Role of *Stenotrophomonas maltophilia* in hospital-acquired infection

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ABSTRACT

Stenotrophomonas maltophilia (previously *Pseudomonas maltophilia, Xanthomonas maltophilia*) is highly resistant to antibiotics. It causes infections that result in increased morbidity, but not usually mortality, in patients with weakened host defences. The increase in *S. maltophilia* nosocomial infections is due to the changing nature of the hospital patient population and to changes in antibiotic usage. Detection, identification and susceptibility testing methods require improvement, and this complicates the comparison of published data. Susceptibility testing should be reserved for those isolates that are clearly associated with disease. Treatment can be difficult and may be complicated by biofilm formation. *S. maltophilia* can both acquire and transfer resistance to antibiotics. Future therapeutic development may be directed against biofilms and efflux mechanisms, in order to render the organism more susceptible to available antimicrobial agents.

KEY WORDS: Bacterial infections.
Drug resistance, bacterial.
Intensive care.
Stenotrophomonas maltophilia.

Introduction

Hospital-acquired infections, otherwise known as nosocomial infections, pose a threat to patient well-being and to the efficient operation of hospitals. The policies used to limit the spread of such infections can lead to the temporary closure of certain facilities, the need to destroy equipment that cannot be sterilised and to extra duties for personnel. This can place significant burdens on hospital resources, reducing their capacity to provide care. Hospitals employ a variety of measures to try to prevent nosocomial infections; however, increasing healthcare costs mean that preventive strategies must show that they are effective in reducing nosocomial infections and also that they are cost effective. Clearly, the key to success lies in the use of current knowledge of nosocomial pathogens.

Nosocomial infection remains the most common type of complication affecting hospital patients. It is caused by a wide variety of microorganisms and, in most developed countries, 6–10% of patients who go into hospital acquire such an infection.[1] Furthermore, more than 20% of patients admitted to European intensive care units (ICUs) develop an ICU-acquired infection.[2] American surveillance data found that 27% of all nosocomial infections in American medical ICUs were due to pneumonia, with 86% of nosocomial pneumonia associated with mechanical ventilation and primarily due to Gram-negative aerobic organisms.[3] Nosocomial pneumonia has been found to increase hospital stay by as much as 14 days.[3]

A patient who has acquired a nosocomial infection will usually require treatment. The optimal treatment of nosocomial infection requires that antimicrobial therapy be started early in the course of infection, using the correct agent, at the most appropriate dose, and for an adequate duration. Such antibiotic prescribing has been shown to significantly reduce mortality, length of ICU and hospital stay and overall costs.[4]

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Choice of appropriate antimicrobial therapy is complicated by a number of factors, particularly use of antibiotics prior to hospitalisation and to resistant pathogens. Resistance to antimicrobial agents is emerging in a wide variety of pathogens, particularly those that cause nosocomial infection.[4] As a consequence of this, increasing resistance, morbidity and mortality due to nosocomial infection is also increasing.[4] One reason for the administration of inappropriate therapy is the presence of Gram-negative bacteria that are resistant to the newer cephalosporins.

The ubiquitous Gram-negative bacillus *Stenotrophomonas maltophilia* is intrinsically resistant to many classes of antibiotic and is a significant nosocomial pathogen, particularly in debilitated patients.[5,6] In a survey of 20 British medical microbiologists conducted in 2000, *S. maltophilia* was voted the ninth most important multidrug-resistant pathogen.[7] Among the Gram-negative bacilli, only *Pseudomonas aeruginosa, Acinetobacter* spp. and *Klebsiella* spp. were judged a greater problem.[7] In the fight against *S. maltophilia* nosocomial infections, the relationship between virulence, transmissibility and antibiotic resistance must first be understood.[8]

Stenotrophomonas maltophilia

Nomenclature

In 1961, *S. maltophilia* was designated *P. maltophilia* on the basis of its flagellar characteristics.[5] In 1983, the new name *Xanthomonas maltophilia* was proposed on the strength of ribosomal RNA (rRNA) homology data,[5] but in 1993 it was moved to the newly formed genus *Stenotrophomonas*, due to the inconsistencies it showed with *Xanthomonas*.[5]

Occurrence

S. maltophilia is an environmental organism found in water, soil and on plants such as fruits, vegetables, flowers and wheat.[5,9] Like *P. aeruginosa*, it is ubiquitous in aqueous environments and can be cultured readily from water sources in homes and hospitals.[5] It has been isolated from well water, river water, raw milk, frozen fish, raw sewage, human and rabbit faeces,[10] and also colonises the gastrointestinal tract.[11]

It has been found as a contaminant of ambulance oxygen humidifier water reservoirs, brushes used for preoperative shaving, chlorhexidine-cetramide disinfectant, EDTA anticoagulant in vacuum blood collection tubes, transducer dome and calibration devices, a cardiopulmonary bypass pump, in ice-making machines, tracheal suction catheters, breathing circuits, 'sterile' water and on the hands of staff.[10]

S. maltophilia has been isolated from various clinical settings, including meningitis,[12] septicaemia,[12] endocarditis,[12] pneumonia,[12,13] peritonitis,[13] urinary tract infection,[12] ocular infection,[12] epididymitis,[12] mastoiditis,[12] soft-tissue and wound infections,[13] cholangitis,[13] osteochondritis,[13] bursitis[13] and paranasal sinusitis.[13]

Culture and identification

S. maltophilia grows on nutrient agar, although most strains require methionine (or cysteine plus glycine) for growth.[14] Isolation from normally sterile body sites is straightforward, and bacteraemia and septicaemia can be detected using standard blood-culture techniques.[5] However, Klärner *et al*. pointed out that problems may occur when using automated blood-culture systems.[15] It should be borne in mind, however, that the data they presented for *S. maltophilia* was drawn from experimental work, and during their one-year clinical study they did not recover a single isolate of *S. maltophilia* from a patient.

