Antibiotic stewardship program in Intensive Care Unit: First report from Iran

Ghoncheh Vahidi, Mostafa Mohammadi1, Lida Shojaei2, Masoud Ramezani1, Sirus Jafari3, Hossein Khalili

ABSTRACT

Introduction: Few data regarding antibiotic stewardship programs in critically ill patients are available. In the present study, the consequence of changing an empirical antibiotic regimen from a carbapenem (meropenem) to a noncarbapenem antibiotic (piperacillin-tazobactam) was evaluated in critically ill patients with a suspicion of sepsis.

Methods: This open-label randomized clinical trial was conducted during May 2015–January 2017 at the general Intensive Care Unit of the Imam Khomeini Hospital Complex, Tehran, Iran. In this study, a carbapenem (meropenem) or a noncarbapenem (piperacillin-tazobactam) antibiotic was considered as an empirical antibiotic regimen in 100 critically ill patients with a suspicion of sepsis. Clinical response and bacterial eradication were defined as primary and secondary outcomes of the study, respectively. Chi-square, Mann–Whitney, and independent sample t-tests were used for comparing variables between the groups. ANOVA was used to compare changes in the mean differences of parameters between the groups. Meaningful difference was indicated as \(P \leq 0.05\).

Results: During the first 72 h of the antibiotic course, the number of patients with clinical response was comparable between piperacillin-tazobactam and meropenem groups (21 [42%] and 25 [50%], respectively, \(P = 0.31\)). Also, at this time, microbial eradication occurred in 13 (54.16%) and 9 (40.90%) patients in piperacillin-tazobactam and meropenem groups, respectively \(P = 0.67\).

Conclusions: Using a carbapenem (meropenem) instead of a noncarbapenem (piperacillin-tazobactam) as an empirical antibiotic regimen did not affect clinical response and bacterial eradication rates in critically ill patients with a suspicion of sepsis.

Key Words: Antibiotic stewardship, meropenem, piperacillin-tazobactam, sepsis

INTRODUCTION

Antibiotics’ discovery was a breakthrough in medicine; lethal infections are being treated easily nowadays.[1] However, extensive use of antibiotics cause pivotal problems including increasing antimicrobial resistance.[2,3] In recent three decades, a dramatic increment in multidrug-resistant (MDR) organisms among hospitalized patients and in communities has been detected. Methicillin-resistant Staphylococcus aureus (MRSA), vancomycin-resistant enterococci, extended-spectrum beta-lactamases (ESBLs)-producing organisms, and carbapenem-resistant enterobacteriaceae (CRE) are now troublesome pathogens.[4] A mortality rate of 58.2% was reported in Iranian patients with MDR Gram-negative infections.[5]

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: reprints@medknow.com

Cite this article as: Vahidi G, Mohammadi M, Shojaei L, Ramezani M, Jafari S, Khalili H. Antibiotic stewardship program in intensive care unit: First report from Iran. Int J Crit Illn Inj Sci 2018;8:83-9.
Increasing resistance to antibiotics, especially carbapenems, led to applying antibiotic stewardship programs in hospitals. Nevertheless, there are few available studies in respect of the final clinical outcome of antimicrobial stewardship programs. The most important factor that should be considered when assessing the final clinical outcome are clinical evaluation of the patients after antibiotic therapy. Few data regarding antibiotic stewardship programs in critically ill patients are available. The goal of this study was to evaluate the consequence of changing an empirical antibiotic regimen from a carbapenem (meropenem) to a noncarbapenem antibiotic (piperacillin-tazobactam) in critically ill patients with a suspicion of sepsis.

**METHODS**

This open-label randomized clinical trial was conducted during May 2015-January 2017 at the general Intensive Care Unit (ICU) of the Imam Khomeini Hospital Complex, Tehran, Iran. The ethical committee of Tehran University of Medical Sciences approved the study protocol and was registered with ID number: IR. TUMS.REC.1395.2751. All the recruited patients or one of their first-degree family members signed informed consent of the study.

