Trends in South Korean antimicrobial use and association with changes in *Escherichia coli* resistance rates: 12-year ecological study using a nationwide surveillance and antimicrobial prescription database

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Abstract

The purpose of this study is to determine the correlation between use of antimicrobials, such as fluoroquinolone, cefoxitin, and cefotaxime, and *Escherichia coli* resistance using a nationwide database. Nationwide data on antimicrobial consumption for 12 years (2002 to 2013) were acquired from a database of subjects (n = 1,025,340) included in the National Health Insurance Service-National Sample Cohort. National antimicrobial resistance rates of *E. coli* were obtained from the Korean Antimicrobial Resistance Monitoring System, which has been administered by the Korean Centers for Disease Control and Prevention since 2002. Fluoroquinolone-resistance rates of *E. coli* isolated from general hospitals have continuously increased since 2002 and were correlated with nationwide fluoroquinolone use (r = 0.82, *P* = 0.0012) or ciprofloxacin use (r = 0.90, *P*<0.0001). Cefotaxime-resistance rates of *E. coli* isolated from general hospitals markedly increased since 2008 and were correlated with nationwide cefotaxime use (r = 0.94, *P*<0.0001) or third-generation cephalosporin use (r = 0.96, *P*<0.0001). Cefoxitin-resistance rates of *E. coli* isolated from general hospitals peaked in 2010 and significantly correlated with cephaparin use at a two-year interval (r = 0.64, *P* = 0.0256). In conclusion, consumption of antimicrobials such as fluoroquinolone, cefoxitin, and cefotaxime is well correlated with the resistance rates of *E. coli* to these agents. This study provides background data for national antimicrobial management policies to reduce antimicrobial resistance.

Introduction

Appropriate antimicrobial use is essential to control the development of microbial resistance. Higher rates of resistance have been reported in high antimicrobial consuming countries [1].
The volumes of antimicrobials used, along with the spread of resistant micro-organisms and genes encoding for resistance, are known to drive antimicrobial resistance. Although antimicrobial use and resistance rates are clearly related [2–4], correlation is not always obvious because of the complexity of resistance ecology [5–7]. Antimicrobial use and resistance rates are not perfectly correlated at national levels or across countries because resistance is affected by several factors, such as the proportion of individuals exposed, the proportion of children in the population, population density, the effects of different drug classes, and differences between bacterial species [8].

Because antimicrobial selective pressures differ among countries not only due to different resistance rates, but also because of discrepancies in medical systems, economic status, and sociological backgrounds, there is a need to investigate the correlation between antimicrobial use and resistance in each unique situation. Although associations between antimicrobial resistance and antimicrobial use according to geographic difference have been reported [1,4], studies on association between antimicrobial resistance and changes in antimicrobial use for long periods are scarce.

Antimicrobial resistance in South Korea is higher than in advanced regions such as the United States and Europe [9–11]. In South Korea, it is easy to obtain medical service since national health insurance for all populations started in 1989, and more antimicrobials are used than in the United States or Europe because prescription practices in clinics are not strictly regulated [12,13].

In our 12-year ecological study using a nationwide surveillance and antimicrobial prescription database, we investigated the correlation between changes in use of third-generation cephalexin, cephemycin, and fluoroquinolone and *Escherichia coli* resistance rates. We focused on *E. coli* because the wide spread multidrug-resistant *E. coli* in community and healthcare facilities has become a serious situation in South Korea [14]. We hope this study will provide background data for the management of national antimicrobial use to reduce antimicrobial resistance.

**Materials and methods**

**Ethics statement**

The study was approved by National Health Insurance Service Ilsan Hospital IRB (NHIMC 2017-03-027). All methods were performed in accordance with the relevant guidelines and regulations. This study used National Health Insurance Service-National Sample Cohort with permission (REQ0000007624).