The problem, however, has more to do with the isolation of the bacterium from specimens taken from body sites with a normal flora. Denton *et al*. were able to show that the use of a selective medium improved the sensitivity of culturing for *S. maltophilia*, when compared to an established procedure that did not use a selective medium.[16]

Their group used a mannitol agar base supplemented with vancomycin (5 mg/L), imipenem (32 mg/L), amphotericin-B (4 mg/L) and bromthymol blue as the pH indicator. *S. maltophilia* does not produce acid from mannitol and could be distinguished clearly from other Gram-negative carbapenam-resistant bacilli isolated on the medium during the study.

Graff and colleagues demonstrated a direct correlation between the frequency of *S. maltophilia* isolation and its density in the sputum of CF patients.[17] Thus, under-reporting of *S. maltophilia* from respiratory specimens of CF patients can occur if inappropriate culture techniques are applied.[17]

Colonies of *S. maltophilia* resemble those of *P. aeruginosa*, being opaque and flat with rugose surfaces and uneven borders. In addition, a yellow or brown diffusible pigment may be produced.[14] They develop a characteristic faint lavender-green colour and strong odour of ammonia when grown on a blood agar medium.[14]

S. maltophilia produces haemolysins that are active against horse and sheep erythrocytes;[18] however, the haemolysis may take three days to appear and may be confined to the area under the colonies. Indophenol oxidase is usually not detected.[14] A partially thermostabile DNase is produced[14,18] and aesculin is hydrolysed.[14] It should be remembered that media used to detect enzymatic activities of non-fermenters, including *S. maltophilia*, should be incubated at 30°C.[14]

S. maltophilia is motile, and cultures to test for motility should be incubated at room temperature, as the synthesis of flagellar proteins is favoured by low temperature.[14] *S. maltophilia* produces acid from maltose but not always from glucose.[5,19,20]

Misidentification of a range of Gram-negative non-fermenters, including *S. maltophilia, Achromobacter xylosoxidans* and the *Burkholderia cepacia*-complex presents a challenge to effective infection control in CF.[21] The misidentification of *S. maltophilia* as *B. cepacia*-complex has been documented.[22,23] The interpretation of DNase tests requires particular attention.[5] Kiska *et al*.,[24] van Pelt *et al*.,[25] Rhoden *et al*.[26] and Otto *et al*.[27] showed that commercial systems used to identify *S. maltophilia* are not equally accurate. *S. maltophilia* can be identified by the Api 20NE system (bioMérieux, Marcy l'Etoile, France).[16,25]

Whitby and colleagues addressed this problem and developed a species-specific rRNA-directed polymerase chain reaction (PCR) technique for the identification of *S. maltophilia*.[9] When used for identification, the method showed a sensitivity and specificity of 100%.[9] They also indicated its potential for detecting *S. maltophilia* in clinical specimens, although this requires more extensive evaluation, particularly with regard to the usefulness of the information generated.[9]

Reference facilities, such as the Laboratory of HealthCare-Associated Infection (LHCAI) in England, are available in certain countries. The LHCAI offers molecular comparison of epidemiologically related isolates using pulsed-field gel electrophoresis (PFGE). It also offers identification of *S. maltophilia* by multiplex PCR.

Susceptibility testing

Susceptibility testing of *S. maltophilia* poses certain problems. These are related to the methods used and the differing results that they produce.[28] Disc diffusion testing is not recommended.[5] Automated susceptibility testing methods have also been shown to have limitations.[29,30] The E-test method or minimum inhibitory concentration (MIC) broth micro-dilution tests may be more useful.[5] No gold-standard or true reference method can be established without a correlative clinical investigation.[30] Such work has not been conducted on *S. maltophilia*. The American NCCLS has a subcommittee that is looking into this problem.[5]

Given these disparate results, Carroll *et al*. contended that all susceptibility testing techniques are inaccurate with *S. maltophilia*.[30] As a result of this situation it can be difficult, if not impossible, to compare published resistance rates if the methods used are not identical. Thus, it is important to

follow locally/nationally accepted procedures. In the UK, the methodology of the BSAC is generally followed. It should be noted that King published a supplement to this method, which describes the modifications to standard procedures required when testing *S. maltophilia*.[31] Essentially, the modifications seem to require MIC determination and incubation at 30°C.[31]

Testing should be reserved for those isolates that are clearly associated with disease, and it may be prudent for laboratories that test these organisms to add an interpretive comment to the effect that susceptibility testing may determine *in vitro* resistance, but may not predict therapeutic efficacy.[30]

Owing to the limited choice of antimicrobials available to treat *S. maltophililia* infections, the emergence of resistance should be monitored carefully.

