Clinical challenges treating *Stenotrophomonas maltophilia* infections: an update

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Stenotrophomonas maltophilia is a non-fermenting, Gram-negative bacillus that has emerged as an opportunistic nosocomial pathogen. Its intrinsic multidrug resistance makes treating infections caused by *S. maltophilia* a great clinical challenge. Clinical management is further complicated by its molecular heterogeneity that is reflected in the uneven distribution of antibiotic resistance and virulence determinants among different strains, the shortcomings of available antimicrobial susceptibility tests and the lack of standardized breakpoints for the handful of antibiotics with *in vitro* activity against this microorganism. Herein, we provide an update on the most recent literature concerning these issues, emphasizing the impact they have on clinical management of *S. maltophilia* infections.

Introduction

Stenotrophomonas maltophilia is an environmental Gram-negative bacillus that has emerged as a cause of a variety of clinical syndromes, mainly pulmonary and bloodstream infections (BSIs).[1–3] *S. maltophilia* primarily impacts vulnerable populations, such as patients with cystic fibrosis (CF), cancer and other conditions leading to an immunosuppressed state.[1,2,4–6] Reported estimates of mortality after *S. maltophilia* infections are mainly derived from retrospective single-centre studies and range from 18% to 69% for all-cause mortality at various timepoints after infection, and from 24% to 58% for attributable mortality.[7–13] Furthermore, *S. maltophilia* has also been recently described as the most common Gram-negative carbapenem-resistant pathogen isolated from BSIs acquired both in the community and in the hospital setting in the USA.[14,15] Despite its undeniable clinical impact, compared with other Gram-negative species, *S. maltophilia* is remarkably understudied (Figure 1). Consequently, important gaps exist in knowledge regarding its genomic and microbiological characteristics (including the assessment of antimicrobial susceptibility) that ultimately impact treatment outcomes of infections caused by *S. maltophilia*.

Clinical epidemiology

Clinical manifestations and risk factors

Due to its relatively low virulence, for many clinicians there is still the question of whether *S. maltophilia* is merely a colonizer or the cause of true infection. Although *S. maltophilia* infection is rare in immunocompetent individuals, this species has been increasingly recognized as an opportunistic pathogen in chronically ill, immunocompromised patients and in persons with CF.[16–19]
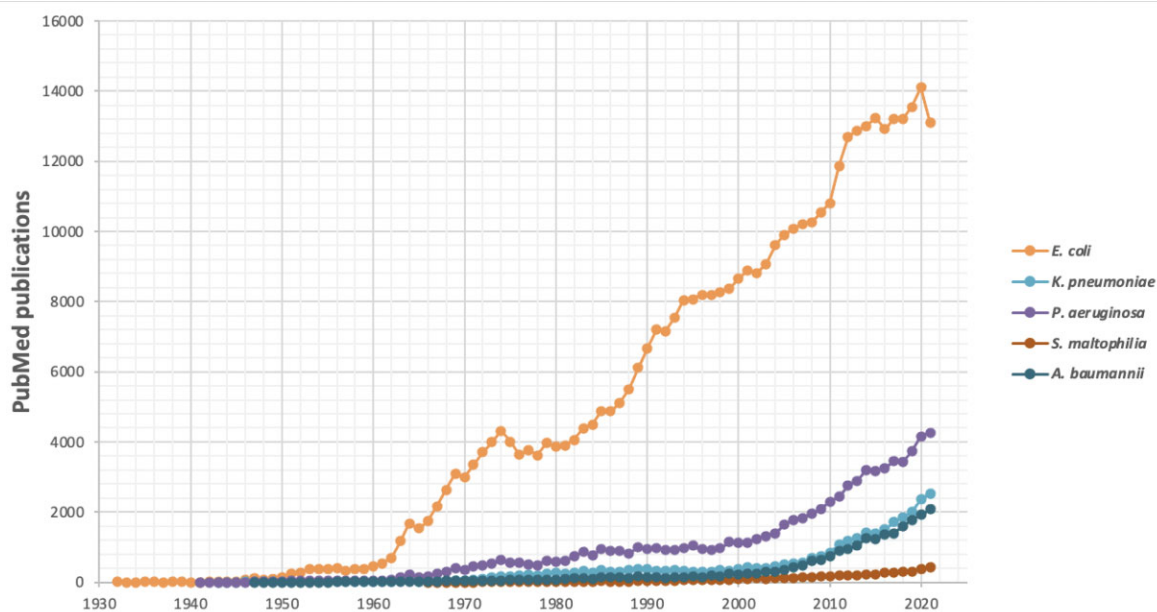
Figure 1. Timeline showing the total number of papers listed in PubMed per year about *E. coli, P. aeruginosa, Klebsiella pneumoniae, Acinetobacter baumannii* and *S. maltophilia.* Search terms used were: "Escherichia AND coli", "Pseudomonas AND aeruginosa", "Klebsiella AND pneumoniae", "Acinetobacter OR baumannii" and "Stenotrophomonas OR maltophilia".

Therefore, identification of *S. maltophilia* from immunosuppressed and debilitated individuals and isolation from a sterile site with signs and symptoms suggestive of infection should not be disregarded.[20]

S. maltophilia is primarily associated with respiratory tract infections, including pneumonia and acute exacerbations of COPD. Isolation of this organism in patients with severe COPD or signs and symptoms of infection, including pneumonia, should not be ignored.[20-24] While identification of this microorganism is frequently delayed awaiting growth of sputum culture, it is not typically covered in empirical antibiotic regimens for acute exacerbation of COPD, leading to higher mortality rates among these patients.[23] A recent retrospective study conducted between January 2017 and September 2019 in Canada showed that 10% of ambulatory patients with COPD have *S. maltophilia* detected in their sputum. Moreover, authors determined that comorbidities, exacerbation, use of oral steroids and carbapenems were risk factors for the presence of *S. maltophilia* in the sputum, and, importantly, that detection of *S. maltophilia* may represent a marker of overall morbidity and a predictor of mortality in patients with COPD.[25]

S. maltophilia is rarely present in the oropharyngeal microbiome of healthy patients but can often be recovered from the oropharynx of hospitalized and CF patients.[26,27] In this population, it causes chronic infection of the airways that contributes to inflammation, lung damage and premature mortality.[4,28,29] *S. maltophilia* can also cause a wide range of infections, including BSIs, skin and soft tissue infections, bone and joint infections, biliary tract infections, urinary tract infections, endophthalmitis, endocarditis, liver abscesses, meningitis and oral cavity infections.[1,2,6,30-33] Importantly, *S. maltophilia* is also a significant pathogen in cancer patients, particularly those with obstructive

lung cancer.[5,34-36] Patients with acute myeloid leukaemia are at particularly high risk for poor outcomes, with overall mortality over 20% in patients with primary bacteraemia and 60% for patients with pneumonia.[10,27,37-39]

Risk factors for infection by *S. maltophilia* include underlying malignancy, the presence of indwelling devices, chronic respiratory disease, immunocompromization, prolonged antibiotic use (especially carbapenems) and long-term hospitalization or admission to ICU.[1,2,6] Univariate analyses have identified ICU stay, central venous or urinary catheter use, prior antibiotic use and mechanical ventilation as risk factors for mortality in hospitalized patients with *S. maltophilia* infections.[40-42] Furthermore, risk factors associated with mortality in patients with *S. maltophilia* bacteraemia include septic shock, ventilation, ICU admission and length of hospital stay ≥30 days.[9,37,43-46] Multivariate analyses include an elevated SOFA score, hypoalbuminaemia, haematological malignancy, quinolone-resistant *S. maltophilia*, septic shock and prior chemotherapy as risk factors for mortality.[37,44,46,47] Mortality risk factors reported for *S. maltophilia* ventilator-associated pneumonia include age and chronic heart failure.[48] Risk factors for *S. maltophilia* pneumonia in ICU patients include higher SOFA score and immunosuppression.[49]