**Study population**

Antimicrobial use in South Korea for 12 years (2002 to 2013) was acquired from a database of subjects from the National Health Insurance Service-National Sample Cohort (NHIS-NSC), a population-based cohort established to provide public health researchers and policy makers with representative, useful information regarding citizens’ utilization of health insurance and health examinations [15]. Informed consent for study participation was exempted according to local institutional review board policy. These data consist of a national sample of 1,025,340 people (male: 513,258, female: 512,082) which account for 2.2% of the total South Korean population as of the 2002 census.

**Nationwide antimicrobial consumption data**

After separation of dispensing and prescribing function policy has been compelled by law in 2000 and all antimicrobials should be used by prescriptions which is electronically transferred
to national health insurance service and accumulated in systemic database in South Korea [16]. Therefore, the data precisely reflect the entire use of antibiotics in South Korea. Systemic antimicrobial prescriptions based on the Anatomical Therapeutic Chemical Classification System (ATC) were included in this study, and amount of use was standardized by Daily Defined Dose (DDD) by expressing data in DDD per 1000 inhabitants daily (DID). This describes the number of people (per a population of 1,000) who use an antimicrobial every day and is an easy way to standardize antimicrobial use, considering dose, form, and frequency of use across antimicrobial products. Ten DID signifies that 1% of the population, on average, might receive a certain drug or group of drugs daily. Antimicrobial use by active ingredient (DDD/1,000 inhabitants/day, DID) can be calculated by following equation [17].

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\text{Amount of antimicrobials used for a year (mg)} = \frac{\text{DDD (mg)} \times 365 \text{ days} \times \text{sample population of the year}}{1,000 \text{ inhabitants}}
\]

**National antimicrobial resistance data**

The data of antimicrobial resistance rates in South Korea were obtained from the Korean Antimicrobial Resistance Monitoring System [14], which has been performed by Korean Centers for Disease Control and Prevention since 2002. These data were obtained from non-duplicated clinical isolates in more than 100 bed-sized general hospitals distributed over all regions of South Korea. Antimicrobial susceptibility tests were done with disk diffusion method or automated minimal inhibition concentration methods. The results were interpreted according to Clinical and Laboratory Standard Institute guidelines [18].

**Statistical analysis**

SAS software, version 9.2 was used for the statistical analysis (SAS Institute, Cary, NC, USA). The correlations between antimicrobial use and resistance were evaluated by correlation analysis, and a p value less than 0.05 was regarded as significant.

**Results**

**Correlation between fluoroquinolone use and resistance rates to fluoroquinolone in *Escherichia coli***

Total fluoroquinolone prescriptions in South Korea increased from 1.445 DID in 2002 to 2.565 DID in 2013. Ciprofloxacin prescriptions in South Korea increased from 0.191 DID in 2002 to 0.675 DID in 2013. Fluoroquinolone-resistance rates of *E. coli* isolated from general hospitals has continuously increased from 30% in 2002 to 42.1% in 2013 and nationwide fluoroquinolone use increased from 1.445 DID in 2002 to 2.565 DID in 2013. Fluoroquinolone-resistance rates of *E. coli* correlated with nationwide total fluoroquinolone use (r = 0.82, P = 0.0012) and ciprofloxacin use (r = 0.90, P<0.0001, Fig 1).

**Correlation of antimicrobial use and resistance rates of *E. coli***

Total third-generation cephalosporin prescriptions in South Korea increased from 0.338 DID in 2002 to 1.457 DID in 2013. Cefotaxime prescriptions in South Korea increased from 0.020 DID in 2002 to 0.053 DID in 2013. Total fourth-generation cephalosporin prescriptions in South Korea increased from 0.002 DID in 2002 to 0.046 DID in 2013. Cefotaxime-resistance rate of *E. coli* isolated from general hospitals has continuously increased from 10% in 2004 to 28.7% in 2013. Cefotaxime-resistance rate correlated with nationwide third-generation cephalosporin use (r = 0.96, P<0.0001) and cefotaxime use (r = 0.94, P<0.0001). Cefotaxime-
Correlation between cephamycin use and resistance rates to cefoxitin in *Escherichia coli*

