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

Iain J. Abbott, MBBS[1]   Anton Y. Peleg, MBBS, PhD, MPH, FRACP[2,3]

[1] Victorian Infectious Diseases Reference Laboratory, Peter Doherty Institute, Victoria, Australia
[2] Department of Infectious Diseases, The Alfred Hospital, Victoria, Australia
[3] Department of Microbiology, Monash University, Clayton, Victoria, Australia

Address for correspondence Iain J. Abbott, MBBS, Victorian Infectious Diseases Reference Laboratory, Doherty Institute, 792 Elizabeth Street, Melbourne, Victoria, Australia 3000 (e-mail: iainabbott@gmail.com).

Abstract

Keywords

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

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.

Nonfermenting Gram-negative bacteria (GNB) are typified by *Pseudomonas* and *Acinetobacter* species, which are widely distributed in natural environments, including soil, water, rhizosphere, and agriculture. Less is known about other nonfermenters, such as *Stenotrophomonas maltophilia*, *Burkholderia cepacia* complex, and *Achromobacter xylosoxidans*, which largely share the same environmental niche and are increasingly being recognized as emerging pathogens in hospitalized, immunocompromised, and cystic fibrosis (CF) patients.

Classification and Taxonomy

The taxonomy of this group of organisms continues to change as more information is gathered (see ►**Fig. 1**). *S. 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
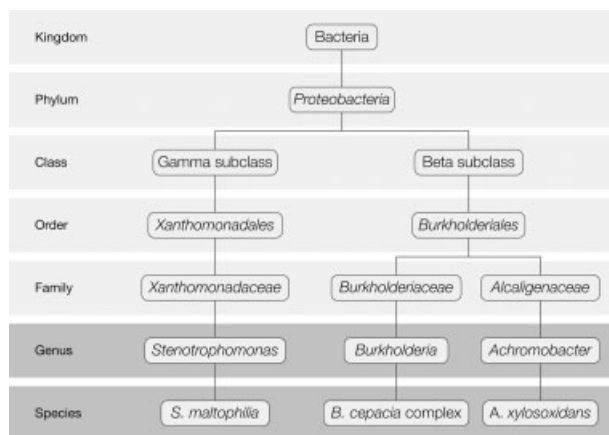
Fig. 1 Taxonomy of *Stenotrophomonas maltophilia*, *Burkholderia cepacia* complex, and *Achromobacter xylosoxidans*.

S. maltophilia may represent a "complex" of species.[1,2] 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**).[3] *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 IIID) based on the polymorphism of the *recA* gene.[4,5] In CF, patients colonized with *B. cenocepacia*, especially lineage IIIA, have a higher mortality following lung transplantation.[6–9] *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.[10–12]

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 *Pseudomonas* and *Acinetobacter* species accounted for the majority (82.7%).[13] 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%.[13] Amongst cancer patients at the MD Anderson Cancer Centre,[14] 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.[15]

The proportion of CF patients colonized with traditional pathogens has largely remained stable over time, with *P. aeruginosa* isolated in 60 to 80% of patients, and methicillin-sensitive *Staphylococcus aureus* in 30 to 60%, while the prevalence of *B. cepacia* complex remains low (3–5%) with a declining incidence.[16,17] There is, however, an increasing prevalence of *S. maltophilia* (4–15%), *A. xylosoxidans* (3–8%), nontuberculous mycobacteria (5–13%), and methicillin-resistant *S. aureus* (17.2%).[16,17] In a French regional CF center, over 5,000 sputa were collected from 300 CF patients. The incidence of *Pseudomonas* was 59%, *S. maltophilia* 18.9%, *B. cenocepacia* 13.8%, and *A. xylosoxidans* 6.9%. Coinfection with two or more of these pathogens was noted to be common.[10] In a multicenter study from Australia and New Zealand, CF patients colonized with *B. cepacia* complex were investigated. The authors identified *B. multivorans* in 29.3% and *B. cenocepacia* in 45.7%, with some geographic variability.[18] Some CF centers in Australia are dominated instead by *B. multivorans* (A.Y. Peleg, written personal communication, July 2014). Multilocus sequence typing scheme has demonstrated that several different *Achromobacter* species and genogroups can infect patients with CF, although less is known about the possible differences in tropism and pathogenicity between the different species.[11,12,19]

Person-to-person transmission of these multidrug-resistant pathogens, especially among CF patients, remains a concern. Unlike *B. cepacia* complex, where evidence for cross-transmission is well reported,[20] less is known for *S. maltophilia* and *A. xylosoxidans*. However, case reports have documented incidences of patient cross-transmission.[10,21,22]

All three organisms are capable of causing a variety of infections, including bacteremia, pneumonia, meningitis, urinary tract infections, and nosocomial infections from contaminated environmental sources (e.g., medications, nebulizers, dialysis fluids, saline solution, disinfectants, and contact lens fluid) have been reported. A major virulence factor of these organisms is their ability to produce and survive within biofilms.[23–27] Biofilm production is associated with resistance to environmental factors by promoting intimate attachment to surfaces, resistance to phagocytic activity and other host immune factors, shielding from antimicrobial activity and enhanced spread across surfaces via bacterial motility. In polymicrobial infections, interspecies interactions have been demonstrated such that different species within the same biofilm can respond to each other's signaling systems and provide survival advantages to the entire polymicrobial community.[28–30]

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

Table 1 *Burkholderia cepacia* complex species[a]

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

Abbreviation: CF, cystic fibrosis.