Lastly, in patients with haematological malignancies, oral colonization with *S. maltophilia* and cumulative antibiotic use are significantly associated with a subsequent *S. maltophilia* infection.[27,50] In this regard, a risk score for acquisition of *S. maltophilia* BSI in the haematological malignancy population was recently developed to identify patients who may benefit from early, effective therapy for *S. maltophilia*. This score incorporates five variables readily available to clinicians, namely, acute leukaemia, absolute neutrophil count category, mucositis as determined by

an oncologist, central venous catheter present and $\geq$3 days of carbapenem therapy within the previous 3 months.[51]

Community-acquired infections

Community-acquired infections caused by *S. maltophilia* have been reported for child and adult patients. These include bacteraemia, ocular infections, respiratory tract infections, wound/soft tissue infections, urinary tract infections, conjunctivitis, otitis and cellulitis.[2,32] In the community setting, *S. maltophilia* mainly causes infections in patients with underlying conditions such as COPD, CF, malignancy, liver disease, HIV infection, transplantation or other immunosuppressive conditions. Other risk factors for community-acquired infections with *S. maltophilia* include use of indwelling devices, antibiotic treatment, prior hospitalization history and trauma.[1,2,32,52] *S. maltophilia* rarely causes bone or joint infections in the community setting, but cases of spondylodiscitis, arthritis and bursitis have been reported in patients with immunosuppression or other underlying conditions.[53–55]

Severe community-acquired skin infections due to *S. maltophilia* have also been reported in both immunocompetent and immunocompromised patients. These include primary cellulitis, cellulitis-like cutaneous metastasis or cellulitis or metastatic nodular skin lesions, gangrenous cellulitis, ecthyma gangrenosum, soft-tissue necrosis and infected mucocutaneous ulcers.[56–61] Finally, the case of a severe infection in the spinal cord caused by *S. maltophilia* in an immunocompetent 12-year-old child related to dry cupping therapy has been recently documented.[62]

It is clear from these reports that *S. maltophilia* is a true pathogen that can infect immunocompetent individuals and cause a broad range of infections in the community, including BSIs. Indeed, a recent, retrospective, multicentre cohort study of *S. maltophilia* BSI patients in the USA found that *S. maltophilia* is the most common cause of carbapenem-resistant Gram-negative BSI. Surprisingly, >40% of these infections were identified as community-onset, defined in this study as infections with an index date that was $\leq$3 days after hospital admission with no evidence of previous contact with a healthcare setting. Because *S. maltophilia* is not included in most surveillance studies for antimicrobial resistance, this is an important epidemiological fact for physicians considering empirical treatment in septic patients.[15]

As an environmental organism, *S. maltophilia* is found as the dominant species that usually outcompete the rhizospheric bacterial populations.[63–65] Since environmental and clinical strains are genetically closely related, soil might be a likely source for community-acquired infections.[66] In addition, items such as sink drains, faucets, water, sponges and contact lens storage cases have been identified as environmental sources of *S. maltophilia,* reflecting the ability of this pathogen to survive on any humid surface, form biofilm and colonize humid surfaces.[1,2,52] Furthermore, *S. maltophilia* is increasingly being reported in companion animals, birds, fish, reptiles, insects and marine invertebrates, as commensal, pathogen or endocytobiont based on its recovery from a healthy or an infected animal.[1,67–77] Importantly, a recent molecular study found common phylogenetic traits among *S. maltophilia* strains isolated from animals and human clinical strains.[78] This and other reports suggest that animals could be a significant reservoir for *S. maltophilia* that causes infection in humans.[76,77,79]

Polymicrobial infections

S. maltophilia is often part of polymicrobial infections; the rate of isolation of this pathogen as a component of a mixed infection ranges from 33% to 70%.[42,80,81] Some of the bacterial species that are commonly detected in these infections are *Enterococcus* sp., coagulase-negative *Staphylococcus*, *Escherichia coli*, *Acinetobacter* spp., *Pseudomonas putida*, *Pseudomonas aeruginosa*, *Klebsiella* spp., and *Enterobacter cloacae*.[1,77,81] In these infections, the pathogenic role of *S. maltophilia* is difficult to ascertain, as other more virulent pathogens may be more important in this regard.

In polymicrobial infections, interactions between members can affect the prognosis of the infection. For instance, *P. aeruginosa* and *S. maltophilia* can produce biofilm in the lungs, creating a thriving environment for them both. In this respect, a higher mortality rate has been reported for pneumonia patients coinfected with *P. aeruginosa* and *S. maltophilia*.[82] On the contrary, interaction between *Aspergillus fumigatus,* another microbe that can be found alongside *S. maltophilia* in the human respiratory tract, seems to the antagonistic.[83,84] In mixed biofilms of *A. fumigatus* and *S. maltophilia*, *S. maltophilia* significantly delayed growth of the fungus hyphae.[85] The degree of antagonism also appears to be strain dependent.[86] In case of BSIs, the effect of monomicrobial versus polymicrobial infections seems to be the opposite. A recent retrospective study that reviewed 10 year data for *S. maltophilia* bacteraemia in hospitalized adults at Mayo Clinic Hospital (MN, USA) noted worse mortality in patients with monomicrobial *S. maltophilia* bacteraemia compared with polymicrobial bloodstream infections.[81] Nevertheless, regardless of the type of infection (mono- or polymicrobial), several studies agreed on the significant reduction in mortality risk when *S. maltophilia*-active therapy was initiated empirically.[11,80,81,87,88]

Global epidemiology data

Due to the worldwide ubiquity of *S. maltophilia* in the environment, its burden in serious infections is equally global. *S. maltophilia* is among the top six bacterial species isolated from patients with pneumonia who are in ICUs, and it is the leading carbapenem-resistant Gram-negative pathogen isolated from BSIs in the USA. In Latin America, *S. maltophilia* is among the top 10 pathogens causing pneumonia. Similarly, in Europe, *S. maltophilia* is also ranked in the top 10 pathogens most frequently isolated from hospitalized pneumonia patients, and in the Asia-Pacific region is one of the top four pathogens associated with intra-abdominal infections.[15,89–93]

On the other hand, the increasing reports of isolates resistant to drugs with historically good susceptibility rates like trimethoprim/sulfamethoxazole, ceftazidime, ticarcillin/clavulanate, fluoroquinolones and minocycline warrant discovery of novel compounds and/or novel combination therapies for *S. maltophilia*.[2,5,94,95] Increasing resistance to trimethoprim/sulfamethoxazole, historically the drug of choice for treatment of *S. maltophilia*, is concerning. Results from the SENTRY antimicrobial surveillance programme of pneumonia patients in US and European hospitals showed that during 2009–12, 96.3% of 302 *S. maltophilia* isolates were

susceptible to trimethoprim/sulfamethoxazole.[91] A recent study of 106 strains collected in Brazil reported that 78% of the strains were susceptible to trimethoprim/sulfamethoxazole. Remarkable, all strains resistant to trimethoprim/sulfamethoxazole also displayed resistance to ceftazidime (100%), ticarcillin/clavulanate (87%) and levofloxacin (52%).[96] In China, a study compared the antibiotic resistance profile of 300 clinical *S. maltophilia* isolates collected between two periods: 2005–09 and 2010–14. Significant increases in resistance were observed, from 29.7% to 47.1% for trimethoprim/sulfamethoxazole and from 28.9% to 52.3% for ceftazidime. The percentage of strains susceptible to minocycline was found to be also decreasing, albeit not as dramatically, as it changed from 10.9% to 13.5% between the two time periods studied. Multidrug resistance (most often to minocycline, trimethoprim/sulfamethoxazole, and ceftazidime) also increased from 11.0% to 31.0% during the two time periods.[97]

