Open Access Maced J Med Sci **electronic publication ahead of print,**
published on April 14, 2019 as https://doi.org/10.3889/oamjms.2019.223

ID Design Press, Skopje, Republic of Macedonia
Open Access Macedonian Journal of Medical Sciences.
https://doi.org/10.3889/oamjms.2019.223
eISSN: 1857-9655
Clinical Science

Resistance Trend, Antibiotic Utilization and Mortality in Patients with *E. coli* Bacteraemia

Amirreza Najmi[1], Fateme Karimi[1], Vijayanarayan Kunhikatta[1], Muralidhar Varma[2], Sreedharan Nair[1*]

[1]Department of Pharmacy Practice, Manipal College of Pharmaceutical Sciences, Manipal Academy of Higher Education, Manipal, Karnataka, India; [2]Department of Medicine, Kasturba Medical College, Manipal Academy of Higher Education, Manipal, Karnataka, India

Citation: Najmi A, Karimi F, Kunhikatta V, Varma M, Nair S. Resistance Trend, Antibiotic Utilization and Mortality in Patients with *E. coli* Bacteraemia. Open Access Maced J Med Sci. https://doi.org/10.3889/oamjms.2019.223

Keywords: Resistance pattern; E. coli; ESBL producing; Empirical therapy; Rational antibiotic use; Mortality

***Correspondence:** Sreedharan Nair. Department of Pharmacy Practice, Manipal College of Pharmaceutical Sciences, Manipal Academy of Higher Education, Manipal, Karnataka. E-mail: nair.sreedhar@manipal.edu

Received: 28-Jan-2019; **Revised:** 18-Mar-2019; **Accepted:** 19-Mar-2019; **Online first:** 14-Apr-2019

Funding: This research did not receive any financial support

Competing Interests: The authors have declared that no competing interests exist

Abstract

BACKGROUND: Incidence of bacteraemia and driving concerns about antibiotic resistance is increasing globally. Risk factors for developing antimicrobial resistance are antibiotic overuse, incorrect dosing and extended duration of administration.

AIM: This study was conducted to examine the prescription and susceptibility pattern of antibiotics in bacteraemia patients with ESBL producing and Non-ESBL-producing *E. coli* and their correlation with mortality.

METHODS: Data were collected from medical records of the patients aged 18 years and above, diagnosed with E. coli bacteremia from January 2013 through July 2017. Institutional ethics committee approval was obtained before the study (IEC 483/2017). Cumulative sensitivity/resistance pattern of isolated microorganisms and DDD/100 bed days of prescribed antibiotics were obtained.

RESULTS: 182 cases of *E. coli* bacteraemia were reviewed. 59.9% (n = 109) were male with an age range of 20-90 years. The mortality rate was 24.9% (n = 44). 55.5% (n = 101) of the isolated organisms were ESBL-producing. A high percentage of resistance to cephalosporins and fluoroquinolones were observed among the patients, and most of the identified isolates were sensitive to the aminoglycosides, carbapenems and β-lactam and β-lactamase inhibitor combinations (BLBLIs).

CONCLUSIONS: Frequent utilisation of the high-end antibiotics and increase in microorganism's resistance to different antibiotics can lead to a worrisome level. Local antibiotic resistance data and consumption policy are essential to prevent and slow down this process. We observed a descending resistance trend for amoxicillin-clavulanic acid combination in our setting to both the ESBL producing and non-producing.

Introduction

Antibiotic resistance can be considered as one of the most critical public health issues in the world [1]. There are different risk factors for developing antimicrobial resistance. Antibiotic overuse, incorrect dosing and extended duration of administration can be among the most important ones [1], [2], [3], [4]. We observe a more challenging situation in less developed countries. In several studies, the inappropriate antimicrobial prescription was observed among the primary care physicians [5], [6], [7], [8] and development of bacterial resistance increases the challenges faced by the physicians to treat the patients [9], [10], [11].

