

Beta-lactam vs Fluoroquinolone Monotherapy for *Pseudomonas aeruginosa* Infection: A Systematic Review and Meta-analysis

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Systematic Review

Keywords: Beta-lactams, fluoroquinolones, Pseudomonas, monotherapy, infection, meta-analysis

Posted Date: April 3rd, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-379835/v1>

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Version of Record: A version of this preprint was published at Antibiotics on December 3rd, 2021. See the published version at <https://doi.org/10.3390/antibiotics10121483>.

Abstract

Introduction: *Pseudomonas aeruginosa* (PA) is a leading cause of healthcare-associated infections. A variety of antibiotic classes are used in the treatment of PA infections, including beta-lactams (BLs) and fluoroquinolones (FQs), given either together in combination therapy or alone in monotherapy. A systematic review and meta-analysis were performed to evaluate the therapeutic efficacy of BL agents versus FQ agents as active, definitive monotherapy in PA infections in adults.

Methods: Comprehensive literature searches of Medline and Scopus electronic databases, alongside hand searches of the Cochrane Database of Systematic Reviews, PubMed, and Google Scholar, were performed without time restriction to identify studies published in English comparing BL and FQ agents given as monotherapy for PA infection in hospitalized adults for which mortality, bacteriological eradication, or clinical response was evaluated. One reviewer screened search results based on pre-defined selection criteria. Two reviewers independently assessed included studies for methodological quality using NIH assessment tools. Two fixed-effects meta-analyses were performed.

Results: A total of 368 articles were screened, and 6 studies involving 338 total patients were included in the meta-analysis. Upon evaluation of methodological quality, 2 studies were rated good, 3 fair, and 1 poor. A meta-analysis of 3 studies demonstrates FQ monotherapy is associated with significantly improved survival compared to BL monotherapy for patients with PA bacteremia (OR, 3.65; 95% CI, 1.27-10.44; $p=.02$). A meta-analysis of 3 studies demonstrates FQ monotherapy is associated with equivalent bacteriological eradication compared to BL monotherapy for PA pneumonia or skin and soft tissue infection (RD, 0.07; 95% CI, -0.09 to 0.24; $p=.39$).

Conclusion: The meta-analyses demonstrate FQ monotherapy significantly improves survival in PA bacteremia and is associated with similar rates of bacteriological eradication in pneumonia and skin and soft tissue infection caused by PA compared to BL monotherapy. However, more research is needed to make meaningful clinical recommendations.

Introduction

Pseudomonas aeruginosa (PA) is a pathogenic gram-negative bacterium and leading cause of healthcare-associated infections (HAIs) around the world [1, 2, 3]. In the United States and Europe, PA accounts for 7.1% and 8.9% of all HAIs, respectively [4, 5]. Meanwhile, some regions within Europe have reported even higher rates [3]. PA is known to cause a variety of serious infections, including nosocomial pneumonia, bloodstream infections, urinary tract infections, and surgical site infections [1, 2, 3], with nosocomial pneumonia and bacteremia having mortality rates greater than 35% [1]. PA has the ability to form biofilms on catheters and tubes [1], putting patients with indwelling catheters and endotracheal tubes at increased risk for infection. Additionally, individuals with bronchiectasis, chronic obstructive pulmonary disease, immunocompromised status, and neutropenia have an increased risk for hospital-

associated PA infection [1, 2, 3]. In particular, it is estimated 70% of adult cystic fibrosis patients are chronically colonized with PA [2].

In addition to its relatively high prevalence and potential for serious infection, multidrug resistant (MDR) PA strains are particularly concerning for human health [6, 7, 8]. Clinically, MDR strains negatively affect patient outcomes and are associated with increased mortality, morbidity [1, 2], and healthcare costs [9]. Given PA poses a significant threat to individual and population health around the world, it is important that clinicians treat PA infections in a way that maximizes patient outcomes and minimizes the selection of resistant isolates.

