Original Article

Safety and Effectiveness of Improving Carbapenem Use via Prospective Review and Feedback in a Multidisciplinary Antimicrobial Stewardship Programme

Christine B Teng, [1,2]*MSc(Clin Pharm), BCPS(AQ-ID)*, Tat Ming Ng, [2]*PharmD, BCPS(AQ-ID)*, Michelle W Tan, [2]*PharmD, BCPS*, Sock Hoon Tan, [2]*BSc(Pharm) (Hon), BCPS*, Mindy Tay, [2]*BSc(Pharm) (Hon)*, Shu Fang Lim, [2]*BSc(Pharm) (Hon)*, Li Min Ling, [3]*MBBS, MRCP*, Brenda S Ang, [3]*MBBS, MPH, FAMS*, David C Lye, [3,4]*MBBS, FRACP, FAMS*

Abstract

Introduction: Antimicrobial stewardship programmes (ASP) can reduce antibiotic use but patient safety concerns exist. We evaluated the safety of prospective carbapenem review and feedback and its impact on carbapenem use and patient outcomes. Materials and Methods: After 3 months implementation of our ASP, we compared patients with and without acceptance of ASP recommendations on the use of carbapenems. Primary outcome was 30-day mortality. Secondary outcomes included duration of carbapenem use, length of hospitalisation, clinical response, microbiological clearance, 30-day re-admission and mortality at discharge. Results: Of 226 recommendations for 183 patients, 59.3% was accepted. De-escalation, switching to oral antibiotics and antibiotic cessation comprised 72% of recommendations. Patients with acceptance of ASP recommendations had lower 30-day mortality and higher end-of-therapy clinical response despite shorter carbapenem duration (*P* <0.05). Predictors of 30-day mortality were Pitt bacteraemia score (adjusted odds ratio [aOR] 1.39, 95% confidence interval [CI], 1.11 to 1.74; *P* = 0.004) and non-acceptance of ASP recommendations (aOR 2.84, 95% CI, 1.21 to 6.64; *P* = 0.016). Conclusion: Our prospective carbapenem review and feedback mainly comprising of reducing carbapenem use is safe.

Ann Acad Med Singapore 2015;44:19-25

Key words: De-escalation, Multifaceted strategies, Pharmacists

Introduction

Multidrug-resistant (MDR) bacteria coupled with a rapidly diminishing antimicrobial pipeline has made antimicrobial resistance an international public health problem.[1-4] Control strategies of MDR bacteria include infection control and antimicrobial stewardship programmes (ASP).[2] The Infectious Diseases Society of America (IDSA) and the Society for Healthcare Epidemiology of America (SHEA) have proposed guidelines for ASP.[5] A recent Cochrane Review demonstrated the effectiveness of ASP in reducing antimicrobial usage and incidence of MDR Gram-negative and *Clostridium difficile* infection.[6]

In Singapore, healthcare-associated infections secondary to MDR bacteria, especially methicillin-resistant *Staphylococcus aureus* and MDR Gram-negatives, is a major concern.[7] Tan Tock Seng Hospital (TTSH), a 1400-bed university teaching hospital in Singapore, established its ASP in January 2009. At the end of 2008, 49% of *Staphylococcus aureus* were methicillin resistant, extended-spectrum beta-lactamases (ESBLs) was detected in 29% of *Escherichia coli* and 40% of *Klebsiella pneumoniae*, and carbapenem resistance was detected in 17% of *Pseudomonas aeruginosa* and 70% of *Acinetobacter baumannii*. A 1-day point prevalence audit of carbapenem use in the 3 largest public hospitals in Singapore including TTSH revealed inappropriate use in 38%. These included failure to de-escalate to a narrow spectrum antibiotic in 36% and non-compliance with hospital carbapenem use criteria in another 30%.[8]

One of the key measures adopted by our ASP is prospective review and feedback on all new carbapenem orders. However, carbapenems are often used in the treatment

