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Therapeutic options for *Stenotrophomonas maltophilia* infections beyond co-trimoxazole: a systematic review

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***Background*: *Stenotrophomonas maltophilia* has emerged as an important opportunistic pathogen, causing infections whose management is often problematic due to its inherent resistance to many antibiotics, making co-trimoxazole the main therapeutic option. However, there are cases in which either due to antimicrobial resistance or allergic reactions and intolerance to co-trimoxazole this antibiotic cannot be administered. We sought to evaluate the available clinical evidence regarding potentially effective alternative antibiotics for the treatment of *S. maltophilia* infections.**

***Methods*: The literature search was performed in the PubMed and Scopus databases. The search string used was '*Stenotrophomonas maltophilia* OR *Xanthomonas maltophilia*'.**

***Results*: Thirty-one case reports and 5 case series were retrieved including a total of 49 patients with a variety of infections. Twenty of 49 cases (40.8%) were treated with ciprofloxacin as monotherapy or in combination with other antibiotics; 12 of 49 cases (24.5%) were treated with ceftriaxone- or ceftazidime-based regimens; and 6 of 49 cases (12.2%) were treated with ticarcillin- or ticarcillin/clavulanate-based regimens. The cure or improvement rates were 18 cases (90%), 8 (75%) and 4 (66.7%), respectively. The remaining 11 patients received various antimicrobials including aminoglycoside-based regimens, carbapenems, levofloxacin, chloramphenicol, aztreonam, minocycline and other β-lactams.**

***Conclusions*: The limited available data suggest that ciprofloxacin, ceftazidime or ceftriaxone, and ticarcillin/clavulanate, alone or in combination with other antibiotics, may be considered as alternative options beyond co-trimoxazole.**

Keywords: ciprofloxacin, ceftazidime, ceftriaxone, antimicrobial resistance, ticarcillin/clavulanate, *Xanthomonas*, *Pseudomonas*

Introduction

Stenotrophomonas maltophilia, formerly known as *Pseudomonas* or *Xanthomonas maltophilia*, is an aerobic, glucose non-fermentative, Gram-negative bacillus[1–4] that is frequently isolated from water, soil, animals, plant materials and hospital equipment.[1,5–14] This bacterium is generally considered to be an opportunistic pathogen,[1,2,13–17] causing various infections, including bacteraemia, urinary tract infections, respiratory tract infections, skin and soft tissue infections, endocarditis, meningitis and ocular infections.[2,13,14,17–20] Although *S. maltophilia* causes mainly nosocomial infections,[1,21] community-acquired infections may also occur.[22] It is also commonly isolated from patients with cystic fibrosis.[23,24]

The population at risk consists mainly of immunocompromised patients, including those with haematological malignancies, critical care patients, patients with central venous catheters or other devices and individuals previously treated with broad-spectrum antibiotics.[14–16,20,25–30] Recent reports indicate that the incidence of *S. maltophilia* infections has increased.[14,15,31,32]

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This fact may be attributed to the increase of the patient population at risk, as a result of the widespread use of chemotherapy and broad-spectrum antibiotics and the adoption of more invasive medical practices.[14,30]

The management of *S. maltophilia* infections is often problematic because this pathogen is frequently inherently resistant to multiple antibiotics, including β-lactams, aminoglycosides, carbapenems and quinolones.[16,17,19,33–35] Two inducible β-lactamases, a zinc-containing penicillinase (L1) and a cephalosporinase (L2) are responsible for the high proportion of resistance to β-lactams.[36–39] The presence of an aminoglycoside acetyl-transferase accounts for the resistance to aminoglycosides.[20,40–44] Furthermore, many isolates possess efflux pumps, which are the main determinants of quinolone resistance.[45–47] Other mechanisms of resistance to quinolones may emerge through spontaneous mutations in outer-membrane proteins.[35,43]

From this perspective, co-trimoxazole appears to be an effective treatment for *S. maltophilia* infections, with susceptibility rates over 90% in most settings.[30,48,49] However, strains resistant to this agent have also been reported.[35,50–52] Although the mechanism of resistance to co-trimoxazole is not well understood, it is considered to be mediated by mobile genetic elements, either plasmids or class I integrons.[53–55]

Additionally, allergic reactions or intolerance to co-trimoxazole are not uncommon, which leads to further limitation of the available treatment options. This is mainly attributed to the nitroso metabolite of sulfamethoxazole, which results in the generation of sulfamethoxazole-specific antibodies, as well as to endogenous glutathione and ascorbate deficiency, which are important for the intracellular reduction of the nitroso metabolite.[56–58] Thus, we sought to critically review the literature to identify alternative antibiotic agents that may be used for the treatment of *S. maltophilia* in various settings and types of patients.

