Emergence of *Stenotrophomonas maltophilia* nosocomial isolates in a Saudi children's hospital

Risk factors and clinical characteristics

Jobran M. Alqahtani, *MBBS, MD.*

ABSTRACT

الأهداف: لوصف الخصائص السريرية للأطفال المرضى والمصابين بعدوى بكتيريا الستينوتروفوموناس المالتوزية في مستشفى أطفال سعودي ، وكذلك لتحديد عوامل الخطر المرتبطة بالعدوى، والتعرف على أنماط مقاومة هذا الميكروب للمضادات الحيوية.

الطريقة: شملت الدراسة 64 معزولة سريرية من بكتيريا الستينوتروفوموناس المالتوزية خلال الفترة من يناير 2015م إلى فبراير 2016م، وتم إجراء اختبارات حساسية هذه المعزولات ل7 من المضادات الحيوية باستخدام الطرق المعيارية.

النتائج: تم تحديد 48 (75%) معزولة كعدوى حقيقية. وكانت أهم أنواع العدوى هي الالتهاب الرئوي وعدوى مجرى الدم في 22 (45.8%) و 14 (29.2%) مريضاً على التوالي. وجدنا أن أهم عوامل الخطر المرتبطة بالعدوى هي الإجراءات الغازية ، والبقاء في المستشفى لفترات طويلة ، و دخول العناية المركزة ، و وجود سرطان الدم الحاد. وكانت المضادات الحيوية الأكثر نشاطا على الميكروب هي (حساسية 100%) rimethoprim/sulfamethoxazole و tigecycline (93.7% sensitivity) .

الخاتمة: أوضحت هذه الدراسة أن بكتيريا الستينوتروفوموناس المالتوزية ميكروب ناشئ هام في حدوث عدوى المستشفيات. ويعتبر التعرف الدقيق على الميكروب وتحديد حساسيته للمضادات الحيوية، إجراءاً حاسماً في علاج المرضى المصابة ومنع انتشار هذه العدوى.

Objectives: To describe the clinical characteristics of pediatric patients colonized or infected by *Stenotrophomonas maltophilia (S. maltophilia)* at a Saudi children's hospital, to identify risk factors associated with infection, and to investigate the antimicrobial resistance patterns of this emerging pathogen.

Methods: In this cross-sectional observational study, 64 non-duplicating *S. maltophilia* strains were isolated in Najran Maternity and Children's Hospital, Najran, Saudi Arabia between January 2015 to February 2016. Antimicrobial susceptibility testing was performed using the reference broth microdilution method.

Results: In this study, 48 (75%) isolates were identified in true infections and 16 (25%) isolates were considered colonization. The main types of *S. maltophilia* infection were pneumonia in 22 (45.8%) patients and bloodstream infection in 14 (29.2%) patients. The significant risk factors included exposure to invasive procedure (p=0.02), and presence of acute leukemia as an underlying disease (p=0.02). The most active antimicrobials were trimethoprim/sulfamethoxazole (100% sensitivity) and tigecycline (93.7% sensitivity).

Conclusions: *Stenotrophomonas maltophilia* is an emerging nosocomial pathogen among pediatric patients. Accurate identification and susceptibility testing of this emerging pathogen are crucial for the management of infected patients and prevention of spread of this nosocomial pathogen.

Saudi Med J 2017; Vol. 38 (5): 521-527
doi: 10.15537/smj.2017.5.16375

From the Department of Pediatrics, College of Medicine, Najran University, Najran, Kingdom of Saudi Arabia.

Received 8th September 2016. Accepted 15th February 2017.

Address correspondence and reprint request to: Dr. Jobran M. Alqahtani, Department of Pediatrics, College of Medicine, Najran University, Najran, Kingdom of Saudi Arabia. E-mail: jobrancv@yahoo.com
ORCID ID: orcid.org/0000-0003-3198-7576

Disclosure. Authors have no conflict of interests, and the work was not supported or funded by any drug company.