[1]Department of Pharmacy, National University of Singapore, Singapore
[2]Department of Pharmacy, Tan Tock Seng Hospital, Singapore
[3]Department of Infectious Diseases, Tan Tock Seng Hospital, Singapore
[4]Yong Loo Lin School of Medicine, National University of Singapore, Singapore
Address for Correspondence:Ms Christine Teng, Department of Pharmacy, Faculty of Science, 18 Science Drive 4, Singapore 117543; Dr Ng Tat Ming, Pharmacy Department, 11 Jalan Tan Tock Seng, Singapore 308433.
Email: christeng@nus.edu.sg; Tat_Ming_Ng@ttsh.com.sg

of serious healthcare-associated infections, and ESBLs are prevalent among healthcare-associated *E. coli* and *K. pneumoniae*, 2 common Gram-negative bacteria in TTSH. Against this background of endemicity with ESBL-producing Enterobacteriaceae with high baseline rates of empiric carbapenem usage, an ASP strategy of prospective review and feedback on carbapenems needs to demonstrate effectiveness and safety. While the Cochrane Review on ASP demonstrated diminished MDR Gram-negative and *C. difficile* infection rates, 4 of 5 studies reporting mortality as a clinical outcome found a non-significant trend towards increased mortality.[6]

In this study, we aim to evaluate the acceptance and safety of ASP recommendation on prospective review and feedback on all carbapenems in our institution.

Materials and Methods

Description of Our Multifaceted, Multidisciplinary ASP

Our ASP was approved by the TTSH Medical Board in January 2009. An ASP committee comprising members from every clinical department, pharmacy, microbiology, infectious diseases (ID), information technology and clinical quality was formed. Our ASP initiatives include: (1) hospital empiric antibiotic guideline for 56 common or important ID conditions, with recommendations for first and second-line antibiotics, criteria for intravenous to oral conversion, total duration of antibiotic(s) and oral antibiotics for de-escalation with negative microbiological cultures, (2) antibiotic renal dose adjustment guidelines, (3) criteria for carbapenem and piperacillin-tazobactam use, (4) criteria for intravenous to oral conversion for highly bioavailable antibiotics, (5) criteria for meropenem to imipenem conversion, and (6) surgical antibiotic prophylaxis guidelines. These guidelines were drafted by an ASP team which comprised 3 ID physicians and 2 ASP pharmacists. They were then reviewed by the Department of ID and endorsed by the TTSH Drug and Therapeutics Committee. All these guidelines are accessible on our intranet via an icon on every hospital computer desktop.

At the inception of the programme, our ASP team visited every clinical department to explain and seek input on the ASP guidelines. Subsequently, ongoing activities include quarterly departmental reports of selected antimicrobial usage and incidence of MDR bacteria sent to heads of departments. An annual ASP update is also presented at a hospital grand round. In addition, an annotated hospital antibiogram is emailed to every hospital doctor annually and made available on our intranet along with the ASP guidelines. Our ASP was developed and implemented according to the IDSA/SHEA 2007 ASP guideline.[5]

As guidelines without active intervention may not be followed widely,[9] we implemented prospective review and feedback on all carbapenems available in TTSH, namely ertapenem, imipenem and meropenem, from April 2009. We reviewed all carbapenem orders according to our criteria for carbapenem use (Table 1). With pertinent positive microbiological cultures, the most narrow-spectrum antibiotic with in vitro activity appropriate for the site of infection is recommended. If patient improves with negative microbiological cultures, de-escalation to narrower spectrum intravenous or oral antibiotic(s) is recommended for the likely ID condition. De-escalation is recommended once patient fulfills pre-specified criteria for clinical stability (Table 1). Patients who fail to improve despite use of carbapenems are referred to the ASP ID physician and recommendations on alternative diagnoses, further investigations and treatment are provided.

