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New strategies against *Stenotrophomonas maltophilia*: a serious worldwide intrinsically drug-resistant opportunistic pathogen

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Stenotrophomonas maltophilia is a worldwide human opportunistic pathogen associated with serious infections in humans, and is most often recovered from respiratory tract infections. In addition to its intrinsic drug resistance, this organism may acquire resistance via multiple molecular mechanisms. New antimicrobial strategies are needed to combat *S. maltophilia* infections, particularly in immunocompromised patients, cystic fibrosis patients with polymicrobial infections of the lung, and in patients with chronic infections. This editorial reports on newer drugs and antimicrobial strategies and their potential for use in treatment of *S. maltophilia* infections, the development of new technologies to detect this organism, and identifies strategies currently in use to reduce transmission of this pathogen.

The WHO lists *Stenotrophomonas maltophilia* as one of the leading drug-resistant pathogens in hospitals worldwide [101]. *S. maltophilia* is an opportunistic multidrug resistant (MDR) Gram-negative bacterium that causes serious infection in immunocompromised patients; this organism is associated with a high mortality rate and is of significant concern in bloodstream infections of cancer patients and in patients with central venous catheters [1]. In 2012, the Study for Monitoring Antimicrobial Resistance Trends program reported *S. maltophilia* as one of the top four pathogens associated with intra-abdominal infections in the Asia-Pacific region (Australia, China, Hong Kong, Malaysia, New Zealand, the Philippines, Singapore, South Korea, Taiwan, Thailand and Vietnam) [2]. In 2012, the SENTRY Antimicrobial Surveillance program reported that *S. maltophilia* is one of the top 10 pathogens causing pneumonia in patients in Latin American medical centers in Brazil, Argentina, Mexico and Chile [3]. Several documented cases of community-acquired *S. maltophilia* infections have also been reported [4].

This MDR organism has been found in soils, plant rhizosphere, animals, water, washed foods and recovered from aqueous-associated surfaces and solutions in the clinical and domestic setting [5]. *S. maltophilia* is not a highly virulent pathogen but is recognized as a significant nosocomial pathogen, and the incidence of hospital-acquired *S. maltophilia* infections is rising [5]. *S. maltophilia* is most frequently recovered from respiratory tract infections and is also found associated with a variety of infections including those of the blood, eye, soft tissue and bone, heart and brain [5].

A significant feature of *S. maltophilia* is its ability to colonize and form biofilms on lung epithelial cells, medical devices and implants used in humans [5,6]. *S. maltophilia* biofilms form on glass and plastics [7]. The rate of *S. maltophilia* biofilm formation can be influenced by the cell's surface ultrastructure [7].

There is considerable discussion about whether *S. maltophilia* is not simply a

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colonizing organism, but one that causes infection and reduces lung function in cystic fibrosis (CF) patients. Mouse model of pneumonia studies have reported that *S. maltophilia* infection resulted in significant early inflammatory response with a high neutrophil count and with high levels of chemoattractant chemokines [8,9]. These results are similar to those found in CF patients with pulmonary disease [9].

In a study using a validated definition of chronic infection, CF patients with chronic *S. maltophilia* infection demonstrated a specific immune response to this pathogen and a significant higher risk of hospitalization for pulmonary exacerbation necessitating antibiotic treatment [10]. A worsening lung function is associated with chronic *S. maltophilia* infection in CF patients [10]. Together, these observations suggest that *S. maltophilia* may be a pathogen in CF patients [10].

S. maltophilia is an intrinsically drug-resistant organism. MDR *S. maltophilia* isolates recovered worldwide have demonstrated resistance to β-lactam drugs, aminoglycosides, quinolones, macrolides, cephalosporins, trimethoprim–sulfamethoxazole (TMX), carbapenems, tetracyclines, chloramphenicol, polymyxins and biocides enabled through a variety of molecular mechanisms including decreased permeability of the outer membrane, multidrug efflux pumps, chromosomally and plasmid-encoded β-lactamases, transposons, integrons and biofilms [1,5,11,12]. It has been suggested that the intrinsic drug resistance of *S. maltophilia* clinical isolates may not be due to the use of antibiotics in the clinical setting [13]. As *S. maltophilia* is an environmental organism, it is plausible that antibiotic resistance genes have been acquired from the natural nonhuman environment [13,14].

