ORIGINAL ARTICLE

ANTIBIOTIC RESISTANCE AMONG CLINICAL ISOLATES OF *STENOTROPHOMONAS MALTOPHILIA* AT A TEACHING HOSPITAL IN RIYADH, SAUDI ARABIA

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Background: *Stenotrophomonas maltophilia* has emerged as a significant pathogen in compromised patients, causing infections which are difficult to treat. This study was carried out to comprehend the recent trend of antimicrobial resistance among clinical isolates of *S. maltophilia* and suggest management guidance for patients in general and in our region in particular**. Methods:** A total of 222 clinical isolates were tested between Jan 2003 to Jun 2009 at King Khalid University Hospital, College of Medicine, King Saud University, Riyadh Saudi Arabia. The organisms were identified as per standard guidelines. Final identification and minimum inhibitory concentration (MIC) was determined by using Microscan®. **Results:** *S. maltophilia* showed absolute resistance to Imipenem. *In vitro*, least resistance was observed against Cotrimoxazole (9.45%) followed by Ceftazidime (57.21%), Piperacillin/Tazobactam (60.82%), Ciprofloxacin (77.03%), Aztreonam (86.03%). Gentamicin showed overall highest resistance (87.39%). The crude mortality rate was 47%. **Conclusion:** Cotrimoxazole is still the most effective agent against *S. maltophilia* but, keeping in view the increasing resistance to first and second line drugs, there is an urgent need for an effective surveillance system. To discourage development of resistance and devise an effective empirical therapy, large scale study should be considered.

Keywords: *Stenotrophomonas maltophilia*, antibiotic resistance, mortality rate, minimum inhibitory concentration

INTRODUCTION

Stenotrophomonas maltophilia, an opportunistic pathogen, has emerged as an important nosocomial pathogen. The spectrum of infections ranges from respiratory and urinary infections to bloodstream infections in hospitalised patients. Patients who are at an increased risk of acquiring infections are those with previous history of antibiotic therapy, patients with severe underlying comorbidities, pneumonia, bloodstream infection, skin infections and surgical-site-related infections, urinary tract infections, endocarditis, meningitis, intra abdominal infections, endophthalmitis, immunocompromised patients, mechanical ventilation, severe mucositis and patients admitted to intensive care units.[1,2]

The infections caused by *S. maltophilia* are difficult to treat because of its intrinsic resistance to a range of different antibiotics. The resistance mechanisms include multi-drug efflux pumps, production of modifying enzymes, and low permeability to various drugs. β Lactam drugs are inactivated by β Lactamases, quinolone resistance is usually mediated by efflux pumps and resistance to amino-glycosides is the result not only of modifying enzymes but also of efflux pumps in addition to temperature dependant resistance due to outer membrane protein changes.[3] The organism produces at least two clinically important inducible β-Lactamases: an L1 (Bush Group 3) zinc-dependant carbapenemase, which is not inhibited by clavulanic acid and an L2 (Bush Group 2e) Cephalosporinase that is inhibited by clavulanic acid. The L1 β-Lactamase hydrolyses most β-Lactam drugs including carbapenems, and only monobactam (Aztreonam) is somewhat resistant to hydrolysis. As a result, Aztreonam may serve as a competitive inhibitor of the L1 enzyme. With the combination of Ticarcillin/Clavulanate, the L2 enzyme is likely to be irreversibly inhibited by clavulanate and the L1 enzyme partially inhibited by Aztreonam.

Cotrimoxazole (SXT) has remained effective as empirical therapy for *S. maltophilia* infections but resistance to this drug has been reported from many countries including Saudi Arabia.[4] Different figures for resistance to SXT have been reported which may be as high as 24%[5] compromising its role in the management of *S. maltophilia* infections.

We reviewed the data in our hospital for the last six and a half years to know about the resistance prevalence to different selected groups of antibiotics in our set up and suggest management guidance for patients in general and in our region in particular.

MATERIAL AND METHODS

The present study was conducted in the Bacteriology Laboratory at King Khalid University Hospital (KKUH), Riyadh, Saudi Arabia. A retrospective analysis was carried out for susceptibility patterns of clinical isolates of *S. maltophilia* that were isolated during a period of six and a half years (Jan 2003–Jun 2009). A total of 222 clinical isolates of *S. maltophilia* were included in this

study. Duplicate specimens from the same sites were excluded and only one specimen per site per patient was considered. Patient's demographic and clinical data including gender, age, ward location, and type of sample were recorded from the laboratory request forms.

