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ORIGINAL ARTICLE

Effects of various antimicrobial stewardship programs on antimicrobial usage and resistance among common gram-negative bacilli causing health care-associated infections: A multicenter comparison

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Abstract *Background:* The effects of various antimicrobial stewardship programs (ASPs) on both antibiotic consumption and resistance among different hospitals within the same insurance system have rarely been investigated.
Methods: This 6-year retrospective study included three medical centers with similar facilities and infection control measures in Taiwan. These hospitals used different types of ASPs: one had a hospital-wide preauthorization requirement by infectious diseases physicians for all broad-spectrum antibiotics, covering all intensive care units; the second used the same

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Gram-negative organisms;
Multidrug-resistant organisms

program, but excluded all intensive care units; and the third used postprescription review only. The nonsusceptibility of unduplicated isolates of gram-negative bacilli causing health care-associated infections and consumption of broad-spectrum antibiotics were analyzed.
Results: Overall, the usage of broad-spectrum antibiotics of all classes escalated significantly over time in all three hospitals, but consumption was lowest under the hospital-wide preauthorization program. Under this ASP, despite a 2-fold increase in the total broad-spectrum antibiotic consumption during study period, some declining trends of resistance were found, including ciprofloxacin-resistant *Pseudomonas aeruginosa* and *Acinetobacter baumannii*, and carbapenem-resistant *P. aeruginosa*. By contrast, the other two hospitals with preauthorization program excluding all intensive care units and postprescription review had similar high broad-spectrum antibiotic consumption, comparable growing trends of resistant strains in general, and the correlations of antibiotic consumption and resistance were basically positive. Carbapenem-resistant *A. baumannii* increased significantly over time in all three hospitals.
Conclusion: This interhospital comparison suggested that hospital-wide preauthorization program is the most effective to reduce key gram-negative bacilli resistance, with the exception of carbapenem-resistant *A. baumannii*.

Introduction

Infections caused by multidrug-resistant organisms (MDROs) are difficult to treat, leading to significant mortality and morbidity, prolonged length of hospital stay, and excessive costs. The rise of antimicrobial resistance with a diminishing antibiotic pipeline poses a serious threat worldwide, especially concerning gram-negative microbes.[1] The overuse or misuse of antimicrobial agents is the vital component in the emergence and spread of MDROs. Antimicrobial stewardship programs (ASPs) have been advocated by many to extend the life expectancy of antimicrobial armamentarium. To date, there is growing evidence demonstrating the benefits of stewardship, including reductions of antimicrobial usage and cost.[2–4] Preprescription approval and postprescription review are two major types of ASPs. However, the long-term effects of these two ASPs have seldom been compared directly, especially across more than one institution.[3,5,6] The menace of MDRO is most serious in critically ill patients at intensive care units (ICUs), and ICUs have been the critical part for the success of ASPs. So far, few studies have been conducted to evaluate the impact of different ASPs with or without covering ICUs.

It is straightforward to predict that the more antimicrobials are used, the higher will be the resistance generated, as Darwinian selection. Many studies have been conducted to assess this association between antibiotic consumption and resistance.[7–17] However, the results have been inconsistent, and the association was not uniform among all antibiotic—organism pairs.[7–17] In addition, only a few studies compared these antimicrobial usage-versus-susceptibility relationships among different institutions simultaneously, and the effects of diverse ASPs among institutions were not surveyed.[18,19] In this study, we investigated the trends of antimicrobial resistance among key health care-associated gram-negative pathogens over a 6-year period and evaluated the relationship between resistance and broad-spectrum antibiotic usage in three medical centers, all of which were within the same insurance system but featured different ASPs.

Methods

This study was approved by the Institutional Ethics Review Boards of all participating hospitals (Kaohsiung Medical University Hospital, Taichung, Taiwan and Taipei Veterans General Hospital, Taipei, Taiwan).

Hospital settings

In this retrospective study, longitudinal multicenter database surveillance was conducted from July 2005 to December 2011. Three academically affiliated medical centers (Hospitals A, B, and C) participated in this study. Each of them has $>$ 1300 beds (the mean bed size, 1903), including $>$ 100 beds in ICUs, and they all provide both primary and tertiary care, including major surgeries, solid organ or hematopoietic stem cell transplantation, and critical care. These three hospitals are located in Taipei, Taichung, and Kaohsiung, the largest three cities in northern, central, and southern Taiwan, respectively.

