Shafa Ortho J. 2016 August; 3(3):e7535. doi: 10.17795/soj-7535.

Published online 2016 July 12. **Review Article**

Antibiotic Prophylaxis in Periprosthetic Joint Infection (PJI): literature Review and World Consensus (Part Seven)

Javad Parvizi,[1,*] Mohammad Ghazavi,[2] and Members of Pre-Op Antibiotics Committee of the Consensus Meeting[3]

[1]Rothman Institute, Thomas Jefferson University, Philadelphia, PA, USA
[2]Bone and Joint Reconstruction Research Center, Shafa Orthopedic Hospital, Iran University of Medical Sciences, Tehran, IR Iran
[3]William Arnold MD PhD; Katherine Belden MD; Goran Bicanic; Stefano Bini MD; Fabio Catani MD; Jiying Chen MD PhD; Mohammad Ghazavi MD FRCSC; Karine M Godefroy MD; Erik Hansen MD; Paul Holham MD; Hamid Hosseinzadeh MD; Kang Il Kim MD; Klaus Kirketerp-Moller MD; Lars Lidgren MD PhD; Jian Hao Lin MD; Jess H Lonner MD; Christopher Moore MD; Panayiotis Papagelopoulos MD; Lazaros Poultsides MD MSc PhD; Khalid Saleh MD MSC FRCSC MHCM; Julia V Salmon MD, Edward Schwarz PhD; Randi Silibovsky MD (US); Jose Stuyck MD; Markus Vogt MD; (International); Annette W Dahl MD; Koji Yamada MD.

[*]*Corresponding author*: Javad Parvizi, Rothman Institute, Thomas Jefferson University, Philadelphia, PA, USA. Tel: +1-2673397813, Fax: +1-2155030580, E-mail: parvizi@aol.com

Received 2016 June 14; **Accepted** 2016 July 08.

Abstract

Context: There is a need to find if patients with poorly controlled diabetes, immunosuppression, or autoimmune disease require different perioperative antibiotic prophylaxis. There is also a need to determine if antibiotic prophylaxis should be different for primary cases, revision cases, hip arthroplasty and knee arthroplasty. The best antibiotic prophylaxis to choose in patients with colonization by carbapenem resistant enterobacteriaceae or multi-drug resistant (MDR)-Acinetobacter spp needs to be determined.
Evidence Acquisition: Delegates in workgroup 3 of the consensus meeting on PJI reviewed English literature for relevant articles. 30 of 221 articles were relevant to the 4 following questions regarding perioperative antibiotic prophylaxis to prevent PJI.
Results: There is no need to use different antibiotic prophylaxis for patients with poorly controlled diabetes, immunosuppression, or autoimmune disease than routine antibiotic prophylaxis. Perioperative antibiotic prophylaxis should be the same for primary and uninfected revision arthroplasty. Perioperative antibiotic prophylaxis should be the same for hips and knees arthroplasties. There is insufficient data to recommend expanded antibiotic prophylaxis in patients known to be colonized or recently infected with multi-drug resistant pathogens.
Conclusions: Based on evidences in the literature and consensus of expert delegates from consensus meeting recommendations for type of antibiotic prophylaxis in patients with poorly controlled diabetes, immunosuppression, or autoimmune disease, primary and uninfected revision arthroplasty, hip or knee arthroplasties and patients known to be colonized or recently infected with multi-drug resistant pathogens were provided.

Keywords: Infection, Joint, Periprosthetic, Arthroplasty

1. Context

Decision making in choosing the appropriate antibiotic prophylaxis for patients with poorly controlled diabetes, immunosuppression, or autoimmune disease, primary or revision cases, hip or knee arthroplasty, patients with colonization by carbapenem resistant enterobacteriaceae or multi-drug resistant (MDR)-Acinetobacter spp. needs to be defined.

2. Evidence Acquisition

From November 2012 till August 2013, 400 delegates from all over the world formed 15 workgroups to review the current literature and find high level evidence for all issues related to PJI. Workgroup No.3 (authors) was assigned to review current literature on perioperative antibiotics. The goal was to find answers and recommendations for more than 264 questions based on the high level evidence if present or reach to a consensus when there is a lack of high level evidence.

After 10 months of hard work by delegates from 58 countries and 100 societies, relevant publications reviewed, communications exchanged and finally a draft was prepared to be presented for vote at the final meeting on 1st of August 2013. The draft included recommendations for management on the basis of high level of evidence if present. Otherwise the cumulative wisdom of 400 delegates from 58 countries and over 100 societies used to reach consensus about practices lacking higher level of evidence.

3. Results:

Question 20: Do patients with poorly controlled diabetes, immunosuppression, or autoimmune disease require a different perioperative antibiotic prophylaxis?

Consensus: No. Routine antibiotic prophylaxis is recommended in these patients.

Delegate Vote: Agree: 90%, Disagree: 9%, Abstain: 1% (Strong Consensus)

Justification: Several studies have demonstrated that diabetes mellitus (DM), especially uncontrolled DM, is a risk factor for postoperative infection in THA and TKA (1-4). A recent retrospective cohort study within the Kaiser Healthcare system found no significant increase in risk of revision or deep infection or revision whether patients had controlled (HbA1c < 7%) or uncontrolled diabetes (HbA1c > 7%). Specifically, compared with patients without DM, there was no association between controlled DM and risk of revision (OR 1.32; 95% CI 0.99 - 1.76).

Similarly, compared to patients without DM, there was no association between uncontrolled DM and risk of revision (OR 1.03; 95% CI 0.68 - 1.54) (5).

Obesity has also been associated with a significant increase in rate of postoperative infection following TJA (6-8).