The organisms were recovered from a variety of clinical specimens including sputum and other respiratory sites, wounds, blood, urine, body fluids, and central venous catheters. These samples were cultured on primary enriched and special media including blood, chocolate agar, and MacConkey medium and incubated overnight at 35 °C. Antibiotic susceptibilities were determined by overnight microdilution method with commercial dehydrated panels provided by Dade Behring MicroScan WalkAway 96 analyser (Sacramento, California USA) as per manufacturer instructions and interpreted according to the CLSI guidelines 2007.[6]

The MicroScan WalkAway 96 system uses standard 96-wells microtitre plates in which growth is detected photometrically for slow growing organisms after 18–24 hr incubation. The inoculation of plates is manual with multipoint in oculator. All organism preparations were incubated in the instrument within the required 30-minute timeline. Identification and Antimicrobial Susceptibility Testing (AST) were performed with Neg BP combo panel type 30. AST results are expressed as susceptible or resistant category.

The following agents were included as group representatives in the study based on their usefulness in the clinical management of the patients: Imipenem (IMP), Gentamicin (GM); Aztreonam (ATM), Ciprofloxacin (CIP), Piperacillin/Tazobactam (TZP), Ceftazidime (CAZ), and Cotrimoxazole (SXT). The MIC was defined as the lowest concentration of the drug that inhibited visible growth. Antimicrobial susceptibility testing results for CAZ, TZP, CIP, and SXT were interpreted using the CLSI criteria (CLSI 2007). For other antimicrobial agents for whom the MIC interpretive breakpoints for *S. maltophilia* were not provided, MIC breakpoints for *Pseudomonas aeruginosa* and other non-Enterobacteriaceae were used.[6] Control strains for susceptibility testing included *Escherichia coli* ATCC 25922, and *P. aeruginosa* ATCC 27853.

RESULTS

A total of 222 specimens were included in the study. Number of specimens in each category is given in Table-1. The highest number of specimens (59%) was from the respiratory system. The patients demographics is given in Table-2, which shows that majority (60.36%) of patients were admitted in one of the ICUs, depicting that patients were either seriously sick or immuno-compromised. The crude mortality rate was 44% (98/222), of which 65% (64/98) of the isolates belonged to respiratory origin (unpublished data). The patients included very young children (newborns) to very old adults (95 yrs) and were from both sexes with male preponderance (M/F ratio being 56.31/43.69).

S. maltophilia showed absolute resistance to Imipenem as expected, followed by Gentamicin (87.39%), Aztreonam (86.03%), Ciprofloxacin (77.03%), Piperacillin/Tazobactam (60.82%) Ceftazidime (57.21%) and Cotrimoxazole (9.45%) (Table-3).

Table-1: Number of specimens from various sites

Site of Specimen	Number	Percentage
Respiratory	131	59.0
Blood	33	14.87
Wounds	36	16.22
Urine	9	4.06
Body Fluids	8	3.6
Central venous catheters	5	2.25

Table-2: Patient demographic details (n=222)

Variables	Number of patients (%)
Gender	
Male	125 (56.30)
Female	97 (43.69)
Age	
≤ 1years	30 (13.51)
>1–20 years	25 (11.26)
>20–50 years	62 (27.92)
>50 years	105 (47.29)
Location	
Non-ICU	68 (30.63)
Outpatient	18 (8.11)
Renal dialysis unit	2 (0.9)
Intensive care units	
Medical	44 (19.82)
Surgical	35 (15.77)
Cardiac	20 (9.0)
Neonatal	18 (8.11)
Paediatric	17 (7.66)

Table-3: Percentage resistance of *S. maltophilia* against selected antimicrobial agents

Antibiotic	Percent resistant
Imipenem	100
Gentamicin	87.39
Aztreonam	86.03
Ciprofloxacin	77.03
Piperacillin/Tazobactam	60.82
Ceftazidime	57.21
Cotrimoxazole	9.45