Pathogenic *Escherichia coli* (*E. coli*) can cause serious diseases, such as urinary tract infections(UTIs) and bacteraemia [12], [13], [14], and incidence of bacteraemia increasing globally [15]. Bacteria which can usually develop the more serious disease is ESBL (Extended-spectrum β-lactamases) producing *E. coli*. ESBLs are enzymes that can hydrolyse penicillins, aztreonam and cephalosporin's [16]. These ESBL producing bacteria showed lesser acceptable clinical outcome in comparison to susceptible (non-ESBL producing bacteria) bacteria [17], [18], [19], [21], which can be related to delay in

appropriate antimicrobial treatment to some extent [22], [23], [24]. The high rate of clinical successes was observed in existing literature with carbapenems administration for ESBL producing bacteria [25], [26], [27], [28]. On the other hand, the use of Cephalosporins [29] and β-lactam–β-lactamase inhibitor combinations [28], [30] have also been suggested recently with ESBL-positive isolates if MICs are below clinical breakpoints. Moderate to high in vitro activity of piperacillin-tazobactam (PTZ) against ESBLs is suggested by several studies [31], [32], [33]. Equivalence between PTZ and carbapenems in the treatment of ESBL infection was demonstrated in some studies [17].

This study was conducted to examine the prescription and susceptibility pattern of antibiotics in bacteraemia patients with ESBL producing and Non-ESBL-producing *E. coli* and their correlation with mortality. Based on the above background, this study focus on the resistance trend, antibiotic utilisation and mortality in patients with *E. coli* bacteraemia.

Material and Methods

In this cross-sectional study, we reviewed data obtained from 182 patients aged 18 years and above who had experienced bloodstream infection with *E. coli* during five years from Jan 2013 through Dec 2017. The Institutional Ethics Committee approval (IEC 483/2017) was obtained before the start of the study.

Bacteremia was defined as the presence of viable bacteria in the bloodstream [34]. Patients were excluded if the presence of *E. coli* was not confirmed by blood culture testing and through microbiology laboratory report. Antibiotic sensitivity results were obtained from the patient medical record [35].

The culture reports and antibiotic resistance pattern were extracted from online microbiology lab reports database and information on antibiotic prescription from the patient's records. The DDD/100 bed days was calculated for the antibiotics by using the AMC tools software.

The data was analysed by SPSS 20.0 software.

Results

Of the 182 patients who met the inclusion criteria, 59.9% (n = 109) of the patients were male, with age range from 20 to 90 years. The mortality rate was 24.9% (n = 44), and mortality rates trends over time are displayed in Figure 1.

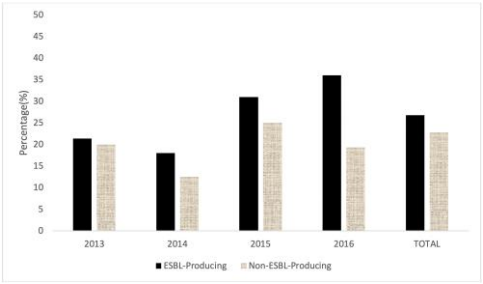

Figure 1: Mortality rate in patients with different types of E.coli isolates over time

The isolated organisms were 55.5% (n = 101) ESBL-producing *E. coli,* and the rest of the organisms were at least sensitive to 4th generation cephalosporins.

Antibiotic sensitivities among the total patient population, viz patients with ESBL producing *E. coli*, patients with non-ESBL producing *E. coli* represented in Table 1.