Currently, a variety of antibiotic classes are used in the treatment of PA infections, including beta-lactams (BLs), fluoroquinolones (FQs), aminoglycosides (AGs), and, rarely, colistin, either together in combination therapy or alone in monotherapy [1]. However, given these choices, no firm standard treatment guideline exists. Empiric therapy with two antipseudomonal agents from different drug classes is recommended for critically ill patients with known or suspected PA bacteremia [10]. After microbiologic susceptibility testing is performed, it is recommended to de-escalate and initiate appropriate definitive therapy with the single agent that is most active against the infecting strain and has the least propensity to select resistance [10]. In practice, the combination of hospital-specific antibiogram data and patient characteristics – including allergies, comorbidities, and renal function – may direct clinicians on which antimicrobial agents to select.

Much effort has focused on comparing the therapeutic efficacy of monotherapy versus combination therapy in the treatment of PA infection, yet the results are generally considered controversial [1, 11]. On the other hand, few systematic reviews have compared the therapeutic effects of different antibiotic classes given as monotherapy for PA infection [12, 13], and none have evaluated BL versus FQ to our knowledge. A systematic review and meta-analysis were performed to evaluate the association between mortality, bacteriological eradication, and clinical success and treatment of PA infection with BL agents versus FQ agents as active, definitive monotherapy in adult inpatients. The goal was that the results would provide clinically relevant information to help guide clinicians on which drug class to select in the definitive treatment of PA infection so that patient outcomes may improve.

Methods

This systematic review and meta-analyses are performed and reported in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocol guidelines [14].

Selection Criteria and Definitions

As an overarching framework, the PICOT (Population, Intervention, Comparison, Outcome, Time) model was implemented to define the inclusion and exclusion criteria for this systematic review and meta-analysis. Studies with populations of adult inpatients infected with PA were included. Studies with comparisons between definitive BL or FQ monotherapy, active against the infecting PA strain, were

eligible for inclusion. Based on precedence in the literature, BL monotherapy was defined as BL ± beta-lactamase inhibitor [15]. Studies that reported outcomes of inpatient mortality, microbiological eradication, or clinical response were eligible for inclusion. No restrictions were placed on year of publication or when the study was performed. No restrictions were placed on geographical location. Case-control, cohort, and randomized controlled studies were all eligible for inclusion. Case reports and case series were excluded. Only available, full-text published studies in English were eligible for inclusion.

Information Sources and Search Strategy

With the assistance of a research librarian, comprehensive literature searches of Medline and Scopus electronic databases were performed in April 2019. Hand searches of the Cochrane Database of Systematic Reviews, PubMed, Google Scholar, and bibliographies of relevant articles and meta-analyses were also performed. The search strategy was formulated by three study investigators (CD, ER, and RW) and executed by a research librarian at Creighton University Health Sciences Library (CUHSL). A combination of key terms and MESH terms were formulated into the search, including beta-lactams (aztreonam, cefepime, ceftazidime, imipenem, meropenem, doripenem, piperacillin, tazobactam, OR piperacillin/tazobactam), fluoroquinolones (ciprofloxacin OR levofloxacin), monotherapy, *Pseudomonas aeruginosa*, *Pseudomonas* infections, *Pseudomonas*, nosocomial, and hospital acquired. A full, detailed record of the search strategy is included in the Supplementary Material.

Screening and Methodological Assessment

The titles and abstracts of the literature search results were screened for eligibility and annotated in Microsoft Word by one study investigator (ER) in accordance with the PICOT-based, predefined selection criteria. Eligible studies were selected, and full-text articles were retrieved via available electronic sources, CUHSL stacks, or interlibrary loan. Full-text versions of the selected studies were reviewed by one investigator (ER) for inclusion in the meta-analysis. The final population of studies included in the meta-analysis were reviewed and assessed for methodological quality and risk of bias independently by two reviewers (ER and RW) using the NIH National Heart, Lung, and Blood Institute Study Quality Assessment Tools for Controlled Intervention Studies or Observational Cohort and Cross-Sectional Studies for randomized control or cohort studies, respectively [16]. These assessment tools include an itemized list of fourteen questions with explanations of their significance but lack a grading algorithm. Reviewers attributed a quality rating of good, fair, or poor based on the number of NIH criteria the study met and the importance of those criteria per NIH guidance. When finished attributing study ratings, reviewers met to discuss the articles and reach consensus on any rating discrepancies. If consensus was not achieved, discrepancies were settled by third party arbitration (CD).