Total cephamycin use was 0.027 DID in 2002 and peaked at 0.071 DID in 2007. After 2007, cephamycin use decreased to 0.046 DID in 2013. Cefoxitin use was 0.003 DID in 2002 and increased to 0.010 DID in 2008. After 2008, cefoxitin use decreased to 0.008 DID in 2013. Cefoxitin-resistance rates of *E. coli* isolated from general hospitals peaked in 2010. This did not correlate with nationwide cephamycin use (r = 0.61, P = 0.0600), but significantly correlated with cephamycin use at a two-year interval (r = 0.64, P = 0.0256, Fig 3A and 3B). Cefoxitin-resistance rate of *E. coli* correlated with nationwide cefoxitin use (r = 0.73, P = 0.0158, Fig 3C).

The correlation between cephamycin use and the resistance rate to cefoxitin in *Escherichia coli*

Total cephamycin use was 0.027 DID in 2002, and peaked to 0.071 DID in 2007. After 2007, cephamycin use decreased to 0.046 DID in 2013. Cefoxitin use was 0.003 DID in 2002, and increased to 0.010 DID in 2008. After 2008, cefoxitin use decreased to 0.008 DID in 2013. Cefoxitin-resistance rates of *E. coli* isolated from general hospitals have peaked in 2010 and decreased after that, which did not correlate with nationwide cephamycin use (r = 0.61, P = 0.0600), but significantly correlated with cephamycin use at 2 year interval (r = 0.64, P = 0.0256, Fig 3A and 3B). Cefoxitin-resistance rates of *E. coli* correlated with nationwide cefoxitin use (r = 0.73, P = 0.0158, Fig 3C).

Discussion

We identified significant correlations between third-generation cephalosporin, cephamycin, and fluoroquinolone use and *E. coli* resistance in a 12-year ecological study using nationwide surveillance and an antimicrobial prescription database.
Previous antimicrobial exposure is a well-known risk factor for infection with ESBL- or AmpC-producing *E. coli* regardless of healthcare-associated or community-associated infections [19–21]. Single center or multicenter studies of correlation between antimicrobial consumption and resistance rates at the facility level could reflect selections of resistant organisms or acquisition of resistant genes in normal colonizers under antimicrobial pressure [22,23]. This data can be used as a background for antimicrobial stewardship programs to reduce unnecessary antimicrobial use and enhance appropriate treatment [24]. The spread of major antimicrobial-resistant pathogens to the community is an emerging problem [25–30], and all antimicrobial use, both in healthcare facilities and the community, contributes to enhancement of resistance [23].

Resistance to third-generation cephalosporins such as cefotaxime or ceftazidime via extended-spectrum β-lactamase (ESBL)-producing *E. coli* has been widespread in hospitals around the world since the late 1980s [31], but a sudden worldwide increase in the mid-2000s as mainly due to sequence type (ST) 131 with resistance to fluoroquinolone and third-
A recent study of molecular epidemiology showed that H30Rx subsets within the ST131-O25-H30 subclone were associated specifically with fluoroquinolone resistance, and CTX-M-15 was widely detected in South Korea [34], the spread of which is an important mechanism of *E. coli* resistance. *E. coli* is a major pathogen involved in urinary tract infection and shows good clinical outcomes [20,35]. However, severe life-threatening infections, such as community-onset bacteremia by ESBL-producing *E. coli*, have increased in South Korea, becoming a concerning problem [34,36,37].