Adult (18–65 years old) patients admitted to the ICU for respiratory or hemodynamic supports following medical problems or surgery were screened. Patients with a suspicion of sepsis who were candidates for empirical antibiotic therapy were recruited. New definition of sepsis and diagnostic criteria were applied in this study. A broad-spectrum antibiotic with antipseudomonal activity was considered as empirical therapy. In patients with risk factors for Gram-positive infections including MRSA, vancomycin was also considered.

In this study, a carbapenem (meropenem) or a noncarbapenem (piperacillin-tazobactam) antibiotic was considered as an empiric antibiotic in patients with a suspicion of sepsis. Immunodeficient individuals and patients with a history of hospitalization or broad-spectrum antibiotic therapy in recent 3 months, allergy to beta-lactam antibiotics, and those with a suspicion of cerebral infections were excluded from the study.

During the study period, 100 patients fulfilled the inclusion criteria and (based on the simple randomization method) were randomly assigned to receive meropenem (50 patients) or piperacillin-tazobactam (50 patients). Patients in the meropenem group received meropenem with a daily dose of 1 g every 8 h. Each dose of meropenem was administered as intravenous infusion during 3 h. Piperacillin-tazobactam, 4.5 g every 8 h (each dose infused over 4 h), was considered for parallel group.

Considering the role of early antibiotic therapy in critically ill patients with a suspicion of sepsis, the empirical regimens were started as soon as possible (during 2 h), and after that, required biological samples for microbiological study (2 blood samples from 2 separate sites with 1 h interval, urine sample, tracheal discharge, and wound sample, if indicated) were collected. Antibiotic dosages were adjusted based on the patients’ renal function. The empirical antibiotic regimens were re-evaluated after 72 h based on the microbiological culture results and clinical status of the patients.

Patients’ demographic data (age, sex, and weight), underlying diseases, drug history, cause of hospital admission, cause of ICU admission, vital signs, hemodynamic and respiratory parameters (heart rate, respiratory rate, blood pressure, pH, PaO₂, PaCO₂, and O₂ saturation), laboratory parameters (complete blood count, electrolytes, renal function tests, erythrocyte sedimentation rate [ESR], C-reactive protein [CRP], and procalcitonin), Acute Physiology and Chronic Health Evaluation II (APACHE II) score, Sequential Organ Failure Assessment (SOFA) score, and Clinical Pulmonary Infection Score (CPIS) were collected from the patients’ medical charts or daily ICU monitoring sheets.

The recruited patients were closely monitored, and changes in vital signs and respiratory, hemodynamic, and laboratory parameters and clinical status were recorded. Duration of antibiotic therapy was defined based on the initial clinical response, culture results, isolated microorganisms, and complications during the ICU course.

Clinical response was defined as the primary outcome of the study. Clinical status of the patients and changes in signs of sepsis including vital signs (fever, tachypnea, and tachycardia), hemodynamic parameters (hypotension), laboratory findings (leukocytosis or leukopenia, and thrombocytopenia), inflammatory biomarkers (ESR, CRP, and procalcitonin), oxygenation parameters (PaO₂, PaCO₂, O₂ saturation, blood pH, and PO₂/FIO₂), radiological findings, and APACHE II, SOFA, and CPIS scores were considered for the assessment of response to the therapy.

Microbiological response was considered as the secondary outcome of the study. Sampling was repeated 72h after starting the antibiotics. In patients who cultures remained positive, the antibiotic regimen was changed and the cultures were repeated. Microbiological response was defined as bacterial eradication.

The recruited patients were followed up for 4 weeks. Duration of antibiotic therapy and 28-day mortality were considered as tertiary end points of the study.
Data analysis was performed by Statistical Package for the Social Sciences (SPSS) version 21 (IBM, Chicago IL, USA). Normally distributed data were detected according to Kolmogorov–Smirnov test. All quantitative data were expressed as mean ± standard deviation or median (interquartile range: 25–75). Categorical variable was presented as percentage. Qualitative data were announced as percentage. Chi-square, Mann–Whitney, and independent sample t-tests were used for comparing variables between the groups. ANOVA was used to compare changes in mean differences of parameters between the groups. Meaningful difference was indicated as $P \leq 0.05$.