In a study of isolates recovered from US centres during 2006–16, the susceptibility of 130 *S. maltophilia* isolates to trimethoprim/sulfamethoxazole ranged from 79% to 96%, being lower in the isolates collected from blood, likely reflecting collection after treatment of the patient with antibiotics, including trimethoprim/sulfamethoxazole. The situation reported for the β-lactams was more dramatic, as the susceptibility to ticarcillin/clavulanate ranged from 18% to 25%. For ceftazidime, the susceptibility reported was from 16% to 43%, being the lowest for isolates collected from CF patients. On the bright side, this analysis also demonstrated excellent susceptibility rates for the novel combination ceftazidime/avibactam and aztreonam, which demonstrated susceptibility rates greater than or comparable to those reported for trimethoprim/sulfamethoxazole.[94] These results confirmed previous findings regarding the *in vivo* and *in vitro* efficacy of ceftazidime/avibactam and aztreonam against *S. maltophilia*.[95,98] Further observational and controlled studies are needed to provide clinical data on the utility and safety of ceftazidime/avibactam and aztreonam therapy.

Molecular epidemiology and genetic makeup of *S. maltophilia*

The molecular epidemiology of *S. maltophilia* strains has been explored using several molecular methods, including pulsed-field gel electrophoresis (PFGE), amplified fragment length polymorphism (AFLP), multilocus sequence typing (MLST) and recently by whole-genome sequencing (WGS). Regardless of the geographical origin of the isolates or the method used, *S. maltophilia* isolates typically show a high level of molecular heterogeneity, which may be related to the wide environmental distribution of this opportunistic pathogen.[99–102] As aforementioned, *S. maltophilia* is found in a wide range of natural habitats, including water, soil, the rhizosphere and animal and human microbiotas.[1,77,103] Nevertheless, associations between defined genomic groups and environmental, animal or human sources have been identified.

The initial genomic characterization of *S. maltophilia* using AFLP suggested an association between some genomic groups and environmental or human sources.[100,101] The so-called genomic groups 4, 9 and 10 contained exclusively environmental strains, whereas genomic groups 1, 6 and 7 included mostly clinical isolates.[100] These findings were not only confirmed but also expanded using the MLST scheme proposed by Kaiser *et al.*[102] Analysis of concatenated MLST loci have proved useful in assessing the population-level diversity of this species.[78,104,105] MLST analysis of strains across multiple French hospitals corroborated the existence of distinct genogroups and observed a preponderance of genogroups 6 and 2.[100–102,104] Predominance of the genomic group 6, and to a lesser extent groups 1 and C, was also observed in our study of clinical *S. maltophilia* strains from multiple institutions in the USA.[94]

WGS has also been applied to investigate hospitals outbreaks. In a recent study, Swedish researchers traced down a sudden increase in isolation frequency of *S. maltophilia* in four patients with pneumonia at an ICU. After a thorough environmental sampling, two outbreak clones, ST361 and ST138, and seven unique ones (mostly from environmental sampling) were identified. Most likely, the outbreak clones originated from two sinks, and transmission was enhanced by a calorimeter shared by three patients. After changing the sink and enhancing disinfection routines of all shared medical devices, cases ceased.[106] In another study, WGS-based typing successfully refuted an outbreak of *S. maltophilia* on a haematopoietic stem cell transplantation ward but revealed that sanitary installations such as shower outlets can be an actual source of *S. maltophilia* transmissions.[107] Similarly to the Swedish study, several new STs were found among the isolated *S. maltophilia* strains. However, two strains belonged to ST94, which is part of the genomic group C, previously reported as associated with human infections.[94,104,107] Beyond the undeniable usefulness of WGS to elucidate potential sources of contamination in hospital outbreaks, these two studies demonstrate the genetic heterogeneity of *S. maltophilia* complex, as numerous new STs were identified within a relatively small sample size. Whether any of these clones has features that render it more epidemic than others is not yet known, but with more use of WGS, certain clones belonging to specific genomic groups may show themselves to be more prone to dispersal than others.

Recently, phylogenetic studies based on WGS have confirmed high intraspecies variability and support the designation of a *S. maltophilia* complex comprising several genogroups. WGS studies also propose the incorporation of the closely related species *Stenotrophomonas pavanii* (16S rRNA sequence identity of >99.1%) into the *S. maltophilia* complex.[100,108–110] A study conducted in France analysed 375 unique *S. maltophilia* complex genomes collected from different sources: 104 from animal, 226 human, 30 environmental and 15 of unknown origin. Phylogenetic analyses identified at least 20 genomic groups; MLST analysis showed most strains in genogroups 1, 3, 6 and C were of human origin, whereas most strains in genogroups 2-b and 5 were of animal origin. Moreover, this work suggested that animal strains play a key role in the diversity of *S. maltophilia* complex and could act as a reservoir for mobile resistance genes.[111] Another recent global phylogenetic study comprising 1305 *S. maltophilia* isolates found that *S. maltophilia* strains can be subdivided into 23 monophyletic lineages, among which genogroup 6 (referred to hereafter as Sm6) was the predominant lineage.[112] In line with previous reports, this study also showed that Sm6 is almost exclusively associated with human infection, and is associated with specific antibiotic resistance and virulence genes.[102,104,112,113] The apparent emergence of strains with

unique genetic backgrounds associated with human pathogenicity may indicate an ongoing process by which *S. maltophilia* adapts to this specific niche. This adaptation process is potentially driven by conditions in the hospital environment that could exert selective pressure for survival of certain strains with new genomic and phenotypic characteristics (e.g. strains producing KatA, involved in resistance to disinfectants).[94,112] Such a shift in ecological niches, from environment to human body, has been documented by recent genomic studies performed on *Legionella pneumophila*. Those studies elegantly demonstrated that contemporary clinical *L. pneumophila* strains arose after multiple, independent events of pathoadaptation of environmental strains to human colonization.[114,115] As will be explained in the next sections, the uneven distribution of resistance and virulence factors among the different lineages of the *S. maltophilia* complex suggest that the same process has been ongoing within this complex. Molecular surveillance is warranted to identify the environmental source and mechanism of spread of lineages of *S. maltophilia* associated with human infection.