Overview of the Prospective Review and Feedback Workflow

The carbapenem order is reviewed initially by the ward pharmacist who performs the initial intervention as indicated. This is escalated to the ASP pharmacist, and subsequently the ID physician, when initial recommendations are not accepted. The ward pharmacists (1 to 2 on each ward), ASP pharmacists (2 full-time equivalents, (FTE)) and ID physicians (0.5 FTE, 1 out of 3 on duty each day) conduct reviews and provide recommendations on every week day during office hours (8 am to 5 pm). Cases that require ID physician review are presented by ASP pharmacists during daily ASP rounds. These rounds usually last for 2 to 3 hours in the afternoon and take place in the patients' wards so as to facilitate individual patient review and discussion with the primary care team. This review and escalation process takes place daily from the day of carbapenem initiation, unless it falls on a weekend or public holiday in which case the review will take place on the next working day, provided the patient is still receiving a carbapenem. Complicated cases may be referred directly to the ASP pharmacist or ID physician. Our ASP reviews the indication for antimicrobial use, renal dose adjustment, opportunity for culture-guided de-escalation, duration of therapy, conversion of meropenem to imipenem, and the need for formal ID consultation. Additional differential diagnoses, investigations, and adjunctive therapy (for example, removal of urinary or central venous catheters, drainage of infected collections) are also recommended, if applicable. All recommendations are entered into the patient's chart and often followed with discussion via telephone or in person with the primary care team.

Evaluation of Acceptance and Safety of Prospective Carbapenem Review and Feedback

To assess the acceptance and safety of ASP recommendation on prospective review and feedback on all carbapenems, we

Table 1. Criteria for Carbapenem Use and Clinical Stability

Empiric Use	Culture-Guided Use
Appropriate criteria A	**Appropriate criteria A**
1. Evidence of sepsis or septic shock (fever >38°C, increased white cell >$10x10^9$/L, or increased C-reactive protein) and 2. Clinically unwell (drowsy/confused, oxygen saturation <92%, systolic blood pressure <90 mmHg or respiratory rate >30 breaths/min) and 3a. Onset of infection: (i) Nosocomial (>48 hours after admission) or (ii) Healthcare-associated (previous admission ≤3 months) or 3b. Isolation of the following within last 3 months: (i) Extended spectrum beta-lactamase (ESBL)-producing Gram-negative bacteria or (ii) AmpC beta-lactamase-producing Gram-negative bacteria (e.g. *Enterobacter*, *Serratia*, *Citrobacter freundii*, *Proteus vulgaris*, *Providencia*, *Morganella*) or (iii) Gram-negative bacteria sensitive to only carbapenems	1. ESBL-producing Gram-negative bacteria or 2. Gram-negative bacteria sensitive only to carbapenem or 3. Non-ESBL-producing bacteria resistant to ceftriaxone and ceftazidime or 4. AmpC beta-lactamase-producing Gram-negative bacteria (e.g. *Enterobacter*, *Serratia*, *Citrobacter freundii*, *Proteus vulgaris*, *Providencia*, *Morganella*) with either: (i) Positive cultures at non-sterile sites resistant to ciprofloxacin and co-trimoxazole (ii) Positive cultures at sterile sites (blood, cerebrospinal fluid, bone) sensitive or resistant to ciprofloxacin and/or co-trimoxazole
Appropriate criteria B	**Appropriate criteria B**
1. Where carbapenem is recommended for empiric therapy in hospital empiric antibiotic guideline	1. Infections by susceptible organisms but use of penicillins and/or cephalosporins is precluded due to allergy and/or intolerance
Criteria of Clinical Stability for De-escalation:	
Consider de-escalation to narrower-spectrum intravenous or oral antibiotic(s) (according to microbiology results or hospital antibiotic guideline) when patient fulfills the following criteria: 1. Afebrile (temperature <38°C for 24 hours) 2. Inotropes are ceased if previously on inotropes 3. Systolic blood pressure returned to baseline or ≥100 mmHg 4. Off mechanical ventilations or fraction of inspired oxygen ≤0.4 5. Respiratory rate <25 breaths/minute and oxygen saturation >92% on room air 6. Reduction in white cell count (if available) 7. Reduction in C-reactive protein (if available)	

collected the following data prospectively on every patient with a carbapenem order reviewed by the ASP team from 1 April to 30 June 2009: age, gender, comorbidities for Charlson's comorbidity score,[10] clinical data for Pitt bacteraemia score at start of carbapenem use,[11] ID diagnosis as assessed by the primary medical team, admission and discharge dates, start and stop dates of carbapenems, dosing as well as reasons for use of carbapenems, renal function, microbiological and radiological reports, ASP recommendations and acceptance, adverse events from carbapenems, and mortality.

