AN OVERVIEW OF THE EMERGING PATHOGEN-
STENOTROPHOMONAS MALTOPHILIA

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ABSTRACT

Stenotrophomonas maltophilia is a multiple-antibiotic-resistant opportunistic pathogen that is being isolated with increasing frequency from patients with health-care-associated infections. S. maltophilia is associated with an ever-expanding spectrum of clinical syndromes. S. maltophilia is resistant to many currently available broad-spectrum antimicrobial agents. The selection of agents for use in the management of S. maltophilia infection presents a challenge to laboratories and clinicians because of the problems associated with susceptibility testing and the inherent resistance of the bacterium to many agents. S. maltophilia will present a major challenge to microbiologists, clinicians, and hospital epidemiologists for some time to come.

KEYWORDS: Stenotrophomonas, pathogen, nosocomial infection.

INTRODUCTION

Nonfermentative gram-negative bacilli are generally saprophytic in nature. Recently it has a remarkable role in hospital acquired infections and in immuno-compromised hosts. But mostly it is associated with hospitalized environments. Among them Pseudomonas aeruginosa, Acinetobacter baumannii has have been larger in population among common nonfermenter pathogens.

Recently there has been a significant role in nonfermentative gram-negative bacilli organisms as they are being isolated from clinical specimens with increasing frequency associated with infections [1]. Non fermenting gram negative bacilli (NFGNB) are inherent resistant to many
antibiotics and are known to produce extended spectrum beta lactamases (ESBL) and metallo betalactamases [2]. Therefore they are considered as MDR organisms. Increase in concern to treat these infections due to NFGNBS as they possess intrinsic mechanisms of resistance to various groups of drugs, especially to carbapenems, which are widely used in clinical practice in health care settings [3].

Nonfermenters occupy only a small percentage of the total clinical isolates, but they require more effort for identification. But on recent survey in all round the world, its population has a drastic increase in it. Other non fermenter having key role in pathogenic rate includes Stenotrophomonas maltophilia, Pseudomonas stutzeri, Burkholderia cepacia, Burkholderia pseudomallei, Moraxella, Achromobacter xylosoxidans, P. oryzihabitans. Mostly all of them are opportunistic human pathogen, commonly affecting immunocompromised patients, such as those with cystic fibrosis or AIDS [4]. Those infections can colonize on different parts of the body, but infections typically target the respiratory tract (e.g. patients with CF or those on mechanical ventilation), causing bacterial pneumonia. Treatment of such infections can be difficult due to multiple antibiotic resistances [5].

**Stenotrophomonas maltophilia**

*S. maltophilia* is an aerobic, nonfermentative, Gram-negative bacterium. *S. maltophilia* is a multi-drug resistant gram-negative bacillus that is an opportunistic pathogen [6, 7]. *Stenotrophomonas* infections have been associated with high morbidity and mortality in severely immunocompromised and debilitated individuals [8, 9]. Most common species under the genus *Stenotrophomonas* are *S.maltophilia* *S. africana*, *S. nitritireducens*. Among them *S. maltophilia* are recognized as important pathogens. Infections caused by other species are relatively infrequent [10].

**Identification of *S. maltophilia* and growth conditions**

*S. maltophilia* are straight or slightly curved non sporulating gram-negative bacilli that are 0.5 to 1.5 mm long. They occur singly or in pairs and do not accumulate poly-β hydroxybutyrateas intracellular granules. They are motile by means of several polar flagella. *S. maltophilia* are catalase-positive, oxidase-negative. The colonies are smooth, glistening, with entire margins and are pale yellow [11]. *S. maltophilia* is an obligate aerobe. Growth does not occur at temperatures lower than 5°C or higher than 40°C and is optimal at 35°C. Margesin and Schinner [12] reported the isolation from an alpine environment of a strain of
the bacterium which was capable of growth at 10°C. Methionine or cystine is required for growth by most but not all strains [13].

On blood agar *S. maltophilia* colonies are rough, dull yellow, dark tan or lavender-green and have an ammonia odor. They are DNase positive, which is a key feature for identification of this organism. A clear zone around colonies on DNase medium is indicative of DNase activity. It takes 72 h for clearing the medium. A pink zone around colonies is observed when toluidine blue DNase agar is used [14]. They grow well on MacConkey agar producing pigmented colonies selected biochemical characteristics and microbiological reactions of *S. maltophilia* are shown Table: 1 [15].

