# DISCREPANCIES BETWEEN VARIOUS METHODS IN SUSCEPTIBILITY TESTING AND EPIDEMIOLOGICAL ANALYSIS OF *STENOTROPHOMONAS MALTOPHILIA* CLINICAL ISOLATES

Aikaterini Masgala, Irene Galani, Maria Souli, Helen Giamarellou
4th Department of Internal Medicine, Molecular Biology Section, University of Athens Medical School, Athens, Greece

SUMMARY

The susceptibility of 25 *Stenotrophomonas maltophilia* (*S. maltophilia*) clinical isolates to four different antimicrobials (trimethoprim/sulfomethoxazole, piperacillin/tazobactam, ceftazidime, ciprofloxacin) were investigated by disk diffusion, E-test and commercial Sensititre and PASCO broth microdilution techniques. Discrepancies between the results of broth microdilution and the other methods studied were characterized as very major, major and minor errors. Using the broth microdilution as the reference method, 24% of the isolates were found susceptible to trimethoprim/sulfamethoxazole, 24% to ceftazidime, 0% to piperacillin/tazobactam and 12% to ciprofloxacin. Good correlation was observed between the two broth microdilution Sensititre and PASCO for all antibiotics tested. Disc diffusion and E-test generated inconsistent results for all agents except trimethoprim/sulfamethoxazole. A great genomic diversity was demonstrated within the *S. maltophilia* strains tested. Although our results confirm that trimethoprim–sulfamethoxazole had some *in vitro* activity against *S. maltophilia*, further clinical studies are necessary to evaluate the clinical efficacy of these compounds for the treatment of *S. maltophilia* infections, since no randomized controlled trials have been carried out and no correlation between the clinical response and susceptibility testing results has been reported. Furthermore, the high genomic diversity observed in the *S. maltophilia* strains indicates the need for careful epidemiological evaluation especially in nosocomial outbreaks.

*Key words:* E-test, disk diffusion, broth microdilution, epidemiological analysis

Address for correspondence: A. Masgala, Tmolou 39, 16233 Vironas, Greece. E-mail: katerina.masgala@gmail.com

## INTRODUCTION

*Stenotrophomonas maltophilia* has emerged over the last decade as an important opportunistic pathogen with intrinsic resistance to many antimicrobials implicated in a variety of infections. Predisposing factors for *S. maltophilia* infections are consumption of broad spectrum antibiotics, use of central venous catheter, leucopenia and use of cytotoxic agents, prolonged hospitalization especially in the Intensive Care Unit (ICU), mechanical ventilation or tracheotomy, hematologic malignancies, cancer and prolonged use of corticosteroids (1, 2). Since it remains a concern for public health, especially for immunocompromised hosts and for patients with cystic fibrosis, various antibiotics alone or in combination have been tested. Trimethoprim-sulfamethoxazole remains the treatment of choice for *S. maltophilia* infections despite the bacteriostatic action and the emergence of resistant strains (3–5).

Although *in vitro* susceptibility methods for *S. maltophilia* have not been so far fully standardized, E-test is a simple method of susceptibility testing and has been shown to be reliable and accurate although Clinical Laboratory Standard Institute (CLSI) recommends broth and agar dilution for the determination of MICs in *S. maltophilia* (6–9).

Therefore and because of the increasing pathogenic potential of this microorganism, we investigated the resistance patterns of 25 not clonal *S. maltophilia* clinical isolates and we compared broth microdilution (Sensititre) results with those from disc diffusion, PASCO broth microdilution and E-test.

## MATERIALS AND METHODS

### Bacterial Isolates

A total of 25 *S. maltophilia* isolates collected from five Greek hospitals were included in the study. Isolates were collected from individual patients in one year period from pus (2), wound infection (3), sputum (7), blood (1), BAL (1), bronchial secretions (9) and urine (2). They were lyophilized and stored at room temperature. Five of the 25 strains studied were obtained from ICUs whereas the rest from medical wards. All isolates were identified by the API 20 NE System (Bio Merieux, Marcy-I-Etoile, France).