Stenotrophomonas maltophilia (*S. maltophilia*) is an aerobic, glucose non-fermentative, Gram-negative bacillus that is widely distributed in various environments and equipment, especially in hospitals.[1,2] This bacterium is increasingly recognized as an emerging global opportunistic pathogen, causing hospital-acquired infections, such as bacteremia, pneumonia, endocarditis, and meningitis, as well as urinary tract, ocular, bone and joint, skin, and soft tissue, and gastrointestinal infections. It is occasionally associated with septic shock in critically ill and immunosuppressed patients; especially in intensive care units (ICUs).[3-6] Infections with *S. maltophilia* are associated with high morbidity and mortality rates. Therapy for these infections represents a significant challenge for clinicians because of the organism's high level of intrinsic resistance to multiple classes of antibiotics, afforded by various mechanisms such as decreased permeability, production of β-lactamases and of aminoglycoside modifying enzymes, or the presence of multidrug efflux pumps.[7] Resistance can also emerge during therapy. Moreover, identification of *S. maltophilia* can be problematic for microbiologists. In many cases, isolation of *S. maltophilia* from clinical specimens may be misidentified as colonization rather than infection.[8,9] Meanwhile, susceptibility testing methods of this organism are difficult. The commonly investigated antibiotics for in vitro activity against *S. maltophilia* include trimethoprim/sulfamethoxazole (SXT), fluoroquinolones, ticarcillin/clavulanate (TIM), minocycline (MI) and tigecycline (TGC).[10] Trends of increasing resistance to these individual antimicrobials have been recently reported in many clinical studies and combined therapeutic regimens are recommended.[11,12] Most clinical and epidemiological studies of *S. maltophilia* have focused on the adult population,[5,8,11,13,14] and only a few reports have described nosocomial infections in pediatric patients.[12,15-17] Moreover, the national data on the antimicrobial susceptibility of *S. maltophilia* in Saudi Arabia is limited. The present study aimed to describe the clinical characteristics of pediatric patients colonized or infected by *S. maltophilia* at a Saudi children's hospital, and to identify risk factors associated with infection, as well as to investigate the antimicrobial resistance patterns of this emerging pathogen. Improved knowledge of these aspects could help the management and selection of empirical therapies for such infections.

Methods. This cross-sectional descriptive study was conducted at Najran Maternity and Children's Hospital, a 250-bed, tertiary care hospital in Najran, a city in southwestern Saudi Arabia, between January 2015 and February 2016. The study was reviewed and approved by the Scientific Research Committee of the College of Medicine, Najran University. The study included children ≤5 years of age who presented with signs and symptoms of healthcare-associated infections, and were admitted to the pediatric ward, or ICUs (neonatal ICU or pediatric ICU). Written consent was obtained from their parents. The demographic and clinical data of the hospitalized children were recorded, including age, gender, type of infection, underlying disease, length of hospital stay, ICU admission, invasive procedure, and antimicrobial therapy within the last 3 months.

Health-care associated infections were defined using criteria of the standard Centers for Disease Control/ National Healthcare Safety definition Network (CDC/ NHSN). Decisions regarding Infection or colonization were made after the following factors were considered: the patient's clinical history, physical findings, body temperature at the time of culture, leukocyte count, C-reactive protein level, culture results of specimens from other sites, clinical course, and response to therapy. Briefly, colonization was defined as the presence of *S. maltophilia* on skin, mucous membranes, in wounds, or in secretions without causing adverse clinical signs or symptoms. A bloodstream infection was considered to be associated with a central venous catheter (CVC) if the patient had a CVC in place at the time of isolation and no other source of infection was identified.[19] Ventilator-associated pneumonia (VAP) was defined as an infection in a child requiring at least 48 hours of mechanical ventilation and developing new and persistent radiographic evidence of focal infiltrates 48 hours or more after the initiation of mechanical ventilation.[18] Urinary tract infection was defined as the isolation of Stenotrophomonas from a catheterized urine sample (>50,000 colony count), and wound infection as the isolation of Stenotrophomonas without any mixed growth from the wound, along with clinical features of wound infection. Conjunctivitis was defined as the presence of a purulent ocular discharge, erythema, and edema of the lids. Neutropenia was defined as an absolute neutrophil count <1500 cells/mm^3 documented at least once during the week before isolation.

