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Brief Original Article

Prospective antimicrobial audit and feedback did not decrease case fatality: Experiences from a hospital in northern Taiwan

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Abstract

Introduction: Although a prospective antimicrobial audit and feedback is an effective strategy in an antibiotic stewardship program, previous researchers have not adequately demonstrated a successful impact on patient outcomes. In this study, the causes of fatalities associated with a prospective antimicrobial audit and feedback were analyzed.

Methodology: Between June and September 2014, applications for 16 target parenteral formulas (including ceftriaxone, ceftazidime, cefepime, piperacillin/tazobactam, vancomycin, teicoplanin, ertapenem, imipenem/cilastatin, meropenem, levofloxacin, moxifloxacin, ciprofloxacin, tigecycline, linezolid, daptomycin, and amikacin), which were not approved by infectious diseases (ID) specialists, were followed up until patients were either discharged or passed away.

Results: Of the 292 cases studied, 193 (66%) were male, with a mean age (standard deviation) of 65.5 (19.3) years. There were five reasons for rejection, including dosage adjustments (37%), no evidence of bacterial infection (28.8%), modifications according to antimicrobial susceptibility (18.8%), target pathogens not being covered (7.2%), and redundant therapy (4.1%). Multiple logistic regression analysis demonstrated that an age greater than 75 years (odds ratio [OR]: 2.58; 95% confidence interval [CI]: 1.32–5.50; p = 0.005) was associated with significant mortality, while urinary tract (OR: 0.26; 95% CI: 0.09–0.70; p = 0.013) and soft tissue/bone infections (OR: 0.18; 95% CI: 0.05–0.61; p = 0.006) were associated with survival. Adjustments according to ID physicians' recommendations were not statistically significant (OR: 0.53; 95% CI: 0.27–1.06; p = 0.074).

Conclusions: Antimicrobial adjustments according to ID physicians' recommendations showed only marginally preventative effects against fatalities.

Key words: prospective antimicrobial audit and feedback; antibiotic stewardship; fatality.

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Introduction

Antibiotic resistance is an increasingly urgent global emergency [1-3]. Powerful selective pressure from antibiotic overconsumption may be an important contribution to antibiotic resistance [1,3]. For instance, Houvinen *et al.* [4] highlighted the development of low-level resistance in streptococci to erythromycin in Finland, because of the limits placed on new macrolide use. In the contrast, the superbug New Delhi Metallo-β lactamase 1-producing (NDM-1) Enterobacteriaceae emerged in communities where broad-spectrum antibiotics were freely sold over the counter [5]. In medical institutions, alarmingly high rates of resistant organisms are prevalent in intensive care units [6], particularly among ventilator-dependent patients [7], since the burden of broad-spectrum antibiotic usage is heavy. At the individual level, patients with higher levels of antibiotic consumption show higher rates of acquiring resistant organisms [8]. More specifically, in Taiwan, patients who acquired penicillin-resistant *Streptococcus pneumoniae* had a 15-day prior history of exposure to antibiotics [9].

In this regard, judicious use of antibiotics may be an important strategy to preserve the effectiveness of antimicrobial agents. The Infectious Diseases Society of America (IDSA) and the Society for Healthcare Epidemiology of America (SHEA) have put forward guidelines for the development and implementation of

antibiotic stewardship programs [10,11]. In late 2011, the Center for Disease Control, R.O.C. (Taiwan CDC) made a national commitment to the containment of antibiotic resistance, and a nationwide antimicrobial stewardship task force was consequently established [12]. Two core strategies were recommended: formulary restriction/preauthorization for certain antibiotics, and prospective antimicrobial audits and feedback. Although the latter was endorsed by expert societies, previous researchers had not adequately demonstrated an impact on patient survival. In this study, the causes of fatalities associated with a prospective antimicrobial audit and feedback were analyzed.