These hospitals have established different strategies to promote the judicious use of antimicrobial agents long before the study period. In Hospitals A and B, preauthorization by an infectious diseases specialist is necessary to prescribe broad-spectrum antibiotics, including beta-lactam/beta-lactamase inhibitor combinations, third- and fourth-generation cephalosporins, glycopeptides, tigecycline, all carbapenems, and all fluoroquinolones. In addition to approving the antimicrobial requests, the infectious diseases specialists also offer direct interaction and feedback to prescribers at the same time. The programs are active 24 hours a day, 7 days a week. All the infectious diseases physicians, including clinical fellows, have

dedicated to enforce these programs. To avoid delay in antibiotic use and jeopardizing patients' outcomes, telephone consultation is permitted, especially in critically ill patients or those with severe sepsis. Otherwise, bedside assessment prior to preauthorization is the general rule. The major difference between Hospitals A and B is in ICUs, where preapproval is required in Hospital A, but not in Hospital B.

In Hospital C, the ASP primarily consists of postprescription review and feedback performed by infectious disease specialists. In all three hospitals, computerized systems were used for prescriptions and approvals to assist implementation of ASPs. Since 2003, all three hospitals have followed the Taiwan Centers for Disease Control guidelines for infection control, and they have been accredited annually as meeting all the standards by the government.[20] During the study period, there were no major outbreaks of health care-associated infections or significant changes implemented in the standard procedures for the prevention of nosocomial infection in these hospitals.

Bacterial identification and drug susceptibility tests

Only unduplicated isolates causing health care-associated infections were analyzed in this study. Isolates from outpatients or community-acquired infections, which are generally beyond the influence of an in-hospital ASP, were not included. Health care-associated infections were determined by the infection control nurses based on the definitions of the Taiwan Centers for Disease Control.[21] Identification and susceptibility testing were performed following the guidelines of the Clinical Laboratory Standards Institute (CLSI) for susceptibility testing.[22] The CLSI released new interpretive criteria for Enterobacteriaceae in 2010, but these new breakpoint values have not been implemented in these three hospitals during the study period.[23] Major pathogens (e.g., *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, and *Acinetobacter baumannii*) were the target of our analysis.

Antibiotic consumption

Antibiotic consumption was calculated by the pharmacy department for all adult wards and expressed as defined daily doses (DDDs) per 1000 patient-days using the World Health Organization anatomical therapeutic chemical classification system of 2009. We focused on broad-spectrum antibiotics, the usual target of ASPs. The antimicrobial agents examined in this study included extended-spectrum cephalosporins (cefotaxime, ceftriaxone, cefoperazone, flomoxef, ceftazidime, cefepime, and cefpirome), piperacillin/tazobactam, class 2 carbapenems (imipenem and meropenem), and antipseudomonal fluoroquinolones (ciprofloxacin and levofloxacin).

Statistical analyses

The trend in the consumption of antimicrobial agents and that in the nonsusceptibility of gram-negative pathogens causing health care-associated infections were analyzed using a linear regression test. Pearson's correlation coefficient was used to determine the relationship between antimicrobial use and resistance. A p value < 0.05 was considered statistically significant (2-tailed test).

Results

Trends of antibiotic consumption

The pooled consumption of broad-spectrum antibiotics among these three medical centers every 6 months is presented in Table S1. From July 2005 to December 2011, the usage of all four classes of antimicrobial agents rose significantly. The most commonly used antimicrobials were extended-spectrum cephalosporins. As shown in Figure 1, the consumption of Class 2 carbapenems with antipseudomonal activity increased most prominently, with increases of 146.3%, 134.3%, and 153.7% observed during the study period at Hospitals A, B, and C, respectively.