Bacteriological methods. *Stenotrophomonas maltophilia* strains were isolated from various clinical specimens including blood, urine, respiratory secretions (tracheal aspirate, and bronchoalveolar lavage), pus, ocular swabs, and tips of CVCs from different patients (one isolate/patient). The isolates were identified by the standard microbiological methods, including microscopy, culture characteristics, catalase, oxidase, aesculin hydrolysis, lysine decarboxylase and DNase,20 the Analytical Profile Index (API) system (bioMérieux, Marcy l'Etoile, France), and the automated Vitek 32 system (bioMérieux, Marcy l'Etoile, France).

Antimicrobial susceptibility testing was performed using the reference broth microdilution method following the guidelines of the Clinical and Laboratory Standards Institute (CLSI).[10] The minimum inhibitory concentrations of 7 antibiotics were determined. The antibiotics tested included TIM, ceftazidime (CAZ), MI, levofloxacin (LVX), TGC, chloramphenicol, and SXT. For TGC, the criteria of ≤1 mg/mL for susceptibility and ≥2.0 mg/mL for resistance were applied based on the clinical breakpoints of the European Committee on Antimicrobial Susceptibility Testing for *Enterobacteriaceae*.[21] The CLSI interpretive criteria for *S. maltophilia* were used for other agents.[10] Intermediately-resistant isolates were considered to be resistant. Quality control was performed using Escherichia coli ATCC 25922, Pseudomonas aeruginosa ATCC 27853 and *Staphylococcus aureus* ATCC 29213.

Statistical analysis. Data were coded, validated, and analyzed using the Student's t-test, the chi squared test, antecedent 95% confidence intervals (95% CI) or Fisher's exact test, where appropriate. All comparisons were 2-tailed, and P values <0.05 were considered statistically significant. All analyses were performed with the Statistical Package for the Social Sciences (SPSS), Version 15.0 (SPSS Inc., Chicago, IL, USA).

Results. Sixty-four non-duplicating *S. maltophilia* strains were isolated during the study period, of which 48 (75%) were identified in true infections and 16 (25%) isolates were considered colonization, because those patients had no infection criteria. The main type of infection associated with *S. maltophilia* was pneumonia in 22 (45.8%) patients, of whom 5 (22.7%) cases had VAP, followed by BSI in 14 (29.2%) patients, of whom 2 (14.3%) patients had CVC-related bacteremia, urinary tract infection in 5 (10.4%) patients, ocular infection in 4 (8.3%) patients, and skin and soft tissue infection in 2 (4.2%) patients. Only one (2.1%) patient had surgical wound infection. The proportions of infecting and colonizing isolates according to the site of isolation are presented in (**Table 1**). Twenty-two (45.8%) *S. maltophilia* isolates from infected patients were obtained from tracheal aspirates, while 14 (29.2%) strains were isolated from blood, 5 (10.4%) from urine, and 4 (8.3%) from ocular discharge. There was no polymicrobial infection in the 48 patients.

The risk factors of *S. maltophilia* infections are listed in **Table 2**. Univariate analysis indicated that patients who were subjected to CVC (p=0.04) or who had acute leukemia as an underlying disease (p=0.02) were significantly infected with *S. maltophilia*. The age, gender, prematurity, underlying diseases other than acute leukemia, mechanical ventilation, and prior antibiotic therapy were not significantly different in infected and colonized patients. The antimicrobials tested, and the percentages of resistant isolates are listed in Table 3. Overall, with the exception of SXT that inhibited all isolates and TGC that inhibited 94% of isolates, more than 75% of isolates was resistant to CAZ and chloramphenicol. The rate of susceptibility to MI was 66.7%, to LVX was 64.7%, and to TIM was 27.1%.

Table 1 - Site of isolation of *Stenotrophomonas maltophilia* nosocomial isolates.

