Stenotrophomonas, Achromobacter, and Nonmelioid Burkholderia Species: Antimicrobial Resistance and Therapeutic Strategies

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Abstract

Stenotrophomonas maltophilia, Achromobacter xylosoxidans, and nonmelioid Burkholderia species, namely, Burkholderia cepacia complex, collectively are a group of troublesome nonfermenters. Although not inherently virulent organisms, these environmental Gram negatives can complicate treatment in those who are immunocompromised, critically ill in the intensive care unit and those patients with suppurative lung disease, such as cystic fibrosis. Through a range of intrinsic antimicrobial resistance mechanisms, virulence factors, and the ability to survive in biofilms, these opportunistic pathogens are well suited to persist, both in the environment and the host. Treatment recommendations are hindered by the difficulties in laboratory identification, the lack of reproducibility of antimicrobial susceptibility testing, the lack of clinical breakpoints, and the absence of clinical outcome data. Despite trimethoprim–sulfamethoxazole often being the mainstay of treatment, resistance is widely encountered, and alternative regimens, including combination therapy, are often used. This review will highlight the important aspects and unique challenges that these three nonfermenters pose, and, in the absence of clinical outcome data, our therapeutic recommendations will be based on reported antimicrobial susceptibility and pharmacokinetic/pharmacodynamic profiles.

Keywords

► antimicrobial resistance
► nonfermenting Gram-negative bacteria
► biofilm
► cystic fibrosis
► immunocompromised patient
► intensive care unit
► antimicrobial susceptibility testing

Classification and Taxonomy

The taxonomy of this group of organisms continues to change as more information is gathered (see – Fig. 1). Stenotrophomonas maltophilia was originally classified within the genus Pseudomonas, but it was reassigned to the Gammaproteobacteria class, initially within the genus Xanthomonas, and subsequently moved to Stenotrophomonas with seven other named species. Genomic subtyping among S. maltophilia isolates demonstrates remarkable diversity suggesting that
S. maltophilia may represent a “complex” of species. The Burkholderia genus, also originally of the genus Pseudomonas, contains more than 60 species and is found within the Betaproteobacteria class and Burkholderiales order. B. cepacia is referred to as a “complex” as it contains at least 17 genetically related species, formally designated as numbered genomovars (see Table 1). B. multivorans (genomovar II) and B. cenocepacia (genomovar III) are the most commonly identified and clinically relevant species within the complex. B. cenocepacia is further split into four phylogenetic lineages (IIIA, IIIB, IIIC, and IID) based on the polymorphism of the recA gene. In CF, patients colonized with B. cenocepacia, especially lineage IIIB, have a higher mortality following lung transplantation. A. xylosoxidans is similarly classified within the Burkholderiales order, but within the Alcaligenaceae family. Although previously assigned to the Alcaligenes genus, A. xylosoxidans now remains the type species within the Achromobacter genus, together with six other named species and multiple genogroups.

Epidemiology, Transmission, and Clinical Significance

Stenotrophomonas, Burkholderia, and Achromobacter species are all ubiquitous environmental organisms found in water, soil, the rhizosphere, and in and on plants. They have a worldwide distribution. SENTRY data from 1997 to 2003 identified 221,084 bacterial isolates, including 11.5% that were nonenteric GNB, of which Stenotrophomonas and Achromobacter species accounted for the majority (82.7%). Of the remaining nonenteric GNB isolated, 3,509 isolates were analyzed, of which S. maltophilia accounted for 59.2%, B. cepacia complex 7.7%, and Achromobacter species 6.7%. Amongst cancer patients at the MD Anderson Cancer Centre, the incidence of S. maltophilia had increased over time, accounting for the 5th most common Gram-negative bacterial isolate. In tropical Australia, bacteremia cases from 2000 to 2010 (over 4,500 cases), S. maltophilia accounted for 1.6% of cases; Achromobacter species 0.2%; and B. cepacia complex was not identified.

