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Original Article

Implementation and outcomes of hospital-wide computerized antimicrobial approval system and on-the-spot education in a traumatic intensive care unit in Taiwan

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KEYWORDS
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Abstract *Background/purpose:* Inappropriate prescribing of antibiotics is a major healthcare problem in intensive care units (ICUs). This study evaluates the impact of a direct hospital-wide computerized antimicrobial approval system (HCAAS) and on-the-spot education for practitioners in a neurosurgical ICU in Taiwan.
Methods: We retrospectively analyzed the medical records monthly of patients who were admitted to the neurosurgical ICU during a period of 7 years and 7 months. A pretest-posttest time series analysis, comparing the three periods: period I (no infectious disease (ID) physician), period II (part-time ID physicians), and period III (full-time ID physician). Antimicrobial consumption and expenditure, incidence of hospital-associated infections, prevalence of healthcare-associated bacterial isolates, in-hospital mortality rates, and indication of antibiotics usage were analyzed.

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Results: Full-time ID physician can increase the consumption of narrow-spectrum antimicrobials (cefazolin, and cefuroxime), and decrease the consumptions of broad-spectrum antimicrobials (ceftazidime, cefepime, and vancomycin) compared to part-time ID physicians. From period I to period III, the expenditure of antimicrobials, incidence of hospital-associated pneumonia, and the in-hospital mortality rates (crude, sepsis-related, and overall infection-related mortality) decreased statistically. The prevalence of extended-spectrum β-lactamase-producing *Escherichia coli* and *Klebsiella pneumoniae*, and Carbapenems-resistant *Pseudomonas aeruginosa* remained at low level after HCAAS implementation. From 2007 to 2009, the rational antibiotics usage continued to increase, resulting from to more prophylaxis and appropriate microbiologic proof, but less empiric antimicrobial therapy.
Conclusion: Implementation of HCAAS and long-term on-the-spot education by full-time ID physician can reduce antimicrobial consumption, cost, and improve inappropriate antibiotic usage whilst not compromising healthcare quality.
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Introduction

About 17%–64% of hospitalized patients receive antimicrobial therapy,[1–3] and 42%–71% of patients receive antibiotics in intensive care units (ICUs).[4–7] Previous research has indicated that total antibiotic consumption is approximately 10 times greater in ICUs than in general hospital wards.[7] Inappropriate antibiotics use is increasing worldwide in hospital settings by around 36%–54% globally,[1–3,8,9] and up to 47%–66% of ICU patients receive inappropriate antibiotics therapy.[5,10] In ICUs, inappropriate antibiotic usage was higher in patients undergoing surgery,[5] while 5%–57% of patients develop nosocomial infections.[7,11] Multidrug resistant (MDR) bacteria, both gram positive cocci and gram negative bacilli (GNB), are increasingly widespread processes in hospital settings.[12,13]

The hospital-wide computerized antimicrobial approval system (HCAAS) was developed in September 2004 at Chang-Gung Memorial Hospital (CGMH), and the implementation of an online antibiotic control program was first reported at CGMH-Taoyuan in Taiwan in 2011.[14] The aim of the study is to evaluate and report the impact of HCAAS and on-the-spot education by infectious disease (ID) physicians in a trauma ICU at CGMH-Chiayi. This study examined the effects of HCAAS on antimicrobial consumption and expenditure, clinical outcomes, antimicrobial resistance of major healthcare-associated bacterial isolates before and after implementation of the system. We also analyzed rates of appropriate antibiotics and indication of antibiotic usage after implementation of the system.

Methods

Study design and setting

The CGMH-Chiayi is a 1300-bed tertiary hospital providing acute and chronic care service in Southern Taiwan. This hospital provides all major services, including medical and surgical subspecialties. Our neurosurgical ICU (NSICU) has twenty hospital beds, which provided for trauma or surgical critical patients. This ICU has been in service since June 2002, however no ID physicians served CGMH-Chiayi until January 2006. HCAAS started in January 2006, with four rotating ID physicians from CGMH-Taoyuan served 12 months (since January 2006 to December 2006). One full-time ID physician has undertaken the work since January 2007 to February 2010. This retrospective study was approved by the Institutional Review Board (Ethics Committee) of CGMH (Document no. 97-1073B and 99-1123C).

All data of patients who were admitted to NSICU from June 2002 to December 2009 were retrospectively reviewed monthly. A pretest-post-test time series analysis, comparing the three periods: period I (no ID physician period, June 2002 to December 2005), period II (part-time ID physicians period, January 2006 to December 2006), and period III (full-time ID physician period, January 2007 to December 2009).

The data included age, sex, duration of ICU stay, incidence of hospital-associated infections (HAIs), prevalence of the major healthcare-associated bacterial isolates, parenteral antimicrobial consumption and cost, rates of appropriate antibiotics, indication of antibiotic usage, and major underlying diseases, but excluded cerebrovascular disease, which was not analyzed.