Site of isolation	Isolates			
	Infected patients (n = 48)		Colonized patients (n = 16)	
	n (%)	95% CI	n (%)	95% CI
Tracheal aspirate	22 (45.8)	31.6 - 60.7	5 (31.3)	12.1 - 58.5
Blood	14 (29.2)	17.4 - 44.3	1 (6.3)	0.3 - 32.2
Urine	5 (10.4)	3.9 - 23.5	4 (25)	8.3 - 52.6
Conjunctiva	4 (8.3)	2.7 - 20.9	4 (25)	8.3 - 52.6
Skin and soft tissue	2 (4.2)	0.7 - 15.4	2 (12.5)	2.2 - 39.6
Surgical site or wound	1 (2.1)	0.1 - 12.5	0 (0)	0.0 - 24.1

Table 2 - Risk factors for *Stenotrophomonas maltophilia* (*S. maltophilia*) infections.

Variable	*S. maltophilia* isolates among:		*P*-value
	Infected patients (n=48)	Colonized patients (n=16)	
Age mean (months)	20.3 ± 14.42	21.8 ± 13.82	0.717
Male (%)	26 (54.2)	9 (56.3)	1.00
Underlying diseases			
Prematurity	10 (20.8)	2 (12.5)	0.714
Acute leukemia	12 (25)	0 (0)	0.052
Congenital heart defects	2 (4.2)	0 (0)	0.407
Neutropenia	4 (8.3)	2 (12.5)	0.635
Mean days of hospital stay	9.7 ± 4.62	7.45 ± 2.31	0.067
ICU admission (%)	15 (31.3)	1 (6.3)	0.052
Prior invasive procedures			
Mechanical ventilation	5 (10.4)	0 (0)	0.320
Central venous catheter	15 (31.3)	1 (6.3)	0.052
Urinary catheter	20 (41.7)	2 (18.8)	0.038
Prior antibiotic therapy	26 (54.2)	6 (37.5)	0.387

Table 3 - Number and percentages of *Stenotrophomonas maltophilia* (*S. maltophilia*) isolates resistant to selected antimicrobial agents.

Antimicrobial agent	*S. maltophilia* isolates (n=48) n (%)
CAZ	44 (91.7)
TIM	35 (72.9)
MI	16 (33.3)
LVX	17 (35.4)
TGC	3 (6.3)
C	34 (70.8)
SXT	0 (0)

CAZ - ceftazidime, TIM - ticarcillin/clavulanate, MI - minocycline, LVX - levofloxacin, TGC - tigacycline, C - chloramphenicol, SXT - trimethoprim-sulfamethoxazole

Discussion. Globally, *S. maltophilia* has become the third most common non-fermentative Gram-negative bacilli responsible for nosocomial infections, behind *P. aeruginosa* and *Acinetobacter species*.[1] Recently, *S. maltophilia* has emerged as an important opportunistic nosocomial pathogen among pediatric patients. The emergence of this pathogen is probably related to advances in medical care that has led to an increase in the number and survival rates of severely ill, debilitated children who are the vulnerable group at the highest risk for acquiring infection by this pathogen.[2,5] *S. maltophilia* has a variety of clinical presentations. Respiratory tract infection, especially VAP, and BSI are the most common infections reported in many clinical and epidemiological studies. The spectrum of the clinical diseases caused by *S. maltophilia* in this study was similar to that observed in other relevant studies.[3,5,11-13]

Differentiation between *S. maltophilia* colonization and infection is difficult for both the clinicians and the microbiologists. Previously, *S. maltophilia* was considered a low-virulence pathogen. Its isolation from the respiratory tract has been frequently interpreted as colonization rather than as infection.[8,9] Many previous studies have found a large proportion of colonizing *S. maltophilia* isolates, with rates of true infection of 13-71%.[13-15,22,23] In this study, 75% of the 64 isolates were identified as true infections. The low rate of colonization in this study may be related to the definitions used. The CDC/NHSN criteria used to define whether an isolate was infecting or not were chosen to give uniformity to the data obtained.[18] Moreover, identification of true *S. maltophilia* infection may be more problematic when *S. maltophilia* is not the only organism isolated. Sattler et al[17] investigated episodes of infection from non-respiratory sites and reported that 70.6% of *S. maltophilia* isolates were from poly-microbial cultures, which yielded other obligate pathogens (*Pseudomonas aeruginosa, Staphylococcus aureus, Klebsiella species* and *Acinetobacter species*). Several factors raise doubts about the significance of *S. maltophilia* in the etiology of poly-