Data Collection and Outcomes Assessed

Unadjusted data were independently manually extracted by two study investigators (ER and RW) and compared in duplicate. Mortality was the primary outcome assessed for observational studies, whereas bacteriological eradication and clinical success were the primary outcomes assessed for controlled studies. These outcomes were selected because they are traditionally used in studies comparing

antimicrobial efficacy and reflect important clinical variables and/or therapeutic efficacy. For studies in which causative organisms of infection other than PA were reported, only PA-specific data were extracted and used in the analysis. If an intent-to-treat (ITT) analysis was reported, ITT data were utilized in the meta-analysis. For mortality, 28-day and 30-day mortalities were included in the same data analysis. Based on consistency among definitions between studies, the definition of microbiological eradication included confirmed eradication and presumed eradication, and the definition of clinical success included clinical cure and improvement. It was planned to stratify the data based on specific agents within a drug class and perform subgroup analyses if possible.

Statistical Analysis

All extracted data were entered manually into Review Manager 5.3. The decision to use a fixed or random-effects meta-analysis was based on between-study heterogeneity as indexed by τ^2 and I^2 . Effect sizes for outcomes from the retrospective cohort studies are reported as odds ratios (OR), whereas effect sizes from the randomized controlled trials are reported as risk differences (RD). All effect sizes are reported along with a 95% confidence interval (CI). Individual study and composite effects are displayed in separate forest plots for each outcome. Following a fixed-effects meta-analysis, publication bias was evaluated visually via funnel plots.

Results

Selected Studies

The literature search resulted in a total of 397 potentially relevant studies for screening, ranging in year of publication from 1981 to 2019 (Fig. 1). Six additional relevant studies were identified via hand searching. Twenty-four articles were selected for full-text review, and ultimately, six studies were included in the systematic review and meta-analysis: three cohort [17, 18, 19] and three randomized control studies [20, 21, 22]. These six studies included 338 total patients.

Figure 1. Flow diagram of study selection process.

Methodological Quality of Studies

Upon evaluation of methodological quality, two studies were rated good, three rated fair, and one rated poor (Table 1). Of the cohort population, study features we identified that increased the risk of bias included failure to report sample size justification and power descriptions, incompletely or inadequately defined outcome measures, and failure to adjust for potentially confounding

variables. Of the randomized control population, study features identified to increase the risk of bias included designs allowing patients to receive non-protocol antimicrobial agents, options to receive vancomycin and/or metronidazole, non-ITT analysis, incomplete or no blinding, dropout rates higher than 20%, failure to report sample size justifications and power descriptions, and study details not reported or inadequately reported (see Appendix).

Study Characteristics

Characteristics of the studies included in the meta-analysis are shown in Table 1. All studies evaluated hospitalized patients. Different from the others, the study design of Siami et al allowed for initially hospitalized patients to be discharged and later evaluated in an outpatient setting. All cohort studies selected patients with bacteremia, while the randomized control studies selected patients with pneumonia [20, 21] or skin infection [22]. In all six studies, the majority of patients were male, and a large proportion of patients were older than 50. Patients selected in the cohort studies shared similar characteristics including malignancy and immunosuppressed status at varying percentages between studies. Ciprofloxacin monotherapy constituted at least part of the FQ arm in all but one study [22]. A variety of BLs were used as monotherapy in the studies, including cephalosporins, carbapenems, and penicillins. All six studies incorporated BL-beta-lactamase drugs in the BL arm. Notably, all but two studies included cases of polymicrobial infections. Furthermore, Kuikka et al excluded cases of polymicrobial bacteremia but reported almost one-fourth of the bacteremia patients had other infections. Although all three randomized control studies defined bacteriological eradication as eradication plus presumed eradication, the definitions of these two terms varied between the studies.

Mortality

A total of 211 patients with PA bacteremia from the three cohort studies were included into the meta-analysis comparing the effects of BL and FQ monotherapy on mortality. Among the six total treatment arms, mortality ranged from 0–32%. Together, 4 patients (9.8%) who received FQ monotherapy died compared to 50 (29.4%) who received BL monotherapy. Results of a fixed-effects meta-analysis indicated that FQ monotherapy resulted in significantly higher survival compared to BL monotherapy (OR, 3.65; 95% CI, 1.27–10.44; $p = .02$; Fig. 2). Visual analysis of the associated funnel plot indicated no apparent publication bias (Fig. 2).