Beyond Human Pathogens

B. cepacia complex, S. maltophilia, and A. xylosoxidans share many beneficial environmental effects (see Fig. 2), although B. cepacia complex is recognized as a pathogen of onions. These organisms produce antimicrobial compounds that protect plants, cause disease in nematodes, and generate factors that promote plant growth. They also have the ability to degrade a wide variety of compounds, including pollutants and heavy metals, enabling these organisms to be effective.
agents of soil bioremediation and phytoremediation.\textsuperscript{31–33} However, the concern to human health is whether the agricultural use of these organisms may present a risk as reservoirs for antibiotic resistance genes. Their ability to multiply in the soil and rhizosphere of plants may be reason enough to consider restricting plants from high-risk patient groups within hospitals (e.g., immunocompromised or CF wards).\textsuperscript{34–36}

### Identification and Antibiotic Susceptibility Testing

All three organisms have similar growth requirements, can have a similar appearance on standard media, and all can be potentially misidentified as each other and as \textit{Pseudomonas} species. Table 2 outlines the basic microbiological characteristics of these organisms. Automated identification using

<table>
<thead>
<tr>
<th>Species</th>
<th>Former designation</th>
<th>Reported sources</th>
</tr>
</thead>
<tbody>
<tr>
<td>\textit{B. cepacia}</td>
<td>Genovar I</td>
<td>Infections in CF and non-CF patients\textsuperscript{b} Environment: soil, rhizosphere, plant, and river water Bioremediation and biocontrol agent</td>
</tr>
<tr>
<td>\textit{B. multivorans}</td>
<td>Genovar II</td>
<td>Infections in CF and non-CF patients Environment: soil, rhizosphere, plant, river water, and contaminant</td>
</tr>
<tr>
<td>\textit{B. cenocepacia}</td>
<td>Genovar III (four lineages, A–D)</td>
<td>Infections in CF and non-CF patients Environment: soil, rhizosphere, plant, river water, and industrial contaminant Biocontrol agent</td>
</tr>
<tr>
<td>\textit{B. stabiliz}</td>
<td>Genovar IV</td>
<td>Infections in CF and non-CF patients Environment: plant, hospital contaminant</td>
</tr>
<tr>
<td>\textit{B. vietnamiensis}</td>
<td>Genovar V</td>
<td>Infections in CF and non-CF patients Environment: soil, rhizosphere, plant, river water, and industrial contaminant Biocontrol agent</td>
</tr>
<tr>
<td>\textit{B. dolosa}</td>
<td>Genovar VI</td>
<td>Infections in CF patients only Environment: rhizosphere, plant</td>
</tr>
<tr>
<td>\textit{B. ambifaria}</td>
<td>Genovar VII</td>
<td>Infections in CF and non-CF patients Environment: soil, rhizosphere Biocontrol agent</td>
</tr>
<tr>
<td>\textit{B. anthina}</td>
<td>Genovar VIII</td>
<td>Infections in CF, non-CF patients and turtles Environment: soil, rhizosphere, river water, and hospital contaminant</td>
</tr>
<tr>
<td>\textit{B. pyrrocinia}</td>
<td>Genovar IX</td>
<td>Infections in CF patients only Environment: soil, rhizosphere, and river water Biocontrol agent</td>
</tr>
<tr>
<td>\textit{B. ubonensis}</td>
<td>Genovar X</td>
<td>Infections in non-CF patients only Environment: soil</td>
</tr>
<tr>
<td>\textit{B. latens}</td>
<td>BCC1</td>
<td>Infections in CF patients only</td>
</tr>
<tr>
<td>\textit{B. diffusa}</td>
<td>BCC2</td>
<td>Infections in CF and non-CF patients Environment: soil and water</td>
</tr>
<tr>
<td>\textit{B. arboris}</td>
<td>BCC3</td>
<td>Infections in CF and non-CF patients Environment: soil rhizosphere, plant, river water, and industrial contaminant</td>
</tr>
<tr>
<td>\textit{B. seminalis}</td>
<td>BCC7</td>
<td>Infections in CF and non-CF patients Environment: soil rhizosphere, plant</td>
</tr>
<tr>
<td>\textit{B. metallica}</td>
<td>BCC8</td>
<td>Infections in CF patients only</td>
</tr>
<tr>
<td>\textit{B. contaminans}</td>
<td>Group K (BCC AT)</td>
<td>Infections in CF patients and sheep Environment: plant</td>
</tr>
<tr>
<td>\textit{B. lata}</td>
<td>Group K</td>
<td>Infections in CF and non-CF patients Environment: forest soil, rhizosphere, plant, river water, and contaminant</td>
</tr>
</tbody>
</table>