microbial infections; namely, the high proportion of poly-microbial isolation in most studies, the co-isolation of pathogens that are well known to cause infection at these sites, and the high cure rate despite inappropriate therapy.[24] The pathogenic role of *S. maltophilia* in poly-microbial infections is still debatable. It is noteworthy that all *S. maltophilia* isolates in this study were mono-bacterial, and more likely to be a cause of infection than colonization.[2,3]

In this study, the predisposing factors associated with *S. maltophilia* infection were similar to those reported by other studies that primarily described *S. maltophilia* isolations among adult patients.[5,11,13,14,16,25] These risk factors included prolonged hospitalization, presence of a CVC, neutropenia, ICU admission, mechanical ventilation, or tracheotomy, prior antibiotic therapy, and underlying disease. It is of particular importance that acute leukemia was recorded as the leading underlying disease in this study associated with *S. maltophilia* infection. In contrast, Sattler et al[17] found that prematurity, primary immunodeficiency, and congenital heart disease were unique and more common risk factors among pediatric patients in their study. In contrast with many previous studies, exposure to antibiotics in this study was found in both infected and colonized patients.[13,14,22,26] Carbapenems are among the classes of antibiotics most frequently associated with *S. maltophilia* isolation.[26] However, several studies have implicated other classes of antibiotics including ampicillin, gentamicin, vancomycin, metronidazole, piperacillin, cephalosporins, and tobramycin, as one of the significant risk factors for the development of *S. maltophilia* colonization and infection.[15,22,23] Cephalosporins, carbapenems, and aminoglycosides are empirically used for pediatric and adult nosocomial infections in our hospital. The management of *S. maltophilia*-associated infection is difficult because many clinical strains of *S. maltophilia* display both intrinsic resistance to various classes of antibiotics such as carbapenems and aminoglycosides, and induced resistance to fluoroquinolones, which are used empirically for nosocomial sepsis. It appears that SXT is the most sensitive antibiotic for *S. maltophilia*-associated infections.[22] In agreement with this finding, all *S. maltophilia* isolates in this study were completely susceptible to SXT. Many case-control studies have actually suggested that SXT protects against *S. maltophilia* infection or colonization.[23,27] However, there is a concern with over using SXT in the neonatal period, as SXT is known to cause adverse events related to bone marrow suppression. Moreover, SXT competes with bilirubin for binding to albumin, and it can increase the level of indirect bilirubin.[28] In a previous study, 23% of *S. maltophilia* infections occurred in the first week of life, but no hyperbilirubinemia was observed.[16] Mutlu et al[16] reported that no adverse side effects, including increased indirect hyperbilirubinemia, were observed with the use of SXT in the neonatal period, and the authors recommended this antibiotic for antimicrobial therapy of *S. maltophilia* pediatric patients including the neonates. In the last few years, several reports have shown that the prevalence of SXT-resistant *S. maltophilia* strains is increasing.[29-32] The SENTRY Antimicrobial Surveillance Program investigated the antimicrobial susceptibility patterns of prominent Gram-negative isolates from pneumonic patients at 28 medical centers in USA, and Europe and the Mediterranean region (EMR) from 2009 to 2012.[33] In this study, the resistance rate to SXT among *S. maltophilia* isolates was 3.7% in the USA and 2.3% in the EMR. The SXT-resistance rates have been reported to be between 8-18% in the Asia-Pacific region.[34] In a recent Saudi study, 2 cases of *S. maltophilia* infection were SXT-resistant.[32] Many clinical studies showed that patients receiving LVX and MI had clinical outcomes similar to those receiving SXT for the treatment of *S. maltophilia* infections,[29,35] and could be alternative therapeutic options. The SENTRY report found that LVX-resistance ranged from 16.2% in the EMR, to 24.9% in the USA, whereas, all isolates from both regions were MI-susceptible.[33] In contrast, less than one third of our isolates were resistant to both drugs. It is worth noting that rapid *in vitro* and *in vivo* resistance to fluoroquinolones might emerge during therapy, and clinical application of MI is still limited.[1] In this study, TGC was the most active antimicrobial agent against *S. maltophilia* isolates (94% susceptibility) after SXT. In a recent SENTRY study in 11 Latin American countries, TGC inhibited 91.5% and 83% of 141 *S. maltophilia* isolates at ≤2 and ≤1 μμg/ml.[36] These findings highlight the in vitro activity of TGC against *S. maltophilia* and this antibiotic can be used as alternative empiric therapy for *S. maltophilia* infection.