HCAAS and on-the-spot education by ID physicians

The HCAAS is an intranet-based application, built under the Health Information System, and is linked to the comprehensive electronic medical records.[10,14,15] Each ID physician was notified when a restricted antimicrobial agent was being prescribed in his pre-assigned region (wards and ICUs). All of the above information was automatically processed in the HCAAS. The prescribing physician was required to provide necessary clinical supporting data that includes clinical history, laboratory reports, culture results, and images for an online review of the ID physicians. After review, the ID physicians briefly discussed the case with the physicians-in-charge prior to making a decision. If a prescription was disapproved, the antimicrobial agent was discontinued by the pharmacy's unit-dose delivery system within 48 h and the prescriber was immediately notified to modify the regimen. If necessary, the ID physicians could still be consulted formally.

Besides the HCAAS, ID physicians visited the NSICU every weekday and Saturday morning starting from January 2006, and discussed with the physicians-in- charge about antibiotic prescription, gave on-the-spot education including rational antibiotics usage, microbial resistance, and infection control. The advice of the appropriate antibiotic choice was based on the probable pathogens in the infection source, patient's underlying diseases, hospital epidemiology (resistant strains surveillance and antibiotic susceptibility testing report), evidence-based medicine and experts' recommendation from literature, guidelines of professional medical societies and textbooks.

Spectrum of antibiotics and indication of antibiotic use

Through the HCAAS, orders of all parenteral antibiotics including antifungal agents in ICUs including narrow-spectrum and broad-spectrum antibiotics were assessed by ID physicians.[10,14–16] Narrow-spectrum antibiotics included non-extended-spectrum cephalosporins (cefazolin, cefuroxime), penicillins (penicillin G, oxacillin, ampicillin), aminoglycosides (gentamicin), lincosamide (clindamycin), nitroimidazole (metronidazole), and folate pathway inhibitors (trimethoprim-sulfamethoxazole). Broad-spectrum antibiotics included extended-spectrum cephalosporins (ceftriaxone, ceftazidime, cefpirome, and cefepime), penicillins (amoxicillin, amoxicillin/clavulanate, ampicillin/sulbactam, piperacillin, and piperacillin-tazobactam), carbapenems (imipenem, meropenem, and ertapenem), monobactams (aztreonam), aminoglycosides (amikacin), fluoroquinolones (ciprofloxacin, levofloxacin, and moxifloxacin), glycopeptides (vancomycin, and teicoplanin), and other antibacterial agents (colistin, tigecycline, linezolid, daptomycin). Piperacillin-tazobactam and levofloxacin were purchased to our hospital after the HCCAS. Anti-fungal agents were not calculated due to insufficient amount. The antibiotic utilization was measured by the total number of grams of the drugs, and the value was converted into defined daily doses (DDD) per 1000 patient-days per month, in accordance with the World Health organization recommendations.[17]

Categories of judgment for antibiotic use

Each ID physician assigned categories I to V of judgment for antibiotic use and followed explicit criteria.[2,9] Category I: the prescription is appropriate. Category II: the prescription is probably appropriate. Category III: a different (usually less expensive or less toxic) antimicrobial is preferred. Category IV: a modified dose or duration of the prescription is recommended. Category V: administration is unjustified. All disagreements were recommended and recorded at medical charts by ID physicians, but these categories were analyzed only in the full-time physician period. De-escalation was defined as either a switch to a narrow spectrum agent or the reduction in the number of antibiotics.[18]

HAIs and antimicrobial resistance of major healthcare-associated bacterial isolates

HAIs, defined as infections that were not present and for which there was no evidence of prior incubation at the time of admission, were identified based on CDC diagnostic criteria for nosocomial infections.[19] The antimicrobial susceptibility profiles of bacterial pathogens were obtained from the Clinical Microbiology Laboratory of CGMH, which is a College of American Pathologists-accredited laboratory. There were no changes in microbiological laboratory techniques during the study period.

End-point measurements

This study was conducted to compare the differences between a new, large hospital in the three different periods with no ID physician, rotating ID physicians, and a full-time ID physician, which had not been previously studied. There were several end-points in this study. First, total consumption of major classes of antimicrobials and expenditure, and in-hospital mortality rates were compared. Second, the incidence of HAIs and prevalence of the most common healthcare-associated antimicrobial-resistant pathogens during ICU stays was assessed. Third, the indication of antibiotics use was compared during the full-time ID physician period. Expiry and critical discharge against medical advice were included in the mortality. The crude mortality was defined as all-cause mortality occurring within ICU stay.

Statistical analysis

The continuous data was compared using one-way analysis of variance (ANOVA) and a Tukey post-hoc test was performed for multiple comparisons (p value < 0.05). All statistical calculations were performed with the Statistical Package for the Social Sciences Windows, version 18.0 (SPSS, Chicago, IL, USA) for Windows, and all values were reported as means $\pm$ standard deviation (SD).

Results

Study population

There were 2208 admissions in period I, 706 admissions in period II, and 1913 admissions in period III. Comparison of these groups indicated that the patients in period III were older, had more chronic airway diseases than period I, and had more malignant diseases than period II (Table 1).

Reduction in antimicrobial consumption and expenditure

In this study, use of narrow-spectrum and broad-spectrum antimicrobials were reviewed (Table 2). In comparison of narrow-spectrum antibiotics between period III and I, the antimicrobial consumption of cefazolin and gentamicin increased to 5.3 times and 3.1 times, respectively, but penicillin G, ampicillin, clindamycin, and metronidazole

Table 1 Patient demographics, hospital associated infections (HAIs[a]), and clinical outcomes in these three periods.