Abbreviation: CF, cystic fibrosis.
\textsuperscript{a}Adapted with permission from Sousa et al.,\textsuperscript{3} Vandamme and Dawyndt,\textsuperscript{78} and Drevinek and Mahenthiralingam.\textsuperscript{79}
\textsuperscript{b}Infections in non-CF patients include reports in immunocompromised patients (malignancy, HIV, and chronic granulomatous disease), immunocompetent individuals (chronic suppurative otitis media, pharyngeal infections, and pediatric neck infections), and hospital-acquired infections in patients with comorbidities (chronic hemodialysis, diabetes mellitus, and congestive heart failure) or those undergoing interventions (prolonged stay in intensive care units, use of central venous catheters, indwelling urinary catheters, and endotracheal tubes) or in the setting of a nosocomial outbreak.
biochemical differentiation (such as API 20 NE [bioMérieux, Marcy l’Etoile, France] and Vitek-2 [bioMérieux, Marcy l’Etoile, France]) can demonstrate low discrimination and misidentifications, especially with CF patient samples.

Modern laboratory identification techniques, such as matrix-assisted laser desorption ionization, time-of-flight mass spectrometry (MALDI-TOF MS) appears to identify and discriminate these organisms well, even with specimens from CF patients. The ability for current versions of MALDI-TOF MS instruments to routinely discriminate between the species within the B. cepacia complex requires further work, but importantly does appear to accurately identify B. cenocepacia. When compared with polymerase chain reaction–restriction fragment length polymorphism (PCR-RFLP) analysis of the recA gene, the Microflex LT MALDI-TOF (Bruker Daltonics GmbH, Leipzig, Germany), under the control of the FlexControl 3.0 software (Bruker Daltonics GmbH) and analyzed by Biotyper 2.0 software (Bruker Daltronics GmbH), produced corresponding discriminatory results, although only the PCR-RFLP method provided a fine discrimination into two lineages (IIIA and IIIB).

A remarkable feature common to these three organisms is the vast array of intrinsic and acquired mechanisms of antibiotic resistance. Intrinsic β-lactamases, a wide range of efflux pump systems, enzymatic modifications, changes in the outer membrane and target site modification are just several of the mechanisms harbored by these organisms. Table 3 outlines these mechanisms in more detail, which may or may not be present in every isolate. Importantly, however, is the ability of these organisms to acquire new resistance determinants (e.g., Sul1 integron that causes trimethoprim–sulfamethoxazole resistance in S. maltophilia) and to rapidly induce resistance (e.g., with the use of fluoroquinolones).

Intrinsic antibiotic resistance patterns in S. maltophilia, B. cepacia complex, and A. xylosoxidans are important for physicians to consider when deciding on empiric therapy. Furthermore, this information assists clinical microbiology laboratories with antibiotic susceptibility testing and the...
Table 3  Mechanisms of antibiotic resistance

