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An in-depth analysis of *stenotrophomonas maltophilia*: A multi-drug-resistant pathogen

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ABSTRACT

Stenotrophomonas maltophilia relates to an aerobic, gram-negative, motile, as well as non-fermentative bacillus widely considered an opportunistic pathogen. In most cases, it leads to infection in persons with *immunosuppression*, malignancies, and organ transplantation. As an organism, *Stenotrophomonas maltophilia* is an opportunist acquired from the environment and has been found to have limited ability to cause infections or colonize patients. Nonetheless, contaminated water of medical instruments in hospital environments are the principal causes of infection. Indeed, *Stenotrophomonas maltophilia has been demonstrated to cause blood stream infections as well as pneumonia with substantial morbidity immuno-suppressed patients. In turn, intrinsic resistance inhibits infection management to various antibiotic classes. Prevention is dependent upon the utilization of modern practices including an emphasis on the antibiotic control use, as well as environmental reservoirs.*

KEYWORDS

Stenotrophomonas maltophilia;
Infection;
Antibiotic;
Immunosuppression

INTRODUCTION

Stenotrophomonas maltophilia refers to an opportunist bacterium, which is acquired from the environment. It is part of the non-fluorescent cluster of pseudomonas cluster of *bacteriae*. In addition, it is considered a frequent colonizer of fluids found in hospital environments including water baths, nebulizers, intravenous fluids, as well as dialysis machines. In most cases, infections cause by this bacterium are usually seen in immuno-weakened individuals especially in instances of prolonged hospital stay, with administration of wide spectrum antibiotics, as well as malignancies. In fact, the most widespread manifestations due to this bacterium involve the soft tissues and skin. Nevertheless, *Stenotrophomonas maltophilia* is the only type or species of this genus (*Stenotrophomonas*) known to cause infections[1]. Initially isolated from pleural fluid in 1943, the organism was labeled bacterium *brookeri*. Later on, the organism was reclassified as Pseudomonas maltophilia and[2] reclassified it leading to the name *Stenotrophomonas maltophilia*. Altogether, the bacterium has several factors making it a cause for concern among professionals today. For instance, its rate of isolation leading to serious infection in immune-weakened individuals is on the rise. Yet in the clinical environment, differentiation between contamination or colonization as well as true infection with the bacterium is repeat-

edly challenging. As cited above, antibiotic treatment is largely inhibited by broad drug resistance, the absence of controlled clinical treatment experiments as well as uncertainties over the value of in-vitro vulnerability testing[3]. In fact, a major challenge in choosing optimal agents emerges when the estabslihed drug choice, in particular *co-trimoxazole*, is not an option because of contraindications including resistance.

Nonetheless, minimal progress has been made regarding identification of risk factors for the contraction of severe *Stenotrophomonas maltophilia* infections including pneumonia, *bacteraemia*, as well as the mortality risk. One of the breakthrough is that management of antibiotic use has been shown as key to prevention of infections in hospital settings. Altogether, *Stenotrophomonas maltophilia* has emerged as a human pathogen increasingly challenging microbiologists, clinicians, as well as infection-management specialists by exhibiting difficult situations. Thus, the aim of this paper revolves around exploring the present knowledge about the bacterium including epidemiology, *pathogenicity*, as well as clinical issues associated with this problematic opportunist.

TAXONOMY, MICROBIOLOGY AND IDENTIFICATION

Stenotrophomonas maltophilia or bacterium booker, was initially isolated decades ago and later on placed in the genus pseudomonas. It would later use the name *xanthomonas* before resting in *Stenotrophomonas* on the onset of the new millennium. Nevertheless, the genus (*Stenotrophomonas*) presently is known to comprise of four species and *maltophilia* is the one the causes human infection. Much information on this species remains unknown, but genetic analysis has suggested that *Stenotrophomonas maltophilia* has adapted over the years to human colonization after losing certain plant pathogenic characteristics. Subsequently, it gained likely human virulence traits[4]. In fact, the closest known sequenced relatives of this bacterium include the plant pathogenic *xanthomonads*. The bacterium isolates from clinical as well as environmental sources represent various genomic clusters – defined through DNA hybridization as well as DNA fingerprinting. In addition, a number of groups including A, B and C have been identified via 16S rRNA sequencing, with the former revealing the highest resemblance to the *Stenotrophomonas maltophilia* bacterium[5]. Several analysis of a group of clinical isolates are under group A and B, with relatively high genetic heterogeneity in the later group. Nonetheless, it remains possible that the first group strains share a number of characteristics favoring the growth of infection. It has been put forward that isolates from specific genomic clusters might be highly adapted to colonizing the respiratory system of individuals suffering from cystic fibrosis[6].