Variable	Period I (N = 2208)	Period II (N = 706)	Period III (N = 1913)
Age (years), mean ± SD[b]	54.4 ± 3.4	55.0 ± 4.1	56.9 ± 2.8†
Male, n (%)	1450 (65.7)	472 (66.9)	1253 (65.5)
Length of ICU[c] stay, (days)	5.1 ± 0.8	4.6 ± 0.6	4.7 ± 0.6
Underlying disease, n (%)			
malignant disease	137 (6.2%)	37 (5.2%)	155 (8.1%)§
cardiovascular disease	69 (3.1%)	29 (4.1%)†	75 (3.9%)
chronic kidney disease	52 (2.4%)	9 (1.3%)	43 (2.2%)
diabetes mellitus	189 (8.6%)	81 (11.5%)	180 (9.4%)
chronic airway disease	20 (0.9%)	10 (1.4%)	37 (1.9%)†
liver cirrhosis	25 (1.1%)	11 (1.6%)	24 (1.3%)
Incidence of HAIs (‰),	9.8 ± 4.2	9.4 ± 4.2	10.4 ± 4.7
HA-BSI[d]	2.6 ± 2.2	1.8 ± 2.1	1.5 ± 1.9
HA-UTI[e]	5.4 ± 3.7	6.4 (3.6)	8.0 ± 4.5†
HA-pneumonia[f]	1.3 ± 1.9	0.7 (1.1)	0.1 ± 0.5†
Mortality rates, n (%)			
Crude mortality	584/2208 (26.4)	151/706 (21.4)	323/1913 (16.9)†
Sepsis-related mortality	45/75 (60.0)	6/15 (40.0)	15/54 (27.8)†
UTI-related mortality	9/141 (6.4)	3/36 (8.3)	8/161(5.0)
Pneumonia-related mortality	52/229 (22.7)	13/78 (16.7)	31/183 (16.9)
Overall infection related mortality	123/411 (29.9)	32/129 (24.8)	70/399 (17.5)†

[a] HAI, hospital associated infection.
[b] SD, standard deviation.
[c] ICU, intensive care unit.
[d] HA-BSI, hospital associated blood stream infection.
[e] HA-UTI, hospital associated urinary tract infection.
[f] HA-pneumonia, hospital associated pneumonia.
Data was presented as mean (standard deviation); Data was compared with ANOVA, †$p < 0.05$ *vs*. PeriodIin the Tukey post hoc test; §$p < 0.05$ *vs*. Period II in the Tukey post hoc test. Data expressed in Mean ± SD.

consumptions decreased ($p < 0.05$). Interestingly, the consumption of cefuroxime decreased in comparison between period II and I, but increased to 4.6 times between period III and II ($p < 0.05$).

In broad-spectrum antibiotics, the antimicrobial consumption of piperacillin, aztreonam, imipenem, ciprofloxacin, and teicoplanin decreased in comparison between period II and I ($p < 0.05$). The consumption of overall antimicrobials, and most major classes broad-spectrum (carbapenems, fluoroquinolones, and glycopeptides) decreased in comparison between period III and I ($p < 0.05$). Although the consumption of ceftazidime, vancomycin, and the class of extended-spectrum cephalosporins increased in comparison between period II and I, all the above antibiotics decreased statistically in comparison between period III and II (Table 2).

The costs (per person per month) of narrow-spectrum, broad-spectrum, and overall antimicrobials decreased 54.8%, 70.4%, and 69.2%, respectively, in comparison between period III and I (Table 3).

In-hospital mortality rates and HAIs

In-hospital monthly crude mortality rates, sepsis related mortality rates, and overall infection related mortality rates showed statistically significant reduction between periods III compared to period I (Table 1).

The hospital-associated urinary tract infection (HA-UTI) rates increased, but the hospital-associated pneumonia (HA-pneumonia) rates decreased in periods III when compared to period I (Table 1).

Hospital-associated antimicrobial resistance profiles

The antimicrobial resistance profiles of the major healthcare-associated bacterial isolates in 8 years were analyzed (Fig. 1). The rate of methicillin-resistant *Staphylococcus aureus* (MRSA) amongst overall *S. aureus* isolates was 60–89% and decreased after implementation of HCAAS, with the lowest rate of 48.5% in 2008. A decrease in isolation of extended-spectrum β-lactamase (*ESBL*)-producing *Escherichia coli* (*E. coli*) and *Klebsiella pneumoniae* (*Kleb. pneumoniae*) was observed over the years with the isolation rates less than 5% in 2008 and 2009. Multidrug-resistant *Acinetobacter baumannii (MDR-Ab)* significantly increased from 0% to 36% before 2007, and decreased to 22% in 2009. Carbapenems-resistant *Pseudomonas aeruginosa* (CR-*Pseudomonas aeruginosa*) remained <5%.