Because of the different ASPs implemented, there was a considerable interhospital variability in the usage of each class of antimicrobial agents, as demonstrated in Figure 1 and Table 1. Piperacillin/tazobactam, carbapenems, and fluoroquinolones were least commonly prescribed at Hospital A (hospital-wide preauthorization requirement ASP) and highest at Hospital C (postprescription review ASP). However, Hospital B featured the greatest consumption of extended-spectrum cephalosporins. Overall, the total amount of broad-spectrum antibiotic use was similarly high at Hospitals B and C, whereas their use was considerably lower in Hospital A (average, 109.25 DDDs/1000 patient-days). The total broad-spectrum antibiotic consumption in Hospital A grew by 94.7% during the study period (from 70.1 DDDs/1000 patient-days to 136.4 DDDs/1000 patient-days), with the most prominent increase observed for fluoroquinolone consumption (from 11.7 DDDs/1000 patient-days to 35.2 DDDs/1000 patient-days).

Trends and comparison of antimicrobial resistance among key gram-negative bacteria

As shown in Table 2, the trends of antimicrobial resistance were highly diverse among the different hospitals. Because of incomplete data on extended-spectrum beta-lactamase-producing strains from Hospital A, the nonsusceptibility rates among *E. coli* and *K. pneumoniae* were obtained only from Hospitals B and C. In general, nonsusceptibility among the *P. aeruginosa* strains stabilized. In Hospital A, which had a hospital-wide preprescription approval program and the lowest consumption rate of antibiotics, the nonsusceptibility of *P. aeruginosa* to ciprofloxacin and Class 2 carbapenems actually decreased over time. In Hospital B, which featured the highest extended-spectrum cephalosporin usage, cefepimenon-susceptibility among *P. aeruginosa* strains increased over time. Likewise, in Hospital C, which had the highest Class 2 carbapenem usage, the nonsusceptibility of *P. aeruginosa* to carbapenem also rose over time. For *A. baumannii*, ciprofloxacin nonsusceptibility decreased overtime in Hospital A. However, the prevalence of carbapenem-resistant *A. baumannii* (CRAB) increased significantly over time in all three hospitals. The trends of