Bacteriological Eradication

A total of 127 patients with PA pneumonia or skin infection from three randomized control studies were included in the meta-analysis comparing the effects of BL and FQ monotherapy on bacteriological eradication. Within six total treatment groups, bacteriological eradication ranged from 25–50%. Together, 28 patients (41.8%) who received FQ monotherapy were found to have culture-confirmed or presumed PA eradication compared to 21 (35.0%) who received BL monotherapy. Results of a fixed-effects meta-analysis indicated that FQ monotherapy was not statistically associated with increased bacteriological eradication compared to BL monotherapy (RD, 0.07; 95% CI, -0.09 to 0.24; $p = .39$; Fig. 3), which was expected given that all of the studies had 95% CIs for their respective RD that included zero. Based on the composite risk difference, the number needed to treat (NNT) was 15, indicating that 15 patients would need to be treated with FQ monotherapy for one patient to benefit over BL monotherapy. Visual analysis of the associated funnel plot indicated no apparent publication bias (Fig. 3).

Clinical Success

Torres et al was the only study to have PA-specific data comparing the effects of BL and FQ monotherapy on clinical response. Twenty-six patients with PA pneumonia were included in the report. Ten patients (71.4%) who received ciprofloxacin monotherapy were found to be clinically cured or improved compared to 8 (66.7%) who received imipenem-cilastatin (RD, 0.05; 95% CI, -0.31 to 0.40; $p = .79$; NNT = 20).

Discussion

A systematic review and meta-analysis of published studies was performed that compared the therapeutic efficacy of BL monotherapy with FQ monotherapy for PA infection in adult inpatients with the purpose of identifying apparent trends with respect to mortality, bacteriological eradication, and clinical success. The results demonstrated patients receiving FQ monotherapy had higher survival in PA bacteremia, but not higher rates of bacteriological eradication in pneumonia and skin and soft tissue infection caused by PA. Based on one study's data of 26 total patients, FQ monotherapy was indicated to have no benefit over BL monotherapy on clinical success rates in PA pneumonia [21].

Unadjusted data were used in the mortality analysis due to the lack of adjusted data accounting for potential confounding variables. Therefore, other inherent risk factors for mortality were not accounted for in the reported data. Wu et al reported patient demographic data specifically for the BL and FQ arms. The BL arm had a greater percentage of patients with septic shock, immunosuppression, and higher mean Pitt bacteremia and APACHE II scores, whereas the FQ arm had a greater percentage of patients with malignancy [19]. Differences in Pitt bacteremia and APACHE II scores were statistically significant, meaning the BL group had more critically ill patients [19]. Unfortunately, treatment arm-specific patient demographics were not reported in the other two studies. In addition to the retrospective nature of the included studies, these discrepancies may have biased our results to an unknown extent.

For the meta-analysis on bacteriological eradication, all included studies reported the presence of polymicrobial infection, which often occurs in patients with ventilator associated pneumonia [20]. This fact likely increased the external validity of the results. All three studies included an unknown percentage of patients who were allowed to receive non-protocol antimicrobials. Two of three studies allowed for the option for protocol-allowed vancomycin and/or metronidazole. These study designs may have introduced a certain level of risk for bias in the results. Although treatment arm-specific patient demographics were reported in all the studies, none of the studies further stratified these data for infection caused by PA specifically. Therefore, we could not determine if any confounding variable existed that would impart a potential advantage or disadvantage for bacteriological eradication.

It is worth noting the Clinical & Laboratory Standards Institute (CLSI) has changed the minimum inhibitory concentration (MIC) cutoffs for ciprofloxacin over time. Since the 1990's, the ciprofloxacin MIC cutoff has decreased, meaning the criteria to be considered "active therapy" is different now for more contemporary studies than it used to be for the studies from the 1990's. Now, it is unclear how this change could have affected the results, but it is important to acknowledge the CLSI change.

Strengths of this meta-analysis include adherence to a well-defined PICOT model, the use of NIH quality assessment tools, and following PRISMA reporting guidelines for systematic reviews and meta-analyses. Additionally, the variations in study year, geography, and patient demographics among included studies enhance the external validity of this study. However, limitations include small sample sizes, differing definitions of terms and outcomes among studies, incomplete data, the lack of grey literature search, and known and unknown discrepancies in patient demographics between treatment arms for infections caused specifically by PA. The latter is explained by the fact that not all studies were designed with the purpose of making direct comparisons between BL and FQ monotherapy or studying PA-specific infection (rather, some examined all causative pathogens of a given infection type). Additionally, the studies evaluated definitive therapy, and the efficacy of empiric therapy could have impacted the results. Consequently, these results should be interpreted with caution.