Stenotrophomonas maltophilia has also been shown to form *biofilms* solely or together with various species. Worth noting is that once the bacterium is growing in *biofilms* it becomes more resistant to antibiotics and phagocytes and thus underlining the challenge it presents to clinicians. Even though *Stenotrophomonas maltophilia* is known to engage in quorum sensing or cell to cell signaling, it does not utilize the standard LuxIR systems associated with gram-negative bacteria. Rather, it utilizes the diffusible signaling factor molecule present in the *xylella* and *xanthomonas* signaling systems. Also worth noting is that diffusible signaling factor disruption contributes to reduced *biofilm* growth, minimized production of extracellular proteases, loss of motility as well as increased susceptibility to heavy metals and various antibiotics. In addition, *Stenotrophomonas maltophilia* is known to modify the *biofilm* configuration, as well as *polymixin* tolerance of pseudomonas *aeruginosa* by diffusible signaling factor signaling. It can also develop small colony variants – a form adapted for survival during chronic infections – which can be challenging to identify in clinical specimens. In sum, culture out of generally sterile body sites is rather straightforward, and *bacteraemia*, as well as sever sepsis may be detected using standard blood culture methods. Additionally, *lecetive media* can enhance culture sensitivity for specimens gotten from non-sterile settings including respiratory secretion out of individuals suffering from cystic fibrosis. Currently, PCR

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use for diagnostic purposes needs further evaluation[7].

PATHOGENICITY

Clinical experience has suggested that whole genome sequencing of this bacterium does not evidence whether the organism is extremely virulent. On the other hand, a number of factors may advance the ability of *Stenotrophomonas maltophilia* to colonize such plastic surfaces as *endotracheal* tubes and catheters as well as human's respiratory tract. The factors consist of a positively charged surface as well as flagella and *fimbrial* adhesions[8]. The outer-layer *lipopolysaccharide* of the bacterium is a virulence feature involved in colonization as well as resistance to various cell-killing techniques. Stimulation through the lipid A part of *lipopolysaccharide* of peripheral blood *monocytes,* as well as alveolar macrophages to generate tumor necrosis factor plays a role as far as the pathogenesis of airway inflammation is concerned[9]. Additionally, *Stenotrophomonas maltophilia* stimulates interleukin-8 expression as well as *polymorphonuclear leucocyte* recruitment. It generates lipases and proteases that are known to have a role in bacterial pathogenesis in various genera as well as some extracellular enzymes including *RNase* and *gelatinase*. Worth noting is that *Stenotrophomonas maltophilia* protease is able to breakdown the protein parts of collagen, fibrinogen and *fibronectin* and therefore may lead to local tissue damage, as well as hemorrhage[10].

