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Clinical impact of non-antibiotic recommendations by a multi-disciplinary antimicrobial stewardship team

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ABSTRACT

Introduction: The multi-disciplinary antimicrobial stewardship team at the study hospital conducts prospective review and feedback on all inpatient orders of piperacillin–tazobactam and carbapenems. In addition, the team provides non-antibiotic recommendations (i.e. additional investigations and infectious disease reviews). This study aimed to describe the impact of these recommendations on patient outcomes.

Methods: Patients on carbapenem and piperacillin–tazobactam who received at least one non-antibiotic recommendation between January 2012 and August 2014 were included in this study. Acceptance and rejection of non-antibiotic recommendations by the managing physician were compared. The primary outcome was 30-d mortality.

Results: Non-antibiotic recommendations were made in 166 patients. There were no differences in baseline characteristics between patients for whom recommendations were accepted and patients for whom recommendations were rejected. Thirty-day mortality (18.0% vs. 34.5%, $P = 0.02$) was significantly lower in patients who had at least one non-antibiotic recommendation accepted. Multi-variate analysis found that Charlson's comorbidity score [odds ratio (OR) 1.20, 95% confidence interval (CI) 1.03–1.42, $P = 0.03$], APACHE II score (OR 1.10, 95% CI 1.01–1.19, $P < 0.01$), hepatobiliary source of infection (OR 10.19, 95% CI 1.44–72.13, $P = 0.02$) and acceptance of at least one non-antibiotic recommendation (OR 0.39, 95% CI 0.17–0.88, $P = 0.02$) were independently associated with 30-d mortality.

Conclusions: During prospective review and feedback of piperacillin–tazobactam and carbapenems, acceptance of non-antibiotic recommendations was found to be associated with a reduction in 30-d mortality.

1. Introduction

Increasing antimicrobial resistance due to inappropriate use is a global concern. Multi-disciplinary antimicrobial stewardship teams have become an integral part of the response to this issue [1,2]. Through prospective review of antibiotic prescriptions and feedback to healthcare providers (e.g. empirical therapy, dose optimisation, de-escalation and duration), antimicrobial stewardship has been shown to improve clinical response, reduce adverse effects and reduce mortality [3–5].

In addition to antibiotic advice, the antimicrobial stewardship team provides non-antibiotic recommendations. This includes advising additional laboratory, microbiological or radiological investigations or bedside consultation from an infectious disease (ID) physician [6]. Unlike antibiotic advice, the impact of non-antibiotic recommendations on patient outcomes has not been widely studied. This study aimed to describe the types of non-antibiotic recommendations made by the antimicrobial stewardship team, and evaluate their effect on patient outcomes when these recommendations were accepted by the managing physician.

2. Methods

2.1. Patients, data collection and outcome definitions

This retrospective study included patients aged >18 y who were prescribed carbapenems or piperacillin–tazobactam, and received one or more non-antibiotic recommendations during prospective review and feedback by the Tan Tock Seng Hospital antimicrobial stewardship team between January 2012 and August 2014.

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Tan Tock Seng Hospital is a 1500-bed acute care university teaching hospital in Singapore. A multi-disciplinary antimicrobial stewardship team was established in 2009. Since 2012, this team has comprised four ID physicians (2–3 h/d rotation) and four full-time pharmacists. Team strategies include prospective review and feedback on all orders of carbapenems and piperacillin–tazobactam [3], implementation of evidence-based hospital-endorsed guidelines on management of infectious diseases and antibiotic dosing, and a computerised clinical decision support system [7]. Following antimicrobial stewardship review, all recommendations are communicated to the primary team through documentation in the patient's chart and a text message to the managing physician. Recommendations are made independently by the pharmacists in 20–30% of cases, with the remainder made by ID physicians during daily rounds.

Data were extracted from electronic medical records, electronic inpatient medication records and the antimicrobial stewardship team database. Data collected included age, gender and source of infection. APACHE II score and age-adjusted Charlson's comorbidity score were calculated to assess disease severity and comorbidities. For patients with multiple reviews during the study period, only the first antimicrobial stewardship review with non-antibiotic recommendations was included in the study in order to address the effects of multiple reviews and recommendations, and to address the immortal time bias of acceptance of recommendations. Non-antibiotic recommendations consisted of ID review or additional investigations: laboratory tests (e.g. procalcitonin, C-reactive protein, full blood count), microbiological tests (e.g. culture and susceptibility testing, *Clostridium difficile* toxin, influenza polymerase chain reaction), radiological imaging and endoscopy (e.g. computed tomography, ultrasound, chest X-ray, echocardiogram). The intentions of these recommendations were recorded and classified as: (1) setting duration and stopping antibiotics; (2) diagnosing infection-related complications or other infections; and (3) diagnosing non-infectious conditions. Each recommendation could have more than one intention. The acceptance of all non-antibiotic recommendations by the managing physician was tracked. Patients were classified into the accepted group if at least one of the non-antibiotic recommendations was executed by the primary team within 48 h of the antimicrobial stewardship review.