It is well-known that a single ST131 strain rapidly expanded and disseminated in most current fluoroquinolone-resistant *E. coli* clinical isolates, which shares ESBL and mutations within the fluoroquinolone resistance-determining regions of gyrA and parC [38]. Therefore, co-selection of third-generation cephalosporin and fluoroquinolone may contribute to the increase in fluoroquinolone and cefotaxime resistance. Cephamycin is not a substrate of ESBL, and resistance to cefoxitin is mediated with AmpC β-lactamase, which results from overexpression of the chromosomal AmpC gene or acquisition of plasmid-mediated AmpC
(pAmpC) determinant [39]. Since Klebsiella pneumoniae with transferrable pAmpC genes was first detected in South Korea in 1988 [40], pAmpC β-lactamase-producing E. coli with cefoxitin resistance has increased in South Korea [41].

Cefoxitin-resistance rates of E. coli isolated from general hospitals have markedly decreased since 2011 in South Korea, regardless of clinical breakpoint changes in CLSI guidelines 2010/2011 [42]. In this study, cefoxitin use decreased after 2008, but resistance rates of E. coli to cefoxitin did not decrease until 2011. Cefoxitin-resistance rates of E. coli did not significantly correlate with nationwide cefoxitin use ($r = -0.61, P = 0.0600$), but showed significant correlation with nationwide cephapemycin use ($r = -0.64, P = 0.0256$) at a two-year interval.

Although the time lag between antibiotic consumption and changes in resistance patterns on a national level is unknown, a period of one to two years has been suggested by other ecological studies [1,4,43]. We suspect that response to cephapemycin antibiotic pressure requires one to two years to influence cephapemycin resistance rates, in accordance with previous studies [1,4,43].

The strong point of this study is analysis based on nationwide surveillance and an antimicrobial prescription database over a long period. Although associations between antimicrobial resistance and antimicrobial use according to geographic difference have been reported several times [1,4], studies about association between antimicrobial resistance and changes of antimicrobial usage for long periods are scarce. National Health Insurance Service (NHIS), a single-insurer system by the government of South Korea, maintains and stores all national records for healthcare utilization and prescriptions. NHIS developed the ‘National Health Information Database’ (NHID) for academic interests, containing personal information, demographics, and medical treatment data for South Korean citizens, which was generated using participants’ medical bill expenses claimed by medical service providers [15]. We used NHIS-NSC, a representative sample database by NHIS with a substantial volume of representative information, which provided large-scale, extensive, stable nationwide antimicrobial prescription data. This nationwide study does have a weak point in the significance of relatedness between antimicrobial consumption and resistance. But ecologically speaking, the density of antimicrobial usage involves the total amount of antimicrobial applied to a geographically defined number of individuals in any setting. Although this study has a less-defined study group compared to a case-control study, it can initiate a strategy of nationwide antimicrobial control in an evidence-based way.

In conclusion, correlations between use of antimicrobials such as fluoroquinolone, cefoxitin, and cefotaxime and E. coli resistance to these agents were observed in this study. This provides background data for national antimicrobial management policies to reduce antimicrobial resistance.

Supporting information
S1 Table. National antimicrobial consumption and resistance rate of Escherichia coli. (XLSX)

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**References**

1. Goossens H, Ferech M, Vander SR, Elseviers M. Outpatient antibiotic use in Europe and association with resistance: a cross-national database study. Lancet (London, England). 2005; 365: 579–587.

2. Cheng AC, Turnidge J, Collignon P, Looke D, Barton M, Gottlieb T. Control of fluoroquinolone resistance through successful regulation, Australia. Emerging infectious diseases. 2012; 18: 1453. https://doi.org/10.3201/eid1809.111515 PMID: 22932272

3. Nasrin D, Collignon PJ, Roberts L, Wilson EJ, Pilotto LS, Douglas RM. Effect of β-lactam antibiotic use in children on pneumococcal resistance to penicillin: prospective cohort study. BMJ. 2002; 324: 28. PMID: 11777803

4. Albrich WC, Monnet DL, Harbarth S. Antibiotic selection pressure and resistance in Streptococcus pneumoniae and Streptococcus pyogenes. Emerging infectious diseases. 2004; 10: 514. https://doi.org/10.3201/eid1003.030252 PMID: 15109426