Methods

Literature search

Two reviewers (P.-E. V. and D. K. M.) independently searched PubMed (25 January 2008) and Scopus (5 February 2008) to identify and screen potentially eligible articles for inclusion in the review. For articles that could not be retrieved through the first search, additional searches were performed by two other reviewers (P.-R. H. and Y.-T. H). The search string used was '*Stenotrophomonas maltophilia* OR *Xanthomonas maltophilia*'. Reference lists of the retrieved articles were also manually searched for other potentially relevant papers. In case of disagreement between the reviewers, consensus was achieved in meetings including at least three authors.

Study selection and data extraction

An article was considered eligible for inclusion if it fulfilled all of the following criteria: (i) it included patients infected with *S. maltophilia*; (ii) it reported data regarding the antibiotic regimen used, which was other than co-trimoxazole; (iii) it reported administration of antibiotics to which the pathogen was susceptible on the basis of antibiograms; (iv) it reported outcome of infection; and (v) it included patients receiving systemic therapy.

Patients who received co-trimoxazole as part of a combination therapy were excluded. Articles published in languages other than English, French, Spanish, German, Italian and Greek were also excluded, as well as conference articles and animal studies.

Data extracted from the evaluable articles were first author and year of publication, co-morbidities, type of infection, antibiotic used and outcome.

Definitions

The outcome of infection was classified according to the authors' evaluation on each article as recovery, improvement or treatment failure. Death was considered as treatment failure if it was attributed to the infection.

All patients were categorized in four groups regarding the administered antibiotic regimen. Each patient could be included in only one group. The categorization of each patient was decided according to the antimicrobial agent that was considered to be the most potent one based on the data provided in each retrieved article.

Results

In Figure S1 [available as Supplementary data at *JAC* Online (http://jac.oxfordjournals.org/)], we present a flow diagram depicting the process of screening and selection of the articles eligible for inclusion. In total, 1203 potentially relevant articles were identified from the PubMed database, while 908 were identified from the Scopus database; 1974 articles were initially excluded after first screening from title and abstract. One hundred and three articles were secondarily excluded because they did not meet with the inclusion criteria. In total, 2077 studies were excluded. Finally, 34 studies were selected for further evaluation and are presented in Tables S1 and S2 [available as Supplementary data at *JAC* Online (http://jac.oxfordjournals.org/)].

Case reports and case series

Of the total 34 selected studies, 29 are case reports, while the remaining 5 are case series. The main characteristics of the included case reports (first author, year of publication, sex and age of the patients, co-morbidities, type of infection, antibiotic treatment and outcome) are presented in Table S1. A total of 31 cases were retrieved; 63% (19/30) of the patients were men. The median age of the patients was 52 years (range 0–80). A summary of the evidence of the published case series regarding alternative treatment for *S. maltophilia* infections is presented in Table S2. Five case series with a total of 18 patients were retrieved. Specific data regarding each patient separately were not reported in the majority of the case series.

Twenty of the 49 cases (40.8%) included in the case reports and case series were treated with ciprofloxacin as monotherapy or in combination with other antibiotics: ceftazidime in 2 cases[59,60] (10%), ceftazidime/gentamicin in 3 cases[60,61] (15%), amikacin in 2 cases[62,63] (10%), ticarcillin/clavulanate in 2 cases[10,64] (10%) and, finally, piperacillin[65], tobramycin[59] and chloramphenicol[66] in 1 case each (5%). In the remaining eight cases,[5–12] ciprofloxacin was used as monotherapy (40%). Among these patients, 17 were cured (85%), 2 patients receiving combination treatment with amikacin died due to the infection (10%) and 1 patient receiving ciprofloxacin combined with ceftazidime and gentamicin improved (5%).

