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Investigation of in vitro activity of colistin and tygecyclin against *Stenotrophomonas maltophilia* isolates

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Abstract

Stenotrophomonas maltophilia has emerged as an important opportunistic pathogen, causing infections whose management is often problematic due to its inherent resistance to many antibiotics. In this study, we aimed to investigate the antimicrobial susceptibility of colistin and tygecyclin as an alternative treatment options for *S. maltophilia* infections. A total of 122 *S. maltophilia* isolates were tested. Minimum inhibitory concentration (MIC) values of colistin and tygecycline were determined by broth microdilution method. Susceptibility of TMP/SMX and levofloxacin (LVX) were determined by disc diffusion method and MIC value of ceftazidime (CAZ) was determined by using E-test. Out of 122 S. maltophilia isolates, 5 (4%) of them were resistant to TMP-SXM. MIC range was 0.125- >512 µg/ml and MIC_{50} 64 µg/ml, MIC_{90} 512 µg/ml for colistin. MIC range for tygecyclin was detected as 0.5- >8, MIC_{50} 2 µg/ml and MIC_{90} 8 µg/ml. Tygecyclin resistance was detected as 66.4% according to the EUCAST guideline and 13.1% according to the USA-FDA breakpoints. And colistin resistance was determined as 86.9% according to both guidelines.

Keywords: colistin, MIC, *S. maltophilia*, tygecyclin

1. Introduction

Stenotrophomonas maltophilia is an important nosocomial pathogen in certain patient populations, particularly in individuals who are immunosuppressed (1). *S. maltophilia* usually appears in immunocompromised and intensive care unit (ICU) patients, also frequently recovered from the respiratory tract of cystic fibrosis patients, and generally associated with infections of the respiratory tract, the organism is also a cause of bacteremia, endocarditis and urinary tract infections (2, 3). *S. maltophilia* infections are associated with high morbidity and mortality with the risk of mortality highest amongst patients receiving inappropriate initial antimicrobial therapy (4).

S. maltophilia is commonly resistant to several antimicrobial agents, including beta-lactams, due to heterogeneous production of b-lactamases (1). Reduced permeability and expression of efflux pumps could enhance this resistance phenotype (5, 6). Trimethoprim/sulfamethoxazole (TMP/SMX) is the main antimicrobial of choice for the treatment of *S. maltophilia* infections with ticarcillin/clavulanate, ceftazidime, minocycline, fluoroquinolones, tigecycline, and the polymyxins are described as alternative therapies (7). TMP/SMX resistance has been described and as high as 10% of isolates in Europe (8, 9). Tigecycline is the first glycylcycline antimicrobial and licensed for clinical use. Tigecycline binds to the 30S ribosomal subunit and inhibits synthesis of protein. It has a wide range of activity against both Gram-positive and Gram-negative organisms (9).

Colistin, also known as polymyxin E, is an old antibiotic and has in vitro activity against some multi-resistant Gram-negative bacteria, including *P. aeruginosa, A. baumannii* and *Klebsiella pneumoniae.* Beta-lactams, aminoglycosides, or quinolones are ineffective, colistin, remain drugs of last choice (10). Colistin has also been shown to possess in vitro activity against *S. maltophilia* strains (83%–88%) of the tested isolates were susceptible to colistin in two recent studies) (8, 11, 12). The aim of this study was to assess the antimicrobial resistance in *S. maltophilia* against colistin and tigecycline.

2. Materials and methods

A total of 122 *S. maltophilia* isolates recovered from hospitalized patients in medical, surgical wards and in intensive care units were tested. Bacterial identification was made by using standard algorithms (microscopy, culture characteristics, oxidase reaction) followed by an automated system (Vitek MS, bioMeriux USA). Minimum inhibitory concentration (MIC) values of colistin and tigecycline were determined for all isolates based on the Clinical Laboratory Standards Institute (CLSI) (13) broth microdilution method. For tigecycline susceptibility fresh cation-adjusted Mueller-Hinton agar was used. Susceptibility of TMP/SMX and levofloxacin (LVX) were determined by disc diffusion method and MIC value of ceftazidime (CAZ) was determined by using E-test.

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Tigecycline breakpoints established by the USA-FDA for Enterobacteriaceae (≤2 / ≥8 µg/ml for susceptibility/resistance) and EUCAST for Enterobacteriaceae (≤1 / >2 µg/ml for susceptibility/resistance) as well as colistin breakpoints established by the CLSI for P. aeruginosa (≤2 / ≥8 µg/ml for susceptibility/resistance), and the EUCAST for P. aeruginosa (≤4 / >4 µg/ml for susceptibility/resistance), were applied for comparison purposes (14-16). MIC50 and MIC90 values were determined for each antimicrobial. TMP/SMX, LVX and CAZ susceptibilities were interpreted according to the CLSI criteria established for *S. maltophilia* (14).

3. Results

Clinical sites of infection for *S. maltophilia* were primarily bloodstream (35.3%) and respiratory tract (33.6%) (Table 1).

Table 1. Distribution of clinical specimen

Specimen	n(%)
Respiratory tract	41 (33.6)
Bloodstream	43(35.3)
Urine	19 (15.6)
Wound	10 (8.2)
Catheter tip	5 (4.1)
Sterile body fluid	2 (1.6)
Conjonktiva	2 (1.6)

Out of 122 S. maltophilia isolates, 5 (4%) of them were resistant to TMP-SXM. LVX and CAZ resistance were determined as 6.5% and 56.5%, respectively.