<table>
<thead>
<tr>
<th>Biochemical tests</th>
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<tbody>
<tr>
<td>1 Indophenol oxidase</td>
<td>Negative</td>
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<td>2 Catalase</td>
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<td>3 Growth at 5°C</td>
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<td>6 Lysine decarboxylase</td>
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<td>7 Ornithine decarboxylase</td>
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<td>8 Methyl red</td>
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<td>9 Voges-Proskauer</td>
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<td>10 Hydrogen sulfide</td>
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<td>11 Reduction of nitrate to nitrite</td>
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<td>12 Citrate</td>
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<td>13 Phenylalanine deaminase</td>
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<td>14 b-Galactosidase (ONPG)</td>
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<td>15 Hydrolysis Esculin</td>
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<td>Gelatin</td>
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<td>DNA</td>
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<td>Starch</td>
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<td>Urea</td>
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**Infections caused by S. maltophilia**

*Stenotrophomonas maltophilia* is a water born organism and has emerged as an important opportunistic pathogen in the debilitated host. *S. maltophilia* is associated with a wide spectrum of clinical syndromes. They are enraging as a known cause of infection in the nosocomial setting [16]. Nosocomial infection remains the most common type of complication affecting hospital patients. The risk factors that have been reportedly associated with this pathogen include intensive care admission, prior use of broad-spectrum antibiotics, mechanical ventilation, malignancy, cystic fibrosis, neutropenia, presence of central venous catheters, prolonged hospitalization, debilitation and immunodeficiency [17].

Bacteremia is a common manifestation of *S. maltophilia* infection [18]. The growth of *S. maltophilia* of respiratory or urinary specimens is therefore sometimes difficult to interpret and not a proof of infection. If, however, it is isolated from sites which would be normally sterile (e.g., blood), then it usually represents true infection. Muder et al [19] report that in their series of 91 patients with *S. maltophilia* bacteremia, 56% did not have a clinically apparent portal of entry but 84% of these individuals had a central venous catheter in place. In study Flaherty et al [20], 3 cases infections caused by *S. maltophilia* and an additional case of both *S. maltophilia* and *Enterobacter cloacae* were isolated from blood cultures. The reason was identified as contaminated O-rings in reprocessed hemodialyzers. Most difficult thing is to differentiate true *S. maltophilia* with that of pseudobacteremia arising from contamination of blood cultures [21]. They have significant role in polymicrobial bacteremia.

*Stenotrophomonas maltophilia* is a common colonizer of the respiratory tract of patients with chronic lung disease, and, another important thing is that in the absence of pneumonia or bacteriemia, is often neglected [22]. The first reported isolation of *S. maltophilia* from the respiratory tracts of patients with cystic fibrosis was in 1975 in Denmark by Frederiksen et al [23]. The respiratory system is the most common site of isolation and infection with *S. maltophilia* [24]. Based on recent studies *S. maltophilia* causes significant mortality in patients with nosocomial pneumonia in other clinical settings, the significance of a positive
respiratory isolate is much less clear [25]. Mostly these infections are frequent in cardiac disease, malignancy, and pulmonary disease (although none had cystic fibrosis). The majority of the patients were immunosuppressed, due to either an underlying disease or drug therapy (particularly with glucocorticoids). Many patients also had a recent or concurrent infection with different pathogens or they developed such an infection during their hospital stay [26].

*S. maltophilia* associated pneumonia is associated with mechanical ventilation, tracheostomy, previous exposure to broad-spectrum antibiotics, the use of respiratory tract equipment such as nebulizers [27, 28]. Haanes *et al.* [29] study about the risk factors for late onset nosocomial pneumonia caused by *S. maltophilia* in critically ill trauma patients.

*S. maltophilia* has been frequently isolated from urine specimens, even though it has been frequently isolated from urine specimens, considered an uncommon cause of urinary tract infection [30, 31]. Isolation of the bacterium from semen specimens from fertile men have been reported in 1980s [32]. Catheter-related –*S. maltophilia* bacteremia responds well to removal of the infected catheter and appropriate antibiotic therapy. In nearly one-third of patients, infection may relapse after prolonged latency Relapse maybe significantly reduced by early (72 h not approximate) catheter removal [33]. Non-CR *S. maltophilia* bacteremia is a serious infection and is associated with a high rate of treatment failure and infection associated deaths [34].

Skin and soft tissue manifestations of *Stenotrophomonas maltophilia* infection are becoming an increasingly recognized entity. Clinical skin presentations include primary cellulitis, metastatic nodular skin lesions or cellulites, gangrenouscellulitis, soft tissue necrosis, ethyma gangrenosum and infected mucocutaneous ulcers [35]. The routes of spread include haematogenous seeding and direct inoculation through mucocutaneous surfaces [36]. Other common infections include umbilical cellulitis [37], prepatellar bursitis, infections of burn wounds [38], cat scratches, and human bite wound [39]. Caylan *et al.* [40] report a case of post-neurosurgical meningitis caused by *S. maltophilia*. Meningitis caused by *S. maltophilia* has been reported extremely rare. Al-Ghamdi *et al.* [41] reported a case of otitis externa due to *S. maltophilia* in a 22-year-old immunocompromised male who had bilateral otalgia and ear discharge, as well as left facial nerve palsy in combination with hearing loss.

**Antimicrobial profiles**

The antibiotic options for the treatment of *S. maltophilia* infections are limited because the bacterium exhibits resistance to many commonly prescribed antibiotics, including beta-
lactam agents, carbapenems and aminoglycosides [42]. Antimicrobial agents selection is crucial in improving the outcome of *S. maltophilia* infections, especially in patients who develop bacteremia [43]. Recent reports say that trimethoprim/sulfamethoxazole is the most effective antimicrobial agent in the treatment of *S. maltophilia* infections [41].