**RESULTS**

During the study period, 136 patients were screened and 36 patients were not included due to positive history for hospitalization, broad-spectrum antibiotic therapy during the past 3 months, and allergy to beta-lactams. Finally, 100 patients were recruited. Baseline characteristics of patients between the groups were comparable [Table 1].

Vital signs; laboratory parameters; APACH and SOFA scores; and inflammatory biomarkers including serum CRP, procalcitonin, and Cr were comparable between the groups. However, patients in piperacillin-tazobactam group had higher ESR level than those in meropenem group ($P = 0.001$) [Table 2].

Respiratory tract was the most common origin of sepsis followed by abdomen, bloodstream, and urinary tract. There was no significant difference between the groups regarding the origin of sepsis ($P = 0.17$). Cultures of the biological samples were negative in 49 (49%) patients. Acinetobacter baumannii, Klebsiella pneumonia, and Pseudomonas aeruginosa were the common isolated microorganisms. Two groups were comparable regarding frequency of these isolates [Table 3]. Based on the antibiotic susceptibility tests, all A. baumannii isolates were resistant to piperacillin-tazobactam. Most of these isolates were sensitive to meropenem. Most P. aeruginosa isolates were resistant to piperacillin-tazobactam and meropenem. Although all K. pneumonia isolates were resistant to piperacillin-tazobactam, they were sensitive to meropenem [Table 4].

Based on the cultures and antibiotic susceptibility patterns, the antibiotic regimen was changed to meropenem in 19 (38%) patients in piperacillin-tazobactam group. In one patient with piperacillin-tazobactam-resistant isolate, antibiotic regimen did not change due to appropriate clinical response. After the culture results became ready, vancomycin, ciprofloxacin, amikacin, and colistin were the common antibiotics that were added to the antibiotic regimens [Table 5].

Although piperacillin-tazobactam was changed to meropenem in 19 patients based on the results of antibiotic susceptibility tests, during the first 72 h of the antibiotic course, the number of patients with clinical response was comparable between piperacillin-tazobactam and meropenem groups (21 [42%] and 25 [50%], respectively, $P = 0.31$). Also at this time, microbial eradication occurred in 13 (54.16%) and 9 (40.90%) of patients in piperacillin-tazobactam and meropenem groups, respectively ($P = 0.67$). However, the remaining cultures became negative during the second 72 h of treatment course or following changing the antibiotic regimens.

Changes in serum procalcitonin levels and SOFA score during the antibiotic therapy were significantly different between meropenem and piperacillin-tazobactam groups [Table 6].

In patients whose cultures became negative after 72 h, duration of antibiotic therapy was 7 days. Longer antibiotic therapy was considered for other patients. In culture-negative patients, duration of antibiotic therapy was determined based on the clinical status.

Duration of antibiotic therapy in piperacillin-tazobactam and meropenem groups was 13 ± 3.81 and 11 ± 4.22 days, respectively ($P = 0.19$). Considering ICU outcome, 33 (66%) and 27 (54%) patients in piperacillin-tazobactam and meropenem groups, respectively, were discharged from the ICU. Mortality rate was comparable between the piperacillin-tazobactam and meropenem groups (34% and 46%, respectively, $P = 0.15$).