This study has some potential limitations related to the small number of *S. maltophilia* isolates from a single center study. Therefore, further epidemiological multi-center studies of longer surveillance duration are necessary to better understand the prevalence and the distribution of *S. maltophilia* associated infections, and prevent the spread of these multi-drug resistant nosocomial isolates.

In conclusion, *S. maltophilia* is an emerging nosocomial pathogen among pediatric patients. It is capable of causing different types of healthcare associated infections. The most important risk factors for *S. maltophilia* infection among hospitalized children are invasive procedures, prolonged hospitalization, and ICU admission. The SXT regimen is an appropriate choice for *S. maltophilia* infection, and TGC could be a useful alternative treatment option specially as part of combination regimens. Accurate identification and susceptibility testing of this emerging pathogen are critical for the management of infected patients and prevention of spread of this nosocomial pathogen.

References

1. Looney WJ, Narita M, Muhlemann K. *Stenotrophomonas maltophilia*: an emerging opportunist human pathogen. ***Lancet Infect Dis*** 2009; 9: 312-323.
2. Brooke JS. *Stenotrophomonas maltophilia*: An emerging global opportunistic pathogen. ***Clin Microbiol Rev*** 2012; 25: 2-41.
3. Abbott IJ, Slavin MA, Turnidge JD, Thursky KA, Worth LJ. *Stenotrophomonas maltophilia*: emerging disease patterns and challenges for treatment. ***Expert Rev Anti Infect Ther*** 2011; 9: 471-488.
4. Garazi M, Singer C, Tai J, Ginocchio CC. Bloodstream infections caused by *Stenotrophomonas maltophilia*: a seven-year review. ***J Hosp Infect*** 2012; 81: 114-118.
5. Pien CJ, Kuo HY, Chang SW, Chen PR, Yeh HW, Liu CC, et al. Risk factors for levofloxacin resistance in *Stenotrophomonas maltophilia* from respiratory tract in a regional hospital. ***J Microbiol Immunol Infect*** 2015; 48: 291-295.
6. Guyot A, Turton TF, Garner D. Outbreak of *Stenotrophomonas maltophilia* on an intensive care unit. ***J Hosp Infect*** 2013; 85: 303-307.
7. Brooke JS. New strategies against *Stenotrophomonas maltophilia*: a serious worldwide intrinsically drug-resistant opportunistic pathogen. ***Expert Rev Anti Infect Ther*** 2014; 12: 1-4.
8. del Toro MD, Rodriguez-Bano J, Herrero M, Rivero A, Garcia-Ordonez MA, Corzo J, et al. Clinical epidemiology of *Stenotrophomonas maltophilia* colonization and infection: a multicenter study. ***Medicine (Baltimore)*** 2002; 81: 228-239.
9. Pakyz AL, Farr BM. Rates of *Stenotrophomonas maltophilia* colonization and infection in relation to antibiotic cycling protocols. ***Epidemiol Infect*** 2009; 137: 1679-1683.
10. Clinical and Laboratory Standards Institute (CLSI). Performance Standards for Antimicrobial Susceptibility Testing. 26th ed. M100S. CLSI: Wayne (PA); 2016.
11. Samonis G, Karageorgopoulos DE, Maraki S, Levis P, Dimopoulou D, Spernovasilis NA, et al. *Stenotrophomonas maltophilia* infections in a general hospital: patient characteristics, antimicrobial susceptibility, and treatment outcome. ***Plos One*** 2012; 7: e37375.
12. Guzoglu N, Demirkol FN, Aliefendioglu D. Haemorrhagic pneumonia caused by *Stenotrophomonas maltophilia* in two newborns. ***J Infect Dev Ctries*** 2015; 9: 533-535.
