15] Wirth and colleagues concluded that there were greater occurrences of QT prolongation assessed by ECG in the moxifloxacin group versus the comparator group.[15] Statistical significance was not examined for adverse effects outcomes in either study.

Cost-Effectiveness of Fluoroquinolones

No relevant evidence regarding the cost-effectiveness of fluoroquinolones was identified.

Guidelines

Two guidelines provide recommendations on the use of fluoroquinolones in the treatment of community-acquired intra-abdominal infections based on varying quality of evidence.[5,17]

The SIS guideline provides recommendations for adults and pediatric patients. For adults, intravenous moxifloxacin or ciprofloxacin plus metronidazole are recommended for the empiric treatment of those with lower-risk infection, with caution advised for those in regions with a high incidence of fluoroquinolone-resistant Escherichia coli (strong recommendation; high quality evidence). Levofloxacin plus metronidazole is recommended where other fluoroquinolones are unavailable (weak recommendation, weak quality evidence). Fluoroquinolone-based regimens in general are recommended for initial empiric antimicrobial therapy in lower risk patients who have had major reactions to beta lactams (weak recommendation; moderate quality evidence).[17]

For pediatric patients, the SIS does not recommend moxifloxacin for empiric treatment unless other options are not available (strong recommendation; weak quality evidence). The SIS recommends ciprofloxacin plus metronidazole (weak recommendation, moderate quality evidence) or levofloxacin (weak recommendation, weak quality evidence) for empiric treatment of children older than one month if other options are not suitable. This is particularly recommended for those who have had life-threatening beta lactam reactions (weak recommendation, moderate quality evidence).[17]

The SIS recommends against empiric use of most fluoroquinolone-based regimens in residents of geographic areas where a high prevalence of extended spectrum beta-lactamase-producing Enterobacteriaceae exists in the community (strong recommendation; moderate quality evidence).

For adults in Turkey with community-acquired intra-abdominal infections of mild to moderate severity, the EKMUD guidelines recommend moxifloxacin monotherapy or combination therapy that includes levofloxacin or ciprofloxacin (good quality evidence).[5] For those considered as high-risk, combinations of metronidazole with ciprofloxacin or levofloxacin are recommended for empiric treatment against gram-negative organisms (good quality evidence).[5] Amoxicillin-clavulanic acid and oral quinolone (moxifloxacin, ciprofloxacin, levofloxacin) are recommended for patients able to accept oral medications in

the recovery period and whose infections are not resistant to these agents (moderate quality evidence).[5]

Limitations

There are a number of key limitations to note with respect to the current report. To begin with, there was limited or no evidence available on the effectiveness and safety of fluoroquinolones for some populations of interest. Pediatric patients were only examined in one small (N = 80) pilot study and statistical significance was not calculated.[15] Complicated intra-abdominal infections and secondary peritonitis were examined but other uncomplicated types of intra-abdominal infection were not examined in clinical studies, and no studies were conducted in Canada. Given that susceptibility to antibiotic resistance differs across regions, it is unclear if the included studies would be generalizable to a Canadian context. In addition, no cost-effectiveness studies were identified for inclusion. Limitations associated with the evidence based guidelines largely stemmed from the lack of clarity in the methodology used to develop the EKMUD guideline.[5] As the EKMUD guideline translated existing recommendations from other guidelines to a Turkish context,[5] it is not clear if findings would be applicable in Canada as well.

Conclusions and Implications for Decision or Policy Making

This report identifies evidence on the clinical effectiveness of fluoroquinolones for the treatment of intra-abdominal infections, and two evidence-based guidelines regarding the use of fluoroquinolones. No evidence was identified for the cost-effectiveness of fluoroquinolones in the treatment of intra-abdominal infections.

Regarding clinical effectiveness, evidence from one systematic review (N = 4,125) demonstrated that fluoroquinolone-based regimens did not differ from beta lactam-based regimens in adults with complicated intra-abdominal infections in terms of effectiveness and safety.[13] Similarly, evidence from the meta-analysis without systematic review and one RCT [14,16] showed that moxifloxacin did not differ from comparators for the treatment of complicated intra-abdominal infections[14] and for secondary peritonitis.[16] Authors of a second RCT did not calculate statistical significance and therefore it is unclear whether moxifloxacin differed from the comparator at test of cure for the treatment of pediatric patients with complicated intra-abdominal infection.[15] Adverse effects were assessed in one meta-analysis without systematic review and one RCT, and evidence suggested rates of adverse events were similar between moxifloxacin and comparator treatment groups.[14,15] The exception was QT prolongation assessed by ECG in the pediatric study, which was judged by the study authors to be greater with moxifloxacin versus comparator treatment, although statistical significance was not calculated.[15]

Two evidence-based guidelines were identified that provide recommendations regarding the use of fluoroquinolones for the empiric treatment of intra-abdominal infections.[5,17] Based on evidence of varying quality, the guidelines development groups recommend fluoroquinolone-based regimens in general; and intravenous moxifloxacin; intravenous ciprofloxacin plus metronidazole; and intravenous levofloxacin plus metronidazole for the treatment of community acquired-intraabdominal infections in adults and children and certain conditions and settings.[5]

Additional research is required to discern the cost-effectiveness of fluoroquinolones for the treatment of intra-abdominal infections.

Although no evidence specific to Canada was identified, the guidelines include recommendations to consider the local context in making decisions about the use of fluoroquinolones in addition to considering effectiveness and safety. In light of the international differences observed in rates of antibiotic resistance, understanding resistance rates in Canada will inform how practitioners interpret included recommendations.