### Molecular Typing

The molecular typing of the *S. maltophilia* isolates was carried out using the Pulse Field Gel Electrophoresis (PFGE) technique. Preparation of agarose plugs containing chromosomal DNA for PFGE analysis was performed as described in the literature and digested with SpeI (New England BioLabs Ltd, Hitchin, Hertfordshire, UK) (10). DNA fragments were separated by PFGE

(pulse times, 5–50 s for 22 h, 1% agarose, 200 V, 10 ºC) in a Gene Navigator apparatus (Pharmacia Biotech AB, Uppsala, Sweden). The band patterns were interpreted according to the Tenover criteria with patterns that differed by two or three bands being defined as closely related subtypes (11).

## Antimicrobial Susceptibility Testing

Antimicrobial susceptibility testing was carried out using the disk diffusion method as described by the CLSI (9). Determination of the MICs was carried out using the PASCO (Becton Dickinson, Sparks, MD) and the Sensititre (Trek Diagnostic Systems, Cleveland, OH) broth microdilution systems and the E-test (AB Biodisks, Solna Sweden) technique according to the respective recommended manufacturer's methodologies for each system. *Escherichia coli* ATCC 25922 and *P. aeruginosa* ATCC 27853 were used as Quality Control (QC) strains. All QC results were within the recommended ranges.

The susceptibility test medium was Mueller–Hinton broth (Cation-Adjusted) or Mueller–Hinton agar (Cation-Adjusted) (Becton Dickinson Microbiology Systems, Cockeysville, Md.). The antimicrobial discs were obtained from Bio-Rad (Richmond, CA, USA) and possessed the following concentrations: piperacillin-tazobactam 100/10 µg, ceftazidime 30 µg, ciprofloxacin 5 µg and trimethoprim-sulfamethoxazole 1.25/23.75 µg.

The minimal inhibitory concentration (MIC) was determined as the lowest antimicrobial concentration inhibiting visible growth after 18 h of incubation at 35 °C.

Interpretive criteria for disk susceptibility testing of *S. maltophilia* isolates are available from Clinical and Laboratory Standards Institute (CLSI) for only minocycline, levofloxacin and trimethoprim/sulfamethoxazole. The performance of other agents that might be approved for therapy, has not been sufficiently studied to establish disk diffusion breakpoints. In terms of MIC interpretation, CLSI recommends additionaly susceptibility breakpoints for ceftazidime and ticarcillin/clavulanic acid (9). The disk diffusion test of ceftazidime and the disk diffusion and broth microdilution results of piperacillin/tazobactam and ciprofloxacin were interpreted according the CLSI criteria established for *Pseudomonas aeruginosa* (9). Agreement between two MIC test methods was defined as MICs that differed by 1 log2 dilution or less and that remained within the same susceptibility or resistance category. Discrepancies were characterized as very major, major and minor errors. A very major error occurred if the isolate was interpreted as resistant by the reference method and susceptible by the tested method. A major error occurred when the interpretation was "susceptible" by the reference method and "resistant" by the tested method. Finally, a minor error occurred when an intermediate result was obtained by one method but not with the other. In our study the Sensititre broth microdilution technique was used as the reference method.

# RESULTS

## Antimicrobial Resistance

The four methods exhibited different susceptibility rates to the four antimicrobial agents against the 25 *S. maltophilia* clinical isolates tested (Table 1). All the QC results were within the recommended breakpoints.

According to Sensititre and PASCO broth microdilution methods, the most effective agent was trimethoprim/sulfamethoxazole with 24% and 32% respectively of the isolates being susceptible to this agent. In contrary piperacillin/tazobactam was the most ineffective agent with none (Sensititre) or only 4% (PASCO) being susceptible. The two broth microdilution methods exhibited the lowest susceptibility rates to all antimicrobial agents, compared to disk diffusion and E-test (Table 1).

The rate of susceptibilities obtained by the disc diffusion and E-test methods showed better agreement as well as those obtained by PASCO and Sensititre broth microdilution systems (Table 1).

The MICs determined by E-test and broth microdilution are shown in Table 2.

The agreement between the E-test results and the broth dilution testing results is shown in Table 3. The lowest agreement was for trimethoprim/sulfamethoxazole (28%) and the highest for piperacillin/tazobactam (64%).