Table 1: Resistance pattern of different E. coli isolates

Antibiotic name	Non-ESBL producing *E. coli* resistance (%)	ESBL producing *E. coli* resistance (%)	All *E. coli* species resistance (%)
Amikacin	1.3	10.9	6.1
Ampicilin/amoxicillin	77.6	100	90.2
Cefotaxime/ceftriaxone	55.8	100	80.9
Cefuroxime	68.4	100	85.6
Cefazolin/cefadroxil	45.5	100	82.4
Cefpirome/cefepime	2.0	100	68
Ciprofloxacin	55.1	95	77.5
Amoxicillin-clavulanic-acid	24.7	93.1	55.6
Trimethoprim-sulphametoxazole	41.6	54.5	48.9
Gentamicin	21.8	50.5	38
Netilmicin	0.0	18.2	12.1
Imipenem	4.3	6.9	6.1
Piperacillin-tazobactam	8.5	29.7	23
Cefoperazone-sulbactam	2.1	22.8	16.2
Colistin	0	0	0

Among the patients with non-ESBL producing *E. coli*, 45 (55.8%) had an organism resistant to cefotaxime. Sensitivity to the colistin, imipenem, amikacin and netilmicin were observed in most of the ESBL enzyme producing as well as non-producing *E. coli* species. Utilisation pattern of antibiotics in terms of DDD/100 bed-days is depicted in Figure 2.

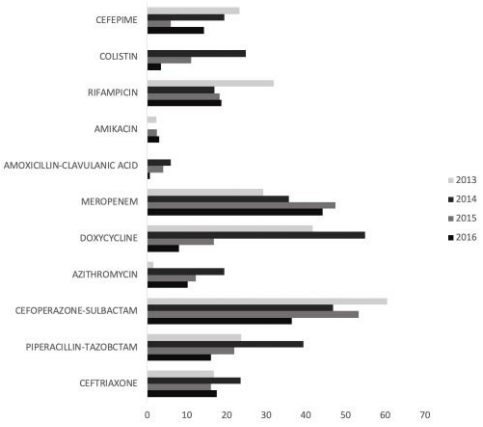

Figure 2: Antibiotic utilisation pattern of patients with E. coli bloodstream infections over time

A group of 40.7% (n = 74) were treated with a cefoperazone-sulbactam combination, and 36.8% (n = 67) were treated with a piperacillin-tazobactam combination and were the most frequently administered antibiotics.

Sixty-two patients (34.1%) received ceftriaxone as empirical therapy. A group of 83.9% (n = 52) of these patients stopped receiving ceftriaxone before the full course of the antibiotic was completed and 35.5% (n = 22) of these patients received a single dose of ceftriaxone after their admission to the hospital. The trend in the change of antibiotic resistance is shown in Figure 3.

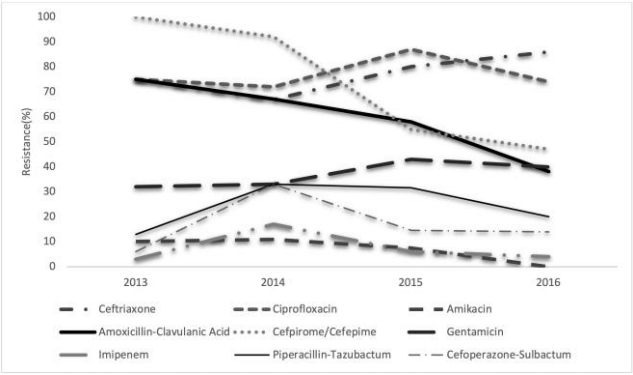

Figure 3: Resistant trends of E. coli isolates to different antibiotics over time

Discussion

ESBL enzyme producing species were dominant in this study, while a lower ratio was reported in other studies [36], [37]. Resistance among *E. coli* species to a variety of antibiotics is increasing. A prior study suggested the use of Ceftriaxone as empirical therapy [29], while we observed an increasing trend of resistance to ceftriaxone among all the reviewed *E. coli* isolates. More than one-third of the patients received ceftriaxone as antimicrobial therapy, and most of them received under-dose medication. This could have affected the increment of cephalosporin's resistance, revealing that added antimicrobial administration control policy may help to overcome antimicrobial resistance.