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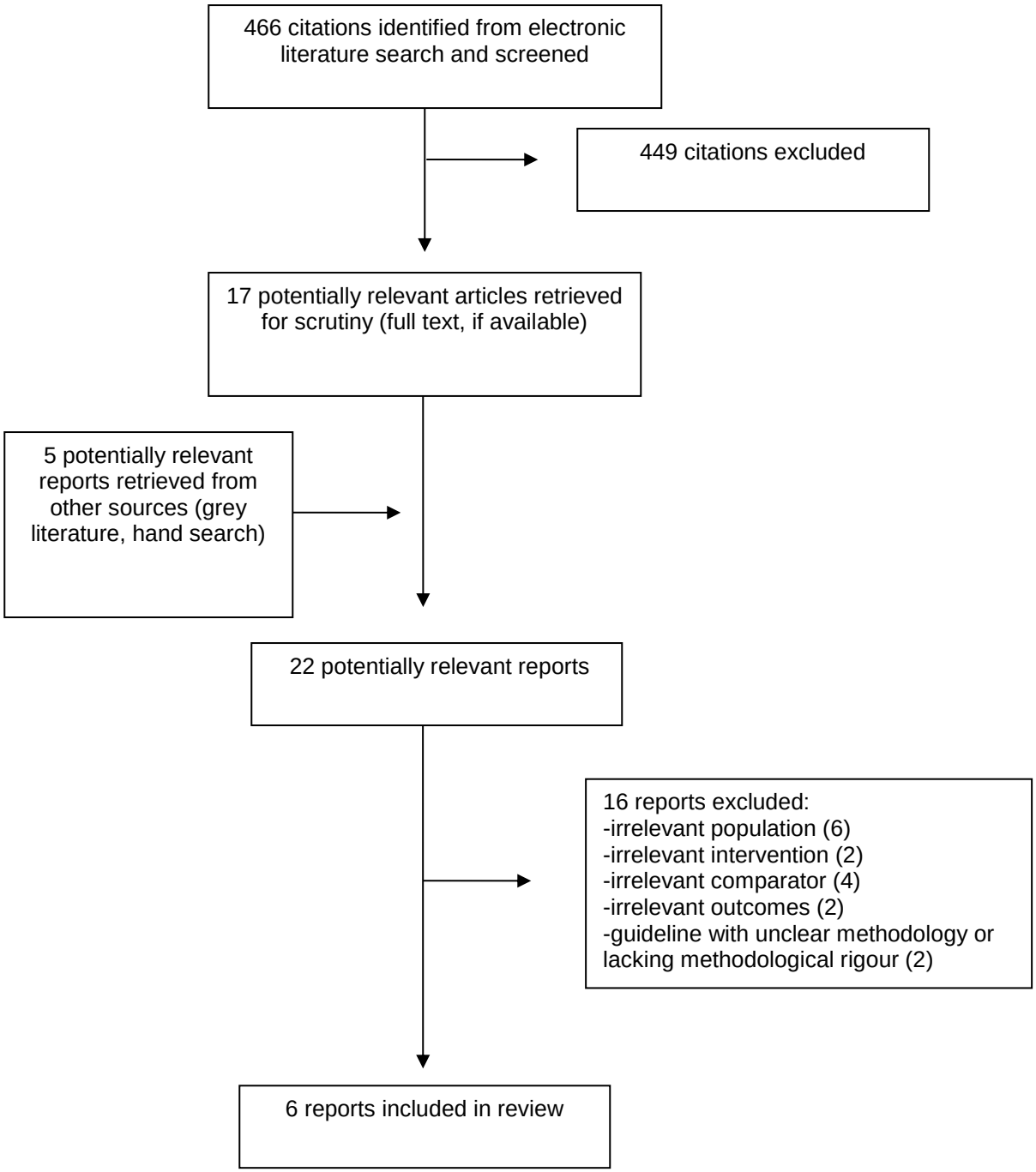
Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 2: Characteristics of Included Meta-Analyses with or without Systematic Review

First Author, Publication Year, Country	Study Designs and Numbers of Primary Studies Included	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
Systematic Review with Meta-Analysis				
Mavros, 2019[13] US	Includes multi-centre RCTs published between 1996 and 2009 Literature searched up to March 2018 Studies that compared regimens that are not recommended for the treatment of patients with cIAI based on the 2017 Infection Society Revised Guidelines on the Management of Intra-Abdominal Infection were excluded	N = 4125 Adult (≥18 yers) patients with cIAI, as defined in individual studies Other population characteristics not provided by review author	Intervention: Fluoroquinolone-based regimen (initiated as IV; could be switched to oral when patient in stable condition) Comparator: Beta lactam-based regimen (initiated as IV; could be switched to oral when patient in stable condition)	Outcomes Clinical Effectiveness: **Treatment success** Defined as sustained resolution or improvement of clinical symptoms and signs attributed to the cIAI, with the absence of surgical site infection requiring systemic antimicrobial treatment at time of test of cure visit AEs: **all-cause mortality; Incidence of treatment-related AEs; severe AEs; withdrawal due to AEs** as defined in each study Measurement tools and properties not reported Follow-up Time to test of cure visit not reported
Meta-Analysis without Systematic Review				
De Waele, 2014[14] Belgium Data were from pooled studies collected in US, Asia, and Europe (specific countries not identified)	Four non-inferiority RCTs were pooled; 3 double-blind, 1 open-label; non-inferiority margin of 10% in 3 studies and 15% in 1 study. Studies conducted between 2000 and 2009	N = 1,229 Eligibility: Age ≥18 years Eligibility for the pooled analysis: -cIAI (i.e., secondary peritonitis) requiring surgery and supportive management; -no other systemic antimicrobial agent	Intervention: IV moxifloxacin 400 mg once daily for up to 14 days in 4 studies; option to switch to per os moxifloxacin 400 mg after a ≥3 days in 2 studies Comparators: i) Piperacillin-tazobactam,	Outcomes Clinical effectiveness outcome: **success rates** at test-of-cure, n (%); defined as "continued resolution or improvement of clinical signs and symptoms related to the infection not requiring any