Appropriate antibiotics usage rates and indication

From 2006 to 2009, the numbers of implementation of HCAAS were 3029 cases (600 in 2006, 595 in 2007, 681 in 2008 and 1153 in 2009). The numbers of approvals were 433 cases (72.2% of total yearly uptake) in 2006, 360 cases

Table 2 The consumption of antimicrobial agents per month (DDD[a]/10^3patient-days) in these three periods.

Variable	Period I (43 months)	Period II (12 months)	Period III (36 months)
Narrow-spectrum antimicrobials	605.3 (192.2)	539.9 (146.3)	621.7 (173.2)
Cefazolin	61.5 (71.2)	221.1 (22.1)†	326.7 (74.6)†§
Cefuroxime	70.7 (49.8)	21.1 (22.8)†	97.6 (73.7)§
Penicillin G	15.1 (14.4)	9.1 (9.2)	1.5 (3.6)†
Ampicilin	27.6 (72.3)	2.5 (7.8)	0.6 (7.9)†
Gentamicin	17.3 (54.8)	94.9 (36)	53.3 (31.1)†§
Clindamycin	62.7 (71.6)	31.0 (22.0)	12.9 (20.3)†
Metronidazole	40.9 (45.0)	20.7 (26.6)	18.8 (18.9)†
Broad-spectrum antimicrobials	743.9 (352.1)	618.0 (120.2)	378.2 (187.0)†§
Cetriaxone	131.6 (100.9)	165.3 (81.3)	144.2 (81.3)
Ceftazidime	51.5 (37.6)	100.8 (33.2)†	53.5 (46.8)§
Cefepime	18.6 (31.0)	21.8 (20.5)	1.0 (3.0)†§
Piperacillin	15.5 (21.7)	1.3 (3.0)†	6.9 (10.8)
Aztreonam	25.5 (38.2)	3.8 (6.4)†	0.2 (1.1)†
Imipenem	104.9 (80.7)	36.5 (35.9)†	15.3 (28.1)†
Meropenem	10.9 (17.5)	19.7 (26.8)	3.2 (9.8)
Amikacin	27.3 (33.9)	9.7 (16.2)	3.7 (7.2)†
Ciprofloxacin	147.2 (139.8)	56.3 (49.3)†	19.2 (20.2)†
Vancomycin	61.4 (53.3)	100.3 (45.3)	51.1 (48.0)§
Teicoplanin	96.6 (70.9)	32.2 (43.5)†	11.0 (16.8)†
Major classes of broad-spectrum antimicrobials			
Extended-spectrum cephalosporins	201.7 (124.9)	287.9 (101.8)†	198.9 (100.2)§
Antipseudomonal penicillins	15.5 (21.7)	11.2 (16.1)	22.4 (19.7)
Carbapenems	115.8 (86.1)	60.1 (38.5)†	28.1 (40.1)†
Fluoroquinolones	147.2 (139.8)	58.7 (47.7)†	22.9 (23.4)†
Glycopeptides	158.0 (75.2)	132.4 (68.5)	62.1 (53.2)†§
Overall antimicrobials	1349.2 (443.6)	1157.9 (188.6)	999.9 (176.9)†

[a] DDD, defined daily dose.
Data was presented as mean (standard deviation); Data was compared with ANOVA, †$p < 0.05$ *vs.* Period I in the Tukey post hoc test; §$p < 0.05$ *vs.* Period II in the Tukey post hoc test.

Table 3 The expenditure of antimicrobial agents (New Taiwan dollar per person per month) in these three periods.

Variable	Period I (N = 2208)	Period II (N = 706)	Period III (N = 1913)
Narrow-spectrum antimicrobials	1144.7 (604.3)	763.7 (258.4)†	517.4 (169.4)†
Broad-spectrum antimicrobials	14088.9 (9148.6)	8082.2 (2165.1)†	4176.3 (2779.2)†
Overall antimicrobials	15233.6 (9466.7)	8845.9 (2347.5)†	4693.7 (2758.6)†

Data was presented as mean (standard deviation); Data was compared with ANOVA, †$p < 0.05$ *vs.* Period I in the Tukey post hoc test; §$p < 0.05$ *vs.* Period II in the Tukey post hoc test.

(60.5%) in 2007, 491 cases (72.1%) in 2008 and 850 cases (73.7%) in 2009 (Table 4).

Between year 2007 and 2009, the ratio of antibiotics usage for prophylaxis increased statistically from 1.2% to 30.4%, while empiric antibiotics usage decreased statistically from 65.7% to 38.4%, and no indication for antibiotics usage decreased statistically from 8.7% to 2.8% (Table 5).

Appropriate antibiotics use rate for prophylaxis showed a statistically significant increase from 0.8% to 28.0% between 2007 and 2009, and for microbial evidence increase from 15.3% to 20.1% between 2007 and 2008. The total numbers of de-escalation were 108 cases (18.2%) in 2007, 115 cases (16.9%) in 2008 and 152 cases (13.2%) in 2009. The total numbers of escalation were 22 cases (3.7%) in 2007, 13 cases (1.9%) in 2008 and 40 cases (3.5%) in 2009 (Table 5).