5. Monnet DL, Archibald UK, Phillips L, Tenover FC, McGowan JJ, Gaynes RP. Antimicrobial use and resistance in eight US hospitals: complexities of analysis and modeling. Intensive Care Antimicrobial Resistance Epidemiology Project and National Nosocomial Infections Surveillance System Hospitals. Infection control and hospital epidemiology. 1998; 19: 388–394. PMID: 9669619

6. Hjaltested EK, Bernatoniene J, Erlendsdottir H, Kaltenis P, Bernatoniene G, Gudnason T, et al. Resistance in respiratory tract pathogens and antimicrobial use in Icelandic and Lithuanian children. Scand J Infect Dis. 2003; 35: 21–26. PMID: 12685879

7. Kahlmeter G, Menday P, Cars O. Non-hospital antimicrobial usage and resistance in community-acquired Escherichia coli urinary tract infection. J Antimicrob Chemother. 2003; 52: 1005–1010. https://doi.org/10.1093/jac/dkg488 PMID: 14613955

8. Turnidge J, Christiansen K. Antibiotic use and resistance—proving the obvious. The lancet. 2005; 365: 548–549.

9. Lee Y, Kim YA, Song W, Lee H, Lee HS, Jang SJ, et al. Recent Trends in Antimicrobial Resistance in Intensive Care Units in Korea. Korean J Nosocomial Infect Control. 2014; 19: 29–36.

10. Sader HS, Farrel DJ, Flamrn RK, Jones RN. Antimicrobial susceptibility of Gram-negative organisms isolated from patients hospitalized in intensive care units in United States and European hospitals (2009–2011). Diagn Microbiol Infect Dis. 2014; 78: 443–448. https://doi.org/10.1016/j.diagmicrobio.2013.11.025 PMID: 24492025

11. Shibayama K, Lee HK, Kim SJ. Comparison of Antibiotic Resistance Rate of Medically Important Microorganisms between Japan and Korea. Ann Clin Microbiol. 2015; 18: 111–118. https://doi.org/10.5145/ACM.2015.18.4.111

12. Lee EK. Analysis of the changes in antibiotic use and resistance. Health Welf Policy Forum. 2003; 77: 72–82.

13. Kim DS, Jang SM, Kim NS. Epidemiologic investigation on antibiotic use defined daily dose. J Korean Acad Manage Care Pharm. 2010; 2: 47–59.

14. Korean Centers for Disease Control and Prevention. Korean Antimicrobial Resistance Monitoring System 2013 annual report. 2013.
15. Lee JY, Lee JS, Park SH, Shin SA, Kim KW. Cohort Profile: The National Health Insurance Service-National Sample Cohort (NHIS-NSC), South Korea. Int J Epidemiol. 2017; 46: e15. https://doi.org/10.1093/ije/dyw319 PMID: 26822938

16. Kim BN. Overview of Antibiotic Use in Korea. Infect Chemother. 2012; 44: 250–262.

17. WHO. Defined Daily Dose. Available: http://www.who.int/medicines/regulation/medicines-safety/toolkit_ddd/en/.

18. CLSI. Performance standards for antimicrobial susceptibility testing, twenty-fifth informational supplement. 27th ed. PA: CLSI; 2017.

19. Zerr DM, Miles-Jay A, Kronman MP, Zhou C, Adler AL, Haaland W, et al. Previous Antibiotic Exposure Increases Risk of Infection with Extended-Spectrum-β-Lactamase - and AmpC-Producing Escherichia coli and Klebsiella pneumoniae in Pediatric Patients. Antimicrob Agents Chemother. 2016; 60: 4237–4243. https://doi.org/10.1128/AAC.00187-16 PMID: 27139486

20. Doi Y, Park YS, Rivera JL, Adams-Haduch JM, Hingwe A, Sordillo EM, et al. Community-associated extended-spectrum β-lactamase-producing Escherichia coli infection in the United States. Clinical Infectious Diseases: An Official Publication of the Infectious Diseases Society of America. 2013; 56: 641–648.