The emergence of new antimicrobial resistance mechanisms in *S. maltophilia* requires monitoring and reporting of antimicrobial susceptibility testing of isolates of this organism. *In vitro* antimicrobial susceptibility testing of *S. maltophilia* isolates continues to be problematic as comparisons of testing methods (e.g., E-tests, disc diffusion, agar dilution) on these isolates are challenging [15,16]. According to the US Clinical and Laboratory Standards Institute guidelines, minimum inhibitory concentration (MIC) breakpoints are available for some antimicrobial agents (e.g., TMX, levofloxacin) but not for all antimicrobial agents tested against this organism [16]. There is a need to establish guidelines for the susceptibility testing of *S. maltophilia* isolates from CF patient with respiratory secretions and for isolates from patients with chronic *S. maltophilia* infections [16]. Currently used antimicrobial breakpoints are established for use against organisms isolated from acute infections and assessed by achievable bloodstream concentration of the antimicrobial, not necessarily reflecting the achievable concentration of the aerosolized drug within the lung environment [16].

There has been an increase in antimicrobial resistance of *S. maltophilia* over recent years, notably to TMX, once a preferred treatment for *S. maltophilia* infections [17]. In a 2012 study of *S. maltophilia* recovered from CF patients, 24.2% of the patients had TMX-resistant isolates [16]. This underscores the need for development of new antimicrobials or new combinations of antimicrobials. Tigecycline and levofloxacin are two newer antimicrobials that alone or in combination with other antimicrobials show promise for their use in CF patients [18–21].

A 2010 review of new antibacterial agents and their potential for use in CF patients reported tigecycline as effective (MIC_{90} of 2 mg/l) against *S. maltophilia* isolates [18]. Synergism of tigecycline with TMX, colistin and amikacin against *S. maltophilia* has been reported. Tigecycline must be used with caution in patients with CF-associated liver disease and/or cirrhosis and should not be used by patients <12 years of age or by pregnant women [18]. In an antimicrobial susceptibility study of 1,586 *S. maltophilia* clinical isolates (predominantly from bloodstream and respiratory tract infections) recovered from medical centers in Europe, North America, Asia and the Pacific region and Latin America, tigecycline was reported as the most effective antibiotic (MIC_{90} values of 2 μg/ml and with a susceptibility rate of >90%) for all regions [19].

In 2011, the pharmacokinetics and safety of an inhaled solution of the fluoroquinolone levofloxacin was assessed for use in CF patients [20]. Clinical trials reported that this drug is well tolerated in human patients with no significant adverse effects, reaching high concentrations (mean C_{max} value of 4,691 mg/l) in sputum and low concentrations (mean C_{max} value of 1.71 mg/l) in serum [20]. A Canadian study in 2011–2012 investigated the antimicrobial susceptibility of 125 CF *S. maltophilia* isolates from sputum and bronchoalveolar lavage grown planktonically and in a biofilm [21]. High-dose levofloxacin (100 mg/l achievable in sputum after aerosolization) alone was effective against planktonic and biofilm grown cultures. Double antibiotic combinations of this high dose of levofloxacin with azithromycin, TMX, ticarcillin–clavulanate or colistin (200 mg/l achievable in CF sputum after aerosolization), demonstrated efficacy against 99% of the planktonic isolates; however, the range of efficacy for these combinations dropped to 58–62% when tested against biofilm grown isolates [21]. Hypoglycemia secondary to levofloxacin has been reported in elderly patients with renal failure [22]. Resistance to levofloxacin appears to be emerging. In the 2012 Study for Monitoring Antimicrobial Resistance Trends study, only 73.5% of the tested *S. maltophilia* isolates associated with intra-abdominal infections demonstrated sensitivity to levofloxacin with no significant difference in susceptibility observed for isolates recovered from nosocomially or community-acquired infections [2]. In 2013, resistance to levofloxacin due to hyperproduction of efflux drug pumps has been identified in *S. maltophilia* isolates from Latin America [23].