ESBL producing *E. coli* species were 93.1% susceptible to carbapenems/imipenem which is supported by other studies [25], [26], [27], [28]. A group of 78.2% and 71.3 sensitivity was observed to the cefoperazone-sulbactam and piperacillin-tazobactam combinations respectively which is supported by other studies as well [28], [30]. Aminoglycosides were found to be effective against the entire reviewed *E. coli* isolates. Netilmicin can be recommended as a superior antimicrobial over gentamicin based on its similar activity and higher safety.

The most frequently prescribed antibiotics were cefoperazone-sulbactam, meropenem and piperacillin-tazobactam respectively. Comparison of the DDD/100 bed days results with the trend in resistance pattern of antibiotics over time revealed that a greater number of antibiotics administered in a specific year, more resistance was observed in the same or next year. The behaviour of the resistance pattern of organisms to antibiotics such as amoxicillin-clavulanic acid, cefepime-cefoperazone-sulbactam and piperacillin-tazobactam can support this claim.

The mortality rate of the patients with ESBL producing *E. coli* bloodstream infection was higher in comparison with non-ESBL producing *E. coli* infections, and it supports the prior studies [17], [18], [19], [20], [21]. The difference in the mortality rate of the ESBL producing and non-ESBL producing organisms has constantly been increasing from 2013, and this can reflect the increase in the ineffectiveness of antimicrobial therapy on resistant organism over time.

E. coli infection is the most prevalent bloodstream infection in our study population. Most of these patients received 3rd gen. cephalosporins empirical therapy and treatment usually continue with a β-lactam and β-lactamase inhibitor combination or carbapenems after releasing of culture sensitivity reports. Due to the high resistance of these isolates to cephalosporins, more appropriate empirical therapy can be selected. ESBL enzyme producing species are the most serious bacterial infection, and they should be treated according to evidence-based culture reports. The ability to identify patients at risk for resistant organisms has important implications. Therefore, an appropriate empirical therapy according to local resistance pattern database should be selected.

We observed a descending resistance trend for amoxicillin-clavulanic acid combination in our setting to both the ESBL producing and non-producing *E. coli* isolates, and its use as empirical therapy for bloodstream infections by *E. coli* organism. Despite high utilisation of cefoperazone-sulbactam, piperacillin-tazobactam and meropenem in our patients, the organisms still show a reliable sensitivity toward these antibiotics as shown in the figure3, and this can support the recommendation of other studies for their utilisation [28], [30].

After all, we should express that the pathogenic microorganisms are getting more susceptible to the older and rarely prescribed antibiotics. Local constantly updated microorganism's resistant data is essential in every hospital and must be prepared and used in antimicrobial treatment guidelines to improve the empirical therapies.

References

1. The evolving threat of antimicrobial resistance Options for action WHO Library Cataloguing-in-Publication Data.

2. Hecker MT, Aron DC, Patel NP, Lehmann MK, Donskey CJ. Unnecessary Use of Antimicrobials in Hospitalized Patients. Arch Intern Med. 2003; 163(8):972. https://doi.org/10.1001/archinte.163.8.972 PMid:12719208

3. 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(15):1897. https://doi.org/10.1001/archinte.161.15.1897 PMid:11493132

4. McGowan JE. Do intensive hospital antibiotic control programs prevent the spread of antibiotic resistance? Infect Control Hosp Epidemiol. 1994; 15(7):478-83. https://doi.org/10.2307/30148498 PMid:7963440

5. Simpson SA, Wood F, Butler CC. General practitioners' perceptions of antimicrobial resistance: a qualitative study. J Antimicrob Chemother. 2006; 59(2):292-6. https://doi.org/10.1093/jac/dkl467 PMid:17110392

6. Kumar S, Little P, Britten N. Why do general practitioners prescribe antibiotics for sore throat? Grounded theory interview study. BMJ. 2003; 326(7381):138. https://doi.org/10.1136/bmj.326.7381.138 PMid:12531847 PMCid:PMC140007