Trimethoprim-sulfamethoxazole (TMP-SMX) has the most potent and reliable *in vitro* activity against *S. maltophilia* [44, 45]. Co-trimoxazole exhibiting more than 90% susceptibility *in vitro* hence it remains the most effective agent against *S. maltophilia* infections, [46]. Reports documented that 98% susceptibility of *S. maltophilia* isolates to TMP-SMX; however, increasing resistance rates (30%–40%) to this agent are being reported [42]. The mechanism(s) of resistance to TMP-SMX is not well understood. These isolates were resistant *in vitro* to imipenem and aminoglycoside and β-lactam antibiotics [47].

The fluoroquinolones are one of the main alternatives to trimethoprim/sulfamethoxazole for the treatment of *S. maltophilia* infections [42]. The quinolones have variable *in vitro* activity against *S. maltophilia*, and newer quinolones, such as moxifloxacin, are superior to older ones, such as ofloxacin and ciprofloxacin [48]. New fluoroquinolones such as clinafloxacin, levofloxacin, gatifloxacin, moxifloxacin, and sitafloxacin show superior *in vitro* activity compared to earlier quinolones [49-51].

Valdezate *et al.* [52] showed that more than 95% of the *S. maltophilia* strains tested were susceptible to the new fluoroquinolones. Clinafloxacin seems to be the most active fluoroquinolone, as shown by Pankuch *et al.* [53]. Weiss *et al* [54], in a comparison of seven fluoroquinolones, showed that clinafloxacin was the most active, inhibiting 95% of the 326 strains analyzed, followed by trovafloxacin (84.3%), moxifloxacin (83.1%), and sparfloxacin (81.5%).

The aminoglycosides, gentamycin, amikacin have poor activity against *S. maltophilia*. Several mechanisms of aminoglycoside resistance have been described, including outer-membrane changes, target modification, aminoglycoside-modifying enzymes, and efflux-mediated mechanisms [55]. Aminoglycosides show poor activity against *S. maltophilia* strains because of the constitutive production of aminoglycoside-modifying enzymes by *S. maltophilia* [56].
Tigecycline is considered to be the drug of choice for these types MDROS. Its a glycylcycline, is a compound that has demonstrated good in vitro activity against S. maltophilia strains [57-59]. The susceptibility to tigecycline (a derivative of minocycline) has also been shown to be high, depending on the interpretative criteria used [60]. Additional clinical experience with the use of tigecycline against S. maltophilia infections is currently scarce [61]. Tigecycline activity was reported for 131 isolates from patients hospitalized in intensive care units (ICUs) in a multi-centre, multi-national survey and for 108 isolates from ICUs in Canada [62, 63].

Antibiotic resistance develops rapidly and therefore, combination therapy is recommended. This is in agreement with a recent study where mortality was significantly lower in patients with Stenotrophomonas maltophilia bacteraemia who were treated with combination therapy. The combination of co-trimoxazole with either ticarcillin/clavulanate or with a third-generation cephalosporin should be considered when an eutropic or a seriously ill patient is to be treated [64]. The majority of clinical isolates of S. maltophilia are inherently resistant to most antimicrobial agents, and as such few therapeutic options remain. The triple combination of co-trimoxazole, rifampicin and carbenicillin has in vitro synergy, but clinical experience is scant [65]. Combination treatment with co-trimoxazole, minocycline and ticarcillin/clavulanate has also been suggested [66]. Ticarcillin-clavulanate is noted to have good activity against Stenotrophomonas maltophilia and is suggested as the agent of choice in individual’s intolerant of TMP-SMX [67]. Antimicrobials that have been used in varying combinations include ticarcillin-clavulanate, minocycline, tigecycline, colistin, chloramphenicol, and cephalosporins [68].

Intrinsic antimicrobial resistance of this organism is a major problem, particularly to aminoglycosides and carbapenems. Multiple efflux pumps and modifications to outer membrane proteins confer variable resistance to a wide range of agents. Chromosomal genes for beta-lactamases affect all beta-lactams including carbapenems. Aminoglycoside acetyl transferase and SmQnr genes (conferring reduced susceptibility to fluoroquinolones) are almost always present [69]. In addition, acquired genes may be present conferring resistance to a wide range of agents, including trimethoprim-sulfamethoxazole (cotrimoxazole). Moreover; the formation of biofilms reduces antimicrobial effectiveness [70].

In conclusion, risk factors for the emergence S. maltophilia infections are acquiring increasing importance in the hospital environment Stenotrophomonas infection was
associated with increased morbidity but not increased mortality, whereas inadequate empiric antibiotic therapy was associated with increased mortality but had no effect on morbidity. Whose eradication is often problematic due to its inherent resistance to many antibiotics and its increased resistance rates. Maintain hygiene is the best method to prevent nosocomial infections. Broad-spectrum antibiotics should be avoided as much as possible in NICU patients, and agent/factor-specific antibacterial treatment should be administered. Early diagnosis and the commencement of appropriate antibiotics reduce mortality.

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