<table>
<thead>
<tr>
<th>Organism</th>
<th>Category</th>
<th>Resistance mechanism</th>
<th>Antimicrobial affected</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>S. maltophilia</em></td>
<td>β-lactamaes</td>
<td>Two chromosomal inducible β-lactamases - L1 (class B) MBL; L2 (class A) serine Plasmid ESBL - TEM-2 penicillinase; CTX-M</td>
<td>Hydrolyses all β-lactams</td>
</tr>
<tr>
<td></td>
<td>Efflux systems</td>
<td>Multidrug efflux systems - SmeDEF; SmeABC; SmrA</td>
<td>Resistance to tetracycline class, chloramphenicol, erythromycin and fluoroquinolone class</td>
</tr>
<tr>
<td></td>
<td>Enzymatic modification</td>
<td>Aminoglycoside-modifying enzymes Smqnr topoisomerase enzyme</td>
<td>Resistance to aminoglycosides and low level intrinsic quinolones</td>
</tr>
<tr>
<td></td>
<td>Changes in the outer membrane</td>
<td>Phosphoglucomutase (SpgM)</td>
<td>Aminoglycosides, polymyxin B and fluoroquinolones</td>
</tr>
<tr>
<td></td>
<td>Target site modification</td>
<td>Protect DNA gyrase and topoisomerases (Smqnr); Class 1 integrons (Sul1 and Sul2)</td>
<td>Resistance to fluoroquinolones; resistance to TMP-SMX</td>
</tr>
<tr>
<td><em>B. cepacia</em> complex</td>
<td>β-lactamases</td>
<td>Chromosomal, inducible Ambler class C (PenA); plus others (Ambler class A + D)</td>
<td>β-lactams</td>
</tr>
<tr>
<td></td>
<td>Efflux systems</td>
<td>RND family efflux transporter</td>
<td>Aminoglycosides, ciprofloxacin, trimethoprim, chloramphenicol</td>
</tr>
<tr>
<td></td>
<td>Enzymatic modification</td>
<td>Aminoglycoside-modifying enzymes; Dihydrofolate reductase</td>
<td>Resistance to aminoglycosides, trimethoprim</td>
</tr>
<tr>
<td></td>
<td>Changes in outer membrane</td>
<td>Lack of binding sites on the lipopolysaccharide layer</td>
<td>Intrinsic resistance to the cationic antimicrobials, polymyxins, and aminoglycosides</td>
</tr>
<tr>
<td></td>
<td>Altered target site</td>
<td>Change in penicillin binding proteins; Mutations in the quinolone resistance-determining region, QRDR (gyrA and parC)</td>
<td>β-lactams; fluoroquinolones</td>
</tr>
<tr>
<td><em>A. xylosoxidans</em></td>
<td>β-lactamases</td>
<td>Intrinsic OXA114, OXA243, and OXA2; Cephalosporinase, blaampC; Acquired carbapenemases (blaam)</td>
<td>β-lactams</td>
</tr>
<tr>
<td></td>
<td>Efflux systems</td>
<td>RNA-type multidrug efflux pumps; AxyABM and AxyXY-OpRZ</td>
<td>Decreased MICs of cephalosporins (except cefepime), aztreonam, fluoroquinolones, chloramphenicol. In innate aminoglycoside resistance and extrudes cefepime, carbapenems, some fluoroquinolones, tetracyclines, and erythromycin</td>
</tr>
<tr>
<td></td>
<td>Enzymatic modification</td>
<td>Aminoglycoside modifying enzymes, AAC(6′)-Ib and aadA1</td>
<td>Aminoglycosides</td>
</tr>
</tbody>
</table>

Abbreviations: ESBL, extended spectrum β-lactamase; MBL, metallo β-lactamase; RND, resistance nodulation division; TMP-SMX, trimethoprim-sulfamethoxazole.
reporting of results (see Table 4). There are subtle differences between intrinsic resistance reports by Clinical and Laboratory Standards Institute (CLSI; M100-S24, appendix B.2) and European Committee on Antimicrobial Susceptibility Testing (EUCAST) and for A. xylosoxidans there is only limited guidance from EUCAST alone, with additional information gathered from other reports in the literature. Clinical breakpoints are limited for these three organisms. It should also be noted that clinical breakpoints provided are based on achievable blood levels of antimicrobials, which may not reflect what can be achieved in the lung, especially in the setting of aerosolized antimicrobials. EUCAST provides clinical breakpoints only for S. maltophilia and only for trimethoprim–sulfamethoxazole. Caution is required in the interpretation of trimethoprim–sulfamethoxazole susceptibility testing by disc diffusion or by a gradient strip method (e.g., Etest [bioMérieux, Marcy l’Etoile, France]) as results should be read at 80% inhibition given the bacteriostatic action of the antibiotic causing a leading edge of growth. EUCAST state that results for other agents should be treated with caution given the lack of data to support a relationship between susceptibility and clinical outcome. CLSI recommends first-line reporting of trimethoprim–sulfamethoxazole, and second line reporting of ticarcillin–clavulanate, ceftazidime, minocycline, levofloxacin, and chloramphenicol. It should be noted that EUCAST considers S. maltophilia to be intrinsically resistant to ceftazidime.

