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Factors associated with treatment failure in patients with diabetic foot infections: An analysis of data from randomized controlled trials

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ABSTRACT

Background: Although several antibiotics have been studied for the treatment of foot infections, their effectiveness has been considered to be similar. The scope of this analysis was the identification of factors that are associated with treatment failure based on evidence from randomized controlled trials (RCTs).

Methods: Two reviewers independently extracted data from published RCTs comparing different antibiotics for diabetic foot infections (DFIs).

Results: The combined observed treatment failure was 22.7% in the 18 RCTs included in the analysis. When different regimens of various antibiotics (penicillins, carbapenems, cephalosporins, and fluoroquinolones) were directly compared in the individual RCTs, they were associated with similar frequency of treatment failure. However, when all patients were combined, carbapenems were associated with fewer treatment failures. Also, treatment failure in patients with DFIs from whom methicillin-resistant *S. aureus* (MRSA) alone or as part of a polymicrobial infection was isolated was more common than in patients from whom other bacteria were isolated [24/68 (35.3%) versus 350/1522 (23%), $p = 0.02$]. Among patients with DFIs due to MRSA the use of linezolid was not associated with better effectiveness in comparison to other antibiotics [treatment failure: 6/19 (31.6%) versus 18/49 (36.7%), $p = 0.69$]. Of interest, treatment failure was similar in patients with and without osteomyelitis [44/169 (26.5%) versus 330/1424 (23.2%), $p = 0.34$].

Conclusions: The isolation of MRSA seems to be a significant factor associated with treatment failure in patients with DFIs. Further research efforts are needed for the identification of additional risk factors for treatment failure and optimization of the management of patients with DFIs.

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1. Introduction

It is estimated that approximately 12–25% of patients with diabetes (both type 1 and type 2) will suffer from diabetic ulcers during the course of the disease [1–3]. The persistence of ulcers (attributable mainly to their pathophysiology) facilitates the development of infections, which in turn represent a major cause of hospitalization as well as fund-consuming

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complications of diabetes, responsible for approximately 15% of the costs associated with the disease [4–6].

The majority of diabetic foot infections are polymicrobial. The number of isolated pathogens varies between studies, with a mean number of 2–5 isolates per episode of infection [7]. Although many antibiotics (as well as combinations of antibiotics), with different spectrum and route of administration, have been used for the empirical treatment of these infections, the best regimen has not been established, yet. Furthermore, it is thought that most of these antibiotics as well as their combinations demonstrate similar effectiveness, irrespective of their spectrum and the susceptibility of the isolated bacteria incorporated to the regimen [7,8].

Following these observations, we sought to identify factors that are associated with treatment failure of DFIs, based on the available evidence from randomized controlled trials.

2. Methods

A search of Pubmed (January 1950 to December 2005) and Cochrane database of controlled trials was performed. Relevant studies were chosen and reviewed for collection of data. References from selected articles were also reviewed. The electronic search was performed after combinations of the terms ''diabetic foot infection'', ''infected diabetic ulcer'', ''osteomyelitis'', or ''skin and soft tissue infections'', with ''linezolid'', ''cephalosporins'', ''penicillins'', ''glycopeptides'', ''carbapenems'', ''fluoroquinolones'' and ''randomized controlled trial''.

Two reviewers independently selected the RCTs that could be eligible for the analysis and extracted the relevant data (KZV and MH). Any discrepancy or disagreement between the reviewers was resolved by consensus in meetings involving all authors. The identified relevant studies were further evaluated. A study was considered to be eligible if it was a randomized controlled trial comparing different antibiotic regimens for their clinical effectiveness for DFIs.

The primary outcomes of the current review were the treatment failure after systemic administration of antibiotics and the reasons (demographic variables, antibiotics, type/severity of infection if available, and bacteria) that could be possibly associated with this failure. Treatment failure was defined as persistence of signs and symptoms consistent with infection of the diabetic foot with or without persistent positive cultures, despite antibiotic administration and, when needed, despite proper surgical intervention. Treatment failure was reported at the end of the study period as defined in each RCT.

Statistical analyses were performed using the ''S-PLUS 6.1'' software. Categorical variables were compared by χ^2; a p-value lower than 0.05 was defined to note statistical significance. Pooled odds ratios and 95% confidence intervals (CI) for all primary and secondary outcomes were calculated, by using both the Mantel–Haenszel fixed effects and the DerSimonian–Laird random effects models. For all analyses, results from the fixed effect model (FEM) are presented only when there was no heterogeneity between RCTs; otherwise results from the random effects model (REM) are presented. Egger's test was used for publication bias testing. The heterogeneity between RCTs was assessed by using a χ^2 test; a p-value lower than 0.10 was defined to note statistical significance in the analysis of heterogeneity.

3. Results

Eighteen RCTs were eligible for inclusion in the analysis [9–26]. The main characteristics and treatment failure outcomes for clinically evaluable patients with DFIs of these RCTs are shown in Table 1. Eleven of the RCTs included in the analysis, were designed to study foot infections in diabetic patients. Seven more RCTs studied the effectiveness of two different antibiotic regimens in patients with skin and soft tissue infections (SSTIs) and included also patients with DFIs (only data regarding the subset of patients with DFIs were further analyzed from these RCTs). Antibiotics were administered intravenously (i.v.) at the beginning of therapy in 15 of the included RCTs. Switch to oral therapy was allowed if improvement was reported. Vancomycin was administered to patients when a methicillin-resistant *Staphylococcus aureus* (MRSA) infection was verified.

Table 2 shows the percentage of patients with treatment failure from all RCTs included in the analysis. Treatment failed in 22.7% of all patients with DFIs included in the analyzed RCTs. Data for the comparison of demographic and other baseline characteristics (age, type of diabetes, duration of disease, presence of complications such as peripheral vascular disease or neuropathy) of patients whose treatment failed were not available for analysis. Data on disease severity were not available.

Several comparisons of treatment failure between different antibiotics and/or groups of antibiotics were performed in order to clarify whether specific agents were associated with worse outcomes. There was not heterogeneity among the identified comparisons. Publication bias using the Egger's test was not detected. The administration of penicillins for the treatment of patients with DFIs was associated with statistically significant more treatment failures than the administration of other classes of antibiotics (12 RCTs, FEM, OR = 1.33, 95% CI 1.02–1.74). However, when the RCT that compared linezolid, with or without aztreonam, with aminopenicillins was excluded, the difference was not significant (11 RCTs, FEM, OR = 1.23, 95% CI 0.90–1.67). No significant difference was found between other classes of compared antibiotics: antipseudomonal penicillins versus other antibiotics [8 RCTs, FEM, OR = 1.24, 95% CI 0.90–1.70], piperacillin/tazobactam versus other antibiotics (7 RCTs, FEM, OR = 1.23, 95% CI 0.88–1.72), aminopenicillins versus other antibiotics (5 RCTs, FEM, OR = 1.37, 95% CI 0.93–2.00), carbapenems versus other antibiotics (4 RCTs, FEM, OR = 0.72, 95% CI 0.46–1.11), and fluoroquinolones versus other antibiotics (4 RCTs, FEM, OR = 0.82, 95% CI 0.48–1.40).

As shown in Table 2, the administration of carbapenems was associated with statistically significant fewer treatment failures when all treated patients included in the RCTs were combined. Table 2 also shows that the treatment failure according to the isolated baseline bacteria (including enterococci and *P. aeruginosa*) was 20–25.6%. However, fewer treatment failures were reported for patients with DFIs from

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