Mechanisms of resistance

Comparative and functional analyses have shown that *S. maltophilia* is equipped with a multitude of genes with proven or potential contribution to antimicrobial resistance.[1,112,116] *S. maltophilia* is intrinsically resistant to a wide range of antibiotics, including most β-lactams, fluoroquinolones, tetracyclines, chloramphenicol, aminoglycosides and trimethoprim (Table 1).[1,2,6]

β-lactam resistance

The main mechanisms of resistance are summarized in Table 2. Intrinsic resistance to β-lactams is mediated by the expression of two inducible β-lactamases: L1, a class B3 metallo-β-lactamase (MBL), and L2, a class A clavulanic acid susceptible cephalosporinase.[1,6,77] L1 MBLs inactivate carbapenems and other β-lactams quite readily and are not inhibited by currently available β-lactamase inhibitors.[117,118] However, an important exception is aztreonam, a monobactam, which is not inactivated by L1 MBLs. L2 β-lactamases are inducible cephalosporinases that confer resistance to extended-spectrum cephalosporins and aztreonam but are susceptible to inhibition by commercially available serine-β-lactamase inhibitors such as clavulanic acid and avibactam.[98,119,120] Different variants of L1 and L2 are described and importantly an association between specific $bla_{L1/L2}$ variants and genogroup Sm6 has been reported.[94,118,120] Considering the remarkably high genetic similarity between *S. maltophilia* and *S. pavanii* (16S rRNA sequence identity of >99.1%), it is not surprising that this species also harbours the genes encoding L1 and L2 β-lactamases, alongside other multidrug efflux pump.[112,121] Therefore, the resistance profile to β-lactams of *S. pavanii* and *S. maltophilia* strains should be similar, and largely depend on the type of L1 and L2 produced, as differences in the hydrolytic capabilities of different L1s and L2s have been reported.[120]

Regulation of the expression of bla_{L1} and bla_{L2} is complex and involves multiple components including membrane-bound and soluble lytic transglycosylases (mLTs and LTs, respectively), the CreBC two-component system and *mrcA* (predicted to encode PBP 1a).[77,122–125] The main mechanism is similar to the induction

Table 1. Natural resistance in *Stenotrophomonas maltophilia* limits therapeutic options

Antibiotic class	Antimicrobial agents	Intrinsic resistance?
β-lactams	Ampicillin, amoxicillin	Yes
	Piperacillin	Yes
	Ticarcillin	Yes
	Ampicillin-sulbactam	Yes
	Amoxicillin/clavulanate	Yes
	Piperacillin/tazobactam	Yes
	Cefotaxime	Yes
	Ceftriaxone	Yes
	Ceftazidime	No
	Cefepime	No
	Aztreonam	Yes
	Imipenem	Yes
	Meropenem	Yes
	Ertapenem	Yes
Polymyxins	Polymyxin B, colistin	No
Aminoglycosides	[a]	Yes
Other	Tetracycline, tigecycline	[b]
	Trimethoprim	Yes
	Trimethoprim/ sulfamethoxazole	No
	Chloramphenicol	No
	Fosfomycin	Yes

Adapted from CLSI M100-S30.[248]
[a]*S. maltophilia* is intrinsically resistant to all aminoglycosides including kanamycin, tobramycin, amikacin and neomycin.
[b]*S. maltophilia* is intrinsically resistant to tetracycline but not to doxycycline, minocycline or tigecycline.

of chromosomally encoded AmpC in *P. aeruginosa* and is summarized in Figure 2. Briefly, the peptidoglycan layer consists of repeated disaccharide subunits of *N*-acetylglucosamine (NAG) and *N*-acetylmuramic acid (NAM) with pentapeptides. Enlargement and growth of the peptidoglycan layer is achieved by a concerted action of both synthetic (e.g. PBPs) and lytic enzymes (e.g. LTs). Hydrolytic activity of LTs produce GlcNac-1,6-anhydro-MurNAc peptides.[122,126] These peptides are transported into the cytoplasm by the AmpG permease, where they are further hydrolysed by NagZ, yielding 1,6-anhydro-muropeptides. To complete the cycle, AmpD further recycles them into UDP-MurNAc pentapeptides, the precursors of peptidoglycan synthesis.[122,127,128]

The transcription regulator *ampR* is located upstream of bla_{L2}, and their promoters overlap. Precursors of peptidoglycan synthesis (UDP-MurNAc-pentapeptide) act as co-effector molecules that upon binding to AmpR prevent expression of the β-lactamases, while allowing transcription of more repressor molecules. However, when the rate of catalysis of peptidoglycan is higher than its synthesis, for instance due to β-lactam-mediated cellular stress, 1,6-anhydro-muropeptides accumulate in the cytoplasm. These muropeptides act as co-effector molecules that competitively bind to AmpR, effectively removing the UDP-MurNAc pentapeptide, and activating bla_{L1} and bla_{L2} transcription.[122,129]

Table 2. Main mechanisms of resistance in *S. maltophilia*

Mechanisms	Resistance mechanisms	Spectrum	Resistance	References
Efflux pumps	SmeABC	AMG, β-lactams, FLQ	Acq	[249]
	SmeDEF	TET, CHL, Macrolides, FLQ, SMX, TMP, SXT, TGC	Int*	[249–252249–252]
	SmeGH	FLQ, β-lactams, TET, PMB	Int*	[116,253]
	SmeIJK	AMG, TET, MIN, CIP, LVX	Int*	[254]
	SmeVWZ	FLQ, CHL, SXT	Int*	[141,252,255]
	SmeYZ	AMG, TET, SXT	Int*	[137,255,256]
	SmrA	FLQ, TET	Int*	[251,257]
	OqxAB	FLQ	Acq	[258]
β-lactamases	L1 Class B3	β-Lactams (except monobactams)	Int	[123,259]
	L2 Class A	Penicillins, cephalosporins	Int	[119,123]
	TEM-2, CTX-M-1	Penicillins, cephalosporins	Acq	[260,261]
Aminoglycoside modifying enzymes	AAC(6′)-Iz	AMK, TOB	Int	[262,263]
	APH (3′)-Iic	KAN, NEO	Int	[264]
	AAC (6′)-Iak	NEO, TOB	Acq	[265]
Other	Sm*qnr*	Quinolones	Int*	[139,252]
	SUL1, SUL2, DfrA	SXT	Acq	[143,144]
	CatB	CHL	Acq	[112]
	tonB[a]	CAZ, FDC	Acq	[131]

Acq, acquired resistance; Int, intrinsic resistance; Int*, overexpression leads to full resistance; AMG, aminoglycosides; FLQ, fluoroquinolones; TET, tetracycline; CHL, chloramphenicol; SMX, sulfamethoxazole; TMP, trimethoprim; SXT, trimethoprim/sulfamethoxazole; TGC, tigecycline; PMB, polymyxin B; MIN, minocycline; CIP, ciprofloxacin; LVX, levofloxacin; AMK, amikacin; TOB, tobramycin; KAN, kanamycin; NEO, neomycin; CAZ, ceftazidime; FDC, cefiderocol.
[a]Mutations in the *tonB* gene lead to reduced susceptibility.

The observation that inactivation of *nagZ* did not completely abolish β-lactamase induction led to the discovery of a *nagZ*-independent mechanism of *bla*$_{L1}$ and *bla*$_{L2}$ regulation.[122,125] In the model proposed by Huang *et al.*,[122] inactivation of the membrane-bound lytic transglycosylase 1 (*mltD1*) results in upregulation of the expression of *mltB1* and *mltD2* in a *creBC*- and *ampNG*-dependent manner. The increased periplasmic MltB1 and MltD2 activity yields to the accumulation of a variety of degraded murein fragments, which are then imported into the cytoplasm by the AmpNG permease system. The imported murein fragments are processed into co-effector molecules by either a NagZ-dependent or a NagZ-independent pathway. As described earlier, in the presence of co-effector molecules, AmpR acts as an activator for the expression of L1 and L2 β-lactamases.[122] Accumulation of NagZ-independent co-effector molecules has also been observed *in vitro* upon inactivation of *mrcA*.[125] Deciphering complex mechanisms governing peptidoglycan synthesis and β-lactamases induction provides valuable knowledge about new molecular targets for antibiotic development.