DISCUSSION

Stenotrophomonas maltophilia has emerged as an important nosocomial pathogen capable of causing respiratory, bloodstream, and urinary infections. The treatment of nosocomial infections by *S. maltophilia* is difficult, as this pathogen shows high levels of intrinsic or acquired resistance to different antimicrobial agents, drastically reducing the antibiotic options available for treatment.[7]

Risk factors for colonisation or infection are frequent use of broad spectrum antibiotics such as

carbapenems in ICU, prolonged hospitalisation, stay in the ICU, mechanical ventilation, indwelling catheters, use of equipment in contact with the respiratory tract, and prematurity.[8]

Almost two third of the isolates have been isolated from respiratory tract origin (59%). According to del Toro *et al*[9], it is difficult to differentiate infection and colonisation in samples from respiratory tract origin. Furthermore, pulmonary isolates are more likely to be classified as colonisers than blood stream and intra abdominal isolates. However, pulmonary nosocomial infections are the most common and their incidence are on the increase,[10–12] and are often associated with high mortality rates[13].

Mortality in *S. maltophilia* infections is defined as death occurring within 14 days of the initial positive culture.[14] A higher mortality rate among patients infected with *S. maltophilia* admitted in the ICU compared with non-ICU settings (44% versus 4.8%) has been reported.[10] In our study the overall mortality rate in ICU compared with non-ICU settings was 44% versus 6%. So, it is imperative to identify patients at high risk in the course of illness and to include Cotrimoxazole (SXT) as therapy in critically ill patients at high risk for mortality once *S. maltophilia* is isolated in sputum (and/or sterile sites).[15]

In our study *S. maltophilia* showed absolute resistance against Imipenem. *S. maltophilia* is intrinsically resistant to carbapenems. Howe *et al*. have shown that both imipenem and meropenem are L1 β-lactamase inducers and, thus, are not-effective against *in vitro* against *S. maltophilia*.[16] Despite the bacteriostatic action and the emergence of resistant strains, Cotrimoxazole (SXT) has been the drug of choice for treatment of *S. maltophilia* infections.[17]

We observed least resistance against Cotrimoxazole (9.5%). It is in contrast with Caylan *et al*[18], who reported least (2.3%) resistance against Cotrimoxazole. This finding could be attributable to decreased usage of the antibiotic in the local setting. However resistance against Ciprofloxacin (75%) and Piperacillin/Tazobactem (59%) is comparable.[18]

In our study an increasing trend in the percent resistance of Gentamicin (87%), Aztreonam (86%), Piperacillin/Tazobactam (60.82%), Ceftazidime (57.21%) and Ciprofloxacin (77%) was observed. This surge in resistance could be because of overlooking an active infection resulting in delayed treatment and suboptimal patient outcomes. On the other hand, indiscriminate treatment of all positive cultures may result in overuse of antibiotics and development of resistance.[15,19]

The results of susceptibility testing from antibiotic surveillance program during 1993–99 showed a high level of resistance against Aztreonam (85.3%) followed by Ciprofloxacin (68.7%), Gentamicin (67.3%), Ceftazidime (36%) and Piperacillin/ Tazobactam (34.7%). However least reported resistance was for Cotrimoxazole (4.7%).[20]

S. maltophilia resistance percentages reported from the ICUs to the SARI (Surveillance of Antimicrobial Use and Resistance in German Intensive Care Units) database were highest for Piperacillin/ Tazobactam 71.6%, followed by Amikacin at 60.7%, Ceftazidime at 38.7% and Ciprofloxacin at 35.8%. Resistance percentages were lowest for Cotrimoxazole (10.3%).[21]

Keeping in view the retrospective nature of the present study, it carries some basic and intrinsic limitations. First of all, the possibility that the physician could have selected an unidentifiable criterion for choice of treatment cannot be excluded. Secondly, information about prior use of antibiotics and prior hospitalisation are also not available. This information is important as these variables play an important role in developing and understanding antimicrobial resistance. Finally, reason for hospitalisation, type and severity of comorbid condition are also not known which would have helped in determining the cause of death.

CONCLUSION

S. maltophilia is an emerging problem in our clinical setup with high crude mortality rate. There is an overall increase in percent resistance noted for the drug of choice compared to the previous data. Co-trimoxazole and/or Ceftazidime in combination with other antibiotics may be considered as alternative options. Large scale effective surveillance system, and infection control procedures are need of the hour to limit the transmission of the resistant clones into the hospital environment.

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