We compared patients with and without acceptance of ASP recommendations. The primary outcome was 30-day mortality from start date of carbapenem use, and secondary outcomes included (1) duration of carbapenem use, (2) length of hospitalisation from start of carbapenem use to discharge, (3) clinical response defined as improvement or resolution of signs and symptoms of initial infection at day 7 and end of therapy, (4) microbiological clearance at day 7, (5) 30-day re-admission, and (6) mortality at hospital discharge.

Statistical Analysis

Descriptive data was presented as mean ± standard deviation (SD), median and range, or percentages, as appropriate. Baseline patient variables and endpoints were compared between groups using Student t-test or Mann-Whitney U test for continuous variables, Chi-square or Fisher exact test for categorical variables, as appropriate. Univariate analysis was performed to evaluate predictive factors for 30-day mortality. Any variable with P <0.20 on univariate analysis was included in a logistic regression model to determine independent associations with 30-day mortality. Statistical analysis was performed using SPSS software version 19. All tests were 2-tailed and a P value <0.05 was regarded as statistically significant. This study was approved by our Institutional Review Board.

Results

In the 3 months after implementation of ASP, 656 courses of carbapenems were ordered, of which 498 were reviewed. Among these, there were 226 ASP recommendations by ward or ASP pharmacists or ID physicians for 183 patients. Our ASP recommendations included de-escalation in 54%; stopping antibiotic, optimising antibiotic and meropenem-to-imipenem conversion in 12% each; and switching to oral

antibiotics in 6% (Table 2). Mean acceptance rate of ASP recommendations was 59.3% (134/226 recommendations for 130/183 patients). The 3 most accepted recommendations pertained to antibiotic optimisation (with additional antibiotics to broaden coverage), de-escalation and switch to oral antibiotics at 66.7%, 65% and 61.5%, respectively.

Baseline demographic and clinical data including age, gender, Charlson's comorbidity and Pitt bacteraemia scores, and ID conditions were similar between patients with and without acceptance of ASP recommendation (Table 3). Patients with acceptance of ASP recommendation had significantly shorter median duration of carbapenem use (3 [range, 1 to 47] vs 7 [range, 1 to 36] days, P <0.001), higher end-of-therapy clinical response (116/130 [89.2%] vs 41/53 [77.4%], P = 0.04) and lower 30-day mortality (15/130 [11.5%] vs 14/53 [26.4%], P = 0.012) (Table 4).

There was no significant difference between patients without and with acceptance of ASP recommendation in 7-day clinical response (36/53 [67.9%] vs 98/130 [75.4%], P = 0.301), mortality at hospital discharge (16/53 [30.2%] vs 24/130 [18.5%], P = 0.082) and median duration of hospitalisation (15 [range, 1 to 236] vs 16 [range, 3 to 230] days, P = 0.564). After excluding patients who died within 30 days after discharge, rate of 30-day re-admission was similar between the 2 cohorts (11/37 [29.7%] vs 32/106 [30.1%], P = 0.958). Repeat microbiological culture was performed in 14 cases without acceptance of ASP recommendation and 27 cases with acceptance; the 7-day microbiological clearance rate was similar (10/14 [71.4%] vs 19/27 [70.4%], P = 0.876) (Table 4).

In the multivariate analysis for predictors of 30-day mortality, Pitt bacteraemia score (adjusted odds ratio [aOR] 1.39, 95% confidence interval [CI], 1.11 to 1.74; P = 0.004) and non-acceptance of ASP recommendation (aOR 2.84, 95% CI, 1.21 to 6.64; P = 0.016) were independently associated with increased risk of 30-day mortality. In the subgroup of patients whose ASP recommendation comprised de-escalation (n = 107), switch to oral antibiotics (n = 8) and stopping antibiotics (n = 19), 30-day mortality was 14/98 (14.3%) with acceptance of ASP recommendation versus 7/36 (19.4%) without acceptance of ASP recommendation (P = 0.467).