Other mechanisms of resistance to β-lactams are described. Recent studies have shown that exposure of *S. maltophilia* to increasing concentrations of ceftazidime resulted in mutation of the *smeH* efflux pump transporter, which ultimately led to resistance to other β-lactam drugs.[130] Remarkably, a recent study has shown that the TonB energy transducer mediates uptake of ceftazidime, and clinical *S. maltophilia* isolates with *tonB* mutations exhibit resistance to siderophore-conjugated lactivicin.[131] Moreover, another recent study has demonstrated that *S. maltophilia* strains can evolve cefiderocol resistance through different genetic pathways. In this work, three *S. maltophilia* blood isolates, susceptible to cefiderocol with MICs ranging from 0.03 to 0.125 mg/L, were subjected to serial passages in escalating concentrations of cefiderocol. Colonies with reduced susceptibility to cefiderocol were recovered in all three genetic background and studied via WGS. WGS analysis revealed isogenic mutations of *tonB*, *smf-1* (encoding a fimbrial protein; Table 3), *tolQ* (a transmembrane transporter) and the *smeT* promoter (encoding a repressor of the MDR efflux pump SmeDEF; Table 2). Notably, these mutations conferred resistance to cefiderocol at MICs of 8–32 mg/L and were stable for ≥4 passages on drug-free medium. The molecular mechanisms of resistance to cefiderocol in these strains is yet to be determined.[132] Results from these two works are worrisome as the emergence of clinical strains of *S. maltophilia* with mutations in *tonB* or in the *smeT* promoter may limit the use of cefiderocol, a recently developed siderophore-conjugated cephalosporin with excellent *in vitro* activity against this species.[133,134]

Aminoglycoside resistance

S. maltophilia is intrinsically resistant to aminoglycosides via the expression of different aminoglycoside modifying enzymes as well as multiple efflux pumps (Table 2).[1,2,6] As in the case of β-lactamases, distribution of these enzymes is not uniform among *S. maltophilia* strains. According to a recent analysis of 1305 *S. maltophilia* genomes, aminoglycoside-phosphotransferases (APHs) were encoded in 66% of strains, distributed in many genogroups like Sm6 and Sm5; aminoglycoside-acetyltransferases (AACs) were encoded in
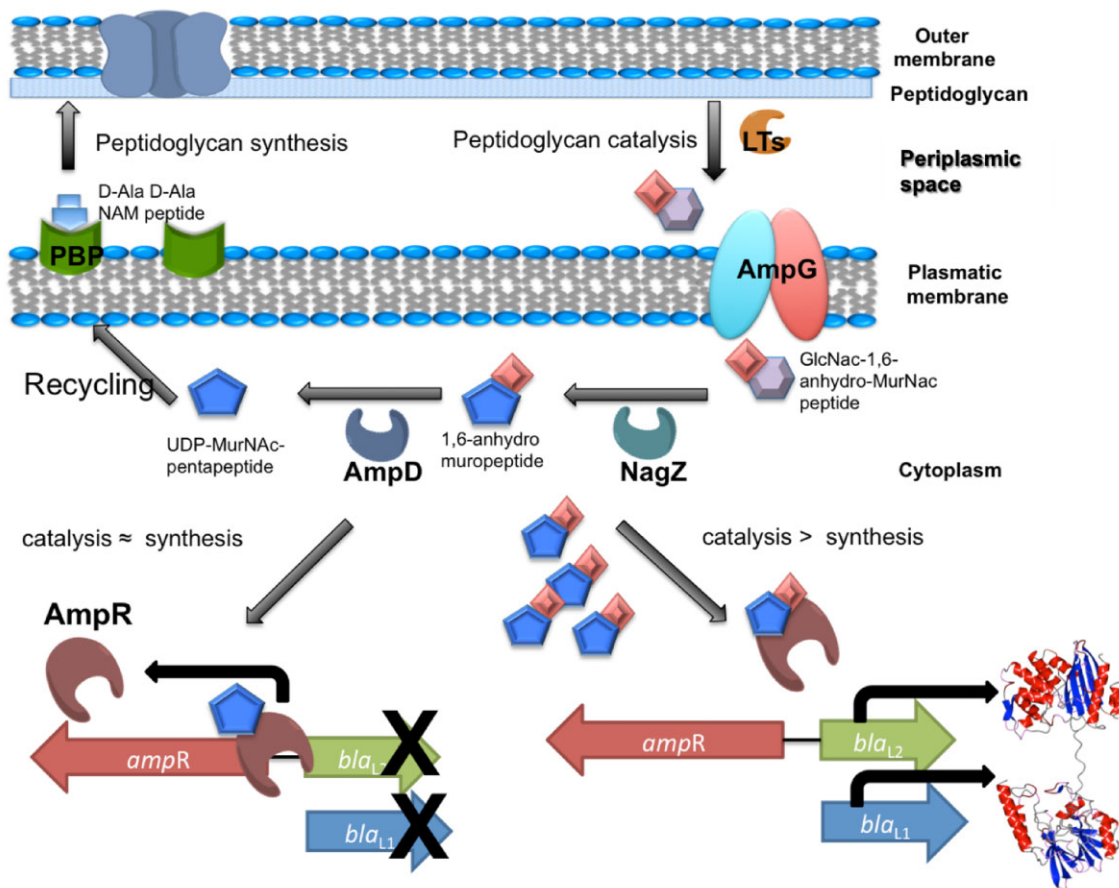
Figure 2. Schematic representation of the coordinated regulation of L1 and L2 expression by the *ampNG-ampDI-nagZ-ampR* regulatory circuit. Enlargement and growth of the peptidoglycan layer is achieved by a concerted action of both synthetic enzymes, like the PBP, and lytic enzymes, like lytic transglycosylases in the periplasmic space, and NagZ and AmpD in the cytoplasm. All these enzymes work together to process peptidoglycan fragments back into the sugar precursor of peptidoglycan synthesis. The AmpR transcription regulator is located upstream of bla_{L2}, and their promoters overlap. Precursors of peptidoglycan synthesis act as co-effector molecules that upon binding to the effector-binding domain of the AmpR, prevent expression of β-lactamases, while allowing transcription of the repressor. However, when the rate of catalysis is higher than the synthesis, for instance due to the action of β-lactams, 1,6-anhydro-muropeptide accumulates and acts as a co-inducer molecule, which upon binding to the repressor causes the complex to relocate upstream of the *bla* genes, allowing the expression of these genes.