| Table 1: Demographic and baseline characteristics of patients |
|-------------------------------------------------------------|
| Parameter | Piperacillin-tazobactam group (n=50), n (%) | Meropenem group (n=50), n (%) | $P$ |
|----------------|---------------------------------------------|-------------------------------|-----|
| Gender | | | |
| Male | 33/50 (66) | 28/50 (56) | 0.20 |
| Female | 17/50 (34) | 22/50 (44) | |
| Age (years) | | | |
| | 55±74 ± 19/29 | 53±42 ± 18/37 | 0.33 |
| Baseline diseases | | | |
| None | 20/50 (40) | 24/50 (48) | 0.73 |
| Cardiovascular diseases | | | |
| None | 12/50 (24) | 14/50 (28) | |
| Renal diseases | | | |
| None | 2/50 (4) | 3/50 (6) | |
| Neurologic diseases | | | |
| None | 3/50 (6) | 2/50 (4) | |
| Endocrine diseases | | | |
| None | 11/50 (22) | 6/50 (12) | |
| Autoimmune diseases | | | |
| None | 2/50 (4) | 1/50 (2) | |
| Cause of hospital admission | | | |
| Surgery | 30/50 (60) | 30/50 (60) | 0.09 |
| Baseline diseases | 9/50 (18) | 15/50 (30) | |
| Autoimmune diseases | 4/50 (8) | 2/50 (4) | |
| Infections | 3/50 (6) | 2/50 (4) | |
| Neurologic diseases | 0/50 (0) | 1/50 (2) | |
| Drug toxicity | 4/50 (4) | 0/50 (0) | |
| Cause of ICU admission | | | |
| Respiratory distress | 20/50 (40) | 17/50 (34) | 0.36 |
| Hemodynamic imbalance | 30/50 (60) | 31/50 (62) | |
| Deep-vein thrombosis | 0/50 (0) | 2/50 (4) | |

ICU: Intensive care unit
DISCUSSION

In this study, the consequence of considering a noncarbapenem antibiotic (piperacillin-tazobactam) as empirical antimicrobial therapy in critically ill patients with a suspicion of sepsis was compared with a carbapenem antibiotic (meropenem). Although piperacillin-tazobactam was changed to meropenem in a considerable percentage of patients, overall, clinical and microbiological responses and 28-day ICU mortality were comparable between patients who received meropenem or piperacillin-tazobactam as empiric antibiotic.

Effectiveness of noncarbapenem antibiotics as empiric therapy was compared with carbapenems in different populations. A prospective study in Japan in 2016 compared piperacillin-tazobactam and meropenem as an empirical antibiotic regimen for patients with neutropenic
Carbapenems are in vitro 6/50 0.44 The same trend 0/50 in vitro 0.06 Day 0 versus day 14 In an 0.60 In another similar study in 2014 in Turkey, meropenem was reported in our country as well. Carabapenems are the treatment of choice for ESBL-producing organisms. However, resistance against carbapenems is significantly increasing worldwide.

Looking for alternative strategies, some available data suggest older agents including polymyxins, fosfomycin, and aminoglycosides, which have their own concerning obstacles such as efficacy and/or toxicity. However, administration of these antibiotics as monotherapy might not be effective enough against CRE isolates. Hence, it would be worthwhile to consider suitable alternatives such as new β-lactam-β-lactamase inhibitors (BLBLIs).

ESBL-producing organisms might be sensitive to old BLBLIs such as piperacillin-tazobactam or amoxicillin-clavulanic acid. However, these antibiotics are not recommended for the treatment of serious infections of ESBL-producing organisms due to the inoculum effect.

In high bacterial load conditions, the efficacy of BLBLI antibiotics decreased significantly. In an in vitro evaluation, piperacillin-tazobactam did not have 99% bactericidal activity against 10^7 colony-forming unit/ml bacteria (high inoculum) in 8 h. In contrast, carbapenems had 99.9% bactericidal activity in 24 h. However, in animal studies, BLBLIs were less efficient than carbapenems, probably due to different pharmacokinetic and pharmacodynamic targets. Thus, it was suggested that BLBLIs may be more reasonable alternatives for low-inoculum infections, while carbapenems are still the treatment of choice specifically as an initial treatment in severe infections with probable high bacterial loads.

It should be considered that inoculum effect was proved as an in vitro finding, so this phenomenon may have no interference or undesirable effects in the in vivo studies. Therefore, it was suggested that BLBLIs and carbapenems may have the same efficiency against bloodstream infections for ESBL-producing organisms.