Sensititre and PASCO broth microdilution showed the closest correlation in terms of ciprofloxacin and ceftazidime since no very major error occurred (Table 4). Furthermore, a low percentage of very major error (4% and 8%) was observed between Sensititre and PASCO broth microdilution for piperacillin/tazobactam and trimethoprim/sulfamethoxazole (Table 4). E-test showed 4% of very major error for piperacillin/tazobactam while for the other agents the percentage of very major errors varied from 12 to 60% (Table 4). Disk diffusion showed high frequency of very major errors for all antibiotics tested (24–44%) (Table 4). There were also a substantial number of minor errors, for E-test and disk diffusion, especially with piperacillin/tazobactam, ceftazidime and ciprofloxacin (Table 4).

***Table 1.*** *Susceptibility of S. maltophilia obtained by the four methods studied*

| Antimicrobial agents | Susceptible isolates (%) (CLSI breakpoint) | | | |
|---|---|---|---|---|
| | Sensititre Broth microdilution | Disc diffusion | PASCO Broth microdilution | E-test |
| Trimethoprim/sulfamethoxazole | 24% (≤2) [a] | 68% (≥16) | 32% (≤2) [a] | 84% (≤2) [a] |
| Piperacillin/tazobactam | 0% (≤16) [bc] | 40% (≥18) [c] | 4% (≤16) [bc] | 12% (≤16) [bc] |
| Ceftazidime | 24% (≤8) | 64% (≥18) [c] | 24% (≤8) | 48% (≤8) |
| Ciprofloxacin | 12% (≤1) [c] | 84% (≥21) [c] | 12% (≤1) [c] | 52% (≤1) [c] |

[a]Based on sulfamethoxazole MIC
[b]Based on Piperacillin MIC
[c]Based on CLSI breakpoint for non Enterobacteriaceae other than *P. aeruginosa*

***Table 2.*** *MICs of* S. maltophilia *strains determined by the E-test method and Sensititre Broth Microdilution*

| | E-test | | | | Sensititre Broth Microdilution | | | |
|---|---|---|---|---|---|---|---|---|
| Antimicrobial agents | MIC range | Resistant isolates (%) | $MIC_{50}$ [c] (mg/l) | $MIC_{90}$ [c] (mg/) | MIC range | Resistant isolates (%) | $MIC_{50}$ (mg/lt) | $MIC_{90}$ (mg/lt) |
| Trimethoprim/sulfamethoxazole [a] | 0.5–32 | 16% | 0.5 | >32 | 0.5–2 | 76% | >2 | >2 |
| Piperacillin/tazobactam [b] | 4–256 | 88% | >256 | >256 | 4-64 | 100% | >64 | >64 |
| Ceftazidime | 1–256 | 52% | 16 | >256 | 1–16 | 76% | >16 | >16 |
| Ciprofloxacin | 1–32 | 48% | 2 | 4 | 1–32 | 88% | 2 | >2 |

[a]Based on sulfamethoxazole MIC
[b]Based on piperacillin MIC
[c]MIC50 and MIC90 defined as the minimal concentration of antibiotic capable of inhibiting 50% and 90% of the isolates tested, respectively.

***Table 3.*** *Correlation of MICs for 25 S. maltophilia isolates obtained by the E test and Broth microdilution methods*

| Antimicrobial agent | No. of isolates for which E-test MICs were within the indicated concentration ($log_2$ dilution) of Broth dilution MICs | | | | | % Agreement within 1 $log_2$ dilution |
|---|---|---|---|---|---|---|
| | ≤-2 | -1 | same | 1 | ≥2 | |
| Trimethoprim/sulfamethoxazole | 17 | 2 (1)[a] | 6 | - | - | 28 |
| Piperacillin/tazobactam | 5 | 1 (0)[a] | 16 | - | 3 | 64 |
| Ceftazidime | 9 | 4 (1)[a] | 11 | - | 1 | 48 |
| Ciprofloxacin | 4 | 11 (0)[a] | 8 | 2 (0) [a] | - | 32 |

[a]In parenthesis the number of the isolates that remained within the same susceptibility or resistance category

The 84% of the ciprofloxacin E-test MICs were within a difference of 1 log2 dilution, compared with those obtained by broth dilution testing, but only 32% of the isolates remained within the same susceptibility or resistance category (Table 3). However, agreement when testing piperacillin/tazobactam (64%) and ceftazidime (48%) was better than agreement for trimethoprim/sulfamethoxazole which was only 28% (Table 3).

