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ORIGINAL ARTICLE

Risk factors for hospital acquisition of trimethoprim–sulfamethoxazole resistant *Stenotrophomonas maltophilia* in adults: A matched case-control study

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Abstract *Background/Purpose:* The emergence of trimethoprim–sulfamethoxazole resistant *Stenotrophomonas maltophilia* (TSRSM) represents a serious threat to patients. The aim of current study was to identify risk factors associated with hospital-acquired TSRSM occurrence in adult inpatients.
Methods: We conducted a matched case-control study in Tri-Service General Hospital, Taipei, Taiwan. From January 2014 through June 2015, case patients with TSRSM and control patients with trimethoprim–sulfamethoxazole susceptible *S. maltophilia* (TSSSM) during hospitalization were identified. Control patients were matched with TSRSM cases for age (within five years), sex, and site of isolation at a ratio of 1:1.
Results: A total of 266 patients were included in our study (133 cases and 133 matched controls). Bivariable analysis showed that previous exposure to fluoroquinolone [odds ratio (OR), 2.693; 95% confidence interval (CI, 1.492–5.884; $p = 0.002$)], length of intensive care unit stay (OR, 1.015 per day; 95% CI, 1.001–1.030; $p = 0.041$), and length of hospital stay (OR, 1.012 per day; 95% CI, 1.002–1.023; $p = 0.018$) prior to *S. maltophilia* isolation were associated with TSRSM occurrence. A multivariable analysis showed that previous exposure to fluoroquinolone (OR, 3.158; 95% CI, 1.551–6.430; $p = 0.002$) was an independent risk factor for TSRSM occurrence after adjustment.

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Conclusion: Previous fluoroquinolone use was an independent risk factor for hospital-acquired TSRSM occurrence in adult inpatients, suggesting that judicious administration of fluoroquinolone may be important for limiting TSRSM occurrence.

Introduction

Stenotrophomonas maltophilia, a nonfermenting gram-negative bacillus, has emerged as a nosocomial pathogen that primarily affects immunocompromised patients.[1–3] The broad spectrum of infections that are associated with *S. maltophilia* include pneumonia and bacteremia, as well as infections of the skin and soft tissue, surgical wounds, and urinary tract.[1,4] The crude mortality rate for *S. maltophilia* infection is around 18%–69%.[5] The treatment of these infections is challenging because *S. maltophilia* is resistant to a variety of structurally unrelated antimicrobial agents.[6,7] *S. maltophilia*'s resistance to antimicrobial agents derives from intrinsic or acquired resistant mechanisms involving β-lactamases, efflux pump systems, enzymatic modification, and target site modification.[7–9]

Trimethoprim–sulfamethoxazole (TMP-SXT) has been the primary treatment for susceptible *S. maltophilia* infections, based on *in vitro* activity and anecdotal reports of favorable clinical outcomes.[6,7,10,11] Although levofloxacin and tigecycline have been considered as alternatives to TMP-SXT for the treatment of *S. maltophilia* infections, more clinical data are still needed to validate their efficacies.[12,13]

Recent antimicrobial susceptibility studies and case series, however, have demonstrated the occurrence of TMP-SXT resistant *S. maltophilia* (TSRSM) in different geographic regions.[14–16] The emergence of TSRSM limits treatment options further and it had been reported that patients with TSRAM were associated with deteriorated clinical outcome.[17,18] Studies of TMP-SXT resistance in uropathogens, mostly *Enterobacteriaceae* strains, revealed that prior TMP-SXT use was associated with TMP-SXT resistance, reflecting selective pressure of TMP-SXT.[19,20] Whether this association in *Enterobacteriaceae* strains is applicable to *S. maltophilia* has remained uncertain.

The prevalence of TSRSM in Taiwan is higher than that in other geographic regions and has been increasing.[14,15,21,22] The majority of TSRSM infections occurred in hospitalized patients, rather than those from community.[18,21,22] Our previous study reported before revealed that patients with TSRSM were associated with prolonged hospitalization indicating increased financial burdens in healthcare systems in Taiwan.[18] This alarming phenomenon in Taiwan highlights an urgent need for effective control and prevention measures that could prevent TSRSM dissemination. The first step in the design of such measures is to identify risk factors that are associated with hospital-acquired TSRSM occurrence. We therefore initiated a matched case-control study to identify risk factors for hospital-acquired TSRSM occurrence in adult hospitalized patients.

Methods

Study design and patient selection

This retrospective matched case-control study was conducted at the Tri-Service General Hospital, which is a tertiary referral center in northern Taiwan with 1700 beds. To identify the individual risk factors for inpatients having hospital-acquired TSRSM, a 1:1 matched case-control study was initiated. The study population included hospitalized adult patients from whom a clinical specimen yielded a *S. maltophilia* isolate for the first time between January 1, 2014 and June 30, 2015, as assessed via electronic records from the microbiological laboratory database. Each patient was included once only. To focus on risk factors for hospital-acquired TSRSM occurrence in adult inpatients, patients with *S. maltophilia* isolated within 48 h of admission were excluded. Patients younger than 18 years old of age were excluded. Patients with TSRSM were assigned to the case group. Patients with TSSSM were identified as potential members of the control group. Matching was performed at a ratio of 1:1 according to sex, age (within five years), and the site of isolation. When more than one control satisfied these conditions, they were randomly chosen with Microsoft Excel 2013® software (Microsoft Corp., Redmond, WA, USA).

Clinical data collections and definitions

Using a computerised data system, clinical information was systematically collected from the medical records of the patients with culture positive TSRSM and the matched controls. The collected information included demographic data, durations of intensive care unit (ICU) and hospital stays prior to *S. maltophilia* isolation, number of admission records during the previous year, comorbidities on admission, indwelling medical devices before *S. maltophilia* isolation during hospitalization, recent therapeutic measures, and previous exposure to antibiotics. The Charlson Comorbidity Index (CCI) was used as an aggregate measure for comorbidities.[23] Previous exposure to antibiotics including prescriptions in the outpatient department was defined as at least 24-h of therapy within the 14 days prior to *S. maltophilia* isolation. Recent chemotherapy within one month before *S. maltophilia* isolation was recorded. Recent surgery was defined as surgery performed in included patients after admission but before *S. maltophilia* isolation.