Resistance mechanisms

S. maltophilia shows high-level intrinsic resistance to a variety of structurally unrelated antibiotics, including β-lactams, quinalones and aminoglycosides.[32]

Multidrug efflux pumps and the impermeable outer membrane contribute to the intrinsic antibiotic resistance of *S. maltophilia*.[33] Some of the multidrug efflux pumps appear to be homologous with those already described in *P. aeruginosa*,[32] while others are different.[34] Alonso and colleagues have shown that *S. maltophilia* strains, in which over- expression of the multidrug efflux pump SmeDEF occurs, are less environmentally 'fit' and are possibly less virulent than wild-type strains.[35] This observation may also apply to the SmeABC multidrug efflux pump.

Most Gram-negative bacilli are quite sensitive to aminoglycoside antibiotics, but *S. maltophilia* is not.[36] Aminoglycoside resistance in *S. maltophilia* is mediated by efflux pumps and enzyme inactivation. The aminoglycoside-modifying enzyme AAC(6′)-Iz acetyltransferase confers resistance to tobramycin, netilmicin, sisiomicin and neomycin.[36] The temperature-dependent variation in susceptibility to aminoglycosides and polymixin B, but not to quinolones, β-lactams and chloramphenicol, is linked to outer membrane lipopolysaccharide characteristics.[33] *S. maltophilia* shows greater resistance to aminoglycosides and polymixin B at 30°C than at 37°C.

Resistance to β-lactam agents is primarily intrinsic and mediated by at least two inducible β-lactamases (L1, an Ambler class-B metallo-β-lactamase [penicillinase], and L2, an Ambler class-A active site serine β-lactamase [cephalosporinase]).[19,37] These two β-lactamases are induced when cells are exposed to β-lactams, and can hydrolyse almost all classes of β-lactam antibiotic.[19,38] Avison *et al*. have recently shown that the production of these two β-lactamases is not coordinated, a finding based on mutant studies that goes against the previously accepted hypothesis.[38]

The results of Valdezate *et al*. suggest that, for quinolones, both permeability and topoisomerase targets in *S. maltophilia* may differ from those in other Gram-negative bacteria.[28]

S. maltophilia can acquire and transfer resistance to antibiotics. Alonso and colleagues have documented the transfer of DNA from Gram-positive bacteria to *S. maltophilia*.[39] They provided evidence that *S. maltophilia* D457 has acquired a cluster of antibiotic and heavy-metal resistance genes from Gram-positive bacteria. Most of these genes are isoforms of genes previously found in *Staphylococcus aureus* plasmids.[39] Furthermore, Barbolla and colleagues have demonstrated the spread of class-1 integrons coding for sulfamethoxazole/trimethoprim resistance in *Stenotrophomonas maltophilia*.[40] Chang *et al*. have suggested that integrons and plasmids do not play a major role in the resistance of *S. maltophilia*.[41]

Pathogenicity

S. maltophilia is distinguished by a high degree of antibiotic resistance, rather than by invasiveness and tissue destruction, and is a major concern, primarily in immunocompromised patients.[2]

S. maltophilia produces DNase, RNase, arbutinase, acetase, esterases, lipases, mucinase, acid and alkaline phosphatases, phosphoamidase, leucine arylamidase and β-glucosidase.[18] Some strains may produce elastase and hyaluronidase.[18] The production of proteases and elastase plays a significant role in bacterial pathogenesis, participating in invasion, tissue damage and host defence evasion.[42] Production of lipases seems to contribute to the virulence of some species associated with pulmonary infections, either by hydrolysing lipid-rich pulmonary tissue components or by triggering an intense inflammatory response.[42]

The *spgM* gene codes for the production of a hexose phosphate mutase, which is required for alginate and thus lipopolysaccharide production.[33] Using a rat lung model, McKay and colleagues showed that a functional *spgM* gene is required for colonisation by *S. maltophilia*, and leads to histopathological changes in the lung.[33] No histopathological changes were observed for mutants lacking a functional *spgM* gene. The gene also confers resistance to complement-mediated cell killing.[33] Thus, outer membrane lipopolysaccharide is an important virulence determinant in *S. maltophilia* and *SpgM* is important for the maintenance of the lipopolysaccharide structure.

Adherence to epithelial cells is central to the initiation of colonisation or invasion of host tissues by many bacteria. This event is often mediated by fibrillar structures called fimbriae or pili. Fimbrial adhesins may mediate direct binding of the bacteria to the host target cell, or may mediate indirect binding by forming cross-link liaisons between bacteria that favour colonisation. All 46 clinical isolates of *S. maltophilia* studied by de Oliveira-Garcia *et al*. produced peritrichous semiflexible fimbriae,[43] which enabled *S. maltophilia* to adhere to cultured epithelial cells and inert materials, resulting in biofilm formation.[43]

Biofilms are composed of a surface-associated community of cells that is enclosed in an extracellular matrix composed of polysaccharides and proteins.[43] Bacterial biofilms are frequently found in persistent infections such as those associated with cystic fibrosis and foreign-body-associated infection.[8] Bacteria growing in biofilms are more resistant to the action of phagocytic cells' antibacterial activity, as well as to the action of antibiotics, than are those that have a planktonic way of life.[8]