6.1% of strains, mostly belonging to the genogroups Sgn4, Sm4b, and Sm15; and aminoglycoside-nucleotidyl-transferases (ANTs) in just 0.4% of all strains studied.[112] Other enzymes implicated in aminoglycoside resistance include the proteases ClpA and HtpX, which were found in 99.3% and 99.8% of the strains investigated, respectively.[112,135] Lastly, it has been shown that mutations in *rplA*, which encodes the largest protein of the 50S ribosomal subunit, induce overexpression of *smeYZ*.[136,137] Strains overexpressing *smeYZ* have been found in the clinic displaying hyper-resistance to all aminoglycosides.[136,138] Overexpression of this efflux pump also contributes to the virulent phenotype observed in murine infection models, suggesting an added fitness advantage in addition to antibiotic resistance.[137]

Quinolone resistance

Resistance of *S. maltophilia* to quinolones is associated with overexpression/mutation of efflux pumps and a chromosomally encoded *qnr* gene (Sm*qnr*) that protects both gyrase and topoisomerase IV from quinolones (Table 2).[1,2,139–141] Unlike other bacteria, clinical isolates of quinolone-resistant *S. maltophilia* do not present mutations in topoisomerases.[142]

Acquired resistance

In addition to its intrinsic resistance mechanisms, *S. maltophilia* has expanded its defence arsenal by acquiring other resistance determinants (Table 2). Several reports describe the increasing presence of *sul1*, *sul2* and *dfrA* genes that contribute to resistance to trimethoprim/sulfamethoxazole. These genes have been found both chromosomally and in plasmids, and often associated with Class 1 integrons and insertion element common region (ISCR) elements, which favour their mobility.[1,143,144] Furthermore, Class 1 integrons carrying multiple antibiotic resistance genes, most commonly against aminoglycosides, have been reported. For instance, Liaw *et al.*[145,146] reported the

Table 3. Main virulence factors of *S. maltophilia*

Role in virulence	Function	Genes	References
Cytotoxic/morphological effects to host cells	Serine protease	*stmPr1*	266,267
	Serine protease	*stmPr2*	266,267
	Fibrinolysin esterase	*k279a*	116
	Phospholipase	*plcN1* (*smlt1755*)	116
Biofilm formation and virulence	DSF-QS system regulator	*rpf-1/rpf-2*	153
Bacterial adhesion/early biofilm formation	Fimbrial protein	*smf-1*	268
	Type IV pilus function	*pilU*	112
Swimming motility/early biofilm formation	Flagellar M ring protein	*flif*	116
Biofilm maturation (alginate biosynthesis)	Phosphoglucomutase	*spgM*	116,269,270
	Glucose-1-phosphate thymidyltransferase	*rmlA*	105,271
	DSF synthase	*rpfF*	85,132
Quorum sensing and swarming motility	LuxR regulator chaperone HchA-associated	*smoR*	112

presence of two Class I integrons carrying (i) *aacA4*, *aadB*, *aacC4* and *aacA6′-1b*—conferring resistance to aminoglycosides—*smr*, *smr/aacA4* and *qac*—resistance to quaternary ammonium—and *cmlA* and *catB*—resistance to chloramphenicol; and (ii) *bla*$_{IMP-8}$—added resistance to β-lactams—and *aac6-II* and *aadA5*—conferring resistance to aminoglycosides, in clinical isolates of *S. maltophilia*.

Mechanisms of virulence and pathogenesis

S. maltophilia possesses multiple virulence factors that allow it to colonize and produce infection (Table 3). Recognized virulence factors include: (i) genes involved in the expression and/or production of pili, flagella, fimbrial structures and adhesins, which contribute to adherence, auto-aggregation, and colonization of biotic and abiotic surfaces; (ii) lipopolysaccharide (LPS), which plays a role in biofilm formation and resistance to antibiotics as well as complement-mediated cell killing; (iii) diffusible signal factor (DSF), fundamental in quorum sensing, which in turn mediates motility, extracellular enzyme production, LPS synthesis, microcolony formation and tolerance toward antibiotics and heavy metal ions; and (iv) extracellular enzymes such as proteases, lipases, esterase and fibrinolysin.[1,116,147]

In addition to these virulence factors, *S. maltophilia* outer membrane vesicles (OMVs) have been investigated for their contribution(s) to pathogenesis. OMVs could act as an indirect form of communication for the pathogen with other bacteria.[77] Secretion of OMVs is stimulated by the antibiotics imipenem and ciprofloxacin, *S. maltophilia* DSF, and, to a lesser degree, *Burkholderia cenocepacia* DSF.[148–150] Proteomic analyses have shown that when OMV secretion is triggered by exposure to imipenem, OMVs are packed with active L1 and by Smlt0387 and Smlt0184, both of which are homologues of Ax21, a sulphated protein that activates plant host defences against *S. maltophilia* infection.[148,151] When secretion is due to stimulation by DSF, the amount of L1 in OMVs decreases significantly, whereas the concentration of Ax21 remains constant.[148] Release of L1 leads to degradation of β-lactams in the external milieu surrounding the bacteria, protecting susceptible bacteria from the action of these antibiotics.[149] In cases of

coinfection, protection could also extend to other species. *In vitro* protection to different species has been demonstrated for OMVs carrying NDM-1.[152]

As with antimicrobial resistance determinants, several important virulence genes are unequally distributed among the lineages. For example, SmoR is involved in quorum sensing and swarming motility of *S. maltophilia*.[153] This virulence determinant is detected in 90% of *S. maltophilia* strains, but when analysed according to lineage, this protein is present in 100% of strains belonging to Sm6.[112] Likewise, KatA, a catalase mediating increased levels of persistence to hydrogen peroxide-based disinfectants, is found in 86.6% of strains. However, this virulence determinant is present in 99% of the strains belonging to the Sm6 and Sm4 lineages and found in only 49% of the strains from Sm3.[112] The predominance of resistance and virulence genes in isolates from Sm6, suggests adaptation to healthcare settings and survival on and in patients.

A recent study analysed allelic variants of the *rpf* gene cluster, responsible for DSF synthesis and perception, in populations of diverse clinical *S. maltophilia* isolates recovered from different geographical regions. This study revealed that the strains harbouring the *rpf-2* allele formed stronger biofilms and demonstrated greater virulence against *Galleria mellonella* larvae than strains harbouring the *rpf-1* variant. Furthermore, assessment of genotypes and virulence revealed a significant link of biofilm-forming ability with genogroup C. Remarkably, greater resistance to β-lactam antibiotics appeared to correlate with the *rpf-1* variant, while the *rpf-2* strains demonstrated greater resistance to colistin.[154] Another study reported variation in replication and persistence of clinical strains of *S. maltophilia* in lung infection models using A/J mice.[155] Further research is needed to determine whether specific mouse strains are more appropriate than others for use as animal models of *S. maltophilia* infection.[77] The uneven distribution of virulence factors among *S. maltophilia* lineages, another proof of its genetic heterogeneity, could result in very different clinical presentations. Therefore, more studies are urgently needed to fully characterize contemporary clinical *S. maltophilia* complex isolates in terms of association with described genomic groups, and virulence and resistance markers that could be used to inform clinical decisions.

Antimicrobial susceptibility testing (AST)

Significant shortcomings in AST affect accurate determination of *S. maltophilia* susceptibility rates to currently approved antibiotic treatment options. The treatment of most Gram-negative bacterial infections hinges on accurate *in vitro* susceptibility testing to predict antimicrobial activity. Unfortunately, for *S. maltophilia* there are many knowledge gaps regarding the accuracy and reproducibility of currently available *in vitro* susceptibility testing methods. For five decades, the internationally recognized reference method for AST of rapidly growing aerobic bacteria is MIC determination using broth microdilution (BMD) according to the International Standards Organization (ISO) 20776-1.[156] BMD methods optimized for *P. aeruginosa* were adapted in the early 2000s by CLSI for use with *S. maltophilia*. Studies conducted as part of the evaluation included a *S. maltophilia* panel of only 10 isolates tested across 8 laboratories, and disc diffusion breakpoints were developed from this dataset.[157]

In vitro susceptibility testing available in a clinical lab must adhere to defined breakpoints and methods for testing. CLSI and EUCAST define MIC breakpoints based on clinical, microbiological, pharmacokinetic (PK) and pharmacodynamic (PD) profiles of the antimicrobials for particular pathogens.[158,159] For *S. maltophilia*, CLSI has defined MIC breakpoints for ceftazidime, levofloxacin, minocycline, trimethoprim/sulfamethoxazole, ticarcillin/clavulanate and chloramphenicol, and very recently approved cefiderocol breakpoints. In contrast, EUCAST only defines MIC and disc breakpoints for trimethoprim/sulfamethoxazole. Lastly, FDA only recognizes ceftazidime breakpoints for *S. maltophilia*.