Despite the satisfactory results following treatment with carbapenems in recent studies, robust increment of resistance in Acinetobacter and Stenotrophomonas species raised considerable concerns. Empirical treatment with BLBLIs such as piperacillin-tazobactam not only successfully controlled infections of ESBL-producing organisms, but also led to preserving the susceptibility of these microorganisms.

Nowadays, serum inflammatory biomarkers are used in the antibiotic stewardship programs to deescalate the antibiotic regimens. Procalcitonin plays a beneficial role as a cost-effective inflammatory marker in making decisions regarding discontinuation or commencement of specific antibiotic treatment in ICU patients.
Antimicrobial stewardship plays a crucial role in modern medicine. It is a coordinated program that mainly focuses on choosing appropriate antibiotics, optimizing patient outcomes, decreasing the adverse effects of antibiotics, and above all the decline in drug resistance. Proper administration of the antimicrobial stewardship was cost saving. A suitable team which at least consists of an infectious disease specialist and a clinical pharmacist is an inevitable part of successful antimicrobial stewardship. Moreover, close collaboration with microbiologists and epidemiologists and specifically government is an additional necessity. De-escalation is a part of antimicrobial stewardship that means shifting from a broad-spectrum antibiotic to a narrow spectrum one. The Australian study which was done in 2005–2008 showed that the antimicrobial stewardship led to increase in the sensitivity of Gram-positive and Gram-negative microorganisms.

This study suffered from some main limitations including study design (open labeled), sample size, heterogeneity of patients, presence of different underlying diseases, concomitant antibiotics, and duration of follow-up.

CONCLUSIONS

Using a carbapenem (meropenem) instead of a noncarbapenem (piperacillin-tazobactam) as an empiric antibiotic did not affect early clinical response, bacterial eradication, and 28-day mortality in critically ill patients with a suspicion of sepsis. Well-designed, blinded, randomized clinical trials in critically ill patients are needed to confirm these findings.

Acknowledgments
The authors would like to thank the nursing staffs of general ICU of Imam Khomeini Hospital for their kind support.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