Adhesion of *S. maltophilia* to abiotic surfaces, such as medical implants and catheters, results in line-related colonisation and infection.[43] In this way, endotracheal tubes, for example, can contribute to pneumonia pathogenesis by allowing direct entry of bacteria into the lung and by providing a surface along the inside of the tube for the

formation of a bacterial biofilm.[3] Organisms that reach the inside of the tube can proliferate easily because this site is not protected by host defences, and antibiotics do not penetrate there.[3] More than three-quarters of endotracheal tubes studied had a biofilm that contained bacteria.[3]

Hanes *et al*. noted that the clinical presentation (temperature, WBC count, presence of purulent aspirates, ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen) of *S. maltophilia* pneumonia was no different to that of pneumonia caused by other Gram-negative bacteria, which indicates that the severity of illness is similar.[44]

During the study of tobramycin solution inhalation therapy (TSI) in CF patients reported by Graff *et al*., the use of TSI to suppress *P. aeruginosa* improved lung function, regardless of *S. maltophilia* culture frequency.[17] However, improvement was not as marked among patients who were persistently co-infected with *S. maltophilia*,[17] indicating that it played an active role in the disease process.

Generalised *S. maltophilia* infection has now been documented,[45] which shows the ability of the organism to disseminate within the body, even if this manifestation is exceptional at this point in time.

Finally, *S. maltophilia* also has the potential for indirect pathogenicity, as it can aid other pathogens. Katayoka *et al*. have shown that β-lactamases produced by *S. maltophilia* can increase the survival of *P. aeruginosa* that are normally susceptible to imipenem when the two organisms grow in culture together.[19]

S. maltophilia infection

Risk factors

The single most important predisposing factor for infection with *S. maltophilia* is the presence of a compromised immune system.[2] Previous broad-spectrum antimicrobial treatment, prolonged hospitalisation, instrumentation, ICU exposure and significant underlying disease are associated with an increased risk of developing *S. maltophilia* infection,[46] which must always be suspected in patients who develop a superinfection while receiving carbapenems.[2]

Previous antibiotic treatment promotes colonisation and infection by antibiotic-resistant bacteria that otherwise may not be able to compete effectively with indigenous microflora. In this way, antibiotic resistance is a relevant colonisation factor when the microorganisms interact with the treated patient. Epidemiological studies have demonstrated that antibiotic therapy is a relevant risk factor for colonisation by *S. maltophilia*.[8]

Sanyal *et al*. showed that a sustained increase in the use of carbapenems in a hospital environment might play a more important role in the acquisition of an *S. maltophilia* infection than previous therapy of the individual patient with a carbapenem.[47] Their data also suggested that third-generation cephalosporins are much less effective in promoting *S. maltophilia* nosocomial infections than are carbapenems.[47]

The work of Schaumann and colleagues supported the finding that pretreatment with a carbapenem is no longer an unequivocal risk factor for *S. maltophilia* infection.[48] They did find that the length of hospital stay proved to be an independent risk factor for acquiring an *S. maltophilia* infection and that its isolation in clinical specimens is associated with longer hospitalisation of patients.[48]

Friedman *et al*. reported that the mean duration of stay prior to bacteraemia was 19 days.[6] *S. maltophilia* pneumonia usually occurs as late-onset nosocomial pneumonia (i.e., beginning after more than five days' hospitalisation).[3] Cefepime exposure and the presence of a tracheostomy were identified as the most significant risk factors for development of *S. maltophilia* ventilator-associated-pneumonia in the retrospective study of trauma patients conducted by Hanes and colleagues.[44]

Nosocomial pneumonia often occurs by aspiration of oropharyngeal flora, and the nature of this changes with time in the hospital but not with duration of mechanical ventilation.[3] The role of endogenous ICU flora, with a high incidence of endemic resistant bacteria, is important in determining the bacteriology of early- or late-onset nosocomial pneumonia, reiterating the importance of detailed knowledge of local ICU microbiology in planning accurate empiric therapy.[3]

Diabetics serve as an example of patients who have underlying disease. Diabetic patients with foot ulcers are often exposed to high levels of antibiotic selective pressure and may develop multiresistant *S. maltophilia* infections for which limb amputation may be the only remaining therapeutic measure.[46]

The compromised immune system of human immunodeficiency virus (HIV) patients increases their risk of acquiring infections, and *S. maltophilia* infection is no exception to this rule. *S. maltophilia* infection is usually associated with an advanced HIV infection, occurring in patients with a previous or concurrent acquired immune deficiency syndrome (AIDS) diagnosis.[49] Therefore, these bacterial infections are related to a concurrent, severe immunodeficiency stage, which was characterised in the study of Calza *et al*. by a mean CD4+ lymphocyte count (±SD) of 72±25.2 cells/μL, while the mean CD4+ cell count (±SD) in the HIV control group without *S. maltophilia* infection was 448±211 cells/μL.[49]

Graff *et al*. found the systemic administration of steroids to be a risk factor for *S. maltophilia* acquisition in CF patients, although inhaled steroids posed no increased risk.[17] The study of Talmaciu and colleagues confirmed this difference.[50]