Patients who only received non-antibiotic recommendations were selected for outcome analysis. The primary objective of this study was to compare 30-d mortality between the patients for whom non-antibiotic recommendations from the antimicrobial stewardship team were accepted and the patients for whom non-antibiotic recommendations were rejected. Secondary objectives were to compare in-hospital mortality, clinical response at 7 d, 30-d re-admission, acquisition of multi-drug-resistant organisms at 30 d, length of hospital stay and duration of reviewed antibiotics.

Patients were defined as achieving a clinical response if all of the following criteria were met by 7 d after the non-antibiotic recommendations: (1) afebrile (<38 °C) for more than 24 h, or a reduction in temperature compared with baseline; (2) systolic blood pressure returned to baseline or ≥100 mmHg; (3) respiratory rate of <25 breaths/min and oxygen saturation >92%; (4) not on mechanical ventilation or fraction of inspired oxygen ≤0.4; and (5) not on any inotropes. Multi-drug-resistant organisms were defined as those resistant to at least three classes of antibiotics [8]. Duration of reviewed antibiotics, length of hospital stay and 30-d mortality were counted from the day of recommendations. When calculating the duration of reviewed antibiotics and length of hospital stay, patients who died before the end of the reviewed antibiotics or hospital stay were excluded.

2.2. Statistical analysis

The level of significance was 0.05, and 95% confidence intervals (CI) are reported for all applicable tests. For continuous variables, between-group comparisons were performed using Mann–Whitney *U*-test. Chi-squared test and Fisher's exact test were used for categorical variables. Univariate analysis was performed to evaluate risk factors for 30-d mortality. Any variable with $P < 0.10$ on univariate analysis was included in a multiple logistic regression model to determine independent associations with 30-d mortality. All statistical analyses were performed using Statistical Package for the Social Sciences (IBM Corp., Armonk, NY, USA). This study was approved by the institutional review board.

3. Results

Among the 166 patients who received non-antibiotic recommendations, there were no differences in baseline characteristics between the patients for whom recommendations were accepted and the patients for whom recommendations were rejected (Table 1). The median age of patients was 75 y [interquartile range (IQR) 63–84 y] and 55.4% were male. The median Charlson's comorbidity score and APACHE II score were 3 (IQR 2–6) and 10 (IQR 8–14), respectively. The most common comorbidities were diabetes mellitus (44.0%), stroke (31.9%), renal impairment (30.7%) and cancer (27.7%). The most common sources of infection were respiratory (41.6%), unknown (27.7%) and urological (13.3%). Overall, the non-antibiotic recommendations were accepted for 111 (66.9%) patients. Recommendations for infectious disease review were accepted for 38 (82.6%) patients. Recommendations for radiological imaging and endoscopy were accepted for 32 (56.1%) patients. Recommendations for microbiological and laboratory tests were accepted for 46 (59.7%) and 36 (69.2%) patients, respectively.

Thirty-day mortality (18.0% vs. 34.5%, $P = 0.02$) was significantly lower in patients for whom at least one non-antibiotic recommendation was accepted. Multi-variate analysis found that Charlson's comorbidity score (OR 1.20, 95% CI 1.03–1.42, $P = 0.03$), APACHE II score (OR 1.10, 95% CI 1.01–1.19, $P < 0.01$), hepatobiliary source of infection (OR 10.19, 95% CI 1.44–72.13, $P = 0.02$) and acceptance of at least one non-antibiotic recommendation (OR 0.39, 95% CI 0.17–0.88, $P = 0.02$) were independently associated with 30-d mortality (Table 2). There were no significant differences in all study outcomes between patients for whom physicians accepted or rejected specific recommendations for ID review, and microbiological and laboratory tests. However, a general trend was observed that

Table 1
Baseline characteristics of patients on piperacillin–tazobactam or carbapenems for whom non-antibiotic recommendations were accepted or rejected.

	Rejected $n = 55$	Accepted $n = 111$	*P*
Age in years, median (IQR)	76 (63–83)	74 (61–84)	0.95
Charlson's score, median (IQR)	3 (2–6)	3 (2–6)	0.52
APACHE II score, median (IQR)	10 (8–15)	10 (8–14)	0.56
Male	27 (49.1)	65 (58.6)	0.25
Comorbidities			
Renal impairment	19 (34.5)	32 (28.8)	0.45
Respiratory disease	8 (14.5)	17 (15.3)	0.90
Dementia	5 (9.1)	11 (9.9)	0.87
Stroke	16 (29.1)	37 (33.3)	0.58
Cardiovascular disease	20 (36.4)	50 (45.0)	0.29
Diabetes mellitus	19 (34.5)	54 (49.8)	0.09
Cancer	18 (32.7)	28 (25.2)	0.31
Source of infection			
Bone and joint	1 (1.8)	4 (3.6)	1.00
Hepatobiliary	1 (1.8)	4 (3.6)	1.00
Intra-abdominal	5 (9.1)	6 (5.4)	0.51
Respiratory	27 (49.1)	42 (37.8)	0.17
Unknown source	16 (29.1)	30 (27.0)	0.78
Urological	5 (9.1)	17 (15.3)	0.27
Skin and soft tissue	2 (3.6)	12 (10.8)	0.15

IQR, interquartile range.