REFERENCES

1. Society for Healthcare Epidemiology of America, Infectious Diseases Society of America, Pediatric Infectious Diseases Society. Policy statement on antimicrobial stewardship by the Society for Healthcare Epidemiology of America (SHEA), the Infectious Diseases Society of America (IDSA), and the Pediatric Infectious Diseases Society (PIDS). Infect Control Hosp Epidemiol 2012;33:322-7.
2. Allenback GL. Survey of Antimicrobial Stewardship Practices in the Western United States: Successes and Challenges. UNLV Theses, Dissertations, Professional Papers, and Capstones; 2014. p. 2054. Available from: https://pdfs.semanticscholar.org/54bf/2d3be96d29c810fa0488c13 3018fa76c443c.pdf. [Last accessed on 2018 Jun 11].
3. Doron S, Davidson LE. Antimicrobial stewardship. Mayo Clin Proc 2011;86:1113-23.
4. Harris PN, Tambyah PA, Paterson DL. B-lactam and β-lactamase inhibitor combinations in the treatment of extended-spectrum β-lactamase producing enterobacteriaceae: Time for a reappraisal in the era of few antibiotic options? Lancet Infect Dis 2015;15:475-85.
5. Malekollahi M, Shojaei L, Khalili H, Doomaniou M. Clinical response and outcome in patients with multidrug resistant gram-negative infections. J Res Pharm Pract 2017;6:44-51.
6. Cucurci DJ; On Behalf of the Latin American Antibiotic use in Intensive Care Unit Group. Antibiotic prescription in Intensive Care Units in Latin America. Rev Argent Microbiol 2011;43:203-11.
7. Edwards S, Emms CE, Campbell HE. Systematic review comparing meropenem with imipenem plus cilastatin in the treatment of severe infections. Curr Med Res Opin 2005;21:785-94.
8. Thuong M, Shorten G, Zaazem P, Girou E, Soussy CJ, Brun-Buisson C, et al. 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. Morris AM. Antimicrobial stewardship programs: Appropriate measures and metrics to study their impact. Curr Treat Options Infect Dis 2014;6:101-12.
10. Morris AM, Brener S, Dresser L, Daneman N, Dellit TH, Avdic E, et al. Use of a structured panel process to define quality metrics for antimicrobial stewardship programs. Infect Control Hosp Epidemiol 2012;33:500-6.
11. Ibrahim OM, Polk RE. Antimicrobial use metrics and benchmarking to improve stewardship outcomes: Methodology, opportunities, and challenges. Infect Dis Clin North Am 2014;28:195-214.
12. Rhodes A, Evans LE, Alhazzani W, Levy MM, Antonelli M, Ferrer R, et al. Surviving sepsis campaign: International guidelines for management of sepsis and septic shock: 2016. Intensive Care Med 2017;43:304-77.
13. Liu C, Bayer A, Cosgrove SE, Daum RS, Fridkin SK, Gorwitz RJ, et al. Clinical practice guidelines by the Infectious Diseases Society of America for the treatment of methicillin-resistant Staphylococcus aureus infections in adults and children: Executive summary. Clin Infect Dis 2011;52:285-92.
14. Sano H, Kobayashi R, Suzuki D, Hori D, Kishimoto K, Kobayashi K, et al. A prospective randomized trial comparing piperacillin/tazobactam with meropenem as empirical antibiotic treatment of febrile neutropenic children and adolescents with hematologic and malignant disorders. Pediatr Blood Cancer 2017;64:e28360.
15. Sezgin G, Acipayam C, Ozkan A, Bayram I, Tanyeli A. Meropenem versus piperacillin-tazobactam as empiric therapy for febrile neutropenia in pediatric oncology patients. Asian Pac J Cancer Prev 2014;15:4549-53.
16. Yamamoto Y, Iizumikawa K, Morinaga Y, Nakamura S, Kurihara S, Inoueura Y, et al. Prospective randomized comparison study of piperacillin/tazobactam and meropenem for healthcare-associated pneumonia in Japan. J Infect Chemother 2013;19:291-8.
17. Oztoprak N, Piskin N, Aydemir H, Celebi G, Akduman D, Keskim AS, et al. Piperacillin-tazobactam versus carbapenem therapy with and without amikacin as empirical treatment of febrile neutropenia in cancer patients: Results of an open randomized trial at a university hospital. Jpn J Clin Oncol 2010;40:761-7.
18. Hirsch EB, Tan VH. Detection and treatment options for Klebsiella pneumoniae carbapenemases (KPCs): An emerging cause of multidrug-resistant infection. J Antimicrob Chemother 2010;65:1119-25.
19. Levy Hara G, Gould I, Endimiani A, Pardo PR, Alkousis G, Hsupeh PR, et al. Detection, treatment, and prevention of carbapenemase-producing Enterobacteriaceae: Recommendations from an International Working Group. J Chemother 2013;25:129-40.
20. Aminzadeh Z, Sadat Kashi M, Shabani M. Bacteriuria by extended-spectrum beta-lactamase-producing Escherichia coli and Klebsiella pneumoniae: Isolates in a governmental hospital in South of Tehran, Iran. Iran J Kidney Dis 2008;2:197-200.
21. Mehran Z, Bahar P, Arab-Halvai Z. High prevalence of carbapenem-resistant Enterobacteriaceae in a tertiary care hospital in Tehran, Iran. J Infect Dev Cities 2010;4:132-8.
22. Zavascki AP, Klee BO, Bulitta JB. Aminoglycosides against carbapenem-resistant Enterobacteriaceae in the critically ill: The pitfalls of aminoglycoside susceptibility. Expert Rev Anti Infect Ther 2017;15:519-26.
23. Morrill HJ, Pogue JM, Kaye KS, LaPlante KL. Treatment options for carbapenem-resistant Enterobacteriaceae infections. Open Forum Infect Dis 2015;2:ofv050.