CLSI provides clinical breakpoints for B. cepacia complex and recommends first-line testing of trimethoprim–sulfamethoxazole, and second line testing of ticarcillin–clavulanate, ceftazidime, meropenem, minocycline, levofloxacin, and chloramphenicol. In contrast, EUCAST recently tried to address their lack of clinical breakpoints for B. cepacia complex, however, determined that there was no evidence to describe a relationship for minimum inhibitory concentration (MIC) and outcome, and were unable to provide guidance. They describe the MIC distributions for relevant antimicrobials to be wide and that susceptibility testing was not reproducible using a routine methodology (i.e., MIC determination by the gradient strip method). A Cochrane review in September 2012 also concluded with similar findings, highlighting that they did not find any randomized controlled trials that compared treatments for exacerbations in CF patients who were infected with B. cepacia complex. They concluded that no conclusions could be drawn from their review and clinicians should continue to assess each patient individually, taking into account in vitro antibiotic susceptibility data, previous clinical responses and their own experience. It should be noted that EUCAST consider B. cepacia complex to be intrinsically resistant to ticarcillin–clavulanate but not piperacillin–tazobactam, while in comparison, CLSI reports intrinsic resistance to piperacillin–tazobactam, do not list ticarcillin–clavulanate in their intrinsic resistance appendix, and do provide clinical breakpoints.
### Table 5 Invitro antimicrobial susceptibility

<table>
<thead>
<tr>
<th></th>
<th><strong>S. maltophilia</strong></th>
<th><strong>B. cepacia complex</strong></th>
<th><strong>A. xylosoxidans</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sens.</strong></td>
<td><strong>Details</strong></td>
<td><strong>Sens.</strong></td>
<td><strong>Details</strong></td>
</tr>
<tr>
<td>Trimethoprim-sulfamethoxazole</td>
<td>34.4 to &gt;90%</td>
<td><strong>Increased resistance in CF population.</strong></td>
<td>0–92%</td>
</tr>
<tr>
<td>Ticarcillin–clavulanate/Piperacillin–tazobactam</td>
<td>11.5 to &gt;70%</td>
<td><strong>Variable rates between drugs. EUCAST reports intrinsic resistance for ticarcillin–clavulanate.</strong></td>
<td>40–100%</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>0–53%</td>
<td><strong>Other cephalosporins resistant.</strong></td>
<td>45–84.7%</td>
</tr>
<tr>
<td>Meropenem</td>
<td>–</td>
<td><strong>Minimal activity of imipenem or doripenem. Ertapenem not active.</strong></td>
<td>52–100%</td>
</tr>
<tr>
<td>Fluoroquinolone class</td>
<td>45–95%</td>
<td><strong>Variable activity; resistance can be readily induced. EUCAST report intrinsic resistance to ciprofloxacin.</strong></td>
<td>–</td>
</tr>
<tr>
<td>Minocycline/Tigecycline</td>
<td>66.7–100%</td>
<td><strong>Tigecycline has poor activity due to drug efflux.</strong></td>
<td>44–51%</td>
</tr>
<tr>
<td>Colistin</td>
<td>37.5–79%</td>
<td><strong>Intrinsic resistance reported</strong></td>
<td>28–70.1%</td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>11.5–82%</td>
<td><strong>Intrinsic resistance reported</strong></td>
<td>22–81.2%</td>
</tr>
</tbody>
</table>

**Abbreviations:** CF, cystic fibrosis; CLSI, Clinical and Laboratory Standards Institute; EUCAST, European Committee on Antimicrobial Susceptibility Testing; TMP, trimethoprim.
Relating to *A. xylosoxidans*, EUCAST does not provide specific guidance beyond their nonspecies-related breakpoints. CLSI provides clinical breakpoints under the section “Other Non-Enterobacteriaceae,” although their specific relevance to *A. xylosoxidans* is debatable.