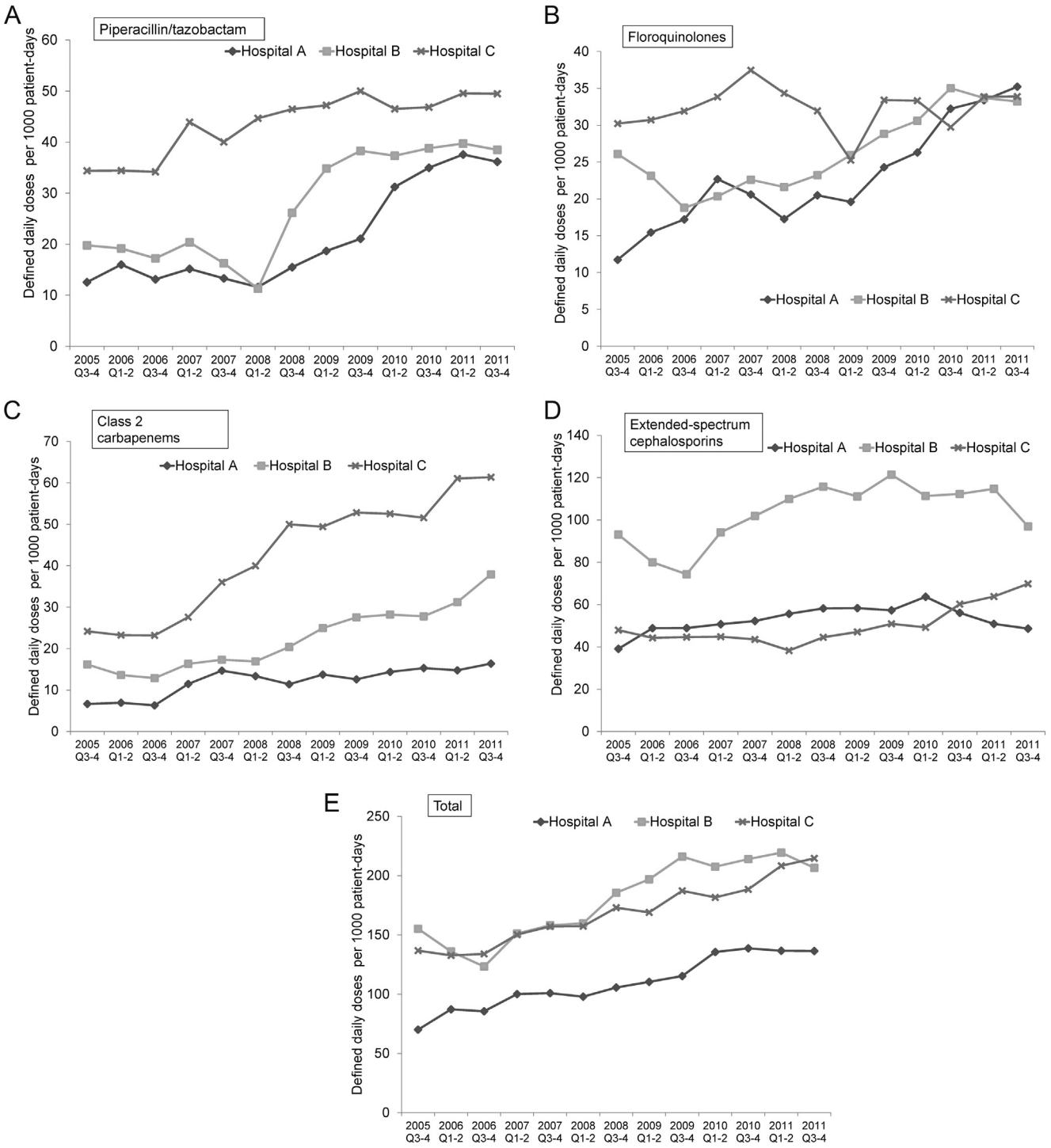

Figure 1. Broad-spectrum antibiotic consumption in defined daily doses/1000 patient-days at each hospital. (A) Piperacillin/tazobactam. (B) Fluoroquinolones. (C) Class 2 carbapenems. (D) Extended-spectrum cephalosporins. (E) Total.

antimicrobial nonsusceptibility among *E. coli* and *K. pneumoniae* strains were similar in Hospitals B and C.

Figure 2 shows the pooled prevalence of resistance during the study period among the different hospitals. Not surprisingly, with the highest extended-spectrum cephalosporins consumption in Hospital B, the prevalence of third-generation cephalosporin-resistant *E. coli* and *K. pneumoniae* was higher in Hospital B. Similarly, piperacillin/tazobactam-resistant *E. coli* and *K. pneumoniae* were more common in Hospital C, whose piperacillin/tazobactam and carbapenem usages were the highest. Carbapenem-resistant *E. coli* was also significantly more common in Hospital C, but its prevalence remained low ($<$ 1%). Among *P. aeruginosa* strains, the nonsusceptibility to piperacillin/tazobactam, ciprofloxacin, cefepime, and carbapenem was lowest in Hospital A. Conversely, the

Table 1 Average consumption of broad-spectrum antibiotics (defined daily doses/1000 patient-days) at three medical centers from July 2005 to December 2011

Hospital	ASP strategy	Piperacillin/tazobactam	Fluoroquinolones	Class 2 carbapenems	Extended-spectrum cephalosporins	Total
A	Preprescription approval, hospital-wide	21.3	22.8	12.2	53.0	109.3
B	Preprescription approval, except ICUs	27.5	26.4	22.4	102.8	179.2
C	Postprescription review	43.7	32.3	42.5	49.9	168.5

ASP = antimicrobial stewardship program; ICU = intensive care unit.

Table 2 Trends in the associations of gram-negative bacteria with health care-associated infection-causing bacteria that are not susceptible to the indicated antimicrobial agent at individual hospitals (Hospitals A, B, and C)

γ	*Pseudomonas aeruginosa*			*Acinetobacter baumannii*			*Escherichia coli*		*Klebsiella pneumoniae*	
Antimicrobial agents	A	B	C	A	B	C	B	C	B	C
Piperacillin/tazobactam	N.S.	N.S.	N.S.	N.S.	0.866	0.73	N.S.	N.S.	N.S.	N.S.
Ciprofloxacin	−0.922	N.S.	N.S.	−0.666	N.S.	N.S.	0.766	0.663	N.S.	N.S.
Carbapenem	−0.608	N.S.	0.625	0.842	0.96	0.603	N.S.	N.S.	0.665	N.S.
Extended-spectrum cephalosporin	N.S.	0.626	N.S.	N.S.	0.817	N.S.	0.739	N.S.	N.S.	N.S.
ESBL-producing							0.828	0.814	N.S.	0.633

ESBL = extended-spectrum beta-lactamases; γ = correlation coefficient; N.S. = not significant.

nonsusceptibility of *A. baumannii* to piperacillin/tazobactam, ciprofloxacin, and cefepime was highest in Hospital A.