Overall, little research has focused specifically on comparing the therapeutic efficacy of BL and FQ drug classes as active, definitive monotherapy for PA infection. To our knowledge, this is the first meta-analysis to do so. The vast majority of systematic reviews compares combination therapy and monotherapy, but results are controversial [1, 11]. Although combination therapy is recommended in certain cases of PA infection for empirical therapy [10, 11], de-escalation to a single active agent is encouraged as this may decrease the potential for adverse events and antimicrobial-associated toxicity and reduce the development of resistance [11]. De-escalation to monotherapy is also consistent with antibiotic stewardship program objectives [23]. Regardless, more research comparing monotherapy in PA infection are needed.

When selecting a preferred drug class for PA infection, no overarching recommendations exist, and our results do not come close to bridging the gap. More likely, no one drug class or antimicrobial agent is the ideal choice. Antimicrobial resistance is in flux and varies by regions, so local antibiogram data are essential to selecting drug therapies. Once PA antimicrobial susceptibility testing is complete, the interplay between patient characteristics and drug features remains critically important in selecting definitive therapy. Furthermore, definitive antimicrobial therapy for PA must minimize the potential for selecting resistance.

On a whole, these results provide insight into the therapeutic efficacy of BL and FQ drug classes as active, definitive monotherapy for PA infection in adult inpatients but fall short of offering definitive answers. The results suggest FQ monotherapy is associated with significantly higher survival rates compared to BL monotherapy, but more rigorous research are required to make definitive conclusions. Clinicians should continue to weigh pros and cons of drug classes and individual agents for a particular patient when selecting definitive therapy for PA infection.

Declarations

FUNDING

This research was supported by the Creighton University School of Medicine 2019 Summer Research Program and funded by a stipend made possible thanks to the generous contributions of alumni Mr. Ronald Yamaguchi and Dr. Kent Yamaguchi.

CONFLICT OF INTEREST

The authors declare there are no conflicts of interest.

Official Statement:

Ethics approval was not required for this study. No consent was required for this study, as the data are from the existing published literature.

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Table

Table 1 is available as a download in the Supplementary Files section.