Patients with CF are infected by a predictable cascade of pathogens, and chronic lung disease is the most common cause of morbidity and mortality.[51] In efforts to treat pulmonary exacerbations and slow the progression of lung disease, CF patients receive multiple courses of oral, intravenous and aerosolised antibiotics. As the life expectancy of CF patients has increased, newly emerging pathogens, such as *S. maltophilia*, have been detected.[51] During the study of CF patients reported by Graff *et al*., inhalation therapy with tobramycin solution (TSI) did not result in a greater risk for isolation of *S. maltophilia* than that seen with standard care alone.[17] In contrast, oral quinolone antibiotic use during the trial was associated with a 2.7-fold increased risk of having a culture positive for *S. maltophilia*.[17]

Colonisation versus infection

Antibiotic treatment should not be started at the colonisation stage to eradicate carriage of *S. maltophilia*, and antibiotics should only be used if clinical and laboratory signs of infection appear.[52] Patients with *S. maltophilia* infection have elevated C-reactive protein values and may have a slightly elevated white blood cell count.[48]

The microbiological diagnosis of pneumonia can be made non-invasively by quantitative or qualitative culture of sputum, tracheal aspirate or invasively by isolation of organisms via bronchoscopy.[3] It must be remembered, however, that oropharyngeal contamination and colonisation may result in positive sputum cultures in the absence of infection.[3] Bronchoscopy techniques include bronchoalveolar lavage (BAL) or protected specimen brushes (PSB), with quantitative cultures, specifically using $\geq 10^3$/mL for PSB and $\geq 10^4$/mL for BAL, to help differentiate infection from colonisation.[3] However, it has been found that guiding management by the results of invasive diagnostic methods led to no improvement in mortality, compared with management guided by non-invasive quantitative culture methods.[3]

Graff *et al*. noted in their study of CF patients that it appeared that a substantial portion of intermittently culture-positive patients in the trial were transiently re-infected with different isolates at different visits and, thus, were not continuously colonised with *S. maltophilia*.[17] It is also possible that the culture-positive patients were being infected with multiple *S. maltophilia* genotypes and that they isolated different genotypes as a result of their culturing techniques.[17] Thus, it is unclear whether any of the factors identified as risks for *S. maltophilia* isolation do, in fact, predispose patients to colonisation/infection or that colonisation is a common, transient and recurring phenomenon among CF patients.[17]

Infection

Although *S. maltophilia* may cause a wide spectrum of human disease, the respiratory tract is the most common site of *S. maltophilia* infection, especially in patients with compromised lung function.[53] In the five continent multi-centre study reported by Gales *et al*., the largest number of isolates came from the respiratory tract, followed by the bloodstream, wounds and the urinary tract, in a decreasing frequency of isolation.[53] However, wound and urinary tract isolates remain relatively rare.[53]

Senol *et al*. showed that the attributable mortality rate for *S. maltophilia* bacteraemia is similar to the attributable mortality rate for other nosocomial bloodstream infections.[54] Friedman *et al*. reported that *S. maltophilia* was cultured from at least one other site in 38% of the episodes of bacteraemia studied, and the most common sites were sputum and central vascular catheters (CVC).[6]

Crispino *et al*. reported that the lower respiratory tract was the only site from which *S. maltophilia* was isolated from their adult ICU patients and that isolation always indicated infection in these patients.[55] In the study by Calza *et al*., most episodes of *S. maltophilia* infection in HIV patients were represented by bacteraemia/sepsis (48/61, 78.7%), followed by pneumonia (five cases, 8.2%) and urinary tract infection (four cases, 6.6%).[49]

Isolation of this organism from a blood culture should prompt a careful review of the patient, with particular emphasis on removal of indwelling CVCs and the commencement of appropriate antibiotic therapy.[6] Friedman *et al*. found the most common characteristics in cases of bacteraemia were the presence of an indwelling CVC and previous antibiotic therapy, and a significant correlation was found between deaths and a failure to remove the CVC or treat with appropriate antimicrobials.[6]

Adherence to the guidelines on CVC use published by O'Grady and colleagues should help to reduce CVC-related infections to a minimum.[56] These guidelines are based on use of appropriate measures and materials, and the education of all those involved in CVC management.[56] It should be noted that the different types of CVC carry different risks of infection.[56] Generally speaking, the mechanical removal of the focus of infection is beneficial in cases of *S. maltophilia* infection.[46]

Cystic fibrosis is characterised by the presence of a chronic endobronchial infection that leads to progressive suppurative obstructive lung disease, which is the primary cause of death in >90% of patients.[17] Optimising antibiotic therapy, against the major CF pathogens, and anti-inflammatory therapy is of the highest priority, as lung disease has a major impact on prognosis.[21]

P. aeruginosa is the most common bacterial pathogen isolated from the CF respiratory tract.[17] However, the microbiological flora of CF lung disease is evolving and *S. maltophilia* is being isolated with increasing frequency from CF respiratory tract secretions.[17] *S. maltophilia* prevalence rates vary considerably between CF centres, with a mean prevalence rate of 4.3–6.4%, but up to 10–25% in single centres.[21] Unlike the pathogenic roles of *P. aeruginosa* and *B. cepacia* in CF, that of *S. maltophilia*, and thus the implications for acquiring the organism, is uncertain.[17,21]

The cohort study of Goss *et al*., in which 1673 CF patients from whom *S. maltophilia* had been isolated were studied, showed that detection of *S. maltophilia* does not affect short-term (three-year) survival.[57] Nonetheless, the problematic antimicrobial resistance patterns of *S. maltophilia* and the pathogenic role of the organism in non-CF disease make the increasing frequency of *S. maltophilia* isolation in CF patients a cause for concern.[17]