[a]Adapted with permission from Sousa et al,[3] Vandamme and Dawyndt,[78] and Drevinek and Mahenthiralingam.[79]

[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.

agents of soil bioremediation and phytoremediation.[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).[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 *Pseudomonas* species. ►**Table 2** outlines the basic microbiological characteristics of these organisms. Automated identification using
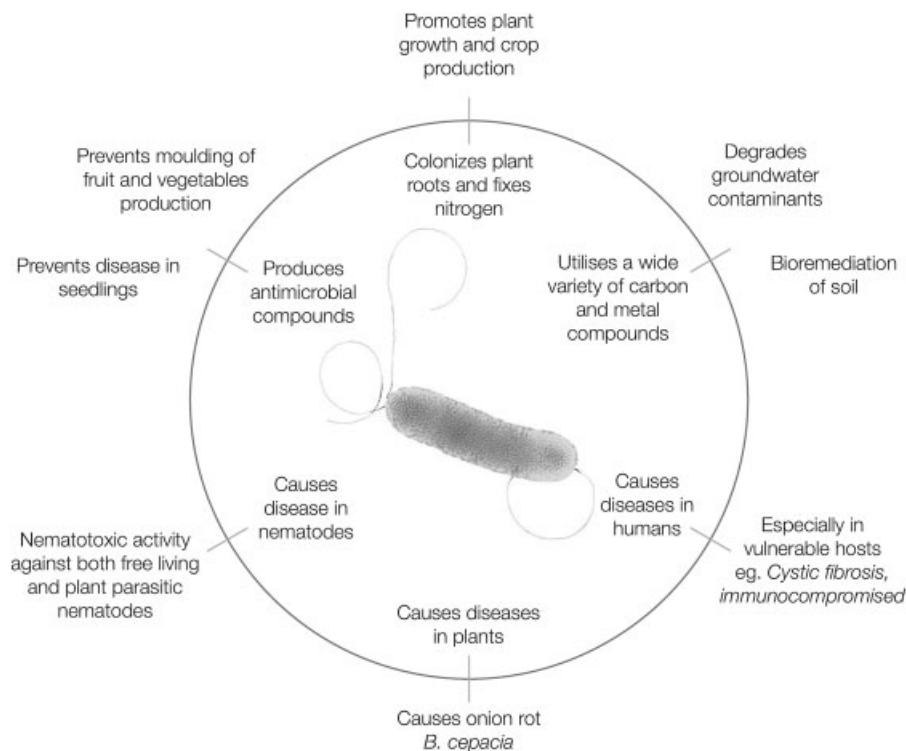
Fig. 2 Beyond human pathogens: biotechnological uses. Adapted with permission from Mahenthiralingam et al[32] and Ryan et al[31]. (Colored transmission electron micrograph of *S. maltophilia* reprinted with permission from Owens B. Silver makes antibiotics thousands of times more effective. Nature News. Macmillan Publishers Ltd, June 19, 2013. Accessed August 9, 2014. Available at http://www.nature.com/news/silver-makes-antibiotics-thousands-of-times-more-effective-1.13232).[99]

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.[37–40] 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.[41–43] 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*.[44] 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).[45]

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 2 Microbiology characteristics of *Stenotrophomonas maltophilia*, *Burkholderia cepacia* complex, and *Achromobacter xylosoxidans*

Aerobic
Nonfermenting gram-negative rod • Appears as a nonlactose fermenting organism on MacConkey agar
Motile
Catalase positive
Oxidase positive • Except *S. maltophilia* which is most often oxidase negative (although reported to be oxidase positive in 20%)
Indole negative
H_2S negative
Urease negative