Discussion

The HCAAS provided a clinician-led, sustainable system for providing antibiotic stewardship in a 3500-bed medical center[14] and another 2700-bed medical center[15] including the trend of most broad-spectrum antibiotics including extended-spectrum cephalosporins, fluoroquinolones, and glycopeptides decreased significantly.

In the current study, the consumption of the class of fluoroquinolones, carbapenems, aztreonam, and teicoplanin decreased statistically in comparison between before and after implantation of HCAAS. Interestingly, the consumption of meropenem, and vancomycin increased, and extended-spectrum cephalosporins increased statistically in comparison between period II and I (Table 2).This increase

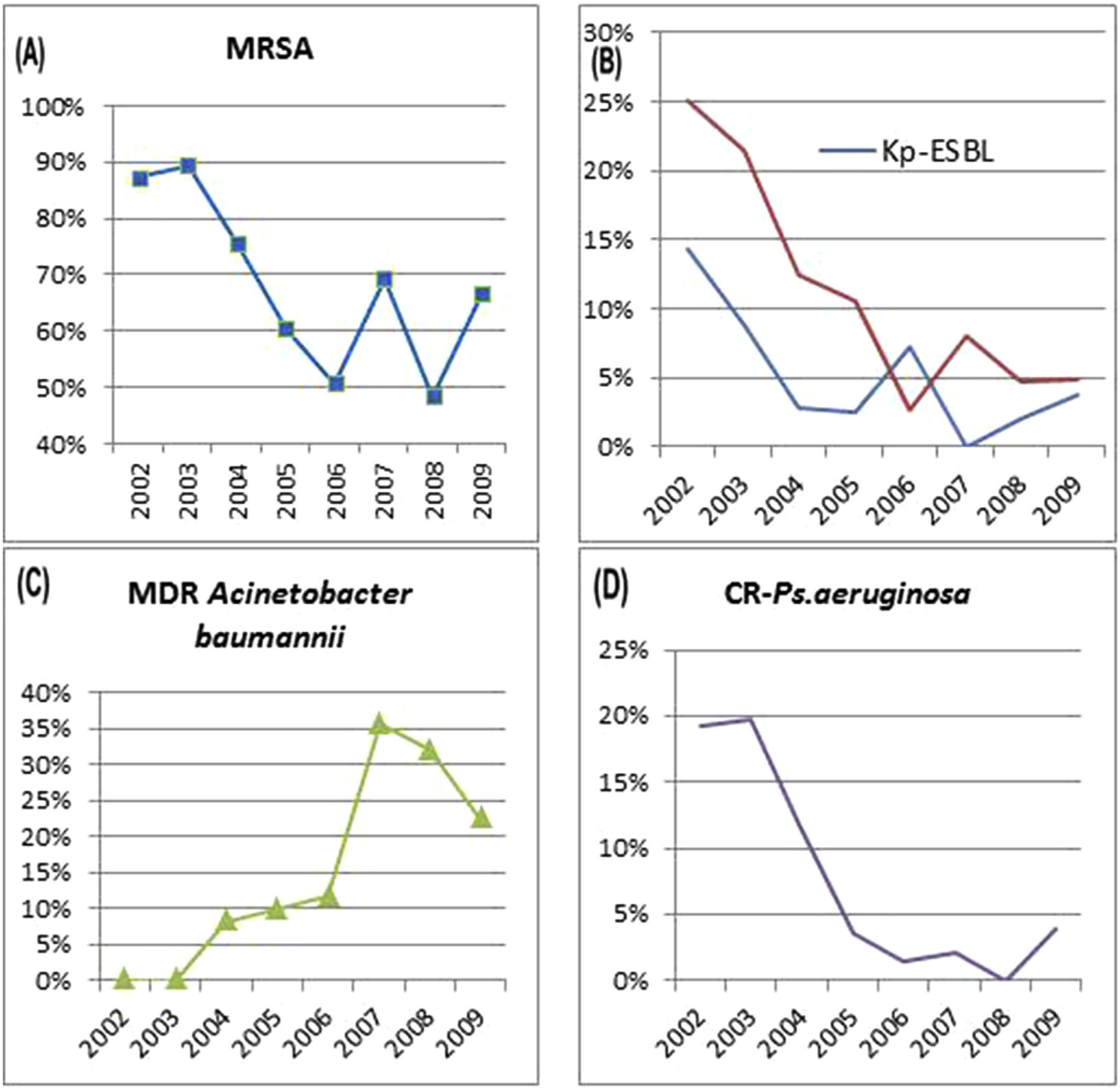

Figure 1. Isolation rates of (A) methicillin-resistant *Staphylococcus aureus* (MRSA) (B) extended-spectrum-lactamase (ESBL)-producing *Escherichia coli* and *Klebsiella pneumoniae* (C) multidrug-resistant (MDR) *Acinetobacter baumannii* and (D) Carbapenems resistant *Pseudomonas aeruginosa*, representing the major healthcare-associated bacterial isolates, at Chang Gung Memorial Hospital (Chiayi, Taiwan) over time.