First Author, Publication Year, Country	Study Designs and Numbers of Primary Studies Included	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
		administered concomitantly with the study drug unless treatment failed; -documented compliance with ≥80% of the study medication given; -no protocol violations influencing treatment efficacy; -successful completion of an assessment at the test-of-cure visit Gender: female, 422 (34.3%); male, 807 (65.7%) Mean age: 47.6 years Mean APACHE II score (severity of illness) (SD): 7.0 (5.0)	3.0g/ 0.375g IV, 4 times / day followed by amoxicillin/ clavulanic acid, 800 mg/ 114mg orally, 2 times / day ii) Ceftriaxone, 2.0, 4 times / day + metronidazole, 500mg IV 3 times / day, followed by amoxicillin clavulanic acid, 500mg/ 125mg orally 3 times / day iii) Ceftriaxone, 2.0g daily + metronidazole, 500mg IV, 2 times / day iv) Ertapenem, 1.0g IV, 4 times / day	antibiotic therapy, and without occurrence of any surgical infection requiring a systemic antibiotic treatment at test-of-cure." (*p*569) AEs **All AEs** and subcategories: **Nausea, diarrhea, abdominal pain, constipation, surgical site infection, post-operative surgical site infection, drug-related AEs occurring in >5 patients in either group, serious AEs, drug-related serious AEs, premature discontinuations due to AEs, deaths** Defined according to MedDRA Preferred Terms Follow-up: Test-of-cure conducted between day 10 and 45 after antibiotic therapy

AE = adverse effects; APACHE = Acute Physiology, Age, Chronic Health Evaluation ; cIAI = complicated intra-abdominal infection; g = grams; IV = intravenous; MedDRA = Medical Dictionary for Regulatory Activities; mg = milligrams; N = sample size; RCT = randomized controlled trial

Table 3: Characteristics of Included Primary Studies

First Author, Publication Year, Country	Study Designs and Numbers of Primary Studies Included	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
Wirth, 2018[15] MOXIPEDIA study Germany	Multi-centre, double-blind, double-dummy, active-controlled parallel group, phase 3 RCT Participants recruited between January 2010 and 2015	N = 451 Median (range) = 13 years (3 months to 17 years); All patients had undergone an initial surgical or interventional radiology procedure with or without postoperative drainage of abdominal cavity at baseline Eligibility: Pediatric patients with cIAI (includes intra-abdominal abscess or macroscopic intestinal perforation with peritonitis)	Intervention: IV moxifloxacin Dose: age and body weight-scaled infusions corresponding to the 400 mg adult dose were administered over 60 minutes; For those aged 3 months to <18 years with BW <45kg, doses ranged from 4mg/kg to 6 mg/kg BW twice daily for those with BW <45kg not exceeding 400mg daily; For those aged ≥12 years with BW ≥45kg dose = 400 mg once daily Duration of treatment: Mean (range) = 8.7 (1-24) days Switching to oral dose was an option for those aged ≥2 yers with body weight ≥20kg, doses were 4mg/kg as 50mg tablets twice daily not exceeding 400mg or 400mg once daily Comparator: IV ertapenem followed by oral amoxicillin/ clavulanate Dose: as per dosing instructions on the label (not further described by Wirth et al.) Duration of treatment: Mean (range) = 8.7 (1 to 14) days	Outcomes Clinical Effectiveness: **Clinical and bacteriologic efficacy** at test of cure AEs: **Cardiac AEs** Measured by standard 12-lead ECG; recordings transmitted to a specified ECG core laboratory for semiautomated and manual verified analyses of ECG parameters; verified by physician expert **Musculoskeletal AEs** Standardized assessment of shoulder, elbow, wrist, hip, knee, ankle, Achilles tendon and patellar tendon at both sides; Parent-report medical history questionnaire AEs defined according to MedDRA version 17.1 Follow-up Assessed at baseline, day 1, day 3-5, day of switch from IV to oral therapy if applicable, end of treatment and test of cure (28 to 42 days after end of treatment); Patients with musculoskeletal AEs at 1 year after end of

First Author, Publication Year, Country	Study Designs and Numbers of Primary Studies Included	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
				treatment were followed up until resolution or up to 5 years
Xu, 2017[16] China	Open-label, parallel-arm, single-centre RCT Conducted between 2012 and 2016	N = 80 Eligibility: Age >18 years; continuous ambulatory peritoneal dialysis patients; Diagnosis of acute peritonitis according to the ISPD guideline	Intervention: Intraperitoneal vancomycin, 1g every 5 days + oral moxifloxacin, 400mg daily (Moxifloxacin taken 2 hours before or 4 hours after aluminum or magnesium containing antacids or iron supplements) Comparator: Intraperitoneal vancomycin, 1g every 5 days + intraperitoneal ceftazidime, 1g daily	Outcomes **Complete cure** Defined as complete resolution of peritonitis with antibiotics alone without relapse within 4 weeks of completion of treatment **Primary treatment failure** Defined as presence of fever, abdominal pain, or turbid peritoneal dialysate, plus total peritoneal white blood cell count > 50% of pretreatment value after 3 days of treatment **Secondary treatment failure** Defined as "treatment failure despite adjustment of antibiotics or changing to second-line antibiotics for at least 3 days in patients with primary treatment failure." (*p*32) **Relapse, recurrent, or repeat peritonitis** episodes Defined according to ISPD guidelines **Peritonitis-related death** Defined as death of patient with active peritonitis, admitted

First Author, Publication Year, Country	Study Designs and Numbers of Primary Studies Included	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
				with peritonitis, or within 2 weeks of peritonitis episode <u>Follow-up</u> 1, 3, 5, 7, 10, 14, and 21 days following initiation of treatment

AE = adverse effects; BW = body weight; cIAI = complicated intra-abdominal infection; ECG = electrocardiography; g = grams; ISPD = International Society for Peritoneal Disease; IV = intravenous; Kg = kilograms; MedDRA = Medical Dictionary for Regulatory Activities; mg = milligrams; RCT = randomized controlled trial;