EPIDEMIOLOGY AND RISK FACTORS OF *STENOTROPHOMONAS MALTOPHILIA*

The bacterium is essentially an environmental organism and can be found in soil, water (natural waters and treatment plants as well as chlorinated distribution systems), and plants. In addition, it has been isolated from animal and human excrements, woodland ticks, frozen fish as well as raw milk. Within the hospital setting, the bacterium has been shown as a contaminant of medical devices including *chlorhexidine-cetrimide* disinfectant, vacuum-blood collection tubes and sterile water. According to Tan et al. (2008) surveys from a number of continents indicates a huge population of patients at risk due to advancing medical technologies. In England and Wales, for instance, the yearly number of blood isolates rose significantly (up to 93 percent) in the last decade or so. The rate of the bacterium isolation also varies considerably across the board as shown by a German study in which 34 ICUs (intensive care unit) showed a rising rate of *Stenotrophomonas maltophilia* infections in some cases and a decrease in others[11]. Nevertheless, acquisition of the bacterium is mostly *nasocomial. Stenotrophomonas maltophilia* molecular typing isolates from hospitalized individuals through pulse-field gel electrophoresis reveals a high genetic variety between most strains and occasional small groups. Such a finding implies that most individuals acquire this bacterium from independent sources – perhaps even before patients enter hospital- and the organism is subsequently selected out of the *commensa*l flora at some stage in antimicrobial exposure[12]. Also worth noting is that *nosocomial* acquisition might result from a common source or via cross-transmission.

Risk factors associated with acquisition of *Stenotrophomonas maltophilia* infection are generally linked to a severely weakened health status, exposure to wide-ranging antimicrobials, medical treatment in which indwelling instruments such as ventilation tubes are used, and long hospitals stays. In addition, chronic obstructive pulmonary ailment as well as the period of antibiotic therapy has been identified as independent risks for *Stenotrophomonas maltophilia* acquired in ICU settings. Bloodstream infection because of *Stenotrophomonas maltophilia* is highly likely in the use of central-venous catheter in hospital treatment, and failure to detach the catheter raises the risk of relapse. Additionally, in persons suffering from cancer, prolonged *chemotheraphy* induced *neutropenia*, as well as receipt of full p*arenteral* nutrition have been linked to *Stenotrophomonas maltophilia* infections. Extended mechanical ventilation has also been associated with *Stenotrophomonas maltophilia* pneumonia. In ad-

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dition, in critically ill trauma patients, pulmonary contusions as well as high injury severity score have been identified as independent signals for multiple occurrences of late-onset *Stenotrophomonas maltophilia* pneumonia. Colonization and infection with the bacterium is favored through exposure to various antimicrobials including *carbapenems, quiolones, cefepime* and *ceftazidime*. Other risk factors associated with *Stenotrophomonas maltophilia* include organ failure, septic shock, as well as high acute physiology and chronic health evaluation. In total, the risk rises with the period of administration as well as the number of antimicrobials administered.

CLINICAL PRESENTATION

By far and large, clinical manifestation of the bacterium infection is pneumonia and then bloodstream infection. Less frequent are wound and urinary tract infections, though are incidents of a rising array of other entities are being reported including meningitis, sinusitis, *endocarditis*, eye infections, arthritis and others[13]. In respiratory tract infection case, *Stenotrophomonas maltophilia* infection is largely among *immunocompromised* individuals. Concomitant isolation of various respiratory pathogens is widespread and complicates understanding. The usefulness of quantitative cultures of *endotracheal spirates* and *broncho-alveolar lavage* fluids is usually limited by latest antimicrobial exposure[14]. Nonetheless, evidence exists suggesting that *Stenotrophomonas maltophilia* can cause pneumonia. A recent survey carried out in a hospital showed that *Stenotrophomonas maltophilia* accounted for approximately 30 cases of *nosocomial* pneumonia[15]. Though clinical presentation of *Stenotrophomonas maltophilia* pneumonia remains non-specific, most patients show respiratory symptoms including *dyspnoea,* cough as well as fever. On radiological tests, pulmonary infiltrates seem lobar with bilateral or unilateral distribution, and uncommon pleural effusions. Rarely are *cavitary* lesions seen and history of lung parenchyma reveals hemorrhage focal lung necrosis in *neutropenic* individuals with *haematological neoplasia*. In those with *cystic fibrosis,* the part played by *Stenotrophomonas maltophilia* in advancement of the disease remains unknown. Mortality rates among persons with *Stenotrophomonas maltophilia* pneumonia ranges between 23 and 77 percent, and the highest rates are observed in patients with concomitant *bacteraemia* and cancer[16].