Table 3 Mechanisms of antibiotic resistance

Organism	Category	Resistance mechanism	Antimicrobial affected
S. maltophilia[1,80]	β-lactamases	Two chromosomal inducible β-lactamases - L1 (class B) MBL; L2 (class A) serine Plasmid ESBL - TEM-2 penicillinase; CTX-M	Hydrolyses all β-lactams
	Efflux systems	Multidrug efflux systems - SmeDEF; SmeABC; SmrA	Resistance to tetracycline class, chloramphenicol, erythromycin and fluoroquinolone class
	Enzymatic modification	Aminoglycoside-modifying enzymes Sm*qnr* topoisomerase enzyme	Resistance to aminoglycosides andlow level intrinsic quinolones
	Changes in the outer membrane	Phosphoglucomutase (SpgM)	Aminoglycosides, polymyxin B and fluoroquinolones
	Target site modification	Protect DNA gyrase and topoisomerases (Smgnr); Class 1 integrons (Sul1 and Sul2)	Resistance to fluoroquinolones; resistance to TMP-SMX
B. cepacia complex[9,32,81–84]	β-lactamases	Chromosomal, inducible Ambler class C (*PenA*); plus others (Ambler class A + D)	β-lactams
	Efflux systems	RND family efflux transporter	Aminoglycosides, ciprofloxacin, trimethoprim, chloramphenicol
	Enzymatic modification	Aminoglycoside-modifying enzymes; Dihydrofolate reductase	Resistance to aminoglycosides, trimethoprim
	Changes in outer membrane	Lack of binding sites on the lipopolysaccharide layer	Intrinsic resistance to the cationic antimicrobials, polymyxins, and aminoglycosides
	Altered target site	Change in penicillin binding proteins; Mutations in the quinolone resistance-determining region, QRDR (*gyrA*and *parC*)	β-lactams; fluoroquinolones
A. xylosoxidans[73,85–88]	β-lactamases	Intrinsic OXA$_{114}$, OXA$_{243}$, and OXA$_2$; Cephalosporinase, *bla*$_{ampC}$; Acquired carbapenemases (*bla*$_{IMP}$)	β-lactams
	Efflux systems	RNA-type multidrug efflux pumps; AxyABM and AxyXY-OprZ	Decreased MICs of cephalosporins (except cefepime), aztreonam, fluoroquinolones, chloramphenicol. Innate aminoglycoside resistance and extrudes cefepime, carbapenems, some fluoroquinolones, tetracyclines, and erythromycin
	Enzymatic modification	Aminoglycoside modifying enzymes, AAC(6')-lb and aadA1	Aminoglycosides

Abbreviations: ESBL, extended spectrum β-lactamase; MBL, metallo β-lactamase; RND, resistance nodulation division; TMP-SMX, trimethoprim-sulfamethoxazole.

Table 4 Intrinsic antibiotic resistance

	S. maltophilia		B. cepacia complex		A. xylosoxidans	
	EUCAST	CLSI	EUCAST	CLSI	EUCAST	Other[a]
Amoxicillin–clavulanate	R	R	R	R	–	R
Ticarcillin–clavulanate	–	–	R	n/r	–	–
Piperacillin–tazobactam	R	R	–	R	–	–
Ceftriaxone	R	R	–	R	R	R
Ceftazidime	R	–	–	–	–	–
Cefepime	R	–	n/r	R	n/r	R
Aztreonam	R	R	n/r	R	n/r	R
Ertapenem	R	R	R	R	R	R
Imipenem	R	R	R	R	–	–
Meropenem	R	R	–	–	–	–
Ciprofloxacin	–	n/r	R	n/r	–	R
Aminoglycoside	R	R	R	R	–	R
Trimethoprim	R	R	R	R	–	R
Trimethoprim–sulfamethoxazole	–	–	–	–	–	–
Fosfomycin	R	R	R	R	–	R
Minocycline/Tigecycline	–	–	–	–	–	–
Colistin	–	–	R	R	–	–
Chloramphenicol	–	–	R	–	–	–

Abbreviations: CLSI, Clinical and Laboratory Standards Institute[46]; EUCAST, European Committee on Antimicrobial Susceptibility Testing[47]; n/r, not reported.
[a]Intrinsic resistance patterns for *A. xylosoxidans* gathered from other reports in the literature.[27,70,71,73,88–90]

reporting of results (see ►**Table 4**). There are subtle differences between intrinsic resistance reports by Clinical and Laboratory Standards Institute (CLSI; M100-S24, appendixB.2)[46] and European Committee on Antimicrobial Susceptibility Testing (EUCAST)[47] 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.[48] 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[49] 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