Table 4: Characteristics of Included Guidelines

Group (and/or First Author), Year, Country	Objective	Guideline Development Group, Intended Users	Recommendations Development and Evaluation Methodology
SIS (Mazuski),[17] 2017 US	"to support clinicians in making appropriate treatment decisions and not designed to supplant the judgement of the individual practitioner." (*p*2)	Task force comprised of members of the Therapeutics and Guidelines Committee and additional individuals from SIS with subject matter expertise Intended users: clinicians	Subjects were selected from the 2010 guideline for updating Task force chair and working group leaders were appointed by SIS Executive Council. Working groups consisted of additional content experts and Therapeutics and Guidelines Committee The task force chose subjects to update from the previous guideline, developed specific questions, and reviewed RCT evidence published between 2000 and 2016 identified by systematic search of Medline. Additional study designs were considered (not systematic) where gaps existed "Because of the limited quantity of methodologically rigorous studies investigating key questions in the management of IAI, the task force did not undertake a detailed statistical analysis for most of these recommendations, but relied on a process of iterative consensus among task force members to develop the recommendations and their final grading." (*p*9) Recommendations were drafted and reviewed by working groups over teleconferences, a face-to-face meeting, and email until consensus was achieved Recommendations were graded according to GRADE Guideline document was reviewed by experts from the SIS, and modified according to reviews by consensus of the task force; it is expected the guideline was externally peer reviewed based on its publication in a scientific journal Task force responded to critiques and forwarded final guideline and supporting materials to SIS Executive Council for final approval.
EKMUD (Avkan-Oguz),[5] 2016 Turkey	"To create a standard clinical pathway for the diagnosis and treatment of patients with IAIs."	The consensus report development group was led by EKMUD, and comprised of 15 experts	Committee met to discuss issues and common practices, delegate subareas among themselves, and screen relevant literature.

Group (and/or First Author), Year, Country	Objective	Guideline Development Group, Intended Users	Recommendations Development and Evaluation Methodology
	(*p*306)	in IAI Intended users: physicians in Turkey involved in diagnosis and management of IAIs	Literature searches of databases were conducted (unclear inclusion criteria). A supplemental questionnaire was circulated to assess surgeons' attitude and ability regarding microbiologic sampling in the diagnosis of intra-abdominal infections Recommendations from existing guidelines were discussed (unclear how identified) "all guidelines do not use the same evidence strength table. Therefore, only the evidence grades which were consistent, recommended in both of these guidelines and were also considered appropriate by our expert panel were included in this consensus report with references to the relevant guidelines." (*p*307) Recommendations were formulated over 4 meetings, using data from Turkey (unclear what type, as no RCTs were identified and no other data or inclusion criteria were discussed) and referring predominately to 2 guidelines, as well as 7 other guidelines Strength of recommendations and quality of evidence was reported based on an unspecified grading system

EKMUD = Infectious Diseases and Clinical Microbiology Specialty Society of Turkey; GRADE = Grading of Recommendations, Assessment, Development and Evaluation; IAI = intra-abdominal infection; RCT = randomized controlled trial; SIS = Surgical Infection Society

Table 5: Grade Recommendations and Level of Evidence for Guidelines

Grade of Recommendation	Quality of Evidence
SIS (Mazuski),[17] 2017	
GRADE system 1. Strong recommendation: "The task force concluded that the intervention is a desirable approach for the care of those patients to whom the question applies. This rating is generally based on moderate to high quality evidence. The conclusion is unlikely to be changed with future research. The magnitude of the effect is also sufficient to justify the recommendation. A strong recommendation was also used to describe interventions that are likely to have a significant effect on patient outcome, even if based on weak evidence. These recommendations are prefaced as ''We recommend.''." 2. Weak recommendation: "The task force concluded that the intervention is a reasonable approach for the care of patients. Not all patients and clinicians, however, would necessarily want to follow the recommendation. A decision not to follow the recommendation is unlikely to result in a major adverse outcome. This rating was generally based on weak to moderate quality evidence. Both the magnitude of the treatment effect and its direction might be altered by future research. These recommendations are prefaced as ''We suggest .''. 3. No recommendation: "The evidence was considered inadequate or too inconsistent to allow any meaningful conclusion to be reached." (*p*9)	GRADE system A. High quality evidence: "The evidence was primarily obtained from RCTs, meta-analyses of such trials, or methodologically sound epidemiologic studies. If the preponderance of evidence is based on studies that do not directly address the question being posed, the overall grade is downgraded to B or C. If there are conflicts in Class A data, the evidence grade is lowered to B or C, depending on the degree of conflict." B. Moderate quality evidence: "The evidence was obtained from lower quality prospective studies, retrospective case control studies, and large observational, cohort, or prevalence studies, and was based on clearly reliable data. If there are significant conflicts in Class B data, the evidence grade is lowered to C." C. Weak quality evidence: "The evidence was obtained from smaller observational studies, studies relying on retrospective or less reliable data, authoritative opinions expressed in reviews, or expert opinions of task force members." D. Insufficient evidence: "There was little or no relevant evidence to address a question, or the evidence reviewed was highly conflicting." (*p*9)
EKMUD (Avkan-Oguz), 2016[5]	
System of unclear origin Grade A: "Good evidence supporting a recommendation for use" Grade B: "Moderate evidence supporting a recommendation for use" Grade C: "Poor evidence supporting a recommendation for use" (*p*307)	System of unclear origin Level I "Evidence from at least one well-designed randomized controlled trial" Level II "Evidence from at least one non-randomized clinical trial" Level III "Evidence from opinions of respected authorities, based on clinical studies, descriptive studies, or reports from expert committees" (*p*307)

GRADE = Grading of Recommendations, Assessment, Development and Evaluation; RCT = randomized controlled trial

Appendix 3: Critical Appraisal of Included Publications

Table 6: Strengths and Limitations of Meta-Analyses with or without Systematic Review using AMSTAR 2[9]

Strengths	Limitations
Mavros, 2019[13]	
• Research questions and inclusion criteria for the review included the components of PICO • Review contained an indirect statement suggesting that the review methods were established prior to the conduct of the review – the reason for not registering the methods was a technical glitch • Review authors used a comprehensive literature search strategy • Study selection and extraction were performed in duplicate • Reasons for exclusion were reported in PRISMA flow diagram • Interventions, comparators, outcomes, and research designs were described in adequate detail • Appropriate methods for statistical combination of results in meta-analysis were performed • Review authors did not account for RoB in individual studies when interpreting the results of the review, however predominately high quality RCTs were included • Adequate investigation of publication bias occurred • RoB was assessed using modified Jadad scale and Cochrane risk of bias tool (reported in online supplement only)	• Review authors did not explain their selection of the study designs for inclusion in the review • A list of excluded studies was not provided • Population characteristics were described in limited detail • Review authors did not report on the sources of funding for the studies included in the review • Review authors did not assess the potential impact of RoB in individual studies on the results of the meta-analyses • Review authors did not discuss the heterogeneity observed in the results of the review • Review authors indicated potential conflicts of interest but did not indicate how conflicts of interest were managed
De Waele, 2014[14]	
• Research questions were clearly described • Included studies were described in adequate detail • Statistical methods used to combine studies were reported • Authors assessed statistical heterogeneity using exploratory methods • Pooled studies were homogenous • Authors disclosed potential conflicts of interest, but did not report how conflicts were managed	• Inclusion criteria were not clear. Outcomes were those commonly assessed by the selected RCTs • Review methods and study selection process were not described • Authors did not explain selection of the study designs for inclusion in the review, and it was not likely to have been systematic • Review authors did not use a comprehensive literature search strategy • It is unclear how the studies were identified or selected for inclusion • RoB in individual studies was not assessed by study authors • Sources of funding for included studies was not reported • Authors used appropriate methods for statistical combination of results • Review authors did not assess the potential impact of RoB in individual studies on the results of the meta-analysis • Authors did not investigate publication bias. It is presumed to present a high RoB given the apparent absence of a systematic search • Authors disclosed potential conflicts of interest, but did not report how conflicts were managed