Correlation between antibiotic consumption and nonsusceptibility rates

The relationships among the different hospitals are presented in Table 3. Class 2 carbapenem usage was consistently correlated with an increased prevalence of CRAB in all institutions. However, some negative correlations also existed (all in Hospital A): fluoroquinolone use with ciprofloxacin-resistant *P. aeruginosa* and *A. baumannii*, piperacillin/tazobactam use with piperacillin/tazobactam-resistant *A. baumannii*, and carbapenem use with carbapenem-resistant *P. aeruginosa*.

Discussion

From 2005 to 2011, among three medical centers in Taiwan, broad-spectrum antibiotic consumption escalated significantly in all four classes, even in the hospital with the hospital-wide preauthorization program. However, the hospital-wide preauthorization program resulted in the lowest broad-spectrum antibiotic usage, and in turn, some declining trends of resistance among important gram-negative pathogens of health care-associated infections, including ciprofloxacin-resistant *P. aeruginosa* and *A. baumannii* and carbapenem-resistant *P. aeruginosa*. By contrast, with less stringent ASPs, the other two medical centers generally had growing trends of resistant strains, and antibiotic consumption and resistance were positively correlated in general.

At first glance, the discrepancies between increasing broad-spectrum antibiotic usage and diminishing resistance rates in Hospital A appeared fairly puzzling, especially in the setting of rapidly escalating fluoroquinolone (200.3% increase) and Class 2 carbapenems consumption (146.3% increase) during the study period. The ASP implemented at Hospital A was hospital-wide preauthorization by infectious diseases physicians. By direct interaction and feedback to prescribers continuously, the use of broad-spectrum antibiotics may be individualized and adjusted over time, with the right duration and right dosage. These benefits, however, were barely reflected by DDD, which is simply designed for comparisons and benchmarking of aggregated consumption and cannot measure individual exposure to antimicrobials. When we considered the limitations of DDD, these paradoxical correlations became somewhat reasonable. Many previous studies evaluated antimicrobial usage-versus-susceptibility relationships within a single institution, and at times the correlations were contradictory.[7,8,11,17] To our knowledge, the impact of ASP types on antimicrobial usage-versus-susceptibility relationships has never been investigated previously. We proposed that the ASPs may play a key role in the relationship between antimicrobial consumption and gram-negative bacilli resistance.

An ASP with a preauthorization requirement and feedback can effectively reduce inappropriate antimicrobial use and cost, and current guidelines recommend this strategy of ASPs.[24] However, the preauthorization program also has several major drawbacks. It requires adequately trained infectious disease specialists and pharmacists to be