Twelve of the 49 cases (24.5%) were treated with ceftriaxone or ceftazidime as monotherapy or in combination with other antibiotics. Six patients received these drugs as monotherapy[60,63,67–70] (50%). In the remaining patients, these agents were combined with netilmicin in two cases[60,71] (16.7%), with amikacin[61] or ampicillin[60] in one case each (8.3%), while in one case both ceftriaxone and ceftazidime were used and combined with tobramycin.[6] Finally, one patient received ceftazidime both intravenously and as 'locked-in' therapy along with ciprofloxacin.[72] Six patients were cured (50%), two patients died (16.7%), two improved (16.7%), one patient developed recurrent peritonitis (8.3%) due to opportunistic pathogens and one developed fungal peritonitis and died 6 weeks later.

Six of the 49 cases (12.2%) were treated with ticarcillin or ticarcillin/clavulanate as monotherapy or in combination with other agents. Ticarcillin was co-administered with tobramycin in one case, which was cured.[14] Ticarcillin/clavulanate was combined with teicoplanin[73] or amikacin[74] in one case each (16.7%). The remaining three of five patients received ticarcillin/clavulanate monotherapy[63] (60%). In three cases, the infection was successfully treated (60%). One patient who received ticarcillin/clavulanate combined with amikacin improved (20%), but died due to the underlying disease and one patient treated with ticarcillin/clavulanate as monotherapy died of infection (20%).

Other therapeutic options included levofloxacin,[75] meropenem,[76] gentamicin alone[77] or combined with piperacillin/tazobactam[78] or chloramphenicol,[79] cefozopran with isepamicin,[80] aztreonam with amoxicillin/clavulanate,[81] minocycline,[82] cefoperazone,[14] imipenem with amikacin[14] and, finally, chloramphenicol plus sulfadimidine.[83] Except for one case treated with imipenem and amikacin in which the treatment failed and another one treated with cefozopran plus isepamicin in which the patient improved, all other patients were cured.

Discussion

The findings of our review suggest that, when the administration of co-trimoxazole for the treatment of patients with *S. maltophilia* infections is not possible, there may be other effective alternative treatments that can be used, namely ciprofloxacin as monotherapy or in combination with other antibiotics, or ceftazidime/ceftriaxone and ticarcillin/clavulanate alone or in combination with other agents. Clinical success rates after the administration of these alternative treatments range from 66.7% to 85% in the limited number of reported cases.

Co-trimoxazole remains the most effective agent against *S. maltophilia* infections, exhibiting more than 90% susceptibility *in vitro*.[30,48,49] Clinical data suggest that co-trimoxazole should be the treatment of choice, despite the reports of emergence of resistance.[50–52] The triple combination of co-trimoxazole, rifampicin and carbenicillin has *in vitro* synergy, but clinical experience is scant.[84] A combination treatment with co-trimoxazole, minocycline and ticarcillin/clavulanate has also been suggested.[52] The combination of co-trimoxazole with either ticarcillin/clavulanate or with a third-generation cephalosporin should be considered when a neutropenic or a seriously ill patient is to be treated.[30] These combinations exhibit *in vitro* synergy whether the isolated pathogens are susceptible to each studied agent or not.[85] However, clinical trials are necessary in order to evaluate the possible correlation of *in vitro* data and the results of therapy in animal models with the infection outcomes in humans. As with other important pathogens, the susceptibility patterns of *S. maltophilia* isolates in each particular population/setting should be taken into consideration when selecting treatment.

It is notable that ciprofloxacin and ceftazidime or ceftriaxone, which were the agents used in the majority of cases, were often administered as monotherapy, with clinical success rates of 100% for ciprofloxacin and 66.7% for ceftazidime or ceftriaxone, proportions that should be interpreted with caution given the limited reported experience. However, *S. maltophilia* has resistance mechanisms for both classes of these antibiotics. Ceftazidime may be inhibited by the production of β-lactamases, as well as by efflux pumps, which reduce the intracellular concentration of the drug. Resistance to quinolones can also be quickly developed by mutations in outer-membrane proteins or via target-site mutation in DNA gyrase.[86] The choice of monotherapy or combination therapy is a controversial issue. Several authors[1,30,33,52,87] suggest that the probability for the emergence of resistance during treatment warrants the consideration of administering antibiotic combinations, especially in neutropenic or immunocompromised patients, who represent the majority of patients at risk.[30,85,88,89] However, treatment recommendations are mainly based on case reports, case series and *in vitro* susceptibility studies.

