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Co-trimoxazole Resistance in Clinical Isolates of *Stenotrophomonas maltophilia*

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A B S T R A C T

Stenotrophomonas maltophilia is increasingly being isolated as a nosocomial pathogen. It is the third most common non-fermenting gram negative bacilli (NFGNB) isolated from the clinical samples especially from the respiratory specimens, blood, urine and pus samples. Though inherently resistant to many groups of antibiotics, its susceptibility to co-trimoxazole is a peculiar character, because of which Co-trimoxazole is considered as the drug of choice for treating these infections. Recently there has been an increase in the incidence of resistance against Co-trimoxazole with variable resistance towards other antibiotics. In the present study 14.2% of the isolates were resistant to Co-trimoxazole. Resistant to other antibiotics was also very high. Ciprofloxacin and Chloramphenicol have shown reasonably good activity against this organism making these drugs as therapeutic alternatives in Co-trimoxazole resistant cases

Introduction

Stenotrophomonas maltophilia is a motile, aerobic, non-fermenting, Gram-negative bacillus. It is isolated from various sources in nature like water, soil, plants, and animals. *S. maltophilia* is an important opportunistic human pathogen, causing nosocomial infections especially in immunocompromised patients. It is the third most common pathogenic non-fermenting gram negative bacilli (NFGNB) worldwide after *Pseudomonas aeruginosa* and *Acinetobacter calcoaceticus -baumannii* complex (Looney *et al.,* 2009, LiPuma *et al.,* 2007). *S. maltophilia* infections include pneumonia, bloodstream infections, urinary tract infections, soft tissue infections, meningitis, and ocular infections.

This pathogen is characterized by intrinsic resistance to multiple classes of antibiotics, due to various mechanisms such as decreased permeability, production of b-lactamases and of aminoglycoside modifying enzymes, or the presence of multidrug efflux pumps (Sanchez *et al.,* 2009).
For a routine laboratory it is always a difficult

task to identify the NFGNB up to the species level, because of which these organisms are frequently under reported. Inherently multidrug resistance nature including resistance to carbapenems necessitates the appropriate identification of this organism and determining the susceptibility patterns. The present study aims at isolating, identifying and determining the susceptibility patterns of *Stenotrophomonas maltophilia* from various clinical specimens in our hospital.

Materials and Methods

Routine bacterial cultures were performed for various samples received in the department of microbiology during the study period of January 2013 to Dec 2014. All the culture positive organisms were identified based on routine biochemical tests.

All the oxidase negative non-fermenting gram negative bacilli (NFGNB) were processed further by performing additional tests like lysine decarboxylase tests, esculin hydrolysis, OF maltose, OF mannitol and pigment production to identify *Stenotrophomonas maltophilia* species(Winn *et al.,* 2006).

Antimicrobial susceptibility testing was performed by the Kirby-Bauer disc diffusion method. The agents tested against *Stenotrophomonas* included ceftazidime (30µg), tigecycline (15 µg), piperacillin/tazobactum (100/10 µg), cefaperazone sulbactum (75/10 µg), amikacin (30 µg), chloramphenicol (30µg), ciprofloxacin (5µg), doxycycline (30µg), andtrimethoprim/ sulfamethoxazole (1.25/23.75 µg), imipenem (10 µg). The results were interpreted according to the Clinical and Laboratory Standards Institute (CLSI) criteria (Wanye, 2011). For the agents where specific CLSI criteria for *S. maltophilia* are not available, the relevant criteria for non-Enterobacteriaceae were used. Escherichia coli ATCC 25922 and Pseudomonas aeruginosa ATCC 27853 were used as quality control strains

Results and Discussion

A total of 297 oxidase negative non-fermenting gram negative bacilli were isolated from various clinical samples during the study period, out of which 21(7%) were identified as *Stenotrophomonas maltophilia* species.

Majority of the *Stenotrophomonas* were isolated from respiratory specimens (57.1%) followed by pus samples (33.3%) and blood (9.5%). Males were predominantly affected (71.4%) followed by females (28.6%) and all these organisms were isolated in the age group of 27years to 65 years.

All the isolates were resistant to imipenem and ceftazidime (100%).Co-trimoxazole resistance was observed in 3(14.2%) out of the 21 isolates. Ciprofloxacin and chloramphenicol resistance was observed in 6(28.5%) isolates each and doxyxycline resistance in 7(33.3%) isolates.