In bloodstream infection case, isolation of *Stenotrophomonas maltophilia* out of a blood culture should require a careful examination of a patient to differentiate between colonization, contamination, and true blood-stream infection. Worth noting is that central-venous lines are the widespread source of *Stenotrophomonas maltophilia* bacterium. Bloodstream infections as well as catheter-related bloodstream infections are usually *polymicrobial*. In addition, the prognosis for catheter-related bloodstream infections is good when prompt removal of an infected catheter is undertaken. On the other hand, in individuals with *haematological* malignancies, *Stenotrophomonas maltophilia* has been linked to breakthrough *bacteraemia.* Lai et al. (2004) approximated a 27 percent mortality rate for *Stenotrophomonas maltophilia* bloodstream infection.

MANAGEMENT OF INFECTIONS RESULTING FROM *STENOTROPHOMONAS MALTOPHILIA*

In-vitro susceptibility examination of *Stenotrophomonas maltophilia* presents a number of technical challenges. A number of standard techniques for the susceptibility examination of *Stenotrophomonas maltophilia to co-trimoxazole* have been published in recent past. Mostly, these standards employ a minimum inhibitory of approximately 2mg/l to signify susceptibility to *co-trimoxazole*. For instance, BSAC (British Society for Antimicrobial Chemotherapy) and American CLSI (Clinical Laboratory Standards Institute) have published standards. The latter standard incorporates broth intensity minimum inhibitory concentration breakpoints for *minocyline, ceftazidime, levofloxacin, minocycline,* as well as *co-trimoxazole*[17]. Nevertheless, confusing is the fact

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that ERAST (Expert Rules in Antimicrobial Susceptibility Testing) consider *Stenotrophomonas maltophilia* to be innately resistant to *ceftazidime* among others. Altogether, the BSAC advises that there exists no data presently to support an association between laboratory susceptibility examination and clinical result with *Stenotrophomonas maltophilia* contamination. Certain antibiotic combinations apply a synergistic impact in vitro against *Stenotrophomonas maltophilia*. The chief tests used include the time-kill, the checkerboard as well as the multiple combination bactericidal examination. Worth noting is that various tests may either give differing or the same outcomes when examining the same strain antibiotic combinations. Another logistical challenge with synergy examination relates to the delay prior outcomes are available, and thus its role in management of individuals is quite limited.

Regarding antimicrobial resistance, *Stenotrophomonas maltophilia* displays high level inherent resistance to various structurally unassociated antibiotics such as *quinolones, tetracycline, aminoglycosides,* heavy metals, as well as disinfectants. Sequencing of some *Stenotrophomonas maltophilia* genomes revealed a number of resistance genes including those encoding for multidrug-efflux pumps and *aminoglycoside-modifying* enzymes. In sum, multidrug-efflux pumps as well as low permeability of the exterior membrane are some of the inherent antibiotic resistance of *Stenotrophomonas maltophilia*[18]. *Stenotrophomonas maltophilia* can also gain resistance via the uptake of resistance genes situated on *transposons, integrons,* and plasmids. Resistance to *quinolones* is referenced primarily through over expression of efflux pumps and perhaps low permeability of the exterior membrane. Recent developments have led to identification of *quinolone*-resistance determinants, but its role remains unclear. Swift emergence of *quinolone* resistance in vivo and in vitro has been witnessed, and this repeatedly coincides with raised resistance to antibiotics belonging to other groups. Resistance of *Stenotrophomonas maltophilia* to *aminoglycosides* may be because of *aminoglycoside*-modifying enzymes, temperature dependent r*esistand,* as well as efflux pumps due to exterior membrane protein transformations. All of these factors have contributed to *Stenotrophomonas maltophilia* emerging as a major threat in medical science.