PICO = Populations, Interventions, Comparators, Outcomes; PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCT = Randomized Controlled Trial; RoB = risk of bias

Table 7: Strengths and Limitations of Clinical Studies using Cochrane RoB 2[10]

Strengths	Limitations
Wirth, 2018[15]	
RoB arising from the randomization process • Allocation sequence was random • No apparent baseline differences between groups RoB due to deviations from the intended interventions (effect of assignment to interventions) • Participants, carers, and people delivering the interventions were not aware of the assigned interventions during the trial • Appropriate analyses were used to estimate the effect of assignment to intervention RoB due to missing outcome data • Data were available for nearly all participants randomized RoB in measurement of the outcome • Method of measuring outcomes was appropriate • Measurement of outcomes unlikely to have differed between intervention groups • Outcome assessors were blinded RoB in selection of the reported result • Blinded outcome data were un-blinded when data-collection was complete • The numerical results were not likely to have been selected on the basis of results from multiple outcome measurements or multiple analyses of the data	RoB arising from the randomization process • Authors did not report allocation concealment RoB in selection of the reported result • Unclear if an analysis plan was pre-specified RoB due to missing outcome data • 26 patients in the intervention group vs 4 in the comparator group did not complete study medication. Reasons in the intervention group were largely due to the outcome of interest, i.e., 15 experienced an AE, parents of 2 patients withdrew consent, 2 protocol violations and 5 for other reasons; reasons in the comparator group were 2 experienced AE and 2 for other reasons RoB in selection of the reported result • Unclear if an analysis plan was pre-specified RoB in selection of the reported result • Unclear if an analysis plan was pre-specified Other • Study was funded and conducted by Bayer. There was no statement included in the publication indicating that the funder's interests did not influence the study conduct or results.
Xu, 2017[16]	
• Allocation sequence was random • No important differences between intervention groups were identified RoB due to deviations from the intended interventions (effect of assignment to intervention) • Authors reported no deviations from the intended intervention • An appropriate analysis was used to estimate the effect of assignment to intervention RoB due to missing outcome data • Outcome data were available for all patients RoB in measurement of the outcomes • Ascertainment of the outcome is not likely to have differed between groups • Assessment of the outcomes was not likely to have been influenced by knowledge of the intervention received RoB in the selection of the reported result • This trial was registered a priori • The numerical results were not likely to have been assessed on the basis of multiple outcome measurements or multiple analyses of the data	RoB arising from the randomization process • Allocation was not concealed from patients or researchers RoB due to deviations from the intended interventions (effect of assignment to intervention) • Participants were aware of their assigned intervention during the trial • Carers and people delivering the intervention delivering the interventions were aware of participants' assigned intervention during the trial RoB in measurement of the outcomes • Method of measuring the outcomes was not described in the article. • Outcome assessors were not blinded to intervention assignment RoB in the selection of the reported result • The analysis plan was not included in the a priori registered protocol

AE = adverse effects; RoB = risk of bias; ITT = intention to treat

Table 8: Strengths and Limitations of Guidelines using AGREE II[11]

Item	Guideline	
	SIS (Mazuski), 2017[17]	EKMUD (Avkan-Oguz), 2016[5]
Domain 1: Scope and Purpose		
1. The overall objective(s) of the guideline is (are) specifically described.	✓	✓
2. The health question(s) covered by the guideline is (are) specifically described.	✓	✓
3. The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.	✓	✓
Domain 2: Stakeholder Involvement		
4. The guideline development group includes individuals from all relevant professional groups.	✓	✓
5. The views and preferences of the target population (patients, public, etc.) have been sought.	X	X
6. The target users of the guideline are clearly defined.	✓	✓
Domain 3: Rigour of Development		
7. Systematic methods were used to search for evidence.	✓	Unclear
8. The criteria for selecting the evidence are clearly described.	X	X
9. The strengths and limitations of the body of evidence are clearly described.	✓	X
10. The methods for formulating the recommendations are clearly described.	✓	X
11. The health benefits, side effects, and risks have been considered in formulating the recommendations.	✓	✓
12. There is an explicit link between the recommendations and the supporting evidence.	✓	X
13. The guideline has been externally reviewed by experts prior to its publication.	✓	X
14. A procedure for updating the guideline is provided.	✓	X
Domain 4: Clarity of Presentation		
15. The recommendations are specific and unambiguous.	✓	✓
16. The different options for management of the condition or health issue are clearly presented.	✓	✓
17. Key recommendations are easily identifiable.	X	✓
Domain 5: Applicability		
18. The guideline describes facilitators and barriers to its application.	✓	✓

Table 8: Strengths and Limitations of Guidelines using AGREE II[11]

Item	Guideline	
19. The guideline provides advice and/or tools on how the recommendations can be put into practice.	✓	X
20. The potential resource implications of applying the recommendations have been considered.	✓	X
21. The guideline presents monitoring and/or auditing criteria.	X	X
Domain 6: Editorial Independence		
22. The views of the funding body have not influenced the content of the guideline.	Unclear	✓
23. Competing interests of guideline development group members have been recorded and addressed.	✓	X