Discussion

Our ASP showed significant impact in improving appropriate carbapenem use which was associated with improved patient outcomes. This improvement occurred before the start of our computerised decision support system for electronic antibiotic prescription in September 2009.[12] A Cochrane Review documented the effectiveness of ASP in modifying antibiotic prescribing. These comprised 6 of 8 studies that increased active antibiotic treatment with controlled before-and-after (CBA) and randomised controlled trial (RCT) design, and 10 of 14 studies with CBA, cluster controlled trial and RCT design, and 26 of 33 studies with interrupted time series (ITS) design which decreased antibiotic use.[6]

The improved clinical outcome from our ASP is highly encouraging. Comparison of patients with and without acceptance of ASP recommendation in our prospective carbapenem review and feedback showed that patients with acceptance of ASP recommendation had higher end-of-therapy clinical response and lower 30-day mortality despite shorter duration of carbapenem use. Illness severity and non-acceptance of ASP recommendation were found to be independent predictors of 30-day mortality. These findings are in contrast to the Cochrane Review, where there was a trend to higher mortality in 4 of 5 studies and significantly higher re-admission in 1 of 4 studies that decreased antibiotic use.[6] The difference in mortality outcomes could be due to different target patient population, antibiotics and specific interventions studied. For example, all patients included in the study by Singh et al[13] were in intensive care units (ICUs), and 20% of patients included in the study by Fraser

Table 2. Types of ASP Recommendations and Acceptance Rates

Type of Recommendation	Ward Pharmacists	ASP Pharmacists	ID Physicians	Total	Total
	n = Accepted/Total (%)	n = Accepted/Total (%)	n = Accepted/Total (%)	n (% Total)	n = Accepted/Total (%)
Total	59/94 (62.8)	42/74 (56.8)	33/58 (56.9)	226 (100)	134/226 (59.3)
De-escalation	33/49	31/49	16/25	123 (54)	80/123 (65.0)
Stopping antibiotics	1/4	2/10	5/12	26 (12)	8/26 (30.8)
Antibiotic optimisation	10/17	5/6	3/4	27 (12)	18/27 (66.7)
Meropenem to imipenem conversion	11/17	0/1	4/8	26 (12)	15/26 (57.7)
Switch to oral antibiotics	1/2	3/6	4/5	13 (6)	8/13 (61.5)
Others	3/5	1/2	1/4	11 (5)	5/11 (45.5)

ASP: Antimicrobial stewardship programme; ID: Infectious disease

Table 3. Baseline Demographic and Clinical Characteristics of Patients with and without Acceptance of ASP Recommendations

Baseline Parameters	Not Accepted (n = 53)	Accepted (n = 130)	*P* Value
Median age, years (range)	70 (34 – 94)	74 (17 – 98)	0.311
Male gender, n (%)	26 (49.1)	63 (48.5)	0.942
Median Charlson's comorbidity score (range)	5 (0 – 12)	5 (0 – 12)	0.890
Median Pitt bacteremia score (range)	0 (0 – 5)	0 (0 – 12)	0.776
Critically ill (Pitt bacteraemia score ≥4), n (%)	4 (8)	8 (6)	0.747
Comorbidities, n (%)			
Hypertension	30 (57)	82 (63)	0.415
Diabetes mellitus	24 (45)	59 (43)	0.990
Dyslipidaemia	17 (32)	53 (41)	0.272
Site of infections, n (%)			
Respiratory	16 (30)	45 (35)	0.564
Intra-abdominal	2 (4)	8 (6)	0.726
Skin/soft tissue	4 (8)	6 (5)	0.479
Hepatobiliary	1 (2)	11 (8)	0.103
Urinary	26 (49)	55 (42)	0.404
Sepsis of unknown source	3 (6)	2 (2)	0.147
Others	1 (2)	3 (2)	0.990

Data are number (%) of patients, unless otherwise indicated. For median values, minimum and maximum values are in parentheses.
ASP: Antimicrobial stewardship programme