## Molecular Typing

The 25 isolates studied, proved by PFGE to have different patterns. Twelve isolates were totally unrelated (differed by seven or more bands) and 13 isolates were probably related (differed by four up to six bands). Among the 13 isolates probably related, only two had the same susceptibility pattern for all methods and for all antibiotics tested (Fig. 1). Those strains originated from the same clinical department.

## DISCUSSION

*S. maltophilia* has risen to prominence in the last few years. Infections caused by this emerging pathogen appear especially in immunocompromised and ICU patients, particularly those catheterized or on mechanical ventilation. *S. maltophilia* is commonly multiresistant to several antimicrobials including β-lactams and aminoglycosides. Trimethoprim/sulfamethoxazole remains by definition the drug of choice for all *S. maltophilia* infections. *In vitro* susceptibility studies have shown that trimethoprim/sulfamethoxazole remains the most active agent against *S. maltophilia* (12). In the present study, 24% of the isolates tested, were susceptible to trimethoprim/sulfamethoxazole when the recommended by the CLSI broth microdilution technique was used (Table 1). However the highest percentage of susceptibility to this agent was obtained with the E-test technique (84%). Comparison of the discordant results between the E-test and broth dilution methods for trimethoprim-sulfamethoxazole demonstrated an unacceptable rate of very major errors (false susceptible) (60%).

The 24% of the isolates of this study was also susceptible to ceftazidime according to broth microdilution technique, percentage that was increased to 48% when E-test was evaluated (Table 1). However, *S. maltophilia* susceptibility testing results concerning ceftazidime are controversial in the literature (13).

Fluoroquinolones which seem to be very promising agents for the management of *S. maltophilia* infections with gatifloxacin, moxifloxacin, gemifloxacin and levofloxacin showing better *in vitro* activity against *S. maltophilia* strains than ciprofloxacin, inhibited only 12% of the isolates (14–16). E-test revealed 52% of susceptibility to the same agent.

In piperacillin/tazobactam broth microdilution show that 100% of the isolates were resistant in accordance with *in vitro* studies that exhibited a high resistance rate of *S. maltophilia* to piperacillin/tazobactam, while 12% of those isolates were susceptible according to E-test (17, 18). Combinations such as ciprofloxacin and piperacillin/tazobactam showed however better *in vitro* activity than piperacillin/tazobactam alone (13).

This study demonstrated an excellent correlation between the dilution methods when evaluating the antimicrobial activity of trimethoprim/sulfamethoxazole, piperacillin/tazobactam and ciprofloxacin against *S. maltophilia* isolates tested.

***Table 4.*** *Correlation of susceptibility methods, using the Sensititre Broth Microdilution as the reference method*

| Antimicrobial agent | Percentage(%) of | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Disc diffution | | | | PASCO Broth microdilution | | | | E-test | | | |
| | VME | ME | mE | TE | VME | ME | mE | TE | VME | ME | mE | TE |
| Trimethoprim/sulfamethoxazole | 44 | 0 | 12 | 56 | 8 | 0 | 0 | 8 | 60 | 0 | 0 | 60 |
| Piperacillin/tazobactam | 24 | 0 | 16 | 40 | 4 | 0 | 4 | 8 | 4 | 0 | 28 | 32 |
| Ceftazidime | 28 | 0 | 20 | 48 | 0 | 0 | 8 | 8 | 16 | 4 | 24 | 44 |
| Ciprofloxacin | 32 | 0 | 48 | 80 | 0 | 0 | 0 | 0 | 12 | 0 | 56 | 68 |