Methodology

Patient samples

Between June and September 2014, antibiotic use at Taoyuan General Hospital was reviewed. Taoyuan General Hospital is a 900-bed regional referral hospital in northern Taiwan. The formulary listed 64 parenteral and oral antibiotics in total, which were monitored monthly for their defined daily dose (DDD). From the antibiotic lists, 16 target parenteral formulae (ceftriaxone, ceftazidime, cefepime, piperacillin/tazobactam, vancomycin, teicoplanin, ertapenem, imipenem/cilastatin, meropenem, levofloxacin, moxifloxacin, ciprofloxacin, tigecycline, linezolid, daptomycin, and amikacin) were prospectively audited by three infectious diseases (ID) physicians. The above antibiotics were prescribed by patients' primary physicians and reviewed by ID specialists within 24 to 48 hours of being in the hospital information system, to verify their rationalities. Prescriptions that were not recommended by ID

Table 1. Demographic characteristics of patients who were given inadequate antibiotics in a regional hospital in northern Taiwan.

Characteristics	Total	Percentage or standard deviation
Case number	292	100%
Male	193	66.1%
Age (years ± SD)	65.5	19.3
Length of hospital stay (days)	24.2	22.6
ICU admission	84	28.8%
Death	77	26.4%
Underlying conditions		
Diabetes	38	13.0%
ESRD	36	12.3%
Malignancies	34	11.6%
Liver cirrhosis	12	4.1%
HIV	4	1.4%
Sites of infection		
Respiratory tract	103	35.3%
Bone and soft tissues	99	33.9%
Sepsis	69	23.6%
Urinary tract	55	18.8%
Intra-abdominal	19	6.5%
Central nervous system	5	1.7%
Mastitis	1	0.3%
Multiple	13	4.5%
Pathogens		
Not identified	111	38.0%
Pseudomonas aeruginosa	38	13.0%
Escherichia coli	35	12.0%
Klebsiella pneumonia	31	10.6%
Staphylococcus aureus	28	9.6%
Acinetobacter baumannii	27	9.2%
Fungus	10	3.4%
Multiple	50	17.1%

ICU: intensive care unit; ESRD: end-stage renal disease; HIV: human immunodeficiency virus

physicians were sent back, with suggestions noted on computers. Patients' outcomes were followed for up to 30 days, until patients were discharged or passed away. The study was approved by the institutional review board of this hospital and informed consent was waived.

Statistical analyses

Demographic data are presented as mean ± standard deviation (SD) for continuous variables, and percentiles for discrete variables. Chi-square tests and student's t-test were used when feasible. Covariates with $p < 0.2$ in the univariate analyses were included in the multivariate logistic regression analyses to determine which covariates predicted fatalities. All statistical analyses were conducted using SAS version 9.3 (SAS Institute, Cary, USA).

Results

Antibiotic consumption in the institution was 850 DDD per thousand patient-days, on average, during the study period. Of 2,069 antibiotic applications, 292 (14.1%) were not recommended by ID specialists (Table 1). Of the patients, 193 (66%) were male, with a mean age (± standard deviation) of 65.5 (± 19.3) years. Among these, 38 (13%) showed a history of diabetes mellitus, 36 (12.3%) were affected by end-stage renal disease (ESRD), 34 (11.6%) had a malignancy, and 12 (4.1%) had liver cirrhosis. Common sites of infection included the respiratory tract, 103 (35.3%) cases; bone and soft tissue, 99 (33.9%) cases; bloodstream, 69 (23.6%) cases; and urinary tract, 55 (18.8%) cases. Commonly identified pathogens were *Pseudomonas aeruginosa*, 38 (13.0%) strains; *Escherichia coli*, 35 (12.0%) strains; *Klebsiella pneumonia*, 31 (10.6%) strains; *Staphylococcus aureus*, 28 (9.6%) strains; and *Acinetobacter baumannii*, 27 (9.2%) strains.

Piperacillin/tazobactam (65, 22.3%), vancomycin (35, 12.0%), ceftriaxone (32, 11.0%), and cefepime (31, 10.6%) were the leading prescriptions that were rejected by ID physicians (Table 2). The five kinds of recommendations for modifications included dosage optimization (108, 37%), no evidence of bacterial infection (84, 28.8%), modifications according to antimicrobial susceptibility (55, 18.8%), potential pathogens not being covered (21, 7.2%), and redundant therapy (12, 4.1%).

Multiple logistic regression analysis showed that patient age greater than 75 years (odds ratio [OR]: 2.58; 95% confidence interval [CI]: 1.32–5.50, $p = 0.005$) was significantly associated with mortality, while urinary tract (OR: 0.26; 95% CI: 0.09–0.70, $p = 0.013$) and soft tissue/bone infections (OR: 0.18; 95% CI: 0.05–0.61, $p = 0.006$), compared with bloodstream infections, were associated with survival (Table 3). Adjustments according to ID physicians' recommendations (OR: 0.53; 95% CI: 0.27–1.06, $p = 0.074$) showed very marginal effects in protection from disease (Table 3).