Table 4. Outcomes of Patients with and without Acceptance of ASP Recommendations

Outcomes	Not Accepted (n = 53)	Accepted (n =130)	*P* Value
Median days of index carbapenem (range)	7 (1 – 36)	3 (1 – 47)	<0.001
7-day clinical response, n (%)	36 (67.9)	98 (75.4)	0.301
End of therapy clinical response, n (%)	41 (77.4)	116 (89.2)	0.040
7-day microbiological response, n (%)	10/14 (71.4)	19/27 (70.4)	0.876
Mortality at hospital discharge, n (%)	16 (30.2)	24 (18.5)	0.082
30-day mortality, n (%)	14 (26.4)	15 (11.5)	0.012
30-day re-admission,* n (%)	11/37 (29.7)	32/106 (30.1)	0.958
Median days of hospitalisation (range)	15 (1 – 236)	16 (3 – 230)	0.564

*Excluded patients who died within 30 days after discharge

et al[14] were haematology-oncology patients. However, only 7.7% of our patients were in ICUs and none were haematology-oncology patients. Reassuringly, our study did not find higher risk for 30-day re-admission.

Despite prospective review and feedback by an ID physician, overall acceptance of our ASP recommendation was relatively low at 59.3%. Anecdotally, many doctors were concerned about the safety of stopping carbapenems in their sick patients. Our evaluation showed that, to the contrary, in patients who achieved clinical stability, it was safe to de-escalate carbapenems when usage is not indicated by microbiological data. Interestingly, while it was not surprising that acceptance rate was more reasonable when we recommended antibiotic optimisation (66.7%) and substitution of meropenem with imipenem (57.7%), acceptance was higher when we advised de-escalation to a narrower spectrum intravenous antibiotic (65%) or oral antibiotic (61.5%) versus cessation of antibiotic (30.8%).

Strategically, ASP may be more effective if short-course de-escalation is adopted similar to the 3-day ciprofloxacin for patients at low risk of ventilator-associated pneumonia.[13]

Prospective review and feedback has been found to be a highly effective strategy in changing prescribing behaviour, albeit labour-intensive.[14-17] We invested in extensive educational efforts in developing and disseminating our ASP guidelines with the hope of achieving earlier appropriate carbapenem use. Inadequate empiric antibiotic is a risk factor for mortality in serious infections in a recent meta-analysis of prospective observational studies.[18] With high rates of ESBLs in our Enterobacteriaceae, early empiric carbapenem in sick septic patients may be appropriate, followed by de-escalation or discontinuation with clinical improvement and microbiological results.[19] Increasingly shorter duration of antibiotics may be adequate for nosocomial pneumonia,[20-22] procalcitonin-guided antibiotic therapy in community-acquired pneumonia[23,24] and sepsis in ICUs.[25,26]

Our study suggest the effectiveness of non-specialised ward pharmacists in implementing ASP using clearly defined criteria in ASP guidelines developed with broad consultation and endorsement by hospital senior management and medical heads of department. The acceptance rate of ward pharmacists' ASP recommendations was 62.8% (Table 2). ASP pharmacists and physicians are scarce resources. We run our hospital-wide ASP with only 2 full-time ASP pharmacists. Specialised pharmacists have been effective in ASP,[27,28] anticoagulation service[29] and heart failure clinics.[30] Our study provided evidence that non-specialised ward pharmacists may be supported to run ASP with a smaller number of ASP pharmacists and ID physicians.

We were able to achieve a 76% review rate of all carbapenem prescribed in the study period. We did not capture specific reasons for courses that were not reviewed. However, due to the inherent workflow of our ASP, a possible reason was the initiation of carbapenems over the weekend or after office hours; patients were no longer receiving the carbapenem when ASP review was to take place during the next working day.

A strength of our study is that we adjusted for potential confounders for comorbidity and illness severity for 30-day mortality by using Charlson's comorbidity and Pitt bacteraemia scores respectively. Pitt bacteremia score has been validated against APACHE II in sepsis in intensive care.[11] Although one of the key rationales for ASP is reducing antibiotic resistance and collateral damage from inappropriate antibiotic use, a limitation of our study is that we did not collect such data. We hope to be able to assess these outcomes in future studies.