VME; very major errors, ME; major errors, mE; minor errors, TE; total errors

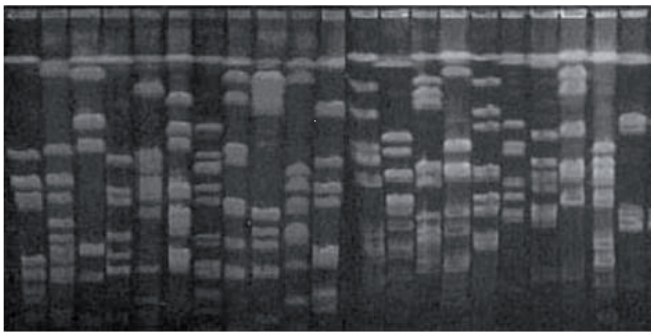

***Fig. 1.*** *PFGE of S. maltophilia strains.*

In contrast to what has been previously demonstrated for different antimicrobial agents, the E-test method exhibited low percentage of agreement with the reference broth dilution method, also for piperacillin/tazobactam, ciprofloxacin and ceftazidime (6). Very major errors occurred at rates of 4, 12 and 16% respectively, indicating that this test is not a reliable method for determining the susceptibility of *S. maltophilia* to this antibiotics.

Susceptibility testing remains problematic for many diagnostic laboratories. Different susceptibilities methods have been tested and have been compared, with controversial results. In this study, we used the broth microdilution as the reference method because of its reliability in susceptibility testing and its convenience (9). To estimate the correlation between the broth microdilution method (Sensititre), which was the reference method, and disk diffusion, E-test and PASCO broth microdilution method, we evaluated the very major errors for all antibiotics tested.

The agar dilution method has been considered by some investigators the best susceptibility method for *S. maltophilia* and it has been applied as the reference method in many studies (5, 13, 19, 20). Using the agar dilution as the reference method Pankuch et al. (21) compared E-test, disk diffusion and broth microdilution. Low rates of essential agreement and high rates of very major and major errors occurred especially for piperacillin/tazobactam. Comparing agar dilution with E-test and disk diffusion methods Apri et al. (3) found high frequency of very major discrepancies for disk diffusion method than with the other methods. However, the susceptibility of *S. maltophilia* to trimethoprim/sulfamethoxazole and ciprofloxacin could be reliably determined by all the diffusion methods tested. Carroll et al. (22) compared disk diffusion and E-test with commercial broth mirodilution and in house microdilution method. Disc diffusion and E-test had the closest correlation for the beta-lactams, doxycycline, ciprofloxacin and trimethoprim/sulfamethoxazole. The commercial broth mirodilution and in house microdilution method generated inconsistent results for all agents except trimethoprim/sulfamethoxazole. E-test and agar dilution had an overall agreement of 94% for all antimicrobials tested in a study conducted by Yao et al. (6). Krueger et al. compared disk diffusion with broth microdilution and they reported poor correlation for ciprofloxacin and trimethoprim/sulfamethoxazole (23). In *S. maltophilia* strains isolated from cystic fibrosis patients, E-test or microdilution method have been found both appropriate for determining the accurate susceptibility pattern which is very important for this difficult to treat group of patients (8, 24).

It is obvious that no agreement exists between the results of any of the studies including ours. Emergence of *S. maltophilia* as a nosocomial pathogen is increasingly apparent. As was observed in our study, *S. maltophilia* strains have high genetic diversity even when isolated from the same medical ward. The different genotypes of this pathogen have been observed in many studies. Data obtained from epidemiological surveys that were conducted to investigate *S. maltophilia* nosocomial outbreaks, showed a high genomic diversity within the species of *S. maltophilia* (25, 26). The different genetic patterns of this opportunistic pathogen have been confirmed in recent studies and it might be related to the high potential environmental distribution of *S. maltophilia* (25, 19, 20).

## CONCLUSION

Using the broth microdilution technique, we found a relatively low percentage of strains (24%) being susceptible to trimethoprim-sulfamethoxazole. This is in agreement with previous *in vitro* reports (27, 28) that question the appropriateness of trimethoprim-sulfamethoxazole therapy alone especially for serious *S. maltophilia* infections.

Nevertheless, *in vitro* testing will not resolve the issue of clinical adequacy, so further controlled trials need to be conducted to evaluate the correlation between the susceptibility testing results and the clinical outcome.

The high genomic diversity of the *S. maltophilia* clinical isolates that has been observed in many studies including ours, makes obvious the need for careful epidemiological evaluation especially in nosocomial outbreaks.

Since the number of the clinical strains in the study is small, further studies are necessary to confirm the obtained data.

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