13. Xun M, Zhang Y, Li B, Wu M, Zong Y, Yin Y. Clinical characteristics and risk factors of infections caused by *Stenotrophomonas maltophilia* in a hospital in northwest China. ***J Infect Dev Ctries*** 2014; 8: 1000-1005.
14. Asaad AM, Al-Ayed MS, Qureshi MA. Emergence of unusual nonfermenting gram-negative nosocomial pathogens in a Saudi hospital. ***Jpn J Infect Dis*** 2013; 66: 507-511.
15. Arthur C, Tang X, Romero JR, Gossett JG, Harik N, Prodhan P. *Stenotrophomonas maltophilia* infection among young children in a cardiac intensive care unit: a single institution experience. ***Pediatr Cardiol*** 2015; 36:509-515.
16. Mutlu M, Yılmaz G, Aslan Y, Bayramoglu G. Risk factors and clinical characteristics of *Stenotrophomonas maltophilia* infections in neonates. ***J Microbiol Immunol Infect*** 2011; 44: 467-472.
17. Sattler CA, Mason EO, Kaplan SL. Non-respiratory *Stenotrophomonas maltophilia* infection at a children's hospital. ***Clin Infect Dis*** 2000; 31: 1321–1330.
18. Horan TC, Andrus M, Dudeck MA. CDC/NHSN surveillance definition of health care-associated infection and criteria for specific types of infections in the acute care setting. ***Am J Infect Control*** 2008; 36: 309-332.
19. Mermel LA, Allon M, Bouza E, Craven DE, Flynn P, O'Grady NP, et al. Clinical practice guidelines for the diagnosis and management of intravascular catheter-related infection: 2009 Update by the Infectious Diseases Society of America. ***Clin Infect Dis*** 2009; 49: 1-45.
20. In: Murray PR, Baron EJ, Jorgensen JH, Pfaller MA, Yolken RH, editors. Manual of Clinical Microbiology Handbook. Washington (DC): ASM Press; 2003.
21. European Committee on Antimicrobial Susceptibility Testing. Clinical Breakpoints. [Accessed 2011 March 1]. Available from URL: http://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Disk_test_documents/EUCAST_breakpoints_v1.3_pdf.pdf.
22. Fihman V, Le Monnier A, Corvec S, Jaureguy F, Tankovic J, Jacquier H, et al. *Stenotrophomonas maltophilia*-the most worrisome threat among unusual non-fermentative gram-negative bacilli from hospitalized patients: a prospective multicenter study. ***J Infect*** 2012; 64: 391-398.
23. Falagas ME, Kastoris AC, Vouloumanou EK, Rafailidis PI, Kapaskelis AM, Dimopoulos G. Attributable mortality of *Stenotrophomonas maltophilia* infections: a systematic review of the literature. ***Future Microbiol*** 2009; 4: 1103-1109.
24. Boucher HW, Talbot GH, Bradley JS, Edwards JE, Gilbert D, et al. Bad bugs, no drugs: no ESKAPE! An update from the Infectious Diseases Society of America. ***Clin Infect Dis*** 2009; 48: 1-12.
25. Xun M, Zhang Y, Li B, Wu M, Zong Y, Yin Y. Clinical characteristics and risk factors of infections caused by *Stenotrophomonas maltophilia* in a hospital in northwest China. ***J Infect Dev Ctries*** 2014; 8: 1000-1005.
26. Gales AC, Jones RN, Forward KR, Linares J, Sader HS, Verhoef J. Emerging importance of multidrug-resistant *Acinetobacter species* and *Stenotrophomonas maltophilia* as pathogens in severely ill patients: geographic patterns, epidemiological features and trends in the SENTRY Antimicrobial Surveillance Program (1997-1999). ***Clin Infect Dis*** 2001; 32 Suppl 2: 104-113.