AGREE = Appraisal of Guidelines for Research & Evaluation; EKMUD = Infectious Diseases and Clinical Microbiology Specialty Society of Turkey; SIS = Surgical Infection Society

Appendix 4: Main Study Findings and Authors' Conclusions

Table 9: Summary of Findings of Included Meta-Analysis with or Without Systematic Review

Main Study Findings	Authors' Conclusion
Systematic Review and Meta-Analysis	
Mavros, 2019[13]	
Fluoroquinolone-based regimens vs beta lactam-based regimens <u>Clinical effectiveness (ITT)</u> n = 3055 RR = 0.97, 95% CI, 0.94 to 1.01 <u>AEs</u> All-cause mortality N = 3614 RR = 1.04, 95%CI, 0.75 to 1.43 Overall treatment related AEs n = 2801 RR = 0.97, 95% CI, 0.70 to 1.33 Withdrawal due to AEs n = 3380 RR = 1.07, 95%CI, 0.86 to 1.33 *Note:* *(Ps not reported)* *Analyses were also conducted by those clinically evaluable and microbiologically evaluable for clinical effectiveness outcome; data not extracted*	"Overall, the 2 classes of antimicrobials were equally effective and safe. Limited evidence from subgroup analyses suggested slightly lower clinical effectiveness of moxifloxacin when compared to a beta lactam-based regimen in the overall population (based on 4 trials), as well as in the subset of patients with complicated appendicitis (3 trials)." (*p*9) "In conclusion, our meta-analysis suggests that ciprofloxacin/metronidazole is as effective as ceftriaxone/metronidazole and carbapenems for the treatment of cIAIs, while moxifloxacin monotherapy had slightly inferior outcomes, especially in complicated appendicitis. Empiric antimicrobial treatment of patients with cIAIs should be selected in light of the local bacterial epidemiology and patterns of resistance." (*p*12)
Meta-Analysis without Systematic Review	
De Waele, 2014[14]	
<u>Clinical Effectiveness (ITT)</u> *Moxifloxacin n/N (%) vs comparator n/N (%)* 449/609 (73.7%) vs 482/620 (77.7%) Point estimate for the **difference in success rates** (%): -3.96; 95% CI, -7.06 to -1.05, *P* = 0.25 <u>AEs (MedDRA Preferred Terms Event) (ITT)</u> *Moxifloxacin, n (%) vs comparator, n (%)* **All AEs** 410 (67.3%) vs 371 (59.8%) **Nausea** 49 (8.0%) vs 28 (4.5%) **Diarrhea** 39 (6.4%) vs 49 (7.9%) **Abdominal pain** 26 (4.3%) vs 19 (3.1%) **Constipation** 21 (3.4%) vs 19 (3.1%)	"In conclusion, in this pooled analysis it has been observed that moxifloxacin has similar clinical and bacteriologic efficacy and a good safety profile compared with those of other previously approved antibiotic regimens in the treatment of mild-to-moderate secondary peritonitis. Despite certain limitations, the data from this pooled analysis provides support for the use of moxifloxacin as a valuable therapeutic option in the group of patients with advanced cIAIs, which is consistent with current treatment guidelines." (*p*573-574)

Table 9: Summary of Findings of Included Meta-Analysis with or Without Systematic Review

Main Study Findings	Authors' Conclusion
Surgical site infection 65 (10.7%) vs 51 (8.2%) **Post-operative** surgical site infection 10 (1.6%) vs 6 (1.0%) **Drug-related AEs occurring in >5 patients in either group** 127 (20.9%) vs 124 (20.0%) **Serious AEs** 110 (18.1%) vs 88 (14.2) **Drug-related serious AEs** 19 (3.1%) vs 6 (1.0) **Premature discontinuations due to AEs** 31 (5.1%) vs 25 (4.0%) **Deaths** 26 (4.3%) vs 21 (3.4%) *Note: per protocol analysis were also reported for clinical effectiveness outcome; data not extracted*	

AE = adverse effects; cIAI = complicated intra-abdominal infection; ITT = intention to treat; n = subsample size; MedDRA PT = Medical Dictionary for Regulatory Activities Preferred Term; RR = relative risk

Table 10: Summary of Findings of Included Primary Clinical Studies

Main Study Findings	Authors' Conclusion
Wirth, 2018[15]	
Note: statistical significance was not assessed for any outcome Efficacy – Clinical response (modified ITT i.e., all patients valid for safety with had at least one pretreatment causative organism for the primary site of infection or from blood cultures). (n = 246 vs n = 133) *Moxifloxacin n (%) vs ertapenem and amoxicillin/clavulanate n (%)* **Bacteriologic success and clinical cure at time of cure** 208 (84.6%) vs 127 (95.5%) *Note: analysis for safety population not reported by study author. Author reported "Similar results were found in the safety population." (pe210)* **Any clinical failure** 38 (15.4%) vs 6 (4.5%) **Infectious failure** 20 (8.1%) vs 2 (1.5%) **Reoperation** 1 (0.4%) vs 1 (0.7%) **Wound infection** 7 (2.8%) vs 1 (0.7%) **Other** (includes QT interval prolongation and administration of other antimicrobials) 1/246 (0.4%) vs 0 (0%) Incidence rate of AEs (ITT) (n = 301 vs n = 150) *Moxifloxacin n (%; 95%CI) vs comparator n (%; 95%CI)* **Any AE** 175 (58.1%; 95% CI, 52.6% to 63.7%) vs 82 (54.7%; 95% CI, 46.7% to 62.6%) **Any drug-related AE** 43 (14.3%; 95% CI, 10.3% to 18.2%) vs 10 (6.7%; 95% CI, 2.7% to 10.7% **Any serious AE** 20 (6.6%) vs 6 (4.0%) **Severe AE** 12 (4%) vs 3 (2.0%)	"In summary, the sequential administration of MXF treatment was well tolerated in children with cIAIs. The general safety profile and efficacy of MXF was consistent with that in adult patients. However, MXF monotherapy appeared less efficacious than ertapenem followed by amoxicillin/clavulanate, an antimicrobial treatment regimen recommended by evidence-based guidelines for children. These results do not support MXF to be recommended for pediatric patients with cIAIs when alternative efficacious antibiotics with better safety profile are available." (*p*e212)