21. Gross AE, Schooneveld TCV, Olsen KM, Rupp ME, Bui TH, Forsung E, et al. Epidemiology and predictors of multidrug-resistant community-acquired and health care-associated pneumonia. Antimicrob Agents Chemother. 2014; 58: 2562–2568. https://doi.org/10.1128/AAC.02582-14 PMID: 24957843

22. Schjerring S, Krogfelt KA. Assessment of bacterial antibiotic resistance transfer in the gut. International Journal of Microbiology. 2011; 2011: 312956. https://doi.org/10.1155/2011/312956 PMID: 21318188

23. Levy SB, Marshall B. Antibacterial resistance worldwide: causes, challenges and responses. Nat Med. 2004; 10: 122.

24. Nagel J, Kaye KS, LaPlante KL, Pogue JM. Antimicrobial Stewardship for the Infection Control Practitioner. Infect Dis Clin North Am. 2016; 30: 771–784. https://doi.org/10.1016/j.idc.2016.04.012 PMID: 27515147

25. Park SY, Kang CI, Wi YM, Chung DR, Peck KR, Lee NY, et al. Risk factors and molecular epidemiology of community-onset, multidrug resistance extended-spectrum β-lactamase-producing Escherichia coli infections. Korean J Intern Med. 2017; 32: 146–157. https://doi.org/10.3904/kjim.2015.113 PMID: 27093979

26. Burke L, Humphreys H, Fitzgerald-Hughes D. The revolving door between hospital and community: extended-spectrum beta-lactamase-producing Escherichia coli in Dublin. J Hosp Infect. 2012; 81: 192–196. https://doi.org/10.1016/j.jhin.2012.04.021 PMID: 22658893

27. Kim YA, Kim JJ, Kim HJ, Lee KW. Community-onset extended-spectrum-β-lactamase-producing Escherichia coli sequence type 131 at two Korean community hospitals: The spread of multidrug-resistant E. coli to the community via healthcare facilities. International Journal of Infectious diseases: official publication of the International Society for Infectious Diseases. 2017; 54: 39–42.

28. Seybold U, Kourbatova EV, Johnson JG, Halvosa SJ, Wang YF, King MD, et al. Emergence of community-associated methicillin-resistant Staphylococcus aureus USA300 genotype as a major cause of health care-associated bloodstream infections. Clinical Infectious Diseases: An Official Publication of the Infectious Diseases Society of America. 2006; 42: 647–656.

29. Dexter C, Murray GL, Paulsen IT, Peleg AY. Community-acquired Acinetobacter baumannii: clinical characteristics, epidemiology and pathogenesis. Expert Review of Anti-Infective Therapy. 2015; 13: 567–573. https://doi.org/10.1586/14787210.2015.1025055 PMID: 25850806

30. Voulgari E, Poulou A, Dimitroulia E, Politi L, Ranellou K, Gennimata V, et al. Emergence of OXA-162 Carbapenemase- and DHA-1 AmpC Cephalosporinase-Producing Sequence Type 11 Klebsiella pneumoniae Causing Community-Onset Infection in Greece. Antimicrob Agents Chemother. 2015; 60: 1862–1864. https://doi.org/10.1128/AAC.01514-15 PMID: 26666930

31. Paterson DL, Bonomo RA. Extended-spectrum beta-lactamases: a clinical update. Clin Microbiol Rev. 2005; 18: 657–686. https://doi.org/10.1128/CMR.18.4.657-686.2005 PMID: 16223952

32. Johnson JR, Johnston B, Ciabots C, Kuskowski MA, Castanheira M. Escherichia coli sequence type ST131 as the major cause of serious multidrug-resistant E. coli infections in the United States. Clinical Infectious Diseases: An Official Publication of the Infectious Diseases Society of America. 2010; 51: 286–294.