Figures

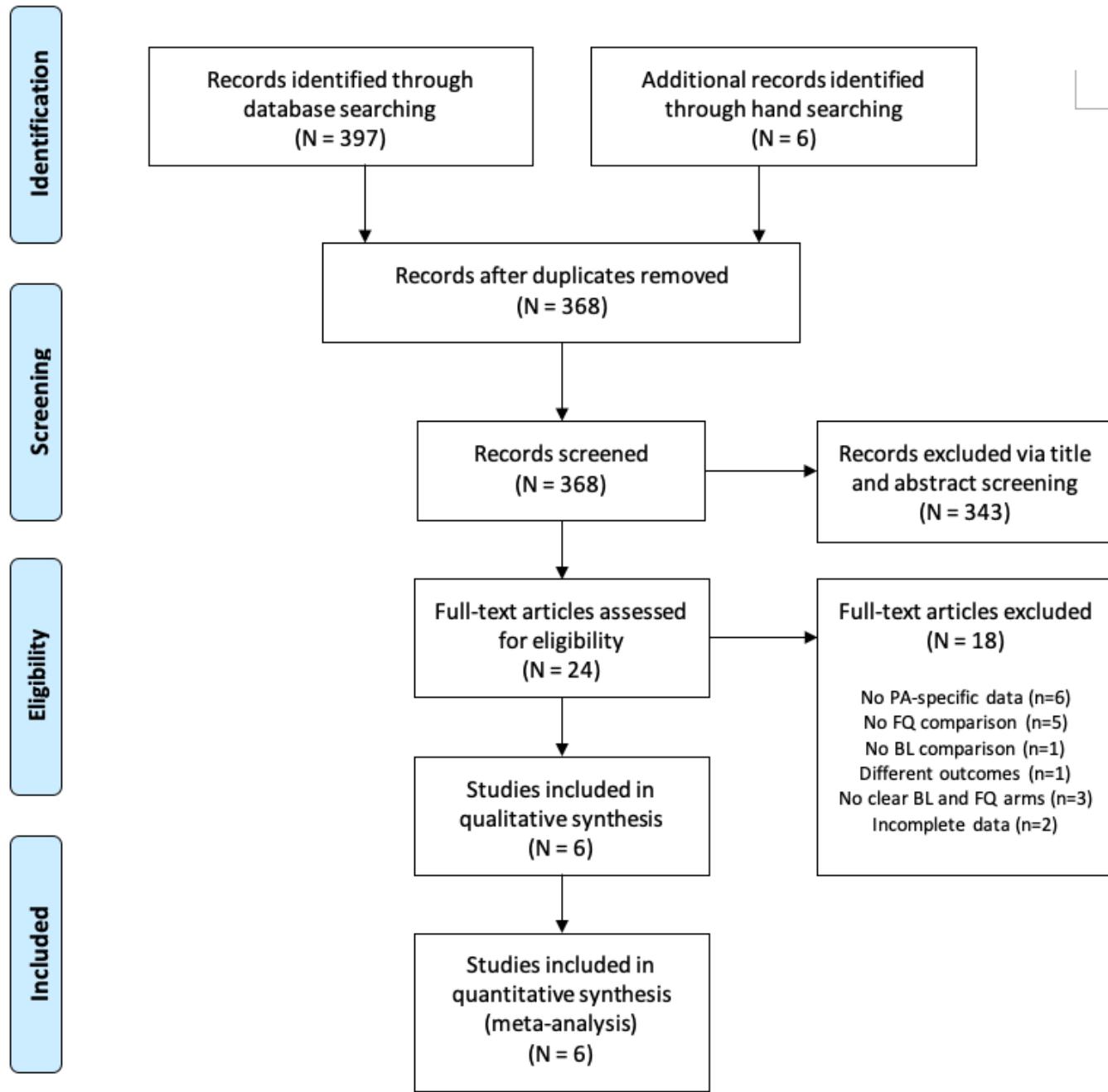


Figure 1

Flow diagram of study selection process.

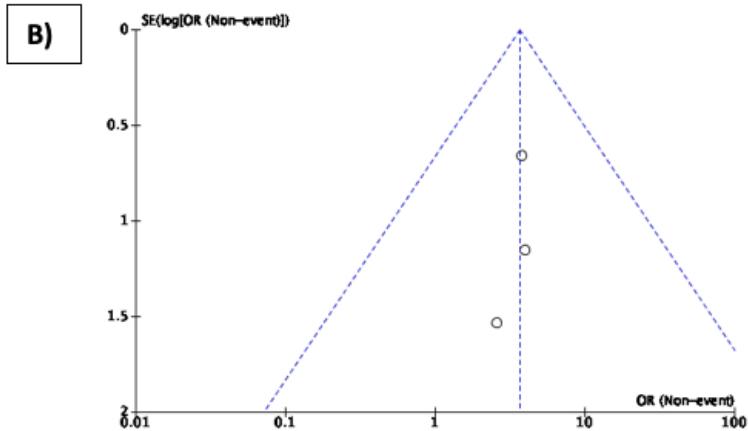
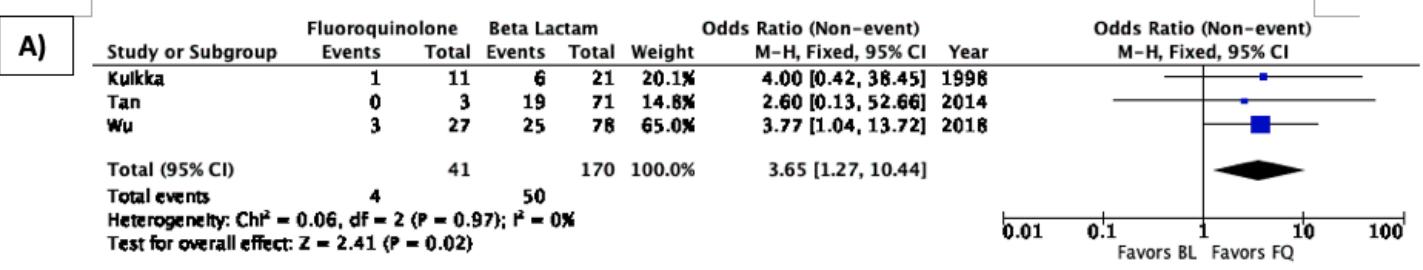


Figure 2. A) Forest plot showing FQ monotherapy is associated with significantly improved survival compared to BL monotherapy using a fixed-effects model. B) Funnel plot showing the studies included in the meta-analysis.