Antimicrobial therapy

Treatment of infections caused by *S. maltophilia* can be difficult because it is intrinsically resistant to most antipseudomonal β-lactam antibiotics, the older quinolones and aminoglycoside agents.[2] *S. maltophilia* is routinely resistant to imipenem and meropenem.[58] Trimethoprim/sulfamethoxazole or β-lactam/β-lactamase inhibitor combinations, mainly aztreonam plus clavulanic acid, remain the most accepted therapy for *S. maltophilia* infection.[28] The most active single drugs *in vitro* against *S. maltophilia* are ticarcillin/clavulanate and trimethoprim/sulfamethoxazole, and the most active combination in synergy studies is ticarcillin/clavulanate plus aztreonam.[58] Trimethoprim-sulfamethoxazole is not bactericidal and resistance may emerge during treatment.[51]

For almost three decades trimethoprim/sulfamethoxazole has been, and remains, the therapy of choice for *S. maltophilia* infection.[2,59] Late-generation cephalosporins and antipseudomonal penicillins may also be useful.[6] Sanyal *et al*. found all the isolates included in the five-year surveillance of their hospital *S. maltophilia* population, between 1993 and 1997, to be sensitive to trimethoprim/sulfamethoxazole and ciprofloxacin.[47] Betriu *et al*. reported a decrease in the percentage of strains resistant to trimethoprim/sulfamethoxazole, but slight rise in the percentage of strains resistant to ciprofloxacin at their hospital in Madrid, Spain, during the period 1995 to 1999.[59] The significant decrease in trimethoprim/sulfamethoxazole

resistance corresponded to a decrease in the use of the drug over the five-year period.[59]

Noteworthy is the observation of Tsiodras and colleagues when examining their cohort of 40 patients with infections due to trimethoprim-sulphamethoxazole-resistant *S. maltophilia*. They concluded that such infection was not associated with an increased risk of death.[46] Antibiotic monotherapy and invasive procedures usually resulted in cure.[46]

The results of the study of *S. maltophilia* nosocomial pneumonia in trauma patients conducted by Haynes *et al*. confirmed that high mortality is associated with inadequate empiric antibiotic therapy.[44] However, *S. maltophilia* pneumonia once again was associated with increased morbidity, but not increased mortality.[44]

Few therapeutic interventions have been successful in affecting the incidence of late-onset ventilator-associated pneumonia (VAP), which carries a higher mortality than early- onset VAP.[3] In patients diagnosed with VAP on the basis of clinical criteria and positive BAL cultures, it has been shown that appropriate treatment given immediately after a clinical diagnosis of nosocomial pneumonia was associated with a significantly lower mortality, compared to inadequate or delayed treatment.[3]

On the basis of currently available information, it would be difficult to recommend withholding antibiotics pending the results of cultures obtained by bronchoscopy if there is a high clinical suspicion of pneumonia.[3] This implies that the laboratory's major role is to provide up-to-date information about the frequency of isolation and resistance levels of local ICU bacteria, in order to provide the best possible basis for selection of empiric therapy. European ICU physicians favoured using invasive microbiological diagnosis only to guide and adjust initial empiric therapy, but not to decide whether or not a ventilated patient has pneumonia, which they felt could be made on clinical grounds.[3] Furthermore, the majority agreed that they would start broad-spectrum antibiotics in a patient with VAP, irrespective of the initial Gram stain, until the results of culture became available.[3]

Increasing resistance to trimethoprim/sulfamethoxazole may prompt the use of newer quinolones, either alone or in combination with other agents.[6] However, there are few data comparing the activity of new and old quinolones.[28] Weiss *et al*. have reported significantly better *in vitro* activity of the newer quinolones trovafloxacin, clinafloxacin and moxifloxacin against 326 clinical isolates of *S. maltophilia*, compared to ciprofloxacin and levofloxacin.[60] The newer quinolones can reach a lung concentration five times their serum concentration, and quinolones exert concentration-dependent killing.[60] They suggested that this improved availability and activity make the newer quinolones an interesting therapeutic option for respiratory tract infections.[60]

Valdezate *et al*. reported the MIC_{90} of the new fluoroquinolones grepafloxacin, trovafloxacin, and moxifloxacin (0.5 mg/mL) to be eight-fold lower than those of ofloxacin and ciprofloxacin (4 mg/mL), and 16- to 128-fold lower than those of pefloxacin, norfloxacin and nalidixic acid (8–64 mg/mL), and concluded that these agents might be considered for treating *S. maltophilia* infections.[28]

In serious infections, triple therapy with either trimethoprim/sulphamethoxazole, carbenicillin and rifampicin or trimethoprim/sulphamethoxazole, minocycline and ticarcillin/clavulanate are said to be synergistic regimens.[6] Prolonged administration of antimicrobial agent may be required in patients with septicaemia.[47]

The multi-centre study of Gales *et al*. showed that among the 842 strains of *S. maltophilia* collected from 43 centres on five continents, resistance to antimicrobials varied with geographical region.[53] Trimethoprim-sulphamethoxazole resistance varied from 2% to 10%, ticarcillin/clavulanate resistance from 10% to 29%, gatifloxacin resistance from 2% to 15% and trovafloxacin resistance from 2% to 13%.[53] Of the 69 strains found to be resistant to trimethoprim-sulphamethoxazole, 77% came from the US and Europe.[53] However, it should be borne in mind that these figures are now five years out of date.