In keeping with our findings, there are reports suggesting that quinolones are indicated when there is documentation of resistance or allergy to co-trimoxazole.[90] According to some *in vitro* studies, moxifloxacin is considered as an effective agent against which low rates of resistance are reported.[91–93] A promising alternative regimen seems to be the combination of moxifloxacin with ticarcillin/clavulanate.[94] However, as we have emphasized, clinical trials evaluating the effectiveness of alternative drugs are warranted.

It should be noted that, as co-trimoxazole remains the drug of choice for *S. maltophilia* infections, some authors suggest that desensitization to co-trimoxazole should be attempted in patients with hypersensitivity to the agent.[95] Landrum *et al.*[96] reported a case of osteomyelitis successfully treated with a combination of co-trimoxazole after desensitization and ticarcillin/clavulanate. Also, Yilmaz *et al.*[95] reported a case of successful management of recurrent cholangitis with co-trimoxazole after desensitization. Data regarding this therapeutic strategy are lacking. However, it should be considered in critically ill patients hypersensitive to co-trimoxazole, especially when other antibiotic regimens have failed.

A common clinical manifestation of *S. maltophilia* infection is bacteraemia, which usually occurs in the setting of serious co-morbidities, including neutropenia and immunosuppression. Bacteraemia is often catheter-associated. Data suggest that catheter removal is important for a favourable outcome.[15,97] Furthermore, especially for cases with bacteraemia, combination therapy with antimicrobials to which the pathogen is susceptible may be considered.[90] When co-trimoxazole cannot be used, administration of ciprofloxacin combined with ticarcillin/clavulanate or ceftazidime may be effective.

S. maltophilia pneumonia is usually ventilator-associated or occurs in neutropenic or immunocompromised patients. Data suggest that treatment recommendations as outlined for bacteraemia are appropriate.[90] Ciprofloxacin-based regimens, ticarcillin/clavulanate or ceftazidime should be considered, taking into account the susceptibility of the isolated pathogen. However, the

majority of patients with positive cultures from the respiratory tract are probably colonized rather than infected.[98,99] Colonization of the respiratory tract may commonly occur in patients with cystic fibrosis or tracheostomy, patients receiving mechanical ventilation and, finally, patients with prolonged stay in critical care units or prolonged exposure to antibiotics.[44,100,101] However, although there are no data to support the need to treat patients colonized with *S. maltophilia*, there is evidence of mortality directly attributed to *S. maltophilia* infections, supporting the need for careful treatment of such infections.[100,102]

The main limitation of our review is that data are provided only from case reports and case series. Clinical trials regarding alternative therapeutic options for *S. maltophilia* infections are not available. Additionally, in the articles reviewed, a variety of antimicrobials were used either as monotherapy or in combination, due to the absence of specific guidelines for the management of *S. maltophilia* infections. Furthermore, there may be a publication bias with regard to the effectiveness of the administered antimicrobials, as case reports presenting a failure of treatment with these agents would be less likely to be published.

In conclusion, *S. maltophilia* has emerged as an important opportunistic pathogen, whose eradication is often problematic due to its inherent resistance to many antibiotics and its increased resistance rates against co-trimoxazole, which is the main therapeutic option. Ciprofloxacin, ceftazidime or ceftriaxone, and ticarcillin/clavulanate, alone or in combination with other antibiotics, may be considered as alternative options, beyond co-trimoxazole. However, clinical trials on this important clinical question are lacking and additional published experience will help in formulating the best evidence-based approach for the treatment of patients with *S. maltophilia* infections when co-trimoxazole cannot be used.

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Transparency declarations

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Supplementary data

Figure S1 and Tables S1 and S2 are available as Supplementary data at *JAC* Online (http://jac.oxfordjournals.org/).

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