Figure 2

A) Forest plot showing FQ monotherapy is associated with significantly improved survival compared to BL monotherapy using a fixed-effects model. B) Funnel plot showing the studies included in the meta-analysis.

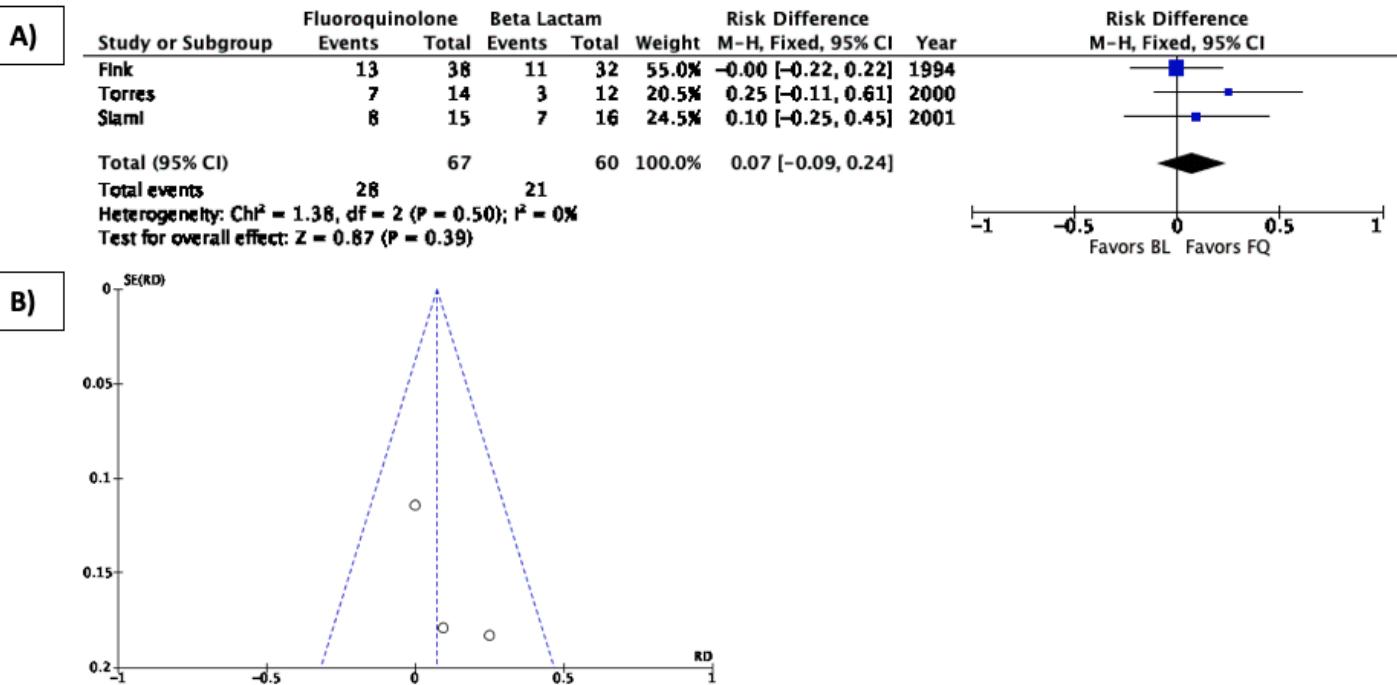


Figure 3. A) Forest plot showing FQ monotherapy is associated with similar bacteriological eradication compared to BL monotherapy using a fixed-effects model. B) Funnel plot showing the studies included in the meta-analysis.

Figure 3

A) Forest plot showing FQ monotherapy is associated with similar bacteriological eradication compared to BL monotherapy using a fixed-effects model. B) Funnel plot showing the studies included in the meta-analysis.

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