Conclusion

Our study showed that a multidisciplinary ASP with core strategies of evidence-based ASP guidelines and prospective review and feedback of carbapenem use led to appropriate and shorter duration of carbapenem use with better clinical response and lower mortality. Importantly, de-escalation of carbapenem appeared to be safe in patients who achieved clinical stability.

Acknowledgements

This work was supported by the National University of Singapore (WBS- R-148-000-112-133 to C.B.T.). It had been presented in part at the 50th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), 12-15 September 2010; Boston, MD. The authors would like to thank Mr Keith Wong for assistance in the collection of data for this study and the TTSH Ward Pharmacists for their commitment and partnership in the stewardship of appropriate antimicrobial use in our hospitalised patients.

REFERENCES

1. Spellberg B, Guidos R, Gilbert D, Bradley J, Boucher HW, Scheld WM, et al. The epidemic of antibiotic-resistant infections: a call to action for the medical community from the Infectious Diseases Society of America. Clin Infect Dis 2008;46:155-64.
2. Siegel JD, Rhinehart E, Jackson M, Chiarello L. The Healthcare Infection Control Practices Advisory Committee. Management of Multidrug-Resistant Organisms In Healthcare Settings, 2006. Centers for Disease Control and Infection. Available from: http://www.cdc.gov/ncidod/dhqp/pdf/ar/mdroGuideline2006.pdf. Accessed 20 August 2011.
3. White AR on behalf of the BSAC Working Party on The Urgent Need: Regenerating Antibacterial Drug Discovery and Development. Effective antibacterials: at what cost? The economics of antibacterial resistance and its control. J Antimicrob Chemother 2011;66:1948-53.
4. ECDC/EMEA Joint Technical Report. The bacterial challenge: time to react. A call to narrow the gap between multidrug-resistant bacteria in the EU and the development of new antibacterial agents. Stockholm: European Centre for Disease Prevention and Control; 2009 Sep. 2009. Report No.: EMEA/576176/2009.
5. Dellit TH, Owens RC, McGowan JE Jr, Gerding DN, Weinstein RA, Burke JP, et al. Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America guidelines for developing an institutional program to enhance antimicrobial stewardship. Clin Infect Dis 2007;44:159-77.
6. Davey P, Brown E, Fenelon L, Finch R, Gould I, Hartmen G, et al. Interventions to improve antibiotic prescribing practices for hospital inpatients. Cochrane Database Syst Rev 2005;4:CD003543.
7. Hsu LY, Tan TY, Jureen R, Koh TH, Krishnan P, Tzer-Pin Lin R, et al. Antimicrobial drug resistance in Singapore hospitals. Emerg Infect Dis 2007;13:1944-7.