Other antibiotics like cefaperazone sulbactum and piperacillin tazobactum were resistant in half of the isolates (47.6 % each). Amikacin resistance was quiet high with 12 out of the 21 isolates (57.1%) being resistant to it. The least resistance was observed for tigecycline with all the isolates being susceptible to it (0% resistance)

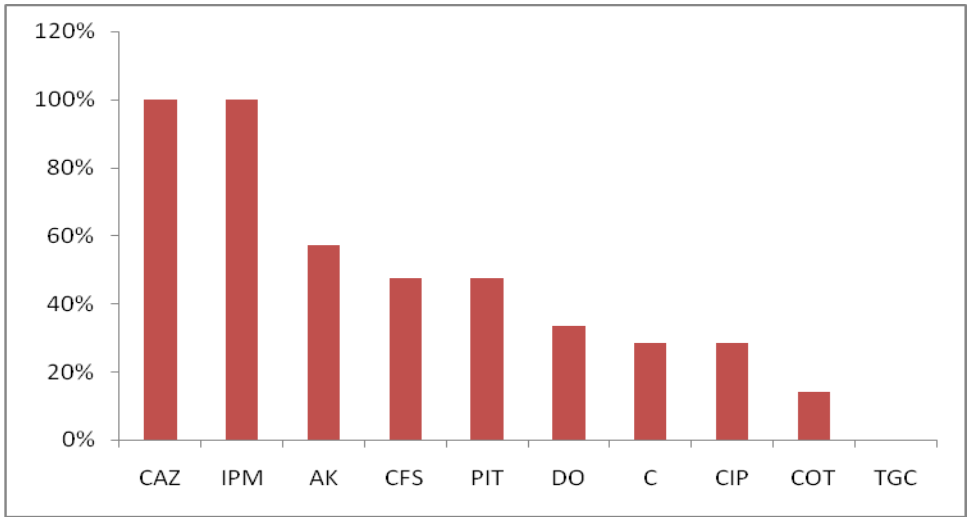
S. maltophilia is an opportunistic multidrug resistant (MDR) Gram-negative bacterium that causes serious infection in immunocompromised patients. Though is not a highly virulent pathogen, it is recognized as a significant nosocomial pathogen and the incidence of these infections in the hospitals are on rise.
This lysine-positive NFGNBs is having a

characteristic contrasting susceptibility pattern to that of *P. aeruginosa* showing sensitivity to co-trimoxazole and resistance towards imipenem. Co-trimoxazole has long been considered as an effective drug for the treatment of these infections, but there has been an increase in antimicrobial resistance of *S. maltophilia* over recent years to this drug which was once a preferred treatment for *S. maltophilia* infections (Gautam *et al.*, 2009; Goldberg *et al.*, 2012). Resistance to co-trimoxazole, over imposed on the inherent multidrug resistance nature to many other antibiotics like aminoglycosides, beta lactams, cephalosporins, carbapenems and many fluoroquinolones makes this organism as an extremely difficult pathogen for the treatment.

Antimicrobial susceptibility testing methods of *S. maltophilia* are also not clearly standardized, and there is poor correlation between disk diffusion and agar dilution results for some agents (Sader, 2005). The European Committee on Antimicrobial Susceptibility Testing (EUCAST) and the British Society for Antimicrobial Chemotherapy (BSAC) report clinical breakpoint data only for trimethoprim–sulfamethoxazole whereas Clinical and Laboratory Standards Institute (CLSI) recommends dilution testing for trimethoprim-sulfamethoxazole, ceftazidime, chloramphenicol, levofloxacin, minocycline, and ticarcillin-clavulanate, and disk diffusion testing for only trimethoprim-sulfamethoxazole, levofloxacin, and minocycline. [EUCAST, 2010, BSAC, 2010] Inspite of the lack of the in vitro guidelines many other antibiotics have been used therapeutically either alone or in combination therapy (Falagas *et al.*, 2008)

In the present study resistance to co-trimoxazole was observed in 14% of the total isolates which is in accordance with the study conducted by Samonis *et al.*, (Samonis *et al.*, 2012) where 13.2% of the isolates were resistant to this antibiotic. In a 2012 study of *S. maltophilia* recovered from cystic fibrosis patients, 24.2% of the patients had TMX-resistant isolates (Milne *et al.*, 2012). The SENTRY Antimicrobial Surveillance Program reported a global resistance rate of 4.7% (1997–2003) (Sader, 2005). This is in contrast with a Taiwanese study of 103 *S. maltophilia* isolates from hospitalized patients, which demonstrated as high as 25% trimethoprim–sulfamethoxazole resistance (Chang *et al.*, 2007).