MIC range was 0.125- >512 µg/ml and MIC_{50} 64 µg/ml, MIC_{90} 512 µg/ml for colistin. For tigecycline, MIC range was detected as 0.5->8, MIC_{50} 2 µg/ml and MIC_{90} 8 µg/ml. Tigecycline resistance was detected as 66.4% according to the EUCAST guideline and 13.1% according to the USA-FDA breakpoints. And colistin resistance was determined as 86.9% according to both guidelines (Table 2).

Susceptibility rates according to the clinical sites were specified in Table 3. Tigecycline susceptibility was determined highest in conjunctiva and sterile body fluids as 50%, however the specimen number is very low (n=2) for these clinical sites. For bloodstream and respiratory tract specimens tigecycline susceptibility was determined as 39.5%-88.4% and 12.2%-78.0%, according to the EUCAST and USA-FDA breakpoints, respectively. The highest colistin susceptibility were determined for bloodstream isolates as 21%. And for catheter tips, conjunctiva and sterile body fluids tigecycline seems more effective than colistin *in vitro.*

Table 2. Resistance rates for tigecycline and colistin according to the EUCAST and CLSI/USA-FDA criteria

	EUCAST	CLSI/USA FDA	MIC_{50} MIC_{90}
	R	R	
Tygecyclin	81 (66.4%)	16 (13.1%)	2 8
Colistin	106 (86.9%)	106 (86.9%)	64 512

Table 3. Distribution of tigecycline and colistin susceptibilities according to the clinical specimens

	Tygecyclin EUCAST(S) CLSI(S)	Colistin (S) EUCAST CLSI
Blood stream (n:43)	39.5% 88.4%	21% 21%
Respiratory tract (n:41)	29.3% 78.0%	12.2% 12.2%
Urine (n:19)	36.8% 79.0%	5.3% 5.3%
Wound (n:10)	30.0% 60.0%	10.0% 10.0%
Catheter tip (n:5)	0% 60.0%	0% 0%
Sterile body fluid (n:2)	50% 100%	0% 0%
Conjunctiva (n:2)	50% 100%	0% 0%

4. Discussion

In this study, in vitro effectiveness of tigecycline and colistin was investigated as an alternative for treatment of *S. maltophilia* isolates that were isolated from clinical samples in our hospital.

S. maltophilia is accepted as a pathogen with gradually increasing importance recently. The reason for this may be increasing number of immune-compromised patients, prolonged hospital stays and increasing use of wide spectrum antibiotics like carbapenems (17). *S. maltophilia* was detected to be the most common non-fermentative bacillus following *P. aeruginosa* and *Acinetobacter spp.* between 1997-2001 and isolation ratio was found as 8% in clinical samples (18).

S. maltophilia may lead to respiratory tract, bloodstream, urinary tract and wound infections. In the studies, *S. maltophilia* was shown to be isolated from different sample types. While vast majority of the isolates were isolated from blood samples in this study, respiratory tract samples, urinary tract samples were the most common in some other studies (19-22).

TMP-SXM has been considered as the first therapeutic option against *S. maltophilia* infections, but this is primarily based on in vitro susceptibility data (7). However, increasing resistance to trimethoprim/sulfamethoxazole has been reported (23, 24), mostly related to the horizontal spread of mobile genetic elements which are carrying resistance genes (25, 26).

The fluoroquinolones are one of the other main alternative treatment options for the *S. maltophilia* infections (7). According to reports, primarily ciprofloxacin, levofloxacin and, particularly, moxifloxacin can have more potent in vitro activity (l5, 27,29). Also, it is reported that resistance to the fluoroquinolones can arise during therapy. In our study, the in vitro resistance to levofloxacin was 6.5% (30-32). Among the beta lactams, ceftazidime is the agent that can be considered as potential therapeutic options against *S. maltophilia*

infections (23). In our study, the susceptibility to this agent was rather low as 43.5%, in agreement with other relevant studies (33).

New treatment options are required due to limited number of antimicrobial agents and resistance development against the agents used for treatment of *S. maltophilia*. Colistin and tigecycline are among these new options. In a study investigating colistin susceptibility in *S. maltophilia* isolates, colistin resistance was found to elevate to 60% in 2010 while it was 8% in 1996. Authors reported that this was associated with increasing use of colistin (34). Colistin resistance was found between 24-100% in a few studies which was conducted with small number of *S. maltophilia* isolates (8, 35-37). Samonis et al. (19) found colistin susceptibility as 91.2%. The clinical breakpoints determined for *P. aeruginosa* by CLSI was used in these studies. Susceptibility method variabilities were reported as the reason for differences in the resistance rates (36). Geographic region and patient population were also reported to be able to be effective on colistin resistance profile (33, 37, 38).

Insa et al. (39) investigated the effectiveness of tigecycline in 120 *S. maltophilia* isolates and found susceptibility of isolates as 98% when they accepted breakpoint value as ≥2µg/ml. Farrel et al. (33) found tigecycline susceptibility as 95% (USA-FDA criteria were used as limit value for tigecycline) in their study investigating tigecycline susceptibility in *S. maltophilia* isolates isolated from different regions of the world. Tigecyclin was found as the most effective agent following TMP-SXM also in this study. Colistin susceptibility was found as 64.6% in the same study (33). Absence of a clinical breakpoint value for *S. maltophilia* in categorical assessment of tigecycline susceptibility and use of different clinical breakpoint influence resistance rates (14-16). When tigecycline susceptibility was evaluated in this study, while resistance rate is 13.1% according to USA-FDA criteria, this value elevated to 66.4% according to EUCAST criteria.

Absence of a specified clinical breakpoints for assessment of colistin and tigecycline susceptibility for *S. maltophilia* isolates seems to be one of the reasons for detecting different susceptibility rates. Determination of clinical breakpoints against these agents with future studies conducted with larger series is suggested to be useful for treatment of *S. maltophilia* infections which is gradually increasing.

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