could be explained, at least in part, by the theory that restricting the use of certain antimicrobial classes may be associated with a compensatory increase in the use of unrestricted antimicrobials, a phenomenon called "squeezing the balloon".[20] Fortunately, a full-time ID physician's service and prolonged education contributed to an increase the consumption of non-extended-spectrum cephalosporins, and a decrease in the consumption of broad-spectrum antimicrobial agents (ceftazidime, cefepime, and vancomycin) (Table 2). The cost reduction for antimicrobial agents were 69.2% in the present study, paralleling to 38.2% in Apisarnthanarak et al. and 19.6% in Erda et al.[2,11]

Lowering the NSICU mortality was an important quality indicator for our study (Table 1). Recent epidemiological data indicate an increasing frequency and awareness of HAIs by antimicrobial-resistant pathogens, especially in ICUs,[21] that have a significant impact on the clinical outcomes and economic expenditure.[22] In past studies, rational antibiotics can reduce HAI rates.[10,11,15,16,23] In the current study, the decreases of the life-threatening infections (HAI-BSI and HAI-pneumonia) were well demonstrated.

Clinical microbiologists provide prompt data on organism identification and pathogen susceptibility patterns. The increased consumptions of carbapenems, extended-spectrum cephalosporins, β-lactams/β-lactamase inhibitors, and fluoroquinolones have been reported to positively correlate with the development of MDR-GNB in a substantial number of studies,[24–26] and the over-consumption of extended-spectrum cephalosporins (particularly ceftazidime) has been reported to potentially increase the prevalence of ESBL-producing *Enterobacteriaceae*.[26] In our study, the prevalence of ESBL-producing *E. coli* and *Kleb. pneumoniae*, and CR-*Pseudomonas aeruginosa* remained at lower level after the HCAAS implementation. However the threaten from MDR-*ab* could not

Table 4 The appropriate rates of various antibiotics indication from year 2007–2009. Data was presented as mean (standard deviation); Data was compared with ANOVA,†$p < 0.05$ *vs.* 2007 in the Tukey post hoc test.

Various indication of antibiotics usage (%)	Year 2007	Year 2008	Year 2009
Appropriate surgical prophylaxis	71.4	92.6	92.0
Appropriate microbial Evidence	62.8 (12.6)	75.7 (16.1)†	68.8 (13.0)
Appropriate empiric Usage	67.5 (6.3)	66.3 (11.3)	68.2 (9.0)
Appropriate antibiotic use	60.5 (6.0)	72.1 (12.8)	73.7 (5.6)†

Note. The appropriate antibiotics indication were adjusted by Apisarnthanarak et al. and Kunin et al.[2,9] Appropriate surgical prophylaxis indicated agreement with the use of appropriate or probably appropriate antimicrobial prophylaxis. Appropriate empiric usage indicated agreement with the use of appropriate or probably appropriate antimicrobial therapy.

be overlooked that even a recent longitudinal multicenter surveillance program in Taiwan indicated a significant increase of MDR-*ab* over the past 10 years.[27] In the present study, the percentage of MDR-*Ab* reached the peak point in 2007, and decreased in 2009 during the implementation of HCAAS (Fig. 1). This phenomenon indicated the importance of strict infection-control measures including the hand-hygiene program, care bundle, monitoring and the inspection of patients infected with resistant pathogens to reduce the secondary spread of resistant organisms and the HAI rate by infection control nurses.

For critically ill patients, timely administration of broad-spectrum antimicrobial agents was crucial for proper coverage of causative pathogens.[10] When patients become stable and the causative pathogens have been identified, de-escalation should be carried out to avoid development of antimicrobial resistance in pathogens.[10] After education and antibiotic-control programs, the incidence of appropriate antibiotic use increased significantly from 58% to 80%,[2] and in ICUs from 66% to 81% at CGMH-Taoyuan.[10] In our study, the rate of agreement dropped from 72.2% in 2006 to 60.5% in 2007, and increased to 73.7% in 2009 (Table 4), reflecting the importance of a full-time ID physician.

According to past studies, 13–36% ICUs patients received antibiotics for prophylaxis.[4,6] The ratio of indication for antibiotics usage, for empiric antibiotics usage and no indication decreased statistically, and for prophylaxis increased statistically significantly in comparison between year 2009 and 2007 (Table 5). With regard to the low rate of surgical prophylaxis in 2007, it was noted that many patients underwent surgery with concomitant fever or abnormal white blood cell counts, and the physicians-in-charge usually assumed infective diseases and ordered the empirical antibiotics, but not prophylaxis.

The increase in the ratio of appropriate microbial agents was noted between 2007 and 2008, but dropped in 2009. It was proposed that on-the-spot education needed to continue, the effectiveness would otherwise decline. Although escalation accounted for only 1.9–3.7% in our study, but it still had a role in patient safety.

Antibiotics ordered empirically were found to be less appropriate than those ordered with evidence of culture and susceptibility results.[5] Between 2007 and 2008, the appropriate ratio of antibiotics usage for microbiologic proof increased statistically from 62.8% to 75.7% (Table 4).

Table 5 Reasons of antibiotic prescription from year 2007–2009.