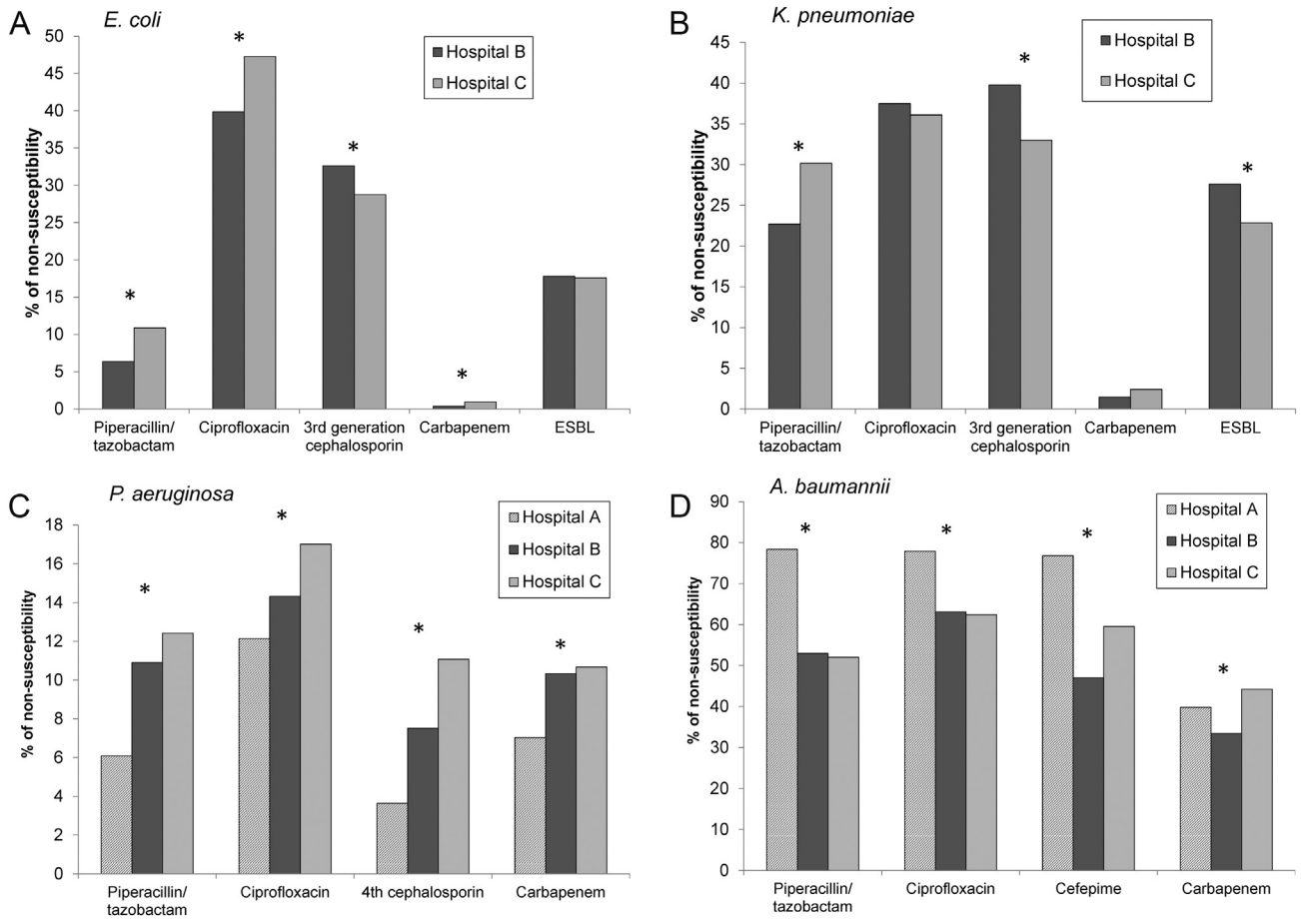

Figure 2. Comparison of non-susceptibility among (A) *Escherichia coli*, (B) *Klebsiella pneumoniae*, (C) *Pseudomonas aeruginosa*, and (D) *Acinetobacter baumannii* at three medical centers. An asterisk indicates that the nonsusceptibility rate is significantly different ($p \leq 0.05$).

Table 3 Relationships between the rates of resistance among nonfermentative gram-negative pathogens causing health care-associated infections and consumption of antibiotics at individual hospital (Hospitals A, B, and C)

γ	*Pseudomonas aeruginosa*			*Acinetobacter baumannii*		
Antimicrobial agents	A	B	C	A	B	C
Piperacillin/tazobactam	N.S.	N.S.	N.S.	−0.571	0.852	0.676
Fluoroquinolones	−0.882	N.S.	N.S.	−0.653	N.S.	N.S.
Class 2 carbapenems	−0.650	N.S.	0.591	0.757	0.927	0.686
Extended-spectrum cephalosporins	N.S.	N.S.	N.S	N.S.	0.767	N.S.

γ = correlation coefficient; N.S. = not significant.

available all day for real-time approvals. Therefore, the preauthorization program is really burdensome and challenging to the labor force, especially for large-scale preauthorization. Moreover, the process of preauthorization is also time consuming, and might delay the timing of initiation of empirical antibiotic therapy, potentially jeopardizing treatment outcomes, especially for critically ill patients. The ethics and legal issues regarding preauthorization in clinical practice are still being debated. To investigate the impacts of preauthorization ASP on patients' clinical outcomes, more information on patient-level data is needed, including high-quality randomized controlled trials. Finally, the preauthorization approach may lead to disputes and may even generate animosity between primary care providers and stewardship team members.[25,26] Like other infection control procedures, ASPs should be individualized. While designing the best ASP program for each institution and patient population, all factors mentioned above should be considered thoroughly.