**Management of Infections**

The first challenge regarding management is to establish the clinical significance of culturing one of these nonfermenters from a clinical specimen. This question is largely irrelevant if these organisms are identified from sterile sites (e.g., cerebrospinal fluid, blood, and joint aspiration), but when they are identified either alone or with other organisms from nonsterile sites (e.g., sputum, wound swabs, and urine cultures), their role in disease may be difficult to ascertain. However, the repeated isolation of these organisms in the context of clinical disease or in unwell patients, antimicrobial therapy directed against these nonfermenters is often warranted. For example, *A. xylosoxidans* can cause a level of inflammation similar to *P. aeruginosa* in chronically infected CF patients and therefore should be treated accordingly.50

Recommendations on specific antibiotic agents for treatment are difficult given the lack of reproducible susceptibility results and minimal clinical data. The fact that these organisms are also frequently part of a mixed infection, especially when it comes to pulmonary involvement, adds to the complexity of management. Reported rates of in vitro antibiotic resistance are very broad depending on patient type and location (see Table 5). In general, isolates from CF patients demonstrate higher rates of resistance than those found in other patient groups.

The suggested first- and second-line agents for treatment, as well as combination therapy options are outlined in Table 6. Individual susceptibility results, patient allergy, and other concurrent conditions will also influence the choice of agent.

**S. maltophilia**

Trimethoprim–sulfamethoxazole remains the first-line therapy for *S. maltophilia*. On the basis of in vitro pharmacodynamics modelling and the bacteriostatic action of trimethoprim–sulfamethoxazole, it is recommended that a higher dose be used (daily dose of 15 mg per kg of the trimethoprim component, split 6 to 8 hourly)51,52 which is more similar to the dose chosen for the treatment of *Pneumocystis jirovecii* pneumonia. In the setting of trimethoprim–sulfamethoxazole resistance, second line agents are available and are often used in combination (see Table 6).53 *S. maltophilia* is inherently resistant to carbapenems, and in fact, use of this class of antibiotic often selects for *S. maltophilia* in patients who are heavily immunosuppressed (e.g.,

<table>
<thead>
<tr>
<th>Organism</th>
<th>First line</th>
<th>Second line</th>
<th>Combination</th>
<th>Alternative combination</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>S. maltophilia</em></td>
<td>Trimethoprim–sulfamethoxazole</td>
<td>Moxifloxacin/levofloxacin</td>
<td>Trimethoprim–sulfamethoxazole PLUS Any 2nd line agent, or ceftazidime</td>
<td>Ticarcillin–clavulanate PLUS Aztreonam PLUS Moxifloxacin/levofloxacin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ticarcillin–clavulanate</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>B. cepacia complex</em></td>
<td>Trimethoprim–sulfamethoxazole Ceftazidime Meropenem</td>
<td>Minocycline Chloramphenicol Ciprofloxacin³</td>
<td>Combination of any 1st line or 2nd line agents</td>
<td>Meropenem PLUS Ceftazidime PLUS Ciprofloxacin PLUS Minocycline, or amikacin PLUS Tobramycin (inhaled)³</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Piperacillin–tazobactam Ticarcillin–clavulanate</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>A. xylosoxidans</em></td>
<td>Piperacillin–tazobactam Meropenem</td>
<td>Ceftazidime Minocycline</td>
<td>Meropenem PLUS Ciprofloxacin/levofloxacin⁴</td>
<td>Meropenem PLUS Minocycline, or levofloxacin⁴ PLUS Chloramphenicol PLUS Colistin (inhaled)⁴</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Meropenem</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Caution should be applied with the use of tigecycline given the 2010 and 2013 US FDA drug safety communications warning not to use tigecycline in pulmonary infections, especially hospital-acquired and ventilator-associated pneumonia, because of increased mortality risk.⁵⁷,⁵⁸* 
*EUCAST report *B. cepacia* complex to be intrinsically resistant to ciprofloxacin.⁵⁹* 
*Inhaled antibiotics have been recommended primarily in pulmonary exacerbations of CF.⁶⁰* 
*Use of newer fluoroquinolones are preferred when used in combination, in preference to ciprofloxacin, given the greater invitro activity,¹³ although intrinsic resistance and poor activity is widely reported across the class.²⁹*
neutropenic patients). The inclusion of a specific biofilm active agent, such as moxifloxacin or levofloxacin has also been shown to be of benefit, although caution should be applied when used as monotherapy because of the risk of rapid induction of resistance. Minocycline and tigecycline have also shown some promise to assist with the treatment of S. maltophilia. The evidence for combination therapy often comes from in vitro synergy testing data, and highlights the need for further research into optimal therapy for this troublesome organism. The combinations are often reported involving trimethoprim–sulfamethoxazole, ticarcillin–clavulanate, moxifloxacin, levofloxacin, aztreonam, ceftazidime, colistin, rifampicin, tigecycline, and minocycline.