Variable cases	Year 2007 (n = 595)	Year 2008 (n = 681)	Year 2009 (n = 1153)
Surgical prophylaxis	7 (1.2)	149 (21.9)†	351 (30.4)†§
Appropriate	5 (0.8)	138 (20.3)†	323 (28.0)†§
Inappropriate	2 (0.3)	11 (1.6)	28 (2.4)†§
Microbiologic documented infection	145 (24.4)	181 (26.6)	327 (28.4)
Appropriate	91 (15.3)	137 (20.1)†	225 (19.5)
Inappropriate	54 (9.1)	44 (6.5)†	102 (8.8)
De-escalation	41 (6.9)	37 (5.4)	59 (5.1)
Escalation	6 (1.0)	4 (0.6)	29 (2.5)
Other reasons not related to the above reasons	7 (1.2)	3 (0.4)	14 (1.2)
Empiric therapy	391 (65.7)	326 (47.9)†	443 (38.4)†§
Appropriate	264 (44.4)	216 (31.7)†	302 (26.2)†
Inappropriate	127 (21.3)	110 (16.2)†	141 (12.2)†
De-escalation	67 (11.3)	78 (11.5)	93 (8.1)
Escalation	16 (2.7)	9 (1.3)	11 (1.0)
Other reasons not related to the above reasons	44 (7.4)	23 (3.4)	37 (3.2)†
No indication	52 (8.7)	25 (3.7)	32 (2.8)†

Data were presented as no (%) of cases; Data was compared with ANOVA, †$p < 0.05$ *vs.* 2007 in the Tukey post hoc test; §$p < 0.05$ *vs.* 2008 in the Tukey post hoc test.

In our study, the ratio of rational antibiotics usage increased due to more evidence for appropriate prophylaxis, more appropriate microbiologic proof, and less empiric antimicrobial therapy. If the physicians-in-charge rotation rate had not changed significantly, the gradually increasing incidence of appropriate antibiotics use was predictable but will remain at a certain high point after long term on-the-spot education.

In the original design of the HCAAS, once an antimicrobial regimen had been approved by ID physicians, the prescription remained valid for 7 days,[10] and even if it was not suitable for the patient's new condition. Another important issue was that many of the pathogens isolated were of no clinical relevance due to a status of colonization.[6] Clinical doctors usually ordered antibiotics according to bacterial culture even without evidence for infection. Due to the fact that the full-time ID physician normally visited NSICU almost every day, these unsuitable regimens were adjusted after discussion or consultation with the physicians-in-charge. An antibiotic order without a consultation with ID specialists was more likely to be inappropriate.[5] In our study, implementation of the HCAAS and education can influence antibiotic-prescribing habits.

ID physicians in Taiwan are relatively insufficient, and they often need to take care of many clinical and administrative work. From 2006 to 2009, ID physicians worked mainly in outpatient clinics, performed HCAAS, infection control, regulatory education, and received no loading for heavy inpatient care. This was very different from other branches of CGMH-Taoyuan and CGMH-Kaohsiung.

Overall, this study provided a comprehensive evaluation of a novel, ID specialist-led, and sustainable system to provide antibiotic stewardship in a busy medical ecology. According to the HCAAS, ID physicians can help physicians in charge to review antibiotic prescriptions, and make preliminary recommendations, but cannot completely replace face-to-face communications. More detailed studies over longer periods need strong support by the hospital administrative management.

Implementation of the HCAAS and long-term on-the-spot education by a full-time ID physician at CGMH-Chiayi can reduce consumption of unnecessary antibiotics and improve inappropriate antibiotic usage while not compromising healthcare quality in the trauma ICU.

Limitation

The present study was limited by a short term of only 91 months, and no further data could be analyzed because the NSICU was divided into three ICUs in February 2010.

Conflicts of interest

All authors have no conflicts of interest to declare.