To avoid the pitfalls of preauthorization, Hospital B implemented a modified program, with formulary unrestricted in ICU areas, where patients are all in a critical condition. Although the burdens of antimicrobial utilization and resistance are greatest in ICUs among the hospitals, ASP strategies to reduce the resistance of microbes might not be very successful if ICUs are excluded. In this study,

both consumption of broad-spectrum antibiotics and resistance in Hospital B (postprescription review in the whole hospital) remained as high as those in Hospital C (preauthorization program in the whole hospital except ICUs). This finding, again, underscores the paramount importance of the involvement of ICUs in the success of ASPs.[18,27]

ASPs are designed to encourage appropriate use of antimicrobial agents, improve patient care, and minimize the impact on antimicrobial resistance.[3] Although control of resistance is the ultimate goal of ASPs, it is difficult to measure ASP effectiveness on the reduction of resistance, and such reductions may take years to observe. The interrupted time series analysis is the preferred tool to assess the effectiveness of infection control interventions.[28,29] However, the statistical analysis is complex, and it could still be potentially confounded by multiple infection control measures adopted concurrently.[3] For instance, a decline of the burden of methicillin-resistant *Staphylococcus aureus* has been reported coincidentally in the United States, Europe, and Asia after the implementation of various actions.[1,4,30] Simply attributing the changes in resistance rates to antimicrobial consumption may be arbitrary to some extent.[31] In our study, all participating hospitals had similar sizes, facilities, and infection control procedures. This provided a great opportunity to evaluate the impact of different ASPs. Hospital-wide preauthorization requirement and feedback was associated with the least usage of broad-spectrum antibiotics and a favorable change in *P. aeruginosa* resistance in our study. More studies of inter-hospital comparisons, like our study, would provide more evidence to determine which types of ASPs are more beneficial for both antimicrobial consumption and resistance reduction.

Despite the stable and decreasing trend of non-susceptibility among *P. aeruginosa* strains, the trends for other nonfermentative gram-negative pathogens, namely, *A. baumannii*, was divergent in this study. The emerging and spread of CRAB has become a global challenge.[32] Unexceptionally, the prevalence of CRAB increased remarkably in all three hospitals, including Hospital A. This might be attributable to the high community burden of CRAB in Taiwan, particularly in the central region.[33,34] To control the spread of CRAB, simply reducing antimicrobial selective pressure will not be effective, perhaps because of the sustained survival of *A. baumannii* on environmental surfaces.

As with numerous other reports on antibiotic use and resistance, our study had several common limitations. The relationship between antimicrobial consumption and resistance is multifactorial, complex, and sometimes unpredictable.[7,11,12,35] Antimicrobial resistance in a hospital is believed to be driven by three main factors: hospital antimicrobial use, cross-transmission of resistant organisms, and introduction of resistant strains from the community or other institutions.[36] Most published studies, including ours, failed to assess the contribution of the latter two variables. To correlate antimicrobial resistance with only one variable (antimicrobial use) may be an excessively simplified method of analysis. Second, the DDD does not measure usage volumes received by children or the oral administration of drugs.[37] Third, the relationships between antibiotic use and resistance as assessed using hospital-wide data may be different for specific patient-care units.[15,35] Our data were aggregated from entire hospitals, and investigating the association for individual patient-care areas was not possible. Fourth, we did not compare the incidence rates of health care-associated infections among the three hospitals, which are more likely to be related to infection control instead of appropriate antibiotic use. Finally, some statistically significant correlations between antibiotic use and resistance may have arisen merely by chance from multiple cross-correlations.[38]

In summary, our multicenter study showed that hospital-wide preauthorization requirement and feedback was associated with the lowest usage of broad-spectrum antibiotics and a diminishing trend in *P. aeruginosa* resistance causing health care-associated infections. Meanwhile, impacts of ASPs seemed minimal on CRAB prevalence, which increased remarkably in all institutions. If ICUs are excluded, preprescription approval strategy may not be superior to postprescription review, considering the effects on antibiotic consumption and resistance reduction.

Conflicts of interest

The authors declare that they have no competing interests.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jmii.2015.05.011.