TREATING *STENOTROPHOMONAS MALTOPHILIA*

In fact, selection of an *all-encompassing entimicrobial* regimen for treating *Stenotrophomonas maltophilia* infection remains challenging due to this high-level intrinsic resistance as well as raising resistance prevalence of the opportunistic pathogen. In addition, there remain uncertainties with regard to in-vitro susceptibility examination. The lack of controlled trials gauging treatment regimens in the clinical environment has not helped the matter either[19]. Current treatments are thus built upon historical evidence as well as anecdotes, case report and case series. It is probably a good practice to select a treatment routine, which the clinical isolate is predisposed in in-vitro examinations irrespective of uncertainties regarding the clinical relevance of such outcomes. In sum, in-vitro models imply that combination therapy must be more effective that *monotherapy* counterparts especially for infections that are challenging to treat. However, clinical evidence is still at infancy and a concluding case regarding treatment of *Stenotrophomonas maltophilia* cannot be presented[20].

prevalence

Prevalence of resistance regarding *Stenotrophomonas maltophilia* is widespread probably because of high resistance to antimicrobials. Indeed, increasing resistance trajectory to antimicrobials including *ticarcillin-clavulanate* and *co-trimoxazole* that are recommended for empirical management is worrisome. For instance, the global resistance level to co-trimoxazole was approximated at 4.7 percent in 2003 and levels from Taiwan (25 percent) and Spain (27 percent) stand out[21]. Such levels also indicate the widespread nature of resistance to various antimicrobials. Nevertheless, compounding the matter is that *co-trimoxazole* solely or in combination with others remains the treatment of

choice for culture-proven and suspected *Stenotrophomonas maltophilia* infection basing on high in-vitro susceptibility levels. In-vitro data implies that *co-trimoxazole is bacteriostatic* against this bacterium, and has thus been recommended to treat severe cases. In therapeutic *concentrations, co-trimoxazole* slows down the release of various components from peripheral blood *monocytes* that have been roused by *Stenotrophomonas maltophilia* in vitro, though the clinical significance of such an observation still needs examination[22]. Intolerance or hypersensitivity may limit the application of *co-trimoxazole*, with hypersensitivity mainly linked to *sulfomethoxazole nitroso* metabolite. In sum, swift oral desensitization has been employed successfully to overcome intolerance in those with *Stenotrophomonas maltophilia* infection. The latest f*luoroquinolones* (including *moxifloxacin, clinafloxacin, trovafloxacin,* as well as gatifloxacin) display improved in-vitro activity than *levofloxacin* and ciprofloxacin against *Stenotrophomonas maltophilia*. Quinolones are known to exert concentration dependant killing and the latest quinolones can attain lung concentrations 5-times that attained in serum[23]. However, it remains unclear whether any of the latest *fluoroquinolones* are superior to the rest. In addition, swift emergence of intolerance against q*uinolones* has been evidenced in vivo and in vitro all of which mean it might be far-sighted to employ them together with other active substances.

The tetracycline derivatives including *doxycycline, tigecycline* and *minocycline* have displayed important in-vitro activity against isolates of *Stenotrophomonas maltophilia*, though there exists little clinical understanding with treating the bacterium with these compounds[24]. For instance, the new wide-spectrum *glycylcline tigecycline* can be used to overcome the regular tetracycline resistance intolerance mediated via efflux as well as ribosomal-target modification. In addition, *tigecycline* has been found to have activity against *co-trimoxazole* resistant *Stenotrophomonas maltophilia* in vitro. Thus, *tigecycline* can be considered a substitute therapeutic choice, especially as a component of combination treatment, though clinical understanding remains unavailable. On the other hand, the *aminoglycosides* display poor activity against *Stenotrophomonas maltophilia* probably due to high inherent resistance. In fact, they play virtually no role in *monotherapy – though polymixins* has lately achieved a role in the management of infections caused by *multiresistant gam-negative bacilli*. There have been reports that *Stenotrophomonas maltophilia* is susceptible to *polymixin* B as well as *colistin*, though testing of these drugs remains challenging partly because the clinical value of their in-vitro data remains unknown.

Combination therapy

Despite the absence of clinical tests, management of *Stenotrophomonas maltophilia* with a number of antimicrobials has emerged as a current practice in which *co-trimoxazole* treatment is contraindicated. Nevertheless, the motivation for combination therapy is linked to the high level inherent resistance of the bacterium, rising cases of acquired resistance as well as the *bacteriostatic* activity associated with *co-trimoxazole*. Combination treatment, as a strategy, is supported through in-vitro synergy *experiement* that reveals improved drug combinations activity in comparison to single drugs – this remain true even in scenarios where the isolate is resistant to various tested drugs[25]. Yet, it needs to be emphasized that the extrapolation of these in-vitro outcomes to clinical practice is subjective at best. Altogether, this underlines the challenge presented by *Stenotrophomonas maltophilia*.