Hanberger *et al*. reported *S. maltophilia* resistance rates for strains isolated from ICU patients in different European countries over the period 1990 to 1995.[2] Gentamycin resistance varied from 46% to 89%, imipenem resistance from 94% to 100%, ceftriaxone resistance from 72% to 100%, ceftazidime resistance from 11% to 61%, piperacillin resistance from 45% to 83% and ciprofloxacin resistance from 28% to 100%.[2]

In general, treatment strategies for *S. maltophilia* in CF patients are similar to those used for *P. aeruginosa* or *B. cepacia*-complex, whereby high doses of two or more parenteral agents with different mechanisms of action are used to manage a pulmonary exacerbation.[51] Multi-resistant *S. maltophilia* poses a major problem for optimal antibiotic therapy of CF patients.[21] Combination therapy with antibiotics, shown to be active as single agents *in vitro*, given in two- to four-week courses, is recommended.[21] If the initial therapy for early colonisation/infection of a CF patient does not eradicate the organism, another treatment regimen, including intravenous antibiotics, should be administered.[21]

It is unclear how many different treatment regimens should be used before it is considered impossible to eradicate the organism in a given patient.[21] However, more studies are needed to optimise therapy.[21] While aerosolised high doses of tobramycin or colistin have proved beneficial as suppressive therapy in CF patients chronically infected with *P. aeruginosa*, there are no clinical data to support the use of these treatment modalities for *S. maltophilia*.[51]

In the six-year study (1996–2001) reported by San Gabriel *et al*., in which approximately 14% of all *S. maltophilia* isolates from US CF patients were included, doxycycline was shown to be the most active antibiotic tested (80% of isolates sensitive *in vitro*).[51] Trimethoprim-sulfamethoxazole inhibited only 16% of isolates, but 65% of isolates were inhibited when this was paired with ticarcillin-clavulanate.[51] Ticarcillin-clavulanate alone inhibited 27% of isolates, and ciprofloxacin and piperacillin both inhibited less than 4% of strains each. The authors cautioned that the interpretation of their *in vitro* results into therapeutic measures may well be complicated by factors such as biofilm formation and the effects of stationary-phase growth, which may occur in CF patients' lungs.

Epidemiology

It must be remembered that *S. maltophilia* infection may either be nosocomial or community-acquired.[45,48] Friedman *et al*. reported that 80% of cases of *S. maltophilia* bacteraemia in their tertiary care hospital were nosocomial in origin,[6] and

Calza *et al*. reported 77% of infections from their 10-year study of HIV patients as being nosocomial in origin.[49] Thus, the majority of serious *S. maltophilia* infections are nosocomial. A total of 400 cases of bacteraemia from England and Wales were reported to the Public Health Laboratory Service (PHLS) Communicable Disease Surveillance Centre (CDSC) in 2000.[61] The study of Caylan *et al*. showed that the same strains of *S. maltophilia* may have survived in the hospital environment for a period of 12 months.[62]

Unravelling the transmission routes of microorganisms is generally difficult, as multiple routes are possible, including direct patient-to-patient contact, contact between patients and healthy carriers of the bacterium (e.g., hospital personnel) who acquired colonisation from other patients or from the environment, and direct contact between the patient and environmental sources.

Among US children under two years of age suffering from CF, *S. maltophilia* is already found in throat, sputum and bronchoscopy cultures in 7% of cases.[63] This compares with a general rate of recovery from the sputum of US CF patients of more than 10%.[64] As bacterial strains may undergo substantial phenotypic change during the course of chronic infection, most bacterial organisms in CF patients are typed by genetic methods.[21] Genotyping of *S. maltophilia* in CF centres has not yet indicated transmissibility as a major problem.[21] Döring *et al*. considered normal hygienic precautions to be sufficient for preventing cross-infection with *S. maltophilia* in CF patients, and that placing patients in cohorts is not necessary for preventing transmission of *S. maltophilia*.[21]

Identification of sources, typing of the microorganism in question and case-control studies are used to investigate the epidemiology of a transmission route.[21] Reliable and highly discriminatory typing methods are essential to any microbiological surveillance programme or investigation of transmission routes.[21] 'Fingerprinting' of chromosomal DNA using PFGE or random amplified polymorphic DNA (RAPD) analysis is often used.[21] Reference laboratories are essential to assure the quality standards for species identification and strain typing and to perform techniques not available at the local level, and also facilitate the identification of the spread of epidemic strains at the national and international level.[21]

Laing and colleagues studied *S. maltophilia* isolates from three hospitals for their genetic relatedness and epidemiology.[65] They used PFGE to characterise 80 isolates and demonstrated that each of the nosocomial and community-acquired isolates in two acute-care hospitals were different, making nosocomial transmission very unlikely.[65] However, in the ICU of the third hospital, isolates from six patients had identical profiles, suggesting that spread between patients was occurring, or that a common source of infection was present.[65]

Travassos and colleagues were able to demonstrate probable patient-to-patient transmission of *S. maltophilia* in two different cases.[42] They used RAPD-PCR to establish the relatedness of the isolates.[42] Valdezate et al. were able to demonstrate nosocomial transmission of *S. maltophilia* in five separate instances.[66] They used PFGE to analyse the relatedness of their 139 isolates, all of which came from non-CF patients at the same hospital. Both Valdezate *et al*. and Travassos et al. found a high degree of genetic diversity among strains.[42,66]

Countermeasures

The anti-infectious repertoire includes hygienic measures, epidemiological controls, vaccines and antibiotics.[8] Vaccines are not relevant to the control of opportunistic infection, and antibiotics have been dealt with above.