**B. cepacia Complex**

Similar principles apply as for treatment of S. maltophilia. Trimethoprim–sulfamethoxazole remains a recommended first-line therapy. Higher dosing schedules (15 mg per kg of the trimethoprim component, split 6 to 8 hourly) has again been recommended based on pharmacokinetic and pharmacodynamics data in the critically ill, as well as extrapolated data from B. pseudomallei, the pathogen causing melioidosis. In contrast to S. maltophilia, B. cepacia complex are often sensitive to meropenem, which is another first-line therapy, but are inherently resistant to polymyxin and colistin. Tigecycline demonstrates poor activity against B. cepacia complex owing to drug efflux, although minocycline maintains activity. Combination therapy is often used for patients who are more severely unwell, and includes double and triple combinations of first- and second-line agents (see Table 6). The main alternative therapeutic agents beyond trimethoprim–sulfamethoxazole include ceftazidime and meropenem, either alone or in combination, or with other antimicrobial agents. The role of penicillins, namely, piperacillin–tazobactam and ticarcillin–clavulanate remains controversial given the different intrinsic resistance reports between EUCAST and CLSI, as previously mentioned. Inhaled tobramycin has the potential to achieve high pulmonary concentrations to inhibit B. cepacia isolates, despite widespread resistance reported. As mentioned, CF patients proceeding to lung transplantation, who are colonized or infected with B. cepacia complex (particularly with B. cenocepacia) are at high risk for a poor outcome, manifested by an overwhelming “cephac syndrome.” The highest risk for this is within 3 months following transplant and many lung transplant centers around the world have B. cenocepacia as an absolute contraindication to transplant. If transplantation is performed in the setting of B. cepacia complex colonization or infection, aggressive combination (double and triple) therapy is often used perioperatively.

**A. xylosoxidans**

Less is known about the optimal therapy for *Achromobacter* spp. In addition to the recognized intrinsic antibiotic resistance patterns, acquired resistance is also widely reported. Given the limitations of the clinical microbiology laboratory to interpret antimicrobial susceptibility results, close communication between the treating doctors and the laboratory is required. The most active agents are piperacillin–tazobactam, meropenem, and trimethoprim–sulfamethoxazole, whereas ceftazidime is more active than cefepime. Tetracyclines (e.g., minocycline) have variable activity and may be vulnerable to a multidrug efflux pump. Although specifically for tigecycline, an MIC of 4 μg/mL has been reported in CF patients, suggesting *Achromobacter* to be a poor target for therapy with tigecycline. Aminoglycosides, fluoroquinolones, fosfomycin, and aztreonam all have poor activity. Multidrug-resistant phenotypes and carbapenemase-producing isolates have been reported, especially for the CF patient population, further complicating therapeutic options. Combination therapy has been recommended for the treatment of *A. xylosoxidans* pulmonary exacerbations in CF. Although the use of concurrent inhaled antibiotics, such as inhaled colistin, could also be considered.

**Conclusions**

*S. maltophilia*, *B. cepacia* complex, and *A. xylosoxidans* are remarkable organisms with the ability to live and thrive in hostile environments, including withstanding antibiotic treatment. The widespread use of fluoroquinolones, aminoglycosides, and broad-spectrum β-lactam antimicrobials has created the perfect niche for these opportunistic pathogens. Infection with *Pseudomonas* species, interspecies quorum-sensing and survival within biofilms create unique therapeutic challenges. Successful treatment requires a greater understanding of the clinical consequences of infections with these organisms, together with their innate microbiological characteristics and antimicrobial resistance patterns. At this stage, more clinical data are required to assist with treatment recommendations, and future research should focus on the role of combination therapy.

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**References**


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