7. Welschen I, Kuyvenhoven MM, Hoes AW, Verheij TJM. Effectiveness of a multiple intervention to reduce antibiotic prescribing for respiratory tract symptoms in primary care: randomised controlled trial. BMJ. 2004; 329(7463):431. https://doi.org/10.1136/bmj.38182.591238.EB PMid:15297305 PMCid:PMC514206

8. Goossens H, Ferech M, Vander Stichele R, Elseviers M. Outpatient antibiotic use in Europe and association with resistance: a cross-national database study. Lancet. 2005; 365(9459):579-87. https://doi.org/10.1016/S0140-6736(05)70799-6

9. uz Zaman T, Aldrees M, Al Johani SM, Alrodayyan M, Aldughashem FA, Balkhy HH. Multi-drug carbapenem-resistant Klebsiella pneumoniae infection carrying the OXA-48 gene and showing variations in outer membrane protein 36 causing an outbreak in a tertiary care hospital in Riyadh, Saudi Arabia. Int J Infect Dis. 2014; 28:186-92. https://doi.org/10.1016/j.ijid.2014.05.021 PMid:25245001

10. Shibl A, Al-Agamy M, Memish Z, Senok A, Khader SA, Assiri A. The emergence of OXA-48- and NDM-1-positive Klebsiella pneumoniae in Riyadh, Saudi Arabia. Int J Infect Dis. 2013; 17(12):e1130-3. https://doi.org/10.1016/j.ijid.2013.06.016 PMid:24021566

11. Elabd FM, Al-Ayed MSZ, Asaad AM, Alsareii SA, Qureshi MA, Musa HA-A. Molecular characterization of oxacillinases among carbapenem-resistant Acinetobacter baumannii nosocomial isolates in a Saudi hospital. J Infect Public Health. 2015; 8(3):242-7. https://doi.org/10.1016/j.jiph.2014.10.002 PMid:25466594

12. Russo TA, Johnson JR. Medical and economic impact of extraintestinal infections due to Escherichia coli: focus on an increasingly important endemic problem. Microbes Infect. 2003; 5(5):449-56. https://doi.org/10.1016/S1286-4579(03)00049-2

13. Ron EZ. Distribution and evolution of virulence factors in septicemic Escherichia coli. Int J Med Microbiol. 2010; 300(6):367-70. https://doi.org/10.1016/j.ijmm.2010.04.009 PMid:20510649

14. Wiles TJ, Kulesus RR, Mulvey MA. Origins and virulence mechanisms of uropathogenic Escherichia coli. Exp Mol Pathol. 2008; 85(1):11-9. https://doi.org/10.1016/j.yexmp.2008.03.007 PMid:18482721 PMCid:PMC2595135

15. de Kraker MEA, Jarlier V, Monen JCM, Heuer OE, van de Sande N, Grundmann H. The changing epidemiology of bacteraemias in Europe: trends from the European Antimicrobial Resistance Surveillance System. Clin Microbiol Infect. 2013; 19(9):860-8. https://doi.org/10.1111/1469-0691.12028 PMid:23039210

16. Frakking FNJ, Rottier WC, Dorigo-Zetsma JW, van Hattem JM, van Hees BC, Kluytmans JAJW, et al. Appropriateness of empirical treatment and outcome in bacteremia caused by extended-spectrum-β-lactamase-producing bacteria. Antimicrob Agents Chemother. 2013; 57(7):3092-9. https://doi.org/10.1128/AAC.01523-12 PMid:23612198 PMCid:PMC3697326

17. Tamma PD, Savard P, Pál T, Sonnevend Á, Perl TM, Milstone AM. An Outbreak of Extended-Spectrum β-Lactamase-Producing Klebsiella pneumoniae in a Neonatal Intensive Care Unit. Infect Control Hosp Epidemiol. 2012; 33(06):631-4. https://doi.org/10.1086/665715 PMid:22561722