Table 2. Reasons and antibiotics not recommended by infectious diseases specialists in a regional hospital in northern Taiwan.

Reasons	Number	Percentage
Optimization of dosage	108	37.0%
Adjustment according to sensitivity	55	18.8%
Insufficient reason to justify the prescription	84	28.8%
Potential pathogens not covered	21	7.2%
Duplications	12	4.1%
Others	12	4.1%
Common regimens not recommended		
Piperacillin/tazobactam	65	22.3%
Vancomycin	35	12.0%
Ceftriaxone	32	11.0%
Cefepime	31	10.6%
Ceftazidime	27	9.2%
Ertapenem	26	8.9%

Table 3. Factors related to case fatalities using multiple logistic regression analyses adjusted by sex.

Characteristic factors	Odds ratio	95% confidence interval	P value
Age greater than 75 years	2.58	1.32–5.50	0.005
Urinary tract infection	0.26	0.09–0.70	0.013
Soft tissue or bone infection	0.18	0.05–0.61	0.006
Modification by infectious diseases physicians' recommendation	0.53	0.27–1.06	0.074

Discussion

There are several commonly adopted strategies in antimicrobial stewardship: formulary restrictions, preauthorization, prospective antimicrobial audits with feedback, and antimicrobial cycling [11-14]. Until now, it remains unclear which were the best interventions. It is likely that the effectiveness of each strategy varies because of different settings, sociocultural contexts, and the addition of various parts of care bundles into antibiotic stewardship programs [15].

In this study, 14.1% of prescriptions were not recommended by ID physicians, and among these, 19.1% of their recommendations were not accepted by primary physicians (data not shown); this is similar to a previous study in Taiwan in which the acceptance rate for ID physicians' suggestions was 80.6% [16]. Prospective antimicrobial audits and feedback systems have also shown benefits such as cost-effectiveness [17], reductions in the inappropriate antibiotic prescriptions [10], decreases in antimicrobial consumption [18-19] and "bug-drug" mismatch [20].

Evaluating patients' outcomes in an antibiotic stewardship program is full of challenges. In previous research, a decrease in resistant pathogens, such as *Clostridium difficile* [18], extended-spectrum β-lactamase-producing *E. coli* and *K. pneumonia* [19], and methicillin-resistant *Staphylococcus aureus* (MRSA) [21] was noted. Decreases in hospital stays [22] and improvements in successful treatments [20] have also been reported.

Unfortunately, there is a dearth of information about the impact on patient survival. Wang *et al*. [16] revealed that blood culture-guided, on-line antibiotic stewardship did not impact patient survival. Norwak *et al*. [23] showed that a prospective antimicrobial stewardship did not dampen patients' clinical outcomes. This current study also shows only marginally protective effects (OR: 0.53; 95% CI: 0.27 to 1.06; p = 0.07) on patient survival. There are a number of possible explanations for this. First, the hospitalized population was very old and often had common comorbidities; 14% of patients and their families had accepted hospice care, so the benefits of optimizing antibiotics may have waned due to the above factors. Second, the sample size used in this study was small, and the study was conducted for only a short period of time.

The limitations of this study also warrant discussion. For instance, this was a retrospective observational study, so the results were less powerful for its study framework. Furthermore, this study was conducted in a single referral hospital, and thus any generalizations should be made with caution. Finally, the survival rates of patients who received proper antibiotics from the beginning were not analyzed, so a comparison of the contribution of adequate and inadequate choices of antibiotics to patient survival was not possible.

Conclusions

Because of old age and the ceasing in some patients of aggressive treatments, antimicrobial adjustments according to ID physicians' recommendations showed only marginal effects in reducing fatalities. Under such circumstances, it should be more prudent to prescribe antibiotics.

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Authors' contributions

CYC and CYL equally contributed to the article. SHC conceived and designed the study; MWW, CHC, WYH, YFC and PHT collected the clinical and laboratory data; CYC, CYL and SHC interpreted the data; CYC and CYL drafted the manuscript; and SHC approved the final version.

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