Prevention

It is relieving that prevention of *Stenotrophomonas maltophilia* transmission, a well as *nosocomial* infections is reliant on the same basis of controlling modern infection as devised for other *multiresistant-nosocomial* bacteria. Control programs ought to incorporate surveillance of *Stenotrophomonas maltophilia* isolation as well as infection and surveillance of consumption of antibiotic, barrier safety measures during patient care, antibiotic stewardship programs, and others[26]. Considering that *Stenotrophomonas maltophilia* is everywhere as an environmental microorganism, suitable handling of medical devices, products, as well as maintenance of the setting and water supply can play a part in prevention. In addition, clustering of

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Stenotrophomonas maltophilia cases should instigate epidemiological inquiries including molecular isolates typing (Jiong et al., 2014). Transmission from such common sources as the environment –humid reservoirs or contaminated medical equipment and products should be addressed[27]. In fact, in *Stenotrophomonas maltophilia* associated infections, effective result is linked to administration of drugs to which the bacterium is susceptible, recovery of bone marrow role, removal of contaminated instruments such as catheters, taking adequate preventive as well as isolation measures[11].

CONCLUSION

Stenotrophomonas maltophilia has emerged as a highly opportunistic pathogen influencing primarily the destabilized host including the hospitalized. *Stenotrophomonas maltophilia* also does not seem to be intrinsically virulent. In fact, the bacterium remains an unusual cause of invasive infection. Yet, the ability of this bacterium to colonize the airway epithelia as well as plastic surfaces of indwelling medical equipments has contributed to its emergence as a widespread *nosocomial* pathogen in such crucial settings as the ICU. Studies have pointed out that genetic aspects play a considerable role as far as drug resistance is concerned. the wide variety of antimicrobial drug intolerance genes as well as mobile genetic components found indicate that the bacterium (*Stenotrophomonas maltophilia*) can function as a pool of antimicrobial drug intolerance determinants within clinical setting. This is a challenge of considerable concern among professionals including clinicians and others. The genome series of the bacterium shoes its capacity for environmental variation that presumably leads to its perseverance in vivo. Though not a particularly high virulent organism, the huge number of genes involved, the ability to attach to surfaces of hospital devices and mucosal surfaces means the bacterium is more persistent and challenging to eradicate.

Indeed, differentiating between infection and colonization can be challenging if this bacterium is isolated out of non- sterile places such as wounds and sputum. *Stenotrophomonas maltophilia* may cause pneumonia as well as bloodstream infection with considerable mortality and morbidity levels in immune-compromised individuals. High-level inherent resistance to such first-line drugs as co-trimoxazole affects management of infection. On the other hand, prevention of the bacterium acquisition as well as infection is dependent on the general modern infection control measures. In the case of *Stenotrophomonas maltophilia*, a higher emphasis on antimicrobial consumption control as well as consideration of environmental reservoirs is highly recommended with regard to prevention. Altogether, this report has revealed why *Stenotrophomonas maltophilia* remains an emerging opportunistic pathogen globally. In particular, the rising incidence of community acquired and n*osocomial* is of great concern among immune-compromised persons. This is because this bacterium is linked to high fatality rates. In addition, this article has revealed that much is unknown about the bacterium with regard to combination therapy. Its wide range of resistance to drugs also presents danger to the entire global population. The fact that *Stenotrophomonas maltophilia* is an environmental bacterium present in various habitats (such as plant *Rhizospheres,* foods, animals and water sources) also increases its danger because humans, immune-compromised or otherwise, are increasingly exposed. In sum, though not entirely mitigating, it is essential to employ the available antimicrobials in an appropriate manner, utilize novel agents to which this bacterium is susceptible, as well as strictly enforce control measures to minimize the prevalence of infections.

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