Table 10: Summary of Findings of Included Primary Clinical Studies

Main Study Findings	Authors' Conclusion
Any drug-related serious AE 0 (0%) vs 0 (0%) **Death** 0 (0%) vs 0 (0%) "No relevant differences in incidence rates of the most common AEs were observed between the 2 treatment arms, except for ECG QT prolongation" (*p*e209) *ECG QT/QTc AEs:* **QT prolongation in ECG recordings** 28 (9.3%) vs 4 (2.7%) (95%CI not reported) **Drug related QT prolongation in ECG recordings** 7%; 95% CI, 4.4 to 10.3 vs 1.3%; 95% CI, 0.2 to 4.7 (n not reported) *Note: one event in intervention group assessed as severe AE by investigator* **QTc interval prolongation-related morbidity or mortality** none "Ten patients (3.3%) discontinued MXF early because of uncorrected QT interval prolongation. A case of QTcB (+24 ms) and QTcF (+13 ms) prolongation after 400 mg MXF infusion at Day 1 resolved on the same day after MXF withdrawal." (*p*e210) *Musculoskeletal AEs:* **Musculoskeletal AE** 13 (4.3%; 95% CI, 2.3 to 7.3) vs 5 (3.3%; 95% CI, 1.1 to 7.6) **Forearm fracture** 1(0.3%) vs 0 (95% CIs not reported) **Joint injury** 0 vs 1 (0.7%) (95% CIs not reported) **Ligament sprain** 1 (0.3%) vs 1 (0.7%) (95% CIs not reported) **Muscle strain** 0 vs 1 (0.7%) (95% CIs not reported) **Arthralgia** 9 (3.0%) vs 1(1.3%) [*unclear if the reporting error is in absolute number or percentage for comparator group*] (95% CIs not reported) **Joint swelling** 0 vs 1 (0.7%) (95% CIs not reported)	

Table 10: Summary of Findings of Included Primary Clinical Studies

Main Study Findings	Authors' Conclusion
Musculoskeletal pain 3 (1.0%) vs 0 (95% CIs not reported) **Myalgia** 1 (0.3%) vs 0 (95% CIs not reported) *Note: no musculoskeletal events were reported by the investigators as being related to intervention or comparator treatments*	
Xu, 2017[16]	
Clinical effectiveness (n = 40 vs n = 40) Intervention n (%) vs comparator n (%); OR, 95% CI **Complete cure** 31 (78%) vs 32 (80%); OR = 0.86, 95% CI, 0.30 to 2.52; *P* = 0.8 **Primary treatment failure** 13 (33%) vs 8 (20%); OR = 1.93, 95% CI, 0.70 to 5.34; *P* = 0.2 **Secondary treatment failure** 4 (10%) vs 5 (13%); OR = 0.78, 95% CI, 0.78, 0.19 to 3.14; *P* = 0.7 **Peritonitis-related death** 1 (3%) vs 1 (3%); OR = 1.00, 95% CI, 0.06 to 16.56; *P* = 0.9 **Successive episodes of peritonitis during 3-month follow-up** 7 (18%) vs 3 (8%); OR = 2.62, 95% CI, 0.63 to 10.95; *P* = 0.2 **Outcome of successive episodes of peritonitis** OR = 1.40, 95% CI, 0.88 to 2.24; P = 0.3 **-Transfer to hemodialysis** 2 (29%) vs 0 (0%) **-Maintenance of PD** 5 (71%) vs 3 (100%)	"This pilot study suggests that intraperitoneal vancomycin plus oral moxifloxacin is a safe, well-tolerated, and effective treatment that potentially could be used as a first-line empirical treatment regimen for PD-related peritonitis. Patients appeared to adhere well to the treatment regimen, which would reduce medical expenses compared to daily intraperitoneal antibiotic administration." (*p*36)

AE = adverse effect; CI = confidence interval; cIAI = complicated intra-abdominal infection; ITT = intention to treat; MXF= moxifloxacin; PD = peritoneal dialysis

Table 11: Summary of Recommendations in Included Guidelines

Recommendations	Strength of Evidence and Recommendations
SIS (Mazuski), 2017[17]	
4. Intravenous antimicrobial agents	
4.7a. "We recommend moxifloxacin as an acceptable agent for the empiric treatment of lower-risk adults with CA-IAI, although it should be used with caution in areas of the world where there is a high incidence of fluoroquinolone-resistant E. coli (*Strong recommendation; high quality evidence*). We do not recommend the use of moxifloxacin for empiric treatment of children with IAI unless no other options are available (*strong recommendation; weak quality evidence*)." (*p*28)	4.7a. Strong recommendation; high quality evidence Strong recommendation; weak quality evidence
4.7b. "We recommend ciprofloxacin plus metronidazole as an acceptable regimen for the empiric treatment of lower-risk adults with CA-IAI, although it should be used with caution in areas of the world where there is a high incidence of fluoroquinolone-resistant E. coli (*strong recommendation; high quality evidence*). We suggest that ciprofloxacin plus metronidazole may be used for empiric treatment of children older than one month CA-IAI, if other options are not suitable (*weak recommendation, moderate quality evidence*)." (*p*28-29)	4.7b. Strong recommendation; high quality evidence Weak recommendation, moderate quality evidence
4.7c. "We suggest that levofloxacin plus metronidazole is an acceptable regimen for the empiric treatment of lower-risk adults with CA-IAI, if use of a fluoroquinolone is warranted and it is the only fluoroquinolone available for use (*weak recommendation, weak quality evidence*). We suggest that levofloxacin plus metronidazole may be used for empiric treatment of children older than one month with IAI, if other options are not suitable (*weak recommendation, weak quality evidence*)." (*p*29)	4.7c. Weak recommendation, weak quality evidence Weak recommendation, moderate quality evidence
6. Selection of empiric antimicrobial therapy for adult patients with CA-IAI	
6.1 "We recommend ciprofloxacin plus metronidazole or moxifloxacin monotherapy for the management of CA-IAI in lower-risk patients who have serious b-lactam allergies (*strong recommendation; high quality evidence*), and suggest levofloxacin plus metronidazole as an alternative if no other fluoroquinolone is available (*weak recommendation, weak quality evidence*)." (*p*33)	6.1. Strong recommendation; high quality evidence Weak recommendation; weak quality evidence
6.3. "We do not recommend addition of an adjunctive aminoglycoside or fluoroquinolone to a b-lactam agent for empiric management of CA-IAI in higher-risk patients (*strong recommendation; moderate quality evidence*)." (*p*35)	6.3. Strong recommendation; moderate quality evidence
6.5. "We suggest use of a fluoroquinolone-based regimen for initial empiric antimicrobial therapy of CA-IAI in lower risk patients who have had major reactions to b-lactam antibiotic agents (*weak recommendation; moderate quality evidence*)."	6.5. Weak recommendation; moderate quality evidence