Fig.1 Resistance pattern of *Stenotrophomonas* to various antibiotics



In another study conducted by Arora *et al.,* (2012) in India, it was observed that over a period of years there was a steady increase in the resistance of *Stenotrophomonas* to cotrimoxazole from 9 to 30% of the isolates (Arora *et al.,* 2012).

In general resistance rates to trimethoprim-sulfamethoxazole have been reported to vary geographically (Livermore *et al.,* 2008, Farrell *et al.,* 2010), but were usually less than 20%.In our study also similar results were observed. Development of resistance to trimethoprim–sulfamethoxazole has been reported owing to modified target genes *sul1* and *sul2*. The association of these genes with the mobile genetic elements is of significant concern because of the probability of wide spreading of this resistance (Toleman *et al.,* 2007)

In the present study all the isolates were resistant to imipenem which is expected, as this organism is inherently resistant to imipenem. Though routine susceptibility testing with imipenem is not recommended, observing resistance to this drug in routine sensitivity plates gives us a clue towards identification of this organism. Apart from imipenem, this organism also has shown absolute resistance against ceftazidime in our study. High rates of ceftazidime resistance have been reported by many authors. Samonis *et al.,* reported a resistance rate of 73.5% for the ceftazidime. Milne *et al.,* reported that 90% of the *Stenotrophomonas* isolates were resistant to ceftazidime. EUCAST report *S. maltophilia* to be intrinsically resistant to ceftazidime, regardless of the result of susceptibility testing.

Amikacin resistance was also considerably high in the present study with 52% of the isolates being resistant. This is similar to betriu *et al.,* (Betriu *et al.,* 2001) study where 62.7% of the isolates were resistant to amikacin. In Milne *et al.,* (2012) study 86% of the isolates were resistant to amikacin. In contrast Samonis *et al.,* (2012) observed very high sensitive rate to this antibiotic where 82.4% of the isolates were susceptible to amikacin.

Tigecycline has shown the least resistance in the present study with all the isolates being susceptible to it. Only few studies are available in the literature regarding the tigecycline susceptibility patterns against *Stenotrophomonas*. In an antimicrobial susceptibility study of 1,586 *S. maltophilia* clinical isolates recovered from medical centers in Europe, North America, Asia and the Pacific region and Latin America, tigecycline was reported as the most effective antibiotic with more than 90% of the isolates being susceptible to this drug irrespective of geographical regions (Farrell *et al.,*2010). Tigecycline is a newer antibiotic with only a limited clinical knowledge and evidence regarding the usefulness of this drug in the treatment of *Stenotrophomonas* infections. Though in vitro susceptibility testing showed fruitful results, it cannot be attributed fully to in vivo situations where pharmacokinetics and pharmacodynamic properties play a significant role. Above this, the high cost of this drug also limits its extensive usage in countries like India. Further research needs to be carried out before fully adopting this agent as a therapeutic alternative.

Apart from tigecycline and cotrimoxazole, in the present study ciprofloxacin and chloramphenicaol have also shown good in vitro activity with only 28.5% of the isolates being resistant to these antibiotics. The resistance rates to these two drugs varied from study to study. In Betriu *et al.,* (2001) study the resistant to ciprofloxacin and chloramphenicol was 68.7% and 39.3% respectively where as in Samonis *et al.,* (2012) study the resistance rate was 17.6%

and 16.2% respectively. In Arora *et al.*, (2012) study only 16% of the isolates were resistant to fluoroquinolones.

Doxycycline followed ciprofloxacin with 33.3% resistance which is intermediate between the findings of Milne *et al.*, (2012) and Arora *et al.*, (2012) study where 13.7% and 59% of the isolates were resistant to this antibiotic respectively. Other antibiotics live piperacillin/tazobactum and cefaperazone/ sulbactum have shown equivocal resistance patterns allowing their utility in only half of the isolates (Fig. 1).

The present study highlights the susceptibility patterns of the *Stenotrophomonas* against various antimicrobial agents. Bacteria can develop resistance to any antibiotic in due course of time especially under the intense antibiotic pressure in the hospital setup. Thorough understanding of the local susceptibility patterns along with proper infection control measures will help in the appropriate management of patients and further prevention of the spread of these resistant infections.

To conclude, resistance has been observed in few isolates against trimethoprim-sulfamethoxazole. Still this drug showed good *in vitro* activity against majority of the *S. maltophilia* isolates. Ciprofloxacin and doxycycline can be considered as an effective alternatives especially in co-trimoxazole resistant infections or when the patients are allergic to co-trimoxazole. Though tigecycline is the highly effective antibiotic in the present study, high cost of this drug and limited clinical experience regarding the effectiveness of this antibiotic against *Stenotrophomonas* prevents its wider usage.

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