	S. maltophilia[1,61,80,91,92]		B. cepacia complex[6,13,63,66,91,93,94]		A. xylosoxidans[10,13,40,70,73,89–91,95,96]	
	Sens.	Details	Sens.	Details	Sens.	Details
Trimethoprim–sulfamethoxazole	34.4 to >90%	Bacteriostatic. High doses req. (TMP ≥15mg/kg). Lower susceptibility rates in CF patients.	0–90.7%	Increased resistance in CF population.	0–92%	Increased resistance in CF population.
Ticarcillin–clavulanate/Piperacillin–tazobactam	11.5 to >70%	Bacteriostatic. Clavulanate inhibits L2 β-lactamase. Piperacillin–tazobactam is not effective.	15.6–97.3%	Variable rates between drugs. EUCAST reports intrinsic resistance for ticarcillin–clavulanate. CLSI supply clinical breakpoints for ticarcillin–clavulanate, but report intrinsic resistance for piperacillin–tazobactam.	40–100%	Both ticarcillin–clavulanate and piperacillin–tazobactam are reported to have variable activity.
Ceftazidime	0–53%	Some invitro activity. Clinical success when used in combination.	23–97.3%	Other cephalosporins resistant.	45–84.7%	Other cephalosporins resistant.
Meropenem	–	Intrinsic resistance reported	26–100%	Minimal activity of imipenem or doripenem. Ertapenem not active.	52–100%	All carbapenems appear active, except ertapenem.
Fluoroquinolone class	45–95%	Bacteriocidal, post-antibiotic effect and biofilm activity. Susceptibility rates reflect newer fluoroquinolone activity (e.g., moxifloxacin or levofloxacin) compared with ciprofloxacin.	5.5–71.4%	Variable activity; resistance can be readily induced. EU-CAST report intrinsic resistance to ciprofloxacin.	–	Intrinsic resistance reported. Greater invitro activity of newer fluoroquinolones (moxifloxacin, gatifloxacin, and levofloxacin).
Minocycline/Tigecycline	66.7–100%	Limited clinical experience. Some susceptibility data may be overestimated by applying Enterobacteriaceae clinical breakpoints.	5.5–44.4%	Tigecycline has poor activity due to drug efflux.	44–51%	Efflux pumps may limit the use of tetracyclines. Tigecycline MIC_{90} 4 mg/L suggests *Achromobacter* to be a poor target for therapy with tigecycline.
Colistin	37.5–79%	Variable activity. False susceptibility reported when testing with Etest.	–	Intrinsic resistance reported	28–70.1%	Higher invitro susceptibility rates when tested against higher concentrations achievable by aerosolization.
Chloramphenicol	11.5–82%	Some invitro activity.	–	Intrinsic resistance reported	22–81.2%	Variable activity.

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 6 Suggested treatment options

Organism	First line	Second line	Combination	Alternative combination
S. maltophilia	Trimethoprim–sulfamethoxazole	Moxifloxacin/levofloxacin Ticarcillin–clavulanate Minocycline/tigecycline[a] Colistin (± rifampicin)	Trimethoprim–sulfamethoxazole PLUS Any 2nd line agent, or ceftazidime	Ticarcillin–clavulanate *PLUS* Aztreonam *PLUS* Moxifloxacin/levofloxacin
B. cepacia complex	Trimethoprim–sulfamethoxazole Ceftazidime Meropenem	Minocycline Chloramphenicol Ciprofloxacin[b] Piperacillin–tazobactam Ticarcillin–clavulanate	Combination of any 1st line or 2nd lines agents	Meropenem *PLUS* Ceftazidime PLUS Ciprofloxacin PLUS Minocycline, or amikacin PLUS Tobramycin (inhaled[c])
A. xylosoxidans	Piperacillin–tazobactam Meropenem Trimethoprim–sulfamethoxazole	Ceftazidime Minocycline Colistin Chloramphenicol	Meropenem PLUS Ciprofloxacin/levofloxacin[d]	Meropenem PLUS Minocycline, or levofloxacin[d] PLUS Chloramphenicol PLUS Colistin (inhaled[c])

[a]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.[97,98]
[b]EUCAST report *B. cepacia* complex to be intrinsically resistance to ciprofloxacin.
[c]Inhaled antibiotics have been recommended primarily in pulmonary exacerbations of CF.
[d]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.[70]

neutropenic patients). The inclusion of a specific biofilm active agent, such as moxifloxacin or levofloxacin has also been shown to be of benefit,[23,54,55] although caution should be applied when used as monotherapy because of the risk of rapid induction of resistance.[56–58] Minocycline and tigecycline have also shown some promise to assist with the treatment of *S. maltophilia*.[59,60] 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.[53,59,61]

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,[52] as well as extrapolated data from *B. pseudomallei*, the pathogen causing melioidosis.[62] 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.[16,63–65] 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.[66] 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.[67,68] 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 "cepacia syndrome."[6,7] 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.[69]

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 com-

munication 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.[13,70–72] Tetracyclines (e.g., minocycline) have variable activity and may be vulnerable to a multidrug efflux pump.[73] Although specifically for tigecycline, an MIC_{90} of 4 mg/L has been reported in CF patients, suggesting *Achromobacter* to be a poor target for therapy with tigecycline.[71] 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.[10,26,74] Combination therapy has been recommended for the treatment of *A. xylosoxidans* pulmonary exacerbations in CF.[75] Although the use of concurrent inhaled antibiotics, such as inhaled colistin, could also be considered.[71,76,77]

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. Coinfection 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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