The lack of breakpoints arises because there are many unknowns in the *in vitro* microbiological, clinical and PK/PD data typically used to establish breakpoints. The lack of recognized breakpoints has real impact on patient treatment. For example, because FDA only recognizes ceftazidime *S. maltophilia* breakpoints, FDA clearance of commercial AST devices for this organism for standard-of-care antimicrobials like trimethoprim/sulfamethoxazole is no longer possible.[160,161] Thus, laboratories in the USA perform AST on *S. maltophilia* isolates using commercial systems that were cleared by the FDA prior to 2009, when FDA last allowed the use of CLSI breakpoints on commercial systems, or by using devices off-label for those cleared by FDA after 2009.

Not surprisingly, significant challenges have been noted in clinical evaluations of various AST methods for *S. maltophilia*.[146,162–165] Khan *et al*.[162] recently demonstrated, utilizing a cohort of 109 contemporary isolates, exceedingly poor performance of commercial tests (including disc diffusion) for antimicrobials including ceftazidime and trimethoprim/sulfamethoxazole routinely tested by clinical laboratories (Table 4). While trimethoprim/sulfamethoxazole testing was generally more reliable than ceftazidime, the only method that obtained acceptable performance, according to FDA criteria (i.e. >89.9% agreement and <3% false resistance or false susceptibility) was trimethoprim/sulfamethoxazole disc diffusion. Notably, a follow-up study reported that performance of the commercial, automated methods used in clinical laboratories did not achieve acceptable FDA criteria.[166] Without FDA recognized breakpoints for *S. maltophilia*, there is no pathway to update these systems and improve performance of AST in clinical laboratories in the USA.[160,161] What is unclear from these data is whether the challenges are a result of the commercial methods

Table 4. Analytical performance of commercial antimicrobial susceptibility testing methods for *S. maltophilia*, compared with reference BMD

	Automated MIC	Gradient diffusion	Disc diffusion
Trimethoprim/sulfamethoxazole			
Agreement with reference BMD, %	77–98	97–99	93
VME, %	0–22	10–10	0
ME, %	0–25	0–2	1
Ceftazidime			
Agreement with reference BMD, %	68–71	71–72	76
VME, %	9–44	9–21	9
ME, %	0–21	13–15	6

Modified from Khan *et al*. 2021.[162] Numbers represent ranges across four automated MIC methods, two gradient diffusion tests and one disc diffusion method.
VME, very major errors (proportion of resistant isolates called susceptible);
ME, major errors (proportion of susceptible isolates called resistant).

or due to an imprecise reference standard (BMD) without optimized conditions to detect clinically significant resistance. As aforementioned, *S. maltophilia* BMD methods were adapted from *P. aeruginosa*, and these organisms display important growth and susceptibility differences, not the least is the array of intrinsic resistance mechanisms expressed by *S. maltophilia* that are absent from *P. aeruginosa*.[167] *S. maltophilia* inhibition by antimicrobials is heavily impacted by factors that are not tightly controlled in the ISO BMD method, including nuanced variation of temperature and media composition.[168–171] As highlighted in the molecular mechanisms of resistance and virulence sections, there are potential genetic factors that could drive therapeutic failure and resistance in *S. maltophilia* and there is a knowledge gap in the interplay between the challenges with determining *S. maltophilia* susceptibility and the genotypic differences.

CLSI reviewed *S. maltophilia* breakpoints in 2019 and concluded insufficient data were available by which to make needed updates to CLSI *S. maltophilia* breakpoints.[157] Until there is additional clinical, PK/PD, microbiological and *in vitro* methodology research, it is unlikely additional breakpoints will be recognized for *S. maltophilia*. This means that patients and clinicians will not be able to determine how to prioritize treatment based on accurate *in vitro* susceptibility testing.

In summary, there are many challenges in AST for *S. maltophilia*. It is imperative to establish a reproducible, accurate, sensitive and predictive standard method to detect clinically important susceptibility profiles in contemporary isolates.

Treatment of infections caused by *S. maltophilia*

Prevention and control strategies

S. maltophilia is an environmental, waterborne organism, and as described earlier in this review, exposure to this bacterium can

occur both in and outside the clinical setting. In the healthcare environment, this pathogen has been isolated from suction system tubing of dental chair units, contaminated endoscopes, faucets, sink drains, dental unit waterlines, ice machines and, importantly, intravenous cannula, prosthetic devices, bronchoscope suction valves and nebulizers.[172–179] Furthermore, *S. maltophilia* has been recovered from haemodialysis water and dialysate samples, tap water, bottled water, contaminated chlorhexidine-cetrimide topical antiseptic, hand-washing soap and contact lens solutions.[1,58,77,180–185] Consequently, *S. maltophilia* infections in patients undergoing haemodialysis, using extracorporeal membrane oxygenation or associated with contaminated central venous catheter (CVC) have been reported.[175,186–191] In the later infections, the removal of the CVC is essential for the successful treatment of *S. maltophilia* catheter-associated bacteraemia, along with the appropriate antibiotic therapy.[11,175,187,190,192–195] In addition, a study showed that point-of-use water filtration has significantly reduced healthcare-associated Gram-negative bacterial infections, including due to *S. maltophilia*, in bone marrow transplant recipients.[196]

In summary, as the transmission of *S. maltophilia* to susceptible individuals may occur through direct contact with the source, disinfection of all possible sources is imperative to avoid healthcare-associated infections with this pathogen. This also includes prevention of *S. maltophilia* biofilms on surfaces that can come into contact with humans, as the ability of *S. maltophilia* to adhere to plastics and form biofilm is fundamental for its survival and transmission in the healthcare environment. In this regard, different strategies to inhibit biofilm formation or reduce established biofilms have been investigated. These include antibiotic combinations (azithromycin plus fluoroquinolones, and erythromycin plus levofloxacin, cefoperazone/sulbactam or piperacillin), antibiotics and disinfectant combinations (minocycline and chlorhexidine) and different substances like continuous renal replacement therapy fluids (Accusol 35-bicarbonate-based solution, Prismocitrate citrate-based anticoagulant, 4% trisodium citrate), clofibric acid, celastrol, chlorogenic acid and plant-based compounds.[77,197–202]

Antibiotic treatment

The optimal treatment for *S. maltophilia* infections is not well established and there are currently limited treatment options based on available *in vitro* and clinical data. Moreover, distinguishing colonization from invasive infections with *S. maltophilia* can be difficult. Considering all these challenges, IDSA recently endorsed a guidance document for the treatment of *S. maltophilia* infections.[203] This document provides detailed recommendations for the treatment of *S. maltophilia* infections in both adult and paediatric patients.

Despite the lack of randomized controlled trials comparing trimethoprim/sulfamethoxazole with any other available treatment of *S. maltophilia* infections, trimethoprim/sulfamethoxazole is considered the 'drug of choice' for treating susceptible *S. maltophilia* infections and has been widely used for many years based upon reported *in vitro* activity and favourable clinical outcomes.[204,205] However, there has not always been a good correlation between *in vitro* susceptibility and clinical success. As exposed in this review,

the heterogeneity of clinical *S. maltophilia* strains, with different virulence and resistance factors, in addition to the shortcomings of AST methods currently available and clinical status of the patients could explain the clinical success or failure of trimethoprim/sulfamethoxazole therapy. Besides trimethoprim/sulfamethoxazole, other common options include fluoroquinolones, tetracyclines and selected β-lactams like ceftazidime and ticarcillin/clavulanate. As described above, however, current resistance rates to ceftazidime and ticarcillin/clavulanate render these agents unreliable.