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References

1. Tünger Ö, Dinc G, Özbakkaloglu B, Atman ÜC, Algün Ü. Evaluation of rational antibiotic use. *Int J Antimicrob Agents* 2000; **15**:131–5.
2. Apisarnthanarak A, Danchaivijitr S, Khawcharoenporn T, Limsrivilai J, Warachan B, Bailey TC, et al. Effectiveness of education and an antibiotic-control program in tertiary care hospital in Thailand. *Clin Infect Dis* 2006;**42**:768–75.
3. Erbay A, Colpan A, Bodur H, Cevik MA, Samore MH, Ergönül Ö. Evaluation of antibiotic use in a hospital with an antibiotic restriction policy. *Int J Antimicrob Agents* 2003;**21**:308–12.
4. Bergmans DC, Bonten MJ, Gaillard CA, Tiel FH, Geest S, Leeuw PW, et al. Indications for antibiotic use in ICU patients: a one-year prospective surveillance. *J Antimicrob Chemother* 1997;**39**:527–35.
5. Erbay A, Bodur H, Akinci E, Colpan A. Evaluation of antibiotic use in intensive care units of a tertiary care hospital in Turkey. *J Hosp Infect* 2005;**59**:53–61.
6. Røder BL, Nielsen SL, Magnussen P, Engquist A, Frimodt-Møller N. Antibiotic usage in an intensive care unit in a Danish university hospital. *J Antimicrob Chemother* 1993;**32**:633–42.
7. Curcio DJ. Antibiotic prescription in intensive care units in Latin America. *Rev Argent Microbiol* 2011;**43**:203–11.
8. Thuong M, Shortgen F, Zazempa V, Girou E, Soussy CJ, Brun-Buisson C. Appropriate use of restricted antimicrobial agents in hospitals: the importance of empirical therapy and assisted re-evaluation. *J Antimicrob Chemother* 2000;**46**:501–8.
9. Kunin CM, Tupasi T, Craig WA. Use of antibiotics: a brief exposition of the problem and some tentative solutions. *Ann Intern Med* 1973;**79**:555–60.
10. Wang HY, Chiu CH, Huang CT, Cheng CW, Lin YJ, Hsu YJ, et al. Blood culture-guided de-escalation of empirical antimicrobial regimen for critical patients in an online antimicrobial stewardship programme. *Int J Antimicrob Agents* 2014;**44**:520–7.
11. Arda B, Sipahi OR, Yamazhan T, Tasbakan M, Pullukcu H, Tunger A, et al. Short-term effect of antibiotic control policy on the usage patterns and cost of antimicrobials, mortality, nosocomial infection rates and antibacterial resistance. *J Infect* 2007;**55**:41–8.
12. Johnson AP. Antibiotic resistance among clinically important Gram-positive bacteria in UK. *J Hosp Infect* 1998;**40**:17–26.
13. Boucher HW, Talbot GH, Bradley JS, Edwards JE, Gilbert D, Rice LB, et al. Bad bugs, no drugs: no ESKAPE! an update from the Infectious Diseases Society of America. *Clin Infect Dis* 2009;**48**:1–12.
14. Chan YY, Lin TY, Huang CT, Deng ST, Wu TL, Leu HS, et al. Implementation and outcomes of a hospital-wide computerised antimicrobial stewardship programme in a large medical centre in Taiwan. *Int J Antimicrob Agents* 2011;**38**:486–92.
15. Chen IL, Lee CH, Su LH, Lily YC, Wang YL, Liu JW. Effects of implementation of an on-line comprehensive antimicrobial stewardship program in ICUs: a longitudinal study. *J Microbiol Immunol Infect* 2016;**16**. 1684–1182.
16. Chen IL, Lee CH, Su LH, Tang YF, Chang SJ, Liu JW. Antibiotic consumption and healthcare-associated infections caused by multidrug-resistant gram-negative bacilli at a large medical center in Taiwan from 2002 to 2009: implicating the importance of antibiotic stewardship. *Plos one* 2013;**8**:1–6.

17. WHO Collaborating Centre for Drug Statistics Methodology. *Guidelines for ATC classification and DDD assignment*. Oslo: WHO; 2005.
18. Morel J, Casoetto J, Jospe R, Aubert G, Terrana R, Dumont A, et al. De-escalation as part of a global strategy of empiric antibiotherapy management. A retrospective study in a medico-surgical intensive care unit. *Crit Care* 2010;**14**:R225.
19. Garner JS, Jarvis WR, Emori TG, Horan TC, Hughes JM. CDC definitions for nosocomial infection. *Am J Infect Control* 1988; **16**:128—40.
20. Burk JP. Antibiotic resistance—squeezing the balloon? *JAMA* 1998;**280**:1270—1.
21. Vincent JL, Rello J, Marshall J, Silva E, Anzueto A, Martin CD, et al. International study of the prevalence and outcomes of infection in intensive care units. *JAMA* 2009;**302**:2323—9.
22. Roberts RR, Hota B, Ahmad I, Scott II RD, Foster SD, Abbasi F, et al. Hospital and societal costs of antimicrobial-resistant infections in a Chicago teaching hospital: implications for antibiotic stewardship. *Clin Infect Dis* 2009;**49**:1175—84.
23. Dortch MJ, Fleming SB, Kauffmann RM, Dossett LA, Talbot TR, May AK. Infection reduction strategies including antibiotic stewardship protocols in surgical and trauma intensive care units are associated with reduced resistant gram-negative healthcare-associated infections. *Surg Infect (Larchmt)* 2011; **12**:15—25.
24. Neuhauser MM, Weinstein RA, Rydman R, Danziger LH, Karam G, Quinn JP. Antibiotic resistance among gram-negative bacilli in US intensive care units: implications for fluoroquinolone use. *JAMA — J Am Med Assoc* 2003;**289**:885—8.
25. Rice LB, Eckstein EC, DeVente J, Shlaes DM. Ceftazidime-resistant *Klebsiella pneumoniae* isolates recovered at the cleveland department of veterans affairs medical center. *Clin Infect Dis* 1996;**23**:118—24.
26. Bantar C, Vesco E, Heft C, Salamone F, Krayeski M, Gomez H. Replacement of broad-spectrum cephalosporins by piperacillin/tazobactam: impact on sustained high rates of bacterial resistance. *Antimicrob Agents Chemother* 2004;**48**:392—5.
27. Kuo SC, Chang SC, Wang HY, Lai JF, Chen PC, Shiau YR, et al. Emergence of extensively drug-resistant acinetobacter baumannii complex over 10 years: nationwide data from the Taiwan Surveillance of Antimicrobial Resistance (TSAR) program. *BMC Infect Dis* 2012;**12**:200.