33. Rogers BA, Sidjabat HE, Paterson DL. Escherichia coli O25b-ST131: a pandemic,multiresistant, community-associated strain. J Antimicrob Chemother. 2011; 66: 1–14. https://doi.org/10.1093/jac/dkq415 PMID: 21081548

34. Kim SY, Park YJ, Johnson JR, Yu JK, Kim YK, Kim YS. Prevalence and characteristics of Escherichia coli sequence type 131 and its H30 and H30Rx subclones: a multicenter study from Korea. Diagn Microbiol Infect Dis. 2016; 84: 97–101. https://doi.org/10.1016/j.diagmicrobiol.2015.10.016 PMID: 26643062
35. Doi Y, Adams J, O'Keefe A, Quereshi Z, Ewan L, Paterson DL. Community-acquired extended-spectrum beta-lactamase producers, United States. Emerging Infectious Diseases. 2007; 13: 1121–1123. https://doi.org/10.3201/eid1307.070094 PMID: 18214201

36. Kang CI, Cheong HS, Chung DR, Peck KR, Song J-, Oh M-, et al. Clinical features and outcome of community-onset bloodstream infections caused by extended-spectrum beta-lactamase-producing Escherichia coli. European Journal of Clinical Microbiology & Infectious Diseases: Official Publication of the European Society of Clinical Microbiology. 2008; 27: 85–88.

37. Cha MK, Kang I, Kim SH, Cho SY, Ha YE, Wi YM, et al. Comparison of the microbiological characteristics and virulence factors of ST131 and non-ST131 clones among extended-spectrum β-lactamase-producing Escherichia coli causing bacteremia. Diagn Microbiol Infect Dis. 2016; 84: 102–104. https://doi.org/10.1016/j.diagmicrobio.2015.10.015 PMID: 26632660

38. Johnson JR, Tchesnokova V, Johnston B, Clabots C, Billig M, et al. Abrupt emergence of a single dominant multidrug-resistant strain of Escherichia coli. J Infect Dis. 2013; 207: 919–928. https://doi.org/10.1093/infdis/jis933 PMID: 23288927

39. Pfeifer Y, Cullik A, Witte W. Resistance to cephalosporins and carbapenems in Gram-negative bacterial pathogens. International journal of medical microbiology: IJMM. 2010; 300: 371–379. https://doi.org/10.1016/j.ijmm.2010.04.005 PMID: 20537585

40. Bauernfeind A, Chong Y, Schweighart S. Extended broad spectrum beta-lactamase in Klebsiella pneumoniae including resistance to cephapemycins. Infection. 1989; 17: 316–321. PMID: 2689349

41. Park MJ, Kim TK, Song WK, Kim JS, Kim HS, Lee J. An Increase in the clinical isolation of acquired AmpC β-lactamase-producing Klebsiella pneumoniae in Korea from 2007 to 2010. Annals of Laboratory Medicine. 2013; 33: 353–355. https://doi.org/10.3343/alm.2013.33.5.353 PMID: 24003426

42. Hombach M, Bloemberg GV, Böttger EC. Effects of clinical breakpoint changes in CLSI guidelines 2010/2011 and EUCAST guidelines 2011 on antibiotic susceptibility test reporting of Gram-negative bacilli. J Antimicrob Chemother. 2012; 67: 622–632. https://doi.org/10.1093/jac/dkr524 PMID: 22167240

43. Bergman M, Huikkko S, Pihlajamäki M, Laippala P, Palva E, Huovinen P, et al. Effect of macrolide consumption on erythromycin resistance in Streptococcus pyogenes in Finland in 1997–2001. Clinical Infectious Diseases. 2004; 38: 1251–1256. https://doi.org/10.1086/383309 PMID: 15127336