Fluoroquinolones are commonly used as an alternative for patients infected with trimethoprim/sulfamethoxazole-resistant *S. maltophilia* or those intolerant to trimethoprim/sulfamethoxazole due to adverse side effects.[1,2,206] Studies comparing treatments with fluoroquinolones and trimethoprim/sulfamethoxazole have suggested that levofloxacin has similar efficacy with fewer adverse drug side effects than trimethoprim/sulfamethoxazole.[80,87,207] A recent study used a large electronic health record database from 154 US hospitals to conduct a retrospective comparative effectiveness study of levofloxacin vs trimethoprim/sulfamethoxazole for BSIs and lower respiratory tract infections (LRTIs) due to *S. maltophilia*. Overall, results from 1581 patients demonstrated comparable mortality risk with the use of either levofloxacin or trimethoprim/sulfamethoxazole for the treatment of these serious infections. However, patients with pneumonia treated with levofloxacin compared with trimethoprim/sulfamethoxazole appeared to display greater survival and were discharged sooner.[80] Authors hypothesized that this signal is likely driven by the potential superiority of levofloxacin over trimethoprim/sulfamethoxazole for pneumonia, due to more favourable PK/PD properties, such as a higher concentration in epithelial lining fluid, quicker time-to-peak serum concentration, bactericidality and greater bioavailability of the oral formulation.[208–210] Regarding treatment of BSIs, authors did not find any significant or non-significant trend towards either of the drugs. Lastly, in agreement with other studies, authors reported that *in vitro*-active empirical therapy appeared to be associated with a decreased risk of death overall.[80]

As with other antibiotics, resistance rates to levofloxacin vary geographically, from 10% reported in Hungary, 15%–20% in India, China, Mexico and the USA, and up to 40% in paediatric patients in China.[1,2,15,34,43,211,212] Another concern is that, compared with trimethoprim/sulfamethoxazole, levofloxacin has a higher rate of emergence of resistance. In recent reports, nearly 20% of patients with *S. maltophilia* pneumonia who do not achieve microbiological eradication may develop quinolone resistance after levofloxacin exposure; this compares to 7%–8% for those exposed to trimethoprim/sulfamethoxazole.[213,214] The higher rate of resistance emergence is especially relevant in CF or cirrhotic patients for whom frequent or chronic quinolone exposure is common, and other chronic infections where the duration of antibiotic therapy is longer than 1–2 weeks.[215]

Tigecycline and related tetracycline antibiotics, minocycline, and eravacycline have demonstrated efficacy against *S. maltophilia* in surveillance studies conducted in the last decade.[89,92,216–222] Across data from five surveillance reports, tigecycline exhibited a range of $MIC_{50/90}$ values of 0.5 to 2/2 to 4 mg/L and MIC range of 0.06 to >16 mg/L.[89,218,221–223] Across five surveillance studies, minocycline demonstrated a $MIC_{50/90}$

range of 0.5 to 2/2 to 4 mg/L and a susceptibility rate of 99.5%.[89,92,216,217,224] In addition to its extremely low *in vitro* resistance, minocycline has minimal drug–drug interactions and a relatively good tolerability profile.[215,225] Given that the multidrug efflux pumps that confer resistance to trimethoprim/sulfamethoxazole often confer resistance to quinolones and β-lactams/β-lactamase inhibitors too, but do not appear to affect minocycline susceptibility, minocycline is often utilized in the context of trimethoprim/sulfamethoxazole and levofloxacin resistance.[226] Likewise, eravacycline is increasingly being utilized for the treatment of MDR Gram-negative infections, but data in the management of *S. maltophilia* infections are limited.[227] In several series, the reported MICs for eravacycline are 2- to 4-fold lower than for tigecycline.[228] Notably, eravacycline MICs frequently mirror minocycline for *S. maltophilia*.[218] Lastly, against 1210 *S. maltophilia* isolates recovered worldwide during 2013–17, eravacycline displayed an $MIC_{50/90}$ of 1/2 mg/L and an MIC range of 0.03 to 16 mg/L.[218] In summary, these data suggest that tetracyclines are reasonable therapeutic options against infections caused by *S. maltophilia*.

Ceftazidime and ticarcillin/clavulanate were previously the most effective β-lactam drugs against *S. maltophilia*.[1] However, recent studies have demonstrated a trend in decreasing susceptibility for ceftazidime (47%–75% during 1997–99 to 30.5%–36.8% during 2009–12) and ticarcillin/clavulanate (71%–90% to 27%–46.1% during 2003–08).[91,94,229,230] β-lactamase inhibitors may be able to reverse resistance to some β-lactam antimicrobials, but their use in combination therapies is limited, as only select antimicrobials have shown improved activity when combined with a β-lactamase inhibitor.[77] Mojica *et al.* established the scientific rationale regarding the combination of ceftazidime/avibactam with aztreonam for the treatment of MBL-producing Gram-negative bacteria, including *S. maltophilia*.[94,95,98,231–234] Aztreonam is not hydrolysed by any MBL, and avibactam inhibits other β-lactamases present that would otherwise inactivate aztreonam.[94,95,98,234] Limited clinical data from case reports support the possibility that ceftazidime/avibactam plus aztreonam may be an option for patients with *S. maltophilia* infections.[235,236]

Finally, cefiderocol was approved by the FDA in November 2019 for the treatment of complicated urinary tract infections.[237,238] Against *S. maltophilia*, cefiderocol has exhibited excellent *in vitro* activity, with MIC_{50}, MIC_{90} and MIC ranging from 0.06 to 0.25 mg/L, 0.25 to 0.5 mg/L and <0.03 to 4 mg/L, respectively.[134,239–246] Despite these *in vitro* data, limited clinical trial data have been unexpected.[241,242,246,247] This was the case for the data collected as part of the CREDIBLE-CR trial, a randomized open-label multicentre study comparing cefiderocol to best available therapy. In this trial, only five cases of *S. maltophilia* infection were enrolled, all pneumonia cases and all in the cefiderocol treatment group. In this small sample size, despite low cefiderocol MICs, the treatment response for all five cases was deemed indeterminate and all-cause mortality was 80% (4 of 5) at the end of the study.[247] These data echo the clinical experience of trimethoprim/sulfamethoxazole in the treatment of *S. maltophilia* infections, and highlight the importance of incorporating clinical response as an indicator of treatment success, alongside microbiological response and PK/PD variables, to validate clinical breakpoints.

Summary

S. maltophilia has emerged as a difficult-to-treat opportunistic nosocomial pathogen. As highlighted in this review, the clinical challenges posed by this microorganism extend beyond its intrinsic multidrug resistance, as there are many gaps in our knowledge of this bacterium. More research is required to understand the implication of the molecular heterogeneity of the *S. maltophilia* complex and the clinical relevance of the resistance and virulent determinants within the genomic groups associated with human infections. Likewise, it is imperative to standardize reproducible and accurate ASTs tailored to *S. maltophilia* that allow trustworthy assessment of the antimicrobial profiles of contemporary clinical strains. Moreover, translational PK/PD approaches are also needed to adjust dosing of existing and investigational therapeutic options, targeting different infection sites and aiming to minimize the development of resistance. These models should also consider the dynamics of polymicrobial communities, which are especially relevant in the case of lung infections.

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