Table 11: Summary of Recommendations in Included Guidelines

Recommendations	Strength of Evidence and Recommendations
(*p*36) 6.6. "We recommend against empiric use of most cephalosporin-aztreonam-, or fluoroquinolone-based regimens for empiric antimicrobial therapy of CA-IAI in patients who reside in geographic areas where there is a high prevalence of ESBL-producing Enterobacteriaceae in the community (*strong recommendation; moderate quality evidence*)." (*p*36) 13. <u>Treatment of pediatric IAI</u> 13.1a. "We suggest ciprofloxacin or levofloxacin plus metronidazole as acceptable regimens for empiric treatment of selected pediatric patients with IAI if other agents cannot be used, particularly for those pediatric patients with life-threatening b-lactam reactions (*weak recommendation; moderate quality evidence*)." (*p*54)	6.6. strong recommendation; moderate quality evidence 13.1a. Weak recommendation; moderate quality evidence
EKMUD (Avkan-Oguz), 2016[5]	
<u>Managing community-acquired intra-abdominal infections of mild to moderate severity in adults</u> 20. For adult patients with mild to moderate IAI in Turkey, the use of ertapenem, moxifloxacin or tigecycline monotherapy or combinations of metronidazole with cefazolin, cefuroxime, ceftriaxone, cefotaxime, levofloxacin or ciprofloxacin are preferable to regimens with anti-pseudomonal activity (IDSA, A-I). Because data are scarce concerning the ESBL positivity rate of organisms involved in community-acquired IAIs in Turkey, empiric antibiotics should be selected on an individual hospital basis according to the ESBL rate in local epidemiologic data (10% or higher) or the ESBL risk factors. Furthermore, although Pseudomonas species are isolated in approximately 8% of IAIs, they are less likely to be the causative agent." (*p*313-314) <u>Managing high-risk community-acquired intra-abdominal infection in adults</u> 26. "The empiric use of antimicrobial regimens with broad-spectrum activity against gram-negative organisms is recommended for the treatment of patients with high-risk IAIs as defined by an APACHE II score >15 or the presence of other factors. These agents include meropenem, imipenem-cilastatin, piperacillin-tazobactam, and ceftazidime as single agents or combinations of metronidazole with cefepime, ciprofloxacin or levofloxacin (IDSA, A-I)." (*p*315) <u>Monitoring antimicrobial therapy in patients with intra-abdominal infection</u> **Clinical monitoring**: "During the recovery period, amoxicillin-clavulanic acid and oral quinolone (moxifloxacin, ciprofloxacin, levofloxacin) or oral cefalosporins in combination with	A-I: Good evidence supporting a recommendation for use; Evidence from at least one well-designed randomized, controlled trial A-I: Good evidence supporting a recommendation for use; Evidence from at least one well-designed randomized, controlled trial B-II: Moderate evidence supporting a recommendation for use; Evidence from at least one non-randomized clinical trial

Table 11: Summary of Recommendations in Included Guidelines

Recommendations	Strength of Evidence and Recommendations
metronidazole can be used for patients able to accept oral medications and whose infections are due to bacteria susceptible to such agents (IDSA, B-II).” (*p*318)	

b-lactam = beta-lactam; CA-IAI = community-acquired intra-abdominal infection; E. coli = Escherichia coli; EKMUD = Infectious Diseases and Clinical Microbiology Specialty Society of Turkey; ESBL= extended spectrum beta-lactamase; IAI = intra-abdominal infection; IDSA = Infectious Diseases Society of America

Appendix 5: Additional References of Potential Interest

Other Guidelines – Fluoroquinolones Addressed in Implementation of Recommendations

Sartelli M, Chichom-Mefire A, Labricciosa FM, et al. The management of intra-abdominal infections from a global perspective: 2017 WSES guidelines for management of intra-abdominal infections. *World J Emerg Surg.* 2017;12:29.
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Safety Alerts

Medicines and Healthcare products Regulatory Agency. Fluoroquinolone antibiotics: new restrictions and precautions for use due to very rare reports of disabling and potentially long-lasting or irreversible side effects. *Drug Safety Update*. 2019;12(8). https://www.gov.uk/drug-safety-update/fluoroquinolone-antibiotics-new-restrictions-and-precautions-for-use-due-to-very-rare-reports-of-disabling-and-potentially-long-lasting-or-irreversible-side-effects. Accessed 2019 Apr 24.

Medicines and Healthcare products Regulatory Agency. Systemic and inhaled fluoroquinolones: small increased risk of aortic aneurysm and dissection; advice for prescribing in high-risk patients. *Drug Safety Update*. 2019;12(4) https://www.gov.uk/drug-safety-update/systemic-and-inhaled-fluoroquinolones-small-increased-risk-of-aortic-aneurysm-and-dissection-advice-for-prescribing-in-high-risk-patients. Accessed 2019 Apr 24.

Health Canada. Summary safety review – fluoroquinolones – assessing the potential risk of persistent and disabling side effects. 2017: https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/safety-reviews/summary-safety-review-fluoroquinolones-assessing-potential-risk-persistent-disabling-effects.html. Accessed 2019 Apr 24.

U.S. Food & Drug Administration. FDA drug safety communication: FDA advises restricting fluoroquinolone antibiotic use for certain uncomplicated infections; warns about disabling side effects that can occur together. 2016: http://www.fda.gov/Drugs/DrugSafety/ucm500143.htm. Accessed 2019 Apr 24.