18. Menashe G, Borer A, Yagupsky P, Peled N, Gilad J, Fraser D, et al. Clinical significance and impact on mortality of extended-spectrum beta lactamase-producing Enterobacteriaceae isolates in nosocomial bacteremia. Scand J Infect Dis. 2001; 33(3):188-93. https://doi.org/10.1080/00365540151060806 PMid:11303808

19. Endimiani A, Luzzaro F, Brigante G, Perilli M, Lombardi G, Amicosante G, et al. Proteus mirabilis bloodstream infections: risk factors and treatment outcome related to the expression of extended-spectrum beta-lactamases. Antimicrob Agents Chemother. 2005; 49(7):2598-605. https://doi.org/10.1128/AAC.49.7.2598-2605.2005 PMid:15980325 PMCid:PMC1168714

20. Kang C-I, Kim S-H, Park WB, Lee K-D, Kim H-B, Kim E-C, et al. Bloodstream infections due to extended-spectrum beta-lactamase-producing Escherichia coli and Klebsiella pneumoniae: risk factors for mortality and treatment outcome, with special emphasis on antimicrobial therapy. Antimicrob Agents Chemother. 2004; 48(12):4574-81. https://doi.org/10.1128/AAC.48.12.4574-4581.2004 PMid:15561828 PMCid:PMC529180

21. Paterson DL, Ko W-C, Gottberg A Von, Mohapatra S, Casellas JM, Goossens H, et al. International Prospective Study of Klebsiella pneumoniae Bacteremia: Implications of Extended-Spectrum β-Lactamase Production in Nosocomial Infections. Ann Intern Med. 2004; 140(1):26. https://doi.org/10.7326/0003-4819-140-1-200401060-00008 PMid:14706969

22. Anderson DJ, Engemann JJ, Harrell LJ, Carmeli Y, Reller LB, Kaye KS. Predictors of mortality in patients with bloodstream infection due to ceftazidime-resistant Klebsiella pneumoniae. Antimicrob Agents Chemother. 2006; 50(5):1715-20. https://doi.org/10.1128/AAC.50.5.1715-1720.2006 PMid:16641440 PMCid:PMC1472233

23. Hyle EP, Lipworth AD, Zaoutis TE, Nachamkin I, Bilker WB, Lautenbach E. Impact of Inadequate Initial Antimicrobial Therapy on Mortality in Infections Due to Extended-Spectrum β-Lactamase-Producing Enterobacteriaceae. Arch Intern Med. 2005; 165(12):1375. https://doi.org/10.1001/archinte.165.12.1375 PMid:15983286

24. Tumbarello M, Viale P, Viscoli C, Trecarichi EM, Tumietto F, Marchese A, et al. Predictors of Mortality in Bloodstream Infections Caused by Klebsiella pneumoniae Carbapenemase-Producing K. pneumoniae: Importance of Combination Therapy. Clin Infect Dis. 2012; 55(7):943-50. https://doi.org/10.1093/cid/cis588 PMid:22752516

25. Vardakas KZ, Tansarli GS, Rafailidis PI, Falagas ME. Carbapenems versus alternative antibiotics for the treatment of bacteraemia due to Enterobacteriaceae producing extended-spectrum -lactamases: a systematic review and meta-analysis. J Antimicrob Chemother. 2012; 67(12):2793-803. https://doi.org/10.1093/jac/dks301 PMid:22915465

26. Hsu AJ, Tamma PD. Treatment of Multidrug-Resistant Gram-Negative Infections in Children. Clin Infect Dis. 2014; 58(10):1439-48. https://doi.org/10.1093/cid/ciu069 PMid:24501388

27. Paterson DL, Ko W-C, Von Gottberg A, Mohapatra S, Casellas JM, Goossens H, et al. Antibiotic Therapy for Klebsiella pneumoniae Bacteremia: Implications of Production of Extended-Spectrum -Lactamases. Clin Infect Dis. 2004; 39(1):31-7. https://doi.org/10.1086/420816 PMid:15206050