All those concerned with anything that comes into contact with patients should adhere to hospital hygiene regulations, which must be critically reviewed should the level of nosocomial infection attain unacceptable levels. One reported outbreak of *S. maltophilia* nosocomial infection was traced to the incorrect preparation of a biocide.[67] A review and change of preparation procedures led to the resolution of the outbreak.

The equipment used during instrumentation procedures is particularly worthy of attention. Rogues and colleagues reported an outbreak of *S. maltophilia* colonisation/infection on a surgical ICU, which was resolved by improved disinfection of the temperature sensors used in the servo-controlled humidifiers of the mechanical ventilators when they were serviced between patients.[68]

The study of Denton and colleagues into the role of nebulisers in the colonisation of CF patients by *S. maltophilia* raises a number of interesting points. They showed that 10% of hospital nubulisers yielded cultures of *S. maltophilia*.[64] Almost a quarter of ward environmental sites also yielded cultures of *S. maltophilia*; however, the environmental isolates were genetically distinct from the nebuliser isolates.[64] Furthermore, none of the patients using the contaminated nubulisers had *S. maltophilia* isolated from their sputum during the study period.[64]

The contamination rate of home-use nebulisers has been reported to be similar.[64] The retrospective nature of the study and the environmental sampling at only one point in time may explain the failure to isolate matching strains.[64] None of the patients with contaminated equipment in the study had positive sputum cultures for the bacterium. However, routine sputum culture did not use a selective medium to isolate *S. maltophilia*, whereas a selective medium was used to ascertain the presence of nebuliser and environmental contamination, so the presence of low numbers of *S. maltophilia* in sputum samples may have been missed.[64] Thus the clinical significance of the frequent colonisation of nebuliser equipment by *S. maltophilia* remains uncertain[64]. However, if nebuliser equipment is rinsed in tap water between uses, it is of primary importance that it should be dried thoroughly afterwards.[64]

The results of the study by Lemmen and colleagues showed that written treatment guidelines for nosocomial infections, combined with a bedside infectious disease consulting service, resulted in a reduction in antibiotic administration.[69] Antimicrobial expenditure was reduced by 44.8% without compromising patient outcome or length of stay in the ICU.[69] The implementation of the infectious disease service was extremely cost-effective, saving a total of 24,113 euros in one year.[69] In addition, it contributed to an overall reduction in problematic and multi-resistant pathogens, with a significant decrease in isolation of *S. maltophilia*. The marked reduction in isolation of *S. maltophilia* was associated with a 75% reduction of carbapenem usage during the study period.[69]

Lannotte and colleagues reported on the usefulness of their systematic monitoring of intubated and ventilated paediatric ICU patients.[52] They tested for tracheal bacterial

colonisation twice a week and found five patients colonised with *S. maltophilia* over a four- month period.[52] Molecular typing (RAPD, PFGE) showed that four of the five strains were related.[52] Strict isolation of patients and improved application of hygiene procedures stopped the spread of *S. maltophilia* within two months.[52]

In order to avoid decline in the lung function of CF patients, it has also been suggested that regular microbiological monitoring, early intensive therapy and also perhaps anti-inflammatory therapy is warranted.[21] Although it may not be possible to eradicate bacterial pathogens from airways of patients with CF, it is important to try to remove pathogens such as *S. maltophilia* using antibiotics based on individual sensitivity tests.[21]

Conclusions

S. maltophilia is a highly resistant, ubiquitous environmental bacterium that can cause infections that result in increased morbidity, but not usually mortality, in patients with weakened host defences. The increased occurrence of *S. maltophilia* nosocomial infection is due to the changing nature of the hospital patient population and the changing pressure placed on the hospital microbiological flora due to changes in antibiotic usage.

There is a certain amount of information available to physicians and other healthcare professionals confronted with *S. maltophilia* infection. However, the completeness and comparability of this information is called into question when such factors as the sensitivity of detection methods, accuracy of identification and the meaning of susceptibility testing results are borne in mind.

Hospital hygiene remains a cornerstone in the fight against nosocomial infection. Thoughtful examination of procedures can lead to the reduction or elimination of sources of infection. Systematic surveillance, using appropriate techniques, of patients at risk can lead to timely intervention against, and the containment of, nosocomial *S. maltophilia* infection. Surveillance of antibiotic resistance rates, both locally and regionally, should be used to formulate up-to-date empirical antibiotic therapy guidelines.

In the future, efforts to eliminate biofilm formation may be valuable and could include using new adhesion-resistant materials. Effective antibiotic therapy may require the targeting of efflux mechanisms, in order to render the organism more susceptible to available antimicrobial agents. Information is the key to achieving efficient reduction in the frequency and impact of *S. maltophilia* infection, and the diagnostic medical microbiology laboratory will play a key role in extending our knowledge of this opportunistic pathogen. □

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