24. López-Cerero L, Picón E, Morillo C, Hernández JR, Docobo F, Pachón J, et al. Comparative assessment of inoculum effects on the antimicrobial activity of amoxicillin-clavulanate and piperacillin-tazobactam with extended-spectrum beta-lactamase-producing and extended-spectrum beta-lactamase-non-producing Escherichia coli isolates. Clin Microbiol Infect 2010;16:132-6.

25. Burgess DS, Hall RG. In vitro killing of parenteral beta-lactams against standard and high inocula of extended-spectrum beta-lactamase and non-ESBL producing Klebsiella pneumoniae. Diagn Microbiol Infect Dis 2004;49:41-6.

26. Tamma PD, Rodriguez-Bano J. The use of noncarbapenem β-lactams for the treatment of extended-spectrum β-lactamase infections. Clin Infect Dis 2017;64:972-80.

27. Delitti 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.

28. Paterson DL, Singh N, Gayowski T, Marino IR. Fatal infection due to extended-spectrum beta-lactamase-producing Escherichia coli: Implications for antibiotic choice for spontaneous bacterial peritonitis. Clin Infect Dis 1999;28:683-4.

29. Go ES, Urban C, Burns J, Kreiswirth B, Eisner W, Mariano N, et al. Clinical and molecular epidemiology of Acinetobacter infections sensitive only to polymyxin B and sulbactam. Lancet 1994;344:1329-32.

30. Meyer KS, Urban C, Eagan JA, Berger BJ, Rahal JJ. Nosocomial outbreak of Klebsiella infection resistant to late-generation cephalosporins. Ann Intern Med 1993;119:353-8.

31. Haubitz S, Mueller B, Schuetz P. Streamlining antibiotic therapy with procalcitonin protocols: Consensus and controversies. Expert Rev Respir Med 2013;7:145-57.

32. Westwood M, Ramaekers B, Whiting P, Tomini F, Joore M, Armstrong N, et al. Procalcitonin testing to guide antibiotic therapy for the treatment of sepsis in intensive care settings and for suspected bacterial infection in emergency department settings: A systematic review and cost-effectiveness analysis. Health Technol Assess 2015;19:v-xxv, 1-236.

33. DiazGranados CA. Prospective audit for antimicrobial stewardship in intensive care: Impact on resistance and clinical outcomes. Am J Infect Control 2012;40:526-9.

34. Elligsen M, Walker SA, Pinto R, Simor A, Mubareka S, Rachlis A, et al. Audit and feedback to reduce broad-spectrum antibiotic use among Intensive Care Unit patients: A controlled interrupted time series analysis. Infect Control Hosp Epidemiol 2012;33:354-61.

35. Sick AC, Lehmann CU, Tamma PD, Lee CK, Agwu AL. Sustained savings from a longitudinal cost analysis of an internet-based preapproval antimicrobial stewardship program. Infect Control Hosp Epidemiol 2013;34:573-80.

36. Roberts RR, Hota B, Ahmad I, Scott RD 2nd, 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.

37. Griffith M, Postelnick M, Scheetz M. Antimicrobial stewardship programs: Methods of operation and suggested outcomes. Expert Rev Anti Infect Ther 2012;10:63-73.

38. Group SHASW. Guidelines for Antimicrobial Stewardship in Hospitals in Ireland: HSE Health Protection Surveillance Centre (HPSC); 2009. Available from: https://www.hpsc.ie/a-z/microbiologyantimicrobialresistance/infectioncontrolandhai/guidelines/File, 4116, en.pdf. [Last accessed on 2017 May 05].

39. Jary F, Kaiser JD, Henon T, Leroy J, Patry I, Blasco G, et al. Appropriate use of carbapenems in the Besançon university hospital. Med Mal Infect 2012;42:510-6.

40. Buising KL, Thursky KA, Robertson MB, Black JF, Street AC, Richards MJ, et al. Electronic antibiotic stewardship - Reduced consumption of broad-spectrum antibiotics using a computerized antimicrobial approval system in a hospital setting. J Antimicrob Chemother 2008;62:608-16.