Human immunodeficiency virus (HIV) has also been associated with an alarming rate of postoperative complications, including infection. Parvizi et al. reported on 6 deep infections in 21 HIV-positive patients undergoing TJA. The authors remarked that the immune status of the patients was related to their risk of deep PJI, in that 5 of the 6 patients ultimately developed Acquired Immune Deficiency Syndrome (AIDS) and the CD4 count was significantly lower at 239 $\pm$ 112 μL at latest follow-up for patients who developed infection compared to 523 $\pm$ 171 μL for the study population as a whole (P < 0.001). In this study the authors reported using prophylactic antibiotics (cephalosporins) preoperatively and 3 doses postoperatively and added antibiotic powder (vancomycin and tobramycin) to the cement in 2 patients thought to be at high risk for infection (9).

Similarly, Ragni et al. found a very high postoperative infection rate (26.5%) in 34 TJA in HIV positive hemophiliacs, all of whom had CD4 counts less than 200/μL at time of surgery (10).

Haberman et al. noted an infection rate of 12.7% in their cohort of 41 patients with HIV undergoing TJA, but did not identify any difference in the outcomes relating to CD4 count (11).

Their perioperative antibiotic protocol was a 5 day course of cefuroxime and in all procedures antibiotic-containing cement (Palacos R, Zimmer, Warsaw, IN) was used. In a smaller series of 6 HIV-infected patients undergoing TJA, Wang et al. noted no infectious or other complications.

The authors again used antibiotic (vancomycin)-impregnated bone cement in all cemented cases (12). Unger et al. evaluated the results of 26 TKAs in HIV-positive hemophiliacs and found no cases of deep infection, but it is interesting to note that the average CD4 count of these patients was 463 μL (13).

Hemophilia has historically been considered a risk factor for PJI, due in part to its relation to HIV and AIDS, but also as an independent risk factor. An article by Silva et al. reviewed the long term results of primary TKA in patients with hemophilia and noted an overall prevalence of PJI of 16% with a rate of infection in HIV-positive and HIV-negative patients of 17% and 13% respectively (P = 0.5). The authors perioperative protocol included 3 to 5 days of prophylactic antibiotics and antibiotic cement was not used (14). In contrast, Rodriguez-Merchan reported an infection rate of only 3% of 35 TJA in hemophiliac patients, but used antibiotic-laden bone cement and 2 days of perioperative antibiotic prophylaxis (15).

Asplenic patients are at increased risk of infection by encapsulated bacteria; and although there is evidence to support vaccinations and penicillin prophylaxis in patients under 16 and over 50 years of age, there is no consensus on the appropriate perioperative management of these immunocompromised patients. In a single case report by Shaarani et al. of an asplenic patient who underwent a TKA, the patient ultimately developed a MRSA infection. In this case standard polymethylmethacrylate (PMMA) was used for cementing components and the patient received intravenous prophylactic dose of second generation cephalosporin preoperatively (16).

Renal disease (including renal failure, dialysis dependence, and renal transplant) has been implicated as increasing the risk of PJI. McCleery et al. analyzed the Scottish Arthroplasty Registry in order to determine the rates of PJI in patients with renal failure, those undergoing dialysis, and those with a renal transplant. They found that patients with renal failure had a significantly increased risk of early infection (1.6%, RR 1.52, P = 0.02) and late infection (4.47%, RR 2.2, P < 0.001). Patients on dialysis had a significantly increased risk of late infection (8.0%, RR 3.99, P < 0.001) and early revision (3.7%, RR 4.4, P < 0.001). Renal transplant patients had a significantly increased risk of late infection, despite whether the transplantation occurred before TKA (9.1%, RR 4.5, P = 0.03) or at any time (8.0%, RR 4.0, P = 0.05) (17). Lieberman et al. documented a deep infection rate of 19% in 16 chronic renal dialysis patients and more favorable outcomes in renal transplant patients (18). Sakalkale et al. reported a deep infection rate of 13% in 12 patients with

end-stage renal failure on dialysis who underwent THA. In this study, perioperative prophylactic antibiotics were administered for 2 to 5 days (19). In contrast, other authors have reported no increased rate of infection in patients on chronic hemodialysis undergoing THA (20, 21).

Similarly, liver disease has been associated with increased morbidity following TJA. Pour et al. performed a case control study of 71 non-cirrhotic patients with hepatitis C undergoing TJA and found that this cohort had higher rates of wound drainage following THA when compared to matched controls (15 vs 3.8%, P = 0.03) (22). Orozco et al. recently published a case control study to analyze the effect of fibrosis and thrombocytopenia on the diagnosis of hepatitis C and clinical outcomes. Analyzing 72 patients (77 joint replacements), the authors found that fibrotic hepatitis C patients had higher deep infection rates (21% vs 0%, P = 0.047) and rates of cellulitis (21% vs 0%, P = 0.047), while thromobocytopenia showed a trend towards greater infection (23).

Solid organ transplant (SOT) is a risk factor for PJI due to the need for chronic use of immunosuppressant medications. Vergidis et al. performed a case control study of patients with SOT who developed PJI and compared them to non-infected controls matched by transplant type, prosthetic joint type, and order of organ transplantation or joint implantation. Of 367 patients with both a joint replacement and SOT, there were 12 cases of PJI, of which 8 were renal transplants, 3 were liver transplants, and 1 was a heart transplant patient. Eight infections were caused by gram-positive organisms, 2 were caused by nontuberculous mycobacteria, and the remaining 2 were culture-negative. Of note, patients received perioperative cefazolin, or in cases of colonization or prior infection with MRSA, vancomycin (24). Tannenbaum et al. reported results on 35 TJA in 19 patients with renal or liver transplant and documented an infection in 5 patients who had the joint replacement after the transplantation. There were no infections in patients who had TJA before the organ transplantation. In this series, prