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Published in:
Acta Anaesthesiologica Scandinavica

DOI:
10.1111/aas.13418

Publication date:
2019

Document version:
Accepted manuscript

Citation for published version (APA):

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Quinolones for sepsis. A protocol for a systematic review of randomised clinical trials with meta-analysis and Trial Sequential Analysis

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Abstract

Background: Sepsis is a relatively common and deadly condition, that constitutes a major challenge to the modern health care system. Quinolones are sometimes used in combination with beta-lactam antibiotics for sepsis, but no former systematic review has assessed the benefits and harms of quinolones in patients with sepsis.

Methods: We will perform a systematic review with meta-analysis and Trial Sequential Analysis including randomised clinical trials assessing the effects of quinolones as add on therapy to usual care in children and adults with sepsis. For the assessment of harms, we will also include quasi-randomised studies and observational studies identified during our searches for randomised clinical trials.

Discussion: This systematic review will clarify if there is evidence to support quinolones being part of the standard treatment for sepsis.

Keywords
Sepsis, children, adults, quinolones, septic shock, systematic review, Trial Sequential Analysis

Description of the condition

Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection (1). Sepsis may be caused by a direct microbial invasion, microbial signal molecules, or toxin production (2).

Observational studies suggest that the mortality from sepsis is between 26% and 42% (3-5). Sepsis is considered to be the most frequent cause of death in non-coronary intensive care units (ICU) consuming 50% of critical care resources (3, 4, 6).

Several observational studies have shown increasing incidences of sepsis (currently 300 to 1031 patients per 100,000 population) (5, 7). The mortality rates have only shown a modest decrease (5, 8-10).

An American epidemiologic study of sepsis showed that during the period from 1979 to 2000, Gram-positive bacteria has gradually become more common as causative organisms than Gram-negative bacteria (11). In a recent international study involving 14,000 ICU patients in 75 countries, Gram-negative bacteria were isolated in 62% of patients with severe sepsis who had positive cultures, Gram-positive bacteria in 47%, and fungi in 19% (12). The most common Gram-positive pathogens are *Streptococcus pneumoniae* and *Staphylococcus aureus*. Among Gram negative pathogens, *Escherichia coli*, *Klebsiella* species, and *Pseudomonas aeruginosa* predominate (13).

Description of the intervention

The treatment of sepsis is generally aimed at treating the underlying cause of sepsis as well as the associated complications. Empirical treatment decisions are based on the presumed aetiology and the type of organic dysfunction (e.g. kidney failure, respiratory failure, or heart failure) (14). Conventional therapy therefore consists of antibiotics, fluid resuscitation, vasoactive agents, and other treatments of underlying conditions (15, 16).
Antibiotics are first line treatment for sepsis (15, 16). Antibiotics can be classified based on their: 1) mechanism of action in regards to, whether they treat and prevent bacterial infections by either inhibiting the growth of the bacteria (bacteriostatic) or by killing them (bactericidal); 2) bacterial spectrum (broad or narrow); and 3) chemical structure (e.g. penicillins, macrolides, aminoglycosides, quinolones, tetracyclines, etc.) (17, 18).

Preliminary observational results have indicated that appropriate (defined as the infecting microorganism was subsequently found to be susceptible in vitro to the antibiotic administered) empirical antibiotic treatment (antibiotic treatment initiated before culture results are known) has been shown to halve the fatality associated with sepsis compared to inappropriate empirical antibiotic treatment (19-21). According to guidelines it is recommended to commence broad-spectrum empiric treatment as soon as sepsis is suspected as mortality increases with every hour of delay (15, 16, 22-25). Empiric treatment should be based on the apparent focus, assumed pathogen, assumed susceptibility patterns, drug allergy, altered pharmacodynamics (decreased liver- or kidney function), and risk factors in the specific patient (15, 16, 22, 25).

Antibiotic combination therapy is currently recommended and has until recently been thought to improve survival in most critically ill patients suffering from sepsis and septic shock (15, 16, 24, 26). A meta-analysis, including mostly observational studies as well as few randomised clinical trials, concluded that antibiotic combination therapy for sepsis is effective in the most critically ill patients, but might be harmful in low-risk patients (27). However, a more recent systematic review including randomised clinical trials assessing antibiotic therapy in septic patients admitted to an intensive care unit, showed no difference between antibiotic combination therapy and antibiotic monotherapy in regards to patient mortality and other patient-important outcomes (26). Furthermore, another systematic review including 69 randomised clinical trials showed that the addition of an aminoglycoside to beta lactam antibiotics for sepsis should be discouraged (21). Nevertheless, it is currently suggested to empirically commence a broad-spectrum beta-lactam antibiotic combined either with a fluoroquinolone, a macrolide, or an aminoglycoside depending on the presumed pathogen (15, 16).

**Quinolones**
The first generation of quinolones (flumequine, nalidixic acid) and the subsequently developed fluoroquinolones (cinoxacin and norfloxacin) did not have systemic antibacterial properties and were effective for urinary tract infections (28, 29). The first systemic fluoroquinolones (ciprofloxacin and ofloxacin) mainly provided coverage for Gram-negative bacteria (28, 30). Later, the first systemic broad spectrum fluoroquinolone (temafloxacin) was developed and provided increased coverage for Gram-positive bacteria (28-30). The newest generations of fluoroquinolone (garenoxacin, gatifloxacin, grepafloxacin, sparflaxacin, levofloxacin, and moxifloxacin) are mainly used in the treatment of respiratory infections (15, 16, 28). Quinolones can be administered orally (bioavailability of 80% to 95%) and intravenously (31).

Quinolones are among the most prescribed antibiotics (across indications) (32-35). The use of quinolones has increased in recent years in both adults and children (32, 34-36). The paediatric usage of quinolones has only recently been extended by some regulatory agencies, whereas quinolones have been used for a wide variety of infections in adults (32, 33). Quinolones are currently recommended for patients with severe infections associated with respiratory failure, in patients with septic shock, or if *Pseudomonas aeruginosa* is suspected or verified (15, 16).

Twelve fluoroquinolones (enoxacin, pefloxacin, fleroxacin, sitafloxacin, temafloxacin, lomefloxacin, BAY3118, sparflaxacin, tosufloxacin, trovafloxacin, grepafloxacin, clinafloxacin) have been withdrawn from the market due to severe adverse events including phototoxicity, QT prolongation, hepatotoxicity, and nephrotoxicity (37).

**Bacterial resistance**

Bacterial resistance to antibiotics is an increasing problem in healthcare systems throughout the world (36, 38). Observational studies assessing fluoroquinolone resistance in several bacterial strains suggest increased resistance emerging in conjunction with the increased use of quinolones (36; 39-41). An antimicrobial surveillance program showed that the quinolone susceptibility for all pathogens was significantly higher in children (84%) than in the general population (42). The low resistance rates observed in the pediatric population, is thought to be due to the limited use of fluoroquinolones in children (42). This study found that the quinolone susceptibility for common pathogens, such as *Streptococcus pneumoniae, Enterobacteriaceae*, non-fermentative Gram-negative bacilli, *Enterococcus faecalis*,

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*Pseudomonas aeruginosa, Acinetobacter* species all were above 95% in children under seven years of age (42). Adults have susceptibility rates down to 58.4% for some of the same pathogens (42).

**How the intervention might work**

As the underlying cause of sepsis is most often a bacterial infection, any intervention that kills the bacteria might also have a beneficial effect on the course of sepsis.

Quinolones are a class of broad-spectrum antibiotics that target two bacterial enzymes: DNA gyrase and topoisomerase IV (30, 43-47). Both the DNA gyrase and topoisomerase IV are essential for bacterial DNA replication and hence bacterial survival (43, 44, 46-49). The quinolones form complexes with DNA gyrase and topoisomerase IV and thereby both inhibit these bacterial enzymes and convert them into DNA-damaging agents. Therefore, quinolones exhibit both bactericidal action and bacteriostatic action (30, 45, 48, 49).

The empirical treatment for suspected sepsis should be broad to ensure coverage of any possible pathogen, which typically results in some type of antibiotic combination therapy (15, 16, 50). Theoretically, combination of different antibiotics has several advantages. First, it is thought to provide an enhanced effect beyond the additive effects for the individual therapies (51). Second, it can be used to broaden the spectrum of antibiotic coverage when used empirically to increase the chance of covering the alleged causative bacteria. Third, combination therapy is thought to suppress the development of subpopulations of microorganisms resistant to antibiotics (51, 52).

**Why it is important to do this review**

Sepsis is a relatively common and deadly condition that constitutes a major challenge to the modern health care system. A review comparing 29 randomised clinical trials of fluoroquinolone versus non-quinolones in antibacterial therapy found, that in 22 trials fluoroquinolones had safety profiles equal to that of non-quinolones, in 5 trials fluoroquinolones were significantly less toxic, and in two trials fluoroquinolones seemed to be more toxic than non-quinolones (53). The most common adverse events associated with fluoroquinolones were: gastrointestinal symptoms, such as nausea and diarrhoea, central
nerve system symptoms, such as headache and dizziness, and liver enzyme abnormalities (29, 30, 34). More serious but less common adverse events include hypoglycaemia, QT prolongation, and skin irritation (55). Arthropathy (joint related diseases), such as tendinopathy (tendon disorder that results in pain, swelling, and impaired function) and chondrotoxicity (toxic to cartilage) has also been observed and the latter event is the reason why quinolones have been deprecated in children for many years (56). However, a large retrospective study on quinolone treatment in more than 7000 children from 1997, did not find a significant correlation between selected quinolone treatment and arthropathy (57).

A retrospective propensity-matched cohort study showed that combination therapy using beta-lactam antibiotics in combination with fluoroquinolones was associated with a significant decrease in hospital and intensive care unit mortality and an increase in ventilator free days and vasopressor free days (27). Fluoroquinolones have been shown to be effective in patients with Gram-negative bacteraemia but data is lacking for the empirical treatment of suspected sepsis (58).

Antibiotic combination therapy may theoretically cause enhanced drug toxicity (59). A Cochrane systematic review from 2014 showed that the addition of aminoglycosides to beta-lactam antibiotics lead to an increase in serious adverse events (primarily nephrotoxicity), without having any beneficial effect on mortality or other clinical important outcomes (60). Quinolones are often used as an alternative choice used in addition to beta-lactam antibiotics for suspected sepsis (61). However, the effects of quinolones for sepsis have not been assessed as well as the effects of aminoglycosides. A recently published large randomised clinical trial comparing a quinolone (moxifloxacin) plus meropenem versus meropenem alone showed a trend toward increased mortality in the group receiving the combination of quinolone and meropenem (62).

No former systematic review of randomised clinical trials with meta-analysis and Trial Sequential Analysis has assessed the benefits and harms of quinolones in patients with sepsis (63-75).

Objectives

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To assess the beneficial and harmful effects of quinolones in patients with sepsis.

**Methods**

**Criteria for considering studies for this review**

**Types of studies**

Randomised clinical trials. Trials will be included regardless of publication type, publication status, publication date, and language. We will not specifically search for non-randomised studies (quasi-randomised studies or observational studies). However, if we during the literature search identify non-randomised studies with reports of harmful effects, then we will narratively report these results. We are aware that this selection runs the risks of underestimating the harmful effects of quinolones.

**Types of participants**

We will include adults and children with sepsis (as defined by trialists).

**Types of experimental interventions**

- As experimental intervention we will accept any type of quinolone (second generation and newer). We will include trials comparing quinolones as an add-on therapy to usual care versus usual care. See Table 1 for comparisons.
- We will include trials comparing interventions utilising any route of antibiotic administration (such as oral and intravenous).
- We will accept any antibiotic dosage.

**Types of control interventions**

- As control intervention we will accept placebo or ‘no intervention’ other than a co-intervention such as usual care, treatment as usual or standard care delivered in both
intervention groups, i.e. we will accept any type of co-intervention as long as these co-interventions are planned to be delivered equally in both intervention groups.

**Types of outcomes**

**Primary outcomes**

- All-cause mortality.
- Proportion of participants with one or more serious adverse event. We will define a serious adverse event as any untoward medical occurrence that resulted in death, was life threatening, jeopardised the participant, was persistent, led to significant disability, hospitalisation, or prolonged hospitalisation (76). As we expect the trialists’ reporting of serious adverse events to be heterogeneous and not strictly according to the ICH-GCP recommendations, we will include the event as a serious adverse if the trialists either: 1) use the term 'serious adverse event' but not refer to ICH-GCP, or 2) report the proportion of participants with an event we consider fulfil the ICH-GCP definition (e.g. myocardial infarction or hospitalisation). If several of such events are reported then we will choose the highest proportion reported in each trial.
- Quality of life (any continuous scale used by the trialists).

**Secondary outcomes**

- Treatment failure, defined as recurrence or worsening of clinical signs leading to any modification of the assigned empirical antibiotic treatment.
- Proportion of participants with adverse events considered not to be serious (any non-serious adverse event).

**Exploratory outcomes**

- Individual serious adverse events.
- Individual adverse events considered not to be serious
- Persistent blood cultures (as defined by trialists).

We will use the trial results reported at maximum follow-up.
Search methods for identification of studies

Electronic searches

We will identify trials through systematic searches of the following bibliographic databases: Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library, MEDLINE (Ovid), Embase (Ovid), LILACS (Bireme), and Science Citation Index Expanded (Web of Science, Thomson Reuters) (77). We will also conduct a search of ClinicalTrials.gov (www.ClinicalTrials.gov), the WHO International Clinical Trials Registry Platform (ICTRP) Search Portal (http://apps.who.int/trialsearch/), Turning Research Into Practice (TRIP), Google Scholar, CINAHL, PsycInfo, Scopus, BIOSIS Citation Index (Web of Science, Thomson Reuters), CNKI, VIP, Wanfang, and Sinomed (Chinese biomedical literature database) in order to search for finished trials as well as ongoing trials.

We will search all databases from their inception to the present and we will impose no restriction on language of publication. If we identify any papers in a language not known by the author group, we will seek help. This will be acknowledged in the Acknowledgements section.

We will identify trials through literature searching designed to identify relevant trials as outlined in Chapter 6.4 of the Cochrane Handbook of Systematic reviews of Interventions (78). We will not apply restrictions to language or publication status.

Searching other resources

We will check reference lists of all relevant primary trials and reviews for additional references.

To identify unpublished trials we will also search clinical trial registers of Europe and the USA, websites of pharmaceutical companies, websites of the US Food and Drug Administration (FDA), fda.opentrials.net, and the European Medicines Agency.
We will search for errata or retractions from included studies published in full text on PubMed (www.ncbi.nlm.nih.gov/pubmed) and report the date this was done within the review.

We will scan the following trials registries for ongoing and unpublished trials:

- The World Health Organization International Clinical Trials Registry Platform (WHO ICTRP)
- ClinicalTrials.gov

We will scan the reference lists and citations of included trials and any relevant systematic reviews identified for further references to additional trials.

**Data collection and analysis**

**Selection of studies**

Two review authors (SKK and MM) will independently screen titles and abstracts. We will retrieve all relevant full-text study reports/publication and two review authors (SKK and MM) will independently screen the full text and identify trials for inclusion and identify and record reasons for exclusion of the ineligible studies. We will resolve any disagreement through discussion or, if required, we will consult a third author (JCJ). We will record the selection process in sufficient detail to complete a PRISMA flow diagram (79) and 'Characteristics of excluded studies' table.

**Data extraction and management**

We will use data collection forms for trial characteristics and outcome data which has been piloted on at least one trial in the review. Two review authors (SKK and MM) will extract trial characteristics from included trials. We will extract the following trials characteristics.

1. Methods: trial design, total duration of the trial, number of trial centres and location, trial setting, bias domain items, withdrawals, and date of the trial.
2. Participants: number of participants in each intervention group, mean age, age range, gender, diagnostic criteria, inclusion criteria, and exclusion criteria.

3. Interventions: intervention and comparison.

4. Outcomes: primary and secondary outcomes specified and collected, and time points reported.

5. Notes: funding for trial, and notable conflicts of interest of trial authors.

Two review authors (SKK and MM) will independently extract outcome data from included trials. We will note in the 'Characteristics of included studies' table if outcome data were not reported in a usable way. We will resolve disagreements by consensus or by involving a third author (JCJ). We will double-check that data are entered correctly by comparing the data presented in the systematic review with the study reports. A second review author (MM) will spot-check study characteristics for accuracy against the trial report.

Assessment of risk of bias in included studies

We will generally use the instructions given in the Cochrane Handbook for Systematic Reviews of Interventions (78) in our evaluation of the methodology of the included trials. Two review authors (SKK and MM) will each independently assess the included trials. We will evaluate the methodology in respect of generation of allocation sequence, allocation concealment, blinding of participants and treatment providers, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, for-profit bias, and other bias sources. We will classify the trials according to the following criteria:

Allocation sequence generation

- Low risk: If sequence generation was achieved using computer random number generator or a random numbers table. Drawing lots, tossing a coin, shuffling cards and throwing dice was also considered adequate if performed by an independent adjudicator.
• Unclear risk: If the method of randomisation was not specified, but the trial was still presented as being randomised.
• High risk: If the allocation sequence was not randomised or only quasi-randomised.

Allocation concealment

• Low risk: If the allocation of patients was performed by a central independent unit, on-site locked computer, identical-looking numbered sealed envelopes, drug bottles or containers prepared by an independent pharmacist or investigator.
• Uncertain risk: If the trial was classified as randomised but the allocation concealment process was not described.
• High risk: If the allocation sequence was familiar to the investigators who assigned participants.

Blinding of participants and treatment providers

• Low risk: If the participants and the treatment providers were blinded to intervention allocation and this was described.
• Uncertain risk: If the procedure of blinding was insufficiently described.
• High risk: If blinding of participants and the treatment providers was not performed.

Blinding of outcome assessment

• Low risk of bias: If it was mentioned that outcome assessors were blinded and this was described.
• Uncertain risk of bias: If it was not mentioned if the outcome assessors in the trial were blinded, or the extent of blinding was insufficiently described.
• High risk of bias: If no blinding or incomplete blinding of outcome assessors was performed.

Incomplete outcome data

• Low risk of bias: If missing data were unlikely to make treatment effects depart from plausible values. This could either be: 1) there were no drop-outs or withdrawals for all outcomes, or 2) the numbers and reasons for the withdrawals and drop-outs for all outcomes were clearly stated and could be described as being similar in both groups.
Generally, the trial was judged as at a low risk of bias due to incomplete outcome data if drop-outs were less than 5%. However, the 5% cut-off was not definitive.

- Uncertain risk of bias: If there was insufficient information to assess whether missing data were likely to induce bias on the results.
- High risk of bias: If the results were likely to be biased due to missing data either because the pattern of drop-outs could be described as being different in the two intervention groups or the trial used improper methods in dealing with the missing data (e.g. last observation carried forward).

**Selective outcome reporting**

- Low risk of bias: If a protocol was published before or at the time the trial was begun and the outcomes specified in the protocol were reported on. If there was no protocol or the protocol was published after the trial was begun, reporting of all-cause mortality and serious adverse events would grant the trial a grade of low risk of bias.
- Uncertain risk of bias: If no protocol was published and the outcomes all-cause mortality and serious adverse events were not reported on.
- High risk of bias: If the outcomes in the protocol were not reported on.

**For-profit bias**

- Low risk of bias: if the trial was not financed by a company that might have an interest in a given result.
- Uncertain risk of bias: if there was no description of how the trial was financed.
- High risk of bias: if the trial was financed or have other involvement by a company that might have an interest in a given result.

**Other bias**

- Low risk of bias: the trial appeared to be free of other bias domains (e.g. academic) that could put it at risk of bias.
- Unclear risk of bias: the trial may or may not have been free of other domains that could put it at risk of bias.
- High risk of bias: there were other factors in the trial that could put it at risk of bias (e.g. authors have conducted trials on the same topic).
Overall risk of bias

We assessed overall risk of bias in two groups defined as:

- Low risk of bias: the outcome result was classified as overall 'low risk of bias' only if all of the bias domains described in the above paragraphs were classified as low risk of bias.

- High risk of bias: the outcome result was classified 'high risk of bias' if any of the bias risk domains described in the above excluding 'blinding of participants and personnel' were classified as 'unclear' or 'high risk of bias'.

We will assess the domains 'blinding of outcome assessment', 'incomplete outcome data', and 'selective outcome reporting' for each outcome result. Thus, we can assess the bias risk for each outcome assessed in addition to each trial. Our primary conclusions will be based on the results of our primary outcomes at overall low risk of bias.

The bias risk assessment enable classification of randomised trials with low risk of bias and high risk of bias. The latter trials tend to overestimate positive intervention effects and underestimate negative effects (79-83).

Assessment of bias in conducting the systematic review

We will conduct the review according to this published protocol and report any deviations from it in the 'Differences between protocol and review' section of the systematic review.

Measures of treatment effect

Dichotomous outcomes

We will calculate risk ratios (RRs) with 95% confidence interval (CI) and Trial Sequential Analysis-adjusted CI (see below) for dichotomous outcomes.

Continuous outcomes

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We will calculate the mean differences (MDs) and the standardized mean difference (SMD) with 95% CI and Trial Sequential Analysis-adjusted CI (see below) for continuous outcomes.

**Dealing with missing data**

We will contact investigators and trial sponsors in order to verify key trial characteristics and obtain missing numerical outcome data where possible (e.g. when a study is identified as abstract only).

We will use valid intention-to-treat data if the trialists report these.

**Dichotomous outcomes**

We will not impute missing values for any outcomes in our primary analysis. In two of our sensitivity analyses, we will impute data (see 'Sensitivity analysis').

**Continuous outcomes**

If only change from baseline scores are reported, we will analyse the results together with follow-up scores (78). If standard deviations (SDs) are not reported, we will calculate the SDs using data from the trial if possible.

We will not use intention-to-treat data if the original report did not contain such data. We will not impute missing values for any outcomes in our primary analysis. In our sensitivity analysis for continuous outcomes, we will impute data, see 'Sensitivity analysis'.

**Assessment of heterogeneity**

We visually inspect forest plots to assess signs of heterogeneity and we will explore possible heterogeneity in our prespecified subgroup analyses. We will also inspect trial characteristics across trials to identify clinical heterogeneity. We will assess the presence of statistical heterogeneity by the Chi² test (threshold $P < 0.10$) and measure the quantities of heterogeneity by the $I^2$ statistic (84, 85).

In order to decide whether a meta-analysis should be conducted we will in addition to assessing heterogeneity assess if the subgroup analysis shows different effects and the overall meta-analysis shows significant statistical heterogeneity (78).
Assessment of reporting biases

We will use a funnel plot to assess reporting bias if 10 or more trials are included. We will visually inspect funnel plots to assess the risk of bias. For dichotomous outcomes we will test asymmetry with the Harbord test (86). For continuous outcomes we will use the regression asymmetry test (87) and the adjusted rank correlation (88).

Data synthesis

Meta-analysis

We will undertake this meta-analysis according to the recommendations stated in the *Cochrane Handbook for Systematic Reviews of Interventions* (78). We will use the statistical software Review Manager 5 (89) provided by Cochrane to analyse data.

We will assess our intervention effects with both random-effects meta-analyses (90) and fixed-effect meta-analyses (91). We will primarily use the result closest to zero effect (75). If the two estimates are similar, we will use the estimate with the widest CI. We use three primary outcomes and, therefore, we will consider a P value of 0.025 or less as the threshold for statistical significance (75). For all remaining outcomes we will consider a P value of 0.05 or less as the threshold for statistical significance (75). We will use the eight-step procedure to assess if the thresholds for significance are crossed (75). Our primary conclusion will be based on results with low risk of bias (75). Where data are only available from one trial, we will use Fisher’s exact test (92) for dichotomous data and Student’s t-test (93) for continuous data.

Where multiple trial arms are reported in a single trial, we will include only the relevant arms. If two comparisons are combined in the same meta-analysis, we will halve the control group to avoid double-counting.

Trial Sequential Analysis

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Traditional meta-analysis runs the risk of random errors due to sparse data and repetitive testing of accumulating data when updating reviews. We will therefore perform Trial Sequential Analyses on the outcomes, in order to calculate the required information size and the cumulative Z-curve’s breach of relevant trial sequential monitoring boundaries (64, 94-99). We wish to control the risks of type I errors and type II errors. A more detailed description of Trial Sequential Analysis can be found at http://www.ctu.dk/tsa/.

For dichotomous outcomes we will estimate the required information size based on the observed, un-weighted proportion of patients with an outcome in the control group (the cumulative proportion of patients with an event in the control groups relative to all patients in the control groups), a relative risk reduction of 20 %, an alpha of 2.5%, a beta of 20%, and diversity as suggested by the trials in the meta-analysis. For continuous outcomes we will in the trial sequential analysis use the observed SD, a mean difference of the observed SD/2, a risk of type I error of 2.5% and a risk of type II error of 20%.

**Subgroup analysis and investigation of heterogeneity**

A: Comparison of the aggregated effect of quinolones between trials at a low and at high risk of bias.

B: Comparison of the aggregated effect of quinolones between trials between infants (age <1 year), children (age 1 to 12 year), adolescence (age 12 to18 years), adults (age 18 to 65 years), and elderly (age > 65 years).

C: Comparison of the aggregated effect between trials where interventions added quinolones to different antibiotic regimes:

- a small spectrum beta lactam antibiotic (e.g. oxacillin, cloxacillin, dicloxacillin, nafcillin, methicillin, and penicillin G)

- a broad spectrum beta lactam antibiotics:
  
  o broad spectrum penicillins (e.g. ampicillin, amoxicillin, piperacillin, ticarcillin, carbenicillin and mezlocillin).
- beta lactam drugs plus beta lactamase inhibitors (e.g. clavulanic acid, sulbactam and tazobactam).
- cephalosporins (e.g., cefozolin, cephalxin, cefuroxim, cefotetan, cefoxitin, ceftriaxon, cefotaxim, ceftazidime, cefepime, ceftaline, ceftobiprole, ceftoperazone).
- carbapenems (e.g. imipenem, meropenem, doripenem, ertapenem).
- monobactam (atreonam).

- an aminoglycoside (e.g. gentamycin).

- a glycopeptide (e.g. vancomycin and teicoplanin).

D: Comparison of the aggregated effect between trials from high-income countries compared to trials from low- and middle-income countries as defined by the World Bank (100).

E: Comparison of the aggregated effect between trials based on primary infection focus (e.g. urinary system, lungs, skin, blood, nervous system, unknown, mixed)

F: Comparison of the aggregated effect between trials based on type of quinolone

Sensitivity analysis

To assess the potential impact of the missing data, we will perform the two following sensitivity analyses on the primary outcomes.

- ‘Best-worst-case’ scenario: we will assume that all participants lost to follow-up in the experimental group survived and had no serious adverse event. We assumed that they also had a beneficial event with regard to quality of life (75). We assumed that all of those with missing outcomes in the control group died and had a serious adverse event. We assumed that they also had a harmful event with regard to quality of life (75).

- 'Worst-best-case’ scenario: we will assume that all participants lost to follow-up in the experimental group died and had a serious adverse event. We assumed that they also had a harmful event with regard to quality of life (75). We will assume that all those
participants lost to follow-up in the control group survived and had no serious adverse event. We assumed that they also had a beneficial event with regard to quality of life (75).

When analysing continuous outcomes a ‘beneficial outcome’ will be the group mean plus two standard deviations (SDs) (we will secondly use one SD in another analysis) of the group mean, and a ‘harmful outcome’ will be the group mean minus two SDs (we will secondly use one SD in another analysis) of the group mean (75).

We will present results of both scenarios in our review.

To assess the potential impact of missing SDs for continuous outcomes, we will perform the following sensitivity analysis.

Where SDs are missing and it is not possible to calculate them, we will impute SDs from trials with similar populations and low risk of bias. If we find no such trials, we will impute SDs from trials with a similar population. As the final option, we will impute SDs from all trials.

We will present results of this scenario in our review.

Other post-hoc sensitivity analyses might be warranted if unexpected clinical or statistical heterogeneity is identified during the analysis of the review results (75).

'Summary of findings' table and GRADE

We will create a 'Summary of findings' table using each of the prespecified primary outcomes and secondary outcomes (except non-serious adverse events). We will use the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the quality of a body of evidence as it relates to the studies which contribute data to the meta-analyses for the prespecified outcomes. We will use methods and recommendations described in Section 8.5 and Chapter 12 of the Cochrane Handbook for Systematic Reviews of Interventions (78) using GRADEpro software. We will justify all decisions to down- or up-grade the quality of studies using footnotes and we will make

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comments to aid the reader's understanding of the review where necessary. Firstly, we will present our results in the 'Summary of findings' table based on the results from the trials at low risk of bias, secondly we will present the results based on all trials.

**Discussion**

To our knowledge this will be the first systematic review to assess quinolones for sepsis.

This protocol has a number of methodological strengths. First, our methodology is described in detail in this protocol which will be published before the literature search is initiated. Second, we will conduct the review using the methods recommended by Cochrane and findings and recommendation of additional methodological studies (84). Hence, we will systematically assess the risks of systematic errors via bias risk assessments, and we will conduct Trial Sequential Analyses and properly adjust our thresholds for statistical significance to control the risks of random error. This adds further robustness to our results and conclusions (101). Third, we will use our systematic eight step procedure to assess if the thresholds for statistical and clinical significance are crossed (102).

The underlying bacteria causing sepsis is expected to differ in the different trials as we include trials regardless of location (country). The doses and length of therapy of the antibiotic regimens might also differ between trials, and the trials we will include will possibly use different inclusion criteria. We therefore expect that the clinical heterogeneity between the trials might be high, but it is not certain that clinical heterogeneity will lead to statistical heterogeneity, i.e. that the relative intervention effects will differ between the included trials. We do not expect to include a large number of relevant trials, which potentially will limit the statistical power of this review.

**Contributions of authors**

Steven Kwasi Korang (SKK), Mathias Maagaard (MM), Joshua Feinberg (JF), Anders Perner (AP), Christian Gluud (CG), Janus C Jakobsen (JCJ),

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Conceiving the review: SKK and JCJ

Co-ordinating the review: SKK and JCJ

Undertaking manual searches: SKK and MM

Screening search results: SKK and MM

Organizing retrieval of papers: SKK and MM

Screening retrieved papers against inclusion criteria: SKK and MM

Appraising quality of papers: SKK and MM

Abstracting data from papers: SKK and MM

Writing to authors of papers for additional information: SKK and MM

Providing additional data about papers: SKK and MM

Obtaining and screening data on unpublished studies: SKK and MM

Data management for the review: SKK and MM

Entering data into Review Manager: SKK and MM

RevMan statistical data: SKK and MM

Other statistical analysis not using RevMan: SKK and MM

Interpretation of data: SKK, JF, CG, AP and MM

Statistical inferences: SKK, JF, CG and MM

Writing the review: SKK and MM

Guarantor for the review (one author): SKK

Person responsible for reading and checking review before submission: SKK
Declarations of interest

Steven Kwasi Korang: Had no conflict of interest

Mathias Maagaard: Had no conflict of interest

Joshua Feinberg: Had no conflict of interest

Anders Perner: The Dept of Intensive Care, where AP heads the research unit, receives support for research from CSL Behring, Fresenius Kabi and Ferring Pharmaceuticals

Christian Gluud: No known conflict of interest

Janus C Jakobsen: Had no conflict of interest

References


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76. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) adopts Consolidated Guideline on Good Clinical Practice in the

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Table 1

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<table>
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<th>Comparison</th>
<th>Control</th>
<th>Intervention</th>
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</thead>
<tbody>
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<td>1</td>
<td>Beta-lactam</td>
<td>Beta-lactam + Quinolone</td>
</tr>
<tr>
<td>2</td>
<td>Aminoglycoside</td>
<td>Aminoglycoside + Quinolone</td>
</tr>
<tr>
<td>3</td>
<td>Glycopeptide</td>
<td>Glycopeptide + Quinolone</td>
</tr>
<tr>
<td>4</td>
<td>Any antibiotic regime</td>
<td>Any antibiotic regime + Quinolone</td>
</tr>
<tr>
<td>Comparison</td>
<td>Control</td>
<td>Intervention</td>
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