8. Liew YX, Lee W, Kwa AL, Lye DC, Yeo CL, Hsu LY. Inappropriate carbapenem use in Singapore public hospitals: opportunities for antimicrobial stewardship. Int J Antimicrob Agents 2011;37:87-8.
9. De Souza V, MacFarlane A, Murphy AW, Hanahoe B, Barber A, Cormican M. A qualitative study of factors influencing antimicrobial prescribing by non-consultant hospital doctors. J Antimicrob Chemother 2006;58:840-3.
10. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987;40:373-83.
11. Rhee JY, Kwon KT, Ki HK, Shin SY, Jung DS, Chung DR, et al. Scoring systems for prediction of mortality in patients with intensive care unit-acquired sepsis: a comparison of the Pitt bacteremia score and the Acute Physiology and Chronic Health Evaluation II scoring systems. Shock 2009;31:146-50.
12. Ng T, Teng CB, Ling L, Ang B, Leo YS, Lye D. A Novel, Interactive, Point-of-care Computerized Decision Support for Antibiotic Prescription is Safe and Effective. In: Program and abstract of the 50th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC); 2010 Sep 12-15; Boston, MD.
13. Singh N, Rogers P, Atwood CW, Wagener MM, Yu VL. Short-course empiric antibiotic therapy for patients with pulmonary infiltrates in the intensive care unit. A proposed solution for indiscriminate antibiotic prescription. Am J Respir Crit Care Med 2000;162:505-11.
14. Fraser GL, Stogsdill P, Dickens JD, Jr, Wennberg DE, Smith RP, Jr, Prato BS. Antibiotic optimization. An evaluation of patient safety and economic outcomes. Arch Intern Med 1997;157:1689-94.
15. LaRocco A, Jr. Concurrent antibiotic review programs–a role for infectious diseases specialists at small community hospitals. Clin Infect Dis 2003;37:742-3.
16. Solomon DH, Van Houten L, Glynn RJ, Baden L, Curtis K, Schrager H, et al. Academic detailing to improve use of broad-spectrum antibiotics at an academic medical center. Arch Intern Med 2001;161:1897-902.
17. Carling P, Fung T, Killion A, Terrin N, Barza M. Favorable impact of a multidisciplinary antibiotic management program conducted during 7 years. Infect Control Hosp Epidemiol 2003;24:699-706.
18. Paul M, Shani V, Muchtar E, Kariv G, Robenshtok E, Leibovici L. Systematic review and meta-analysis of the efficacy of appropriate empiric antibiotic therapy for sepsis. Antimicrob Agents Chemother 2010;54:4851-63.
19. Deresinski S. Principles of antibiotic therapy in severe infections: optimizing the therapeutic approach by use of laboratory and clinical data. Clin Infect Dis 2007;45 Suppl 3:S177-83.
20. Kollef MH, Kollef KE. Antibiotic utilization and outcomes for patients with clinically suspected ventilator-associated pneumonia and negative quantitative BAL culture results. Chest 2005;128:2706-13.
21. Micek ST, Ward S, Fraser VJ, Kollef MH. A randomized controlled trial of an antibiotic discontinuation policy for clinically suspected ventilator-associated pneumonia. Chest 2004;125:1791-9.
22. Chastre J, Wolff M, Fagon JY, Chevret S, Thomas F, Wermert D, et al. Comparison of 8 vs 15 days of antibiotic therapy for ventilator-associated pneumonia in adults: a randomized trial. JAMA 2003;290:2588-98.
23. Christ-Crain M, Stolz D, Bingisser R, Müller C, Miedinger D, Huber PR, et al. Procalcitonin guidance of antibiotic therapy in community-acquired pneumonia: a randomized trial. Am J Respir Crit Care Med 2006;174:84-93.
24. Schuetz P, Christ-Crain M, Wolbers M, Schild U, Thomann R, Falconnier C, et al. Procalcitonin guided antibiotic therapy and hospitalization in patients with lower respiratory tract infections: a prospective, multicenter, randomized controlled trial. BMC Health Services Research 2007;7:102.
25. Bouadma L, Luyt CE, Tubach F, Cracco C, Alvarez A, Schwebel C, et al. Use of procalcitonin to reduce patients' exposure to antibiotics in intensive care units (PRORATA trial): a multicentre randomised controlled trial. Lancet 2010;375:463-74.
26. Nobre V, Harbarth S, Graf JD, Rohner P, Pugin J. Use of procalcitonin to shorten antibiotic treatment duration in septic patients: a randomized trial. Am J Respir Crit Care Med 2008;177:498-505.
27. Gentry CA, Greenfield RA, Slater LN, Wack M, Huycke MM. Outcomes of an antimicrobial control program in a teaching hospital. American Journal of Health-System Pharmacy 2000;57:268-74.
28. Hand K. Antibiotic pharmacists in the ascendancy. J Antimicrob Chemother 2007;60 (Suppl 1):i73-6.
29. Tschol N, Lai DK, Tilley JA, Wong H, Brown GR. Comparison of physician- and pharmacist-managed warfarin sodium treatment in open heart surgery patients. Can J Cardiol 2003;19:1413-7.
30. Koshman SL, Charrois TL, Simpson SH, McAlister FA, Tsuyuki RT. Pharmacist care of patients with heart failure: a systematic review of randomized trials. Arch Intern Med 2008;168:687-94.