27. Averbuch D, Cordonnier C, Livermore DM, Mikulska M, Orasch C, Viscoli C, et al. Targeted therapy against multi-resistant bacteria in leukemic and hematopoietic stem cell transplant recipients: guidelines of the 4th European Conference on Infections in Leukemia (ECIL-4, 2011). ***Haematologica*** 2013; 98: 1836-1847.
28. Springer C, Eyal F, Michel J. Pharmacology of trimethoprim-sulfamethoxazole in newborn infants. ***J Pediatr*** 1982; 100: 647-650.
29. Cho SY, Kang CI, Kim J, Ha YE, Chung DR, Lee NY, et al. Can levofloxacin be a useful alternative to trimethoprim-sulfamethoxazole for treating *Stenotrophomonas maltophilia* bacteremia? ***Antimicrob Agents Chemother*** 2014; 58: 581-583.
30. Juhasz E, Pongracz J, Ivan M, Kristof K. Antibiotic susceptibility of sulfamethoxazole-trimethoprim resistant *Stenotrophomonas maltophilia* strains isolated at a tertiary care center in Hungary. ***Acta Microbiol Immunol Hung*** 2015; 62: 295-305.
31. Wei C, Ni W, Cai X, Zhao J, Cui J. Evaluation of Trimethoprim/Sulfamethoxazole (SXT), Minocycline, Tigecycline, Moxifloxacin, and Ceftazidime Alone and in Combinations for SXT-Susceptible and SXT-Resistant *Stenotrophomonas maltophilia* by In Vitro Time-Kill Experiments. ***PloS One*** 2016; 11: e0152132.
32. Al-Jasser AM. *Stenotrophomonas maltophilia* resistant to trimethoprim-sulfamethoxazole: an increasing problem. ***Ann Clin Microbiol Antimicrob*** 2006; 5: 23-25.
33. Sader HS, Farrell DJ, Flamm RK, Jones RN. Antimicrobial susceptibility of Gram-negative organisms isolated from patients hospitalized with pneumonia in US and European hospitals: Results from the SENTRY Antimicrobial Surveillance Program, 2009-2012. ***Int J Antimicrob Agents*** 2014; 43: 328-334.
34. Wu H, Wang JT, Shiau YR, Wang HY, Lauderdale TL, Chang SC, et al. A multicenter surveillance of antimicrobial resistance on *Stenotrophomonas maltophilia* in Taiwan. ***J Microbiol Immuno Infect*** 2012; 45: 120-126.
35. Wang YL, Scipione MR, Dubrovskaya Y, Papadopoulos J. Monotherapy with fluoroquinolone or trimethoprim-sulfamethoxazole for treatment of *Stenotrophomonas maltophilia* infections. ***Antimicrob Agents Chemother*** 2014; 58: 176-182.
36. Sader HS, Castanheira M, Farrell DJ, Flamm RK, Mendes RE, Jones RN. Tigecycline antimicrobial activity tested against clinical bacteria from Latin American medical centers: results from SENTRY Antimicrobial Surveillance Program (2011-2014). ***Int J Antimicrob Agents*** 2016; 48: 144-150.

Authorship entitlement

Excerpts from the Uniform Requirements for Manuscripts Submitted to Biomedical Journals updated November 2003.
Available from www.icmje.org

The international Committee of Medical Journal Editors has recommended the following criteria for authorship; these criteria are still appropriate for those journals that distinguish authors from other contributors.

Authorship credit should be based on 1) substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; 2) intellectual content; and 3) final approval of the version to be published. Authors should meet conditions 1, 2, and 3.

Acquisition of funding, collection of data, or general supervision of the research group, alone, does not justify authorship.

An author should be prepared to explain the order in which authors are listed.