28. Perez F, Bonomo RA. Can We Really Use ss-Lactam/ss-Lactam Inhibitor Combinations for the Treatment of Infections Caused by Extended-Spectrum ss-Lactamase-Producing Bacteria? Clin Infect Dis. 2012; 54(2):175-7. https://doi.org/10.1093/cid/cir793 PMid:22057699

29. Leclercq R, Cantón R, Brown DFJ, Giske CG, Heisig P, MacGowan AP, et al. EUCAST expert rules in antimicrobial susceptibility testing. Clin Microbiol Infect. 2013; 19(2):141-60. https://doi.org/10.1111/j.1469-0691.2011.03703.x PMid:22117544

30. Rodriguez-Bano J, Navarro MD, Retamar P, Picon E, Pascual A. -Lactam/ -Lactam Inhibitor Combinations for the Treatment of Bacteremia Due to Extended-Spectrum -Lactamase-Producing Escherichia coli: A Post Hoc Analysis of Prospective Cohorts. Clin Infect Dis. 2012; 54(2):167-74. https://doi.org/10.1093/cid/cir790 PMid:22057701

31. Hoban DJ, Lascols C, Nicolle LE, Badal R, Bouchillon S, Hackel M, et al. Antimicrobial susceptibility of Enterobacteriaceae, including molecular characterization of extended-spectrum beta-lactamase-producing species, in urinary tract isolates from hospitalized patients in North America and Europe: results from the SMART study 2009-2010. Diagn Microbiol Infect Dis. 2012; 74(1):62-7. https://doi.org/10.1016/j.diagmicrobio.2012.05.024 PMid:22763019

32. Chen Y-H, Hsueh P-R, Badal RE, Hawser SP, Hoban DJ, Bouchillon SK, et al. Antimicrobial susceptibility profiles of aerobic and facultative Gram-negative bacilli isolated from patients with intra-abdominal infections in the Asia-Pacific region according to currently established susceptibility interpretive criteria. J Infect. 2011; 62(4):280-91. https://doi.org/10.1016/j.jinf.2011.02.009 PMid:21382411

33. Marchaim D, Sunkara B, Lephart PR, Gudur UM, Bhargava A, Mynatt RP, et al. Extended-Spectrum β-Lactamase Producers Reported as Susceptible to Piperacillin-Tazobactam, Cefepime, and Cefuroxime in the Era of Lowered Breakpoints and No Confirmatory Tests. Infect Control Hosp Epidemiol. 2012; 33(08):853-5. https://doi.org/10.1086/666632 PMid:22759556

34. Wells BG, Di Piro JT, Schwinghammer TL. CVD. Sepsis and Septic Shock. In: Joseph T. DiPiro, editor. Pharmacotherapy Handbook. 9th ed. Newyork: McGraw-Hill Education, 2014:427-33. PMid:25234570 PMCid:PMC4268415

35. Bauer AW, Kirby WMM, Sherris JC, Turck M. Antibiotic Susceptibility Testing by a Standardized Single Disk Method. Am J Clin Pathol. 1966; 45(4_ts):493-6.

36. Horner C, Fawley W, Morris K, Parnell P, Denton M, Wilcox M. Escherichia coli bacteraemia: 2 years of prospective regional surveillance (2010-12). J Antimicrob Chemother. 2014; 69(1):91-100. https://doi.org/10.1093/jac/dkt333 PMid:24003184

37. Hristea A, Olaru ID, Adams-Sapper S, Riley LW. Characterization of ESBL-producing Escherichia coli and Klebsiella pneumoniae from bloodstream infections in three hospitals in Bucharest, Romania: a preliminary study. Infect Dis (Auckl). 2015; 47(1):46-51. https://doi.org/10.3109/00365548.2014.959043 PMid:25365029