In addition to tigecycline and levofloxacin, ticarcillin/clavulanate has demonstrated efficacy against *S. maltophilia*. In a 2010 study, testing 15 combination pairs of antimicrobials against 80 *S. maltophilia* isolates from Scottish CF patients, ticarcillin/clavulanate with aztreonam, ticarcillin/clavulanate with colistin and ticarcillin/clavulanate with levofloxacin demonstrated the most synergy (91.7, 40.0 and 19.4%, respectively) [16].

The usefulness of *in vitro* antimicrobial testing of *S. maltophilia* isolates is limited, however, as the determined efficacy of the antimicrobial may not be accurate in a polymicrobial infection containing *S. maltophilia* and other organisms such as *Pseudomonas aeruginosa* and *Burkholderia* species. *S. maltophilia* has been co-isolated with *P. aeruginosa* from sputa of CF patients. A diffusible signal factor released by *S. maltophilia* alters the biofilm formation and polymyxin sensitivity of *P. aeruginosa* [24]. This signal factor may be an appropriate target for pharmaceutical intervention in patients co-infected with these pathogens. One unresolved question is, 'What role is *S. maltophilia* playing in its interactions with co-colonizing organisms?' Research is needed to determine if drug resistance is being exchanged between *S. maltophilia* and other co-colonizers within biofilms. Clarification of *S. maltophilia* as a co-colonizer or co-pathogen in polymicrobial infections, such as those often seen in the CF lung, will provide insight for when and how to administer appropriate pharmaceutical therapy to combat these infections.

To further our understanding of the significance of the presence of *S. maltophilia* in human infection, there is a need for continuing to develop technologies to detect this organism. Matrix-assisted laser desorption–ionization time-of-flight mass spectrometry (MALDI–TOF MS) and new molecular biology methods such as PCR–electrospray ionization-quadrupole TOF MS have strengthened our ability to identify pathogens including *S. maltophilia* [25]. MALDI-TOF MS is used by several clinical microbiology laboratories for identification of microbial isolates. The method is relatively fast and low cost and uses a comparison of the data for each isolate with available databases of mass spectra. For some species, MALDI-TOF MS can identify a microbial isolate to a level as low as subspecies and strain. This technique can identify antibiotic resistance through detection of enzymatic activity (e.g., β-lactamase in *S. maltophilia*) of the isolate [25]. PCR–electrospray ionization–quadrupole TOF MS is a new method that identifies bacterial isolates using MS and PCR to detect species-specific DNA [25]. This method could be used to detect genetic heterogeneity of 16S rRNA among different groups of *S. maltophilia* isolates.

Once identification of an isolate as *S. maltophilia* has been achieved, next-generation sequencing of bacterial genomes provides another methodology for use by clinical microbiology laboratories to detect antimicrobial resistance markers and virulence factors present in this pathogen [25]. In addition to sequencing, PCR and RT–PCR are useful for identification of virulence- and antimicrobial resistance-encoding genes in *S. maltophilia* isolates.

Conclusion

Health care workers are becoming more aware of *S. maltophilia* as an emerging opportunistic pathogen. This organism is a common contaminant of water and is able to colonize moist surfaces [5]. Several important measures of prevention must continue to be used by health care personnel in efforts to reduce transmission of this serious pathogen. These measures include hand washing with soap and ensuring appropriate cleaning and disinfection of medical devices used with patients [1,5,12]. Care must be taken to avoid using hospital tap water to wash patient wounds and avoid disposing of potentially and contaminated antimicrobial solutions into sites that can come into contact with susceptible individuals [1,5,12].

Clinicians have an urgent need for new antimicrobial therapies to keep pace with infections of MDR *S. maltophilia*. Treatment therapies with the potential to circumvent or slow the development of antimicrobial resistance include use of antisense RNA to target genes used in virulence [26], phage therapy [27], nanoemulsions [28] and the use of adjuvants to restore antibiotic efficacy [29]. To date, the author is not aware of the use of these therapies against *S. maltophilia* infections in patients; however, it is reasonable to suggest that combinations of these therapies and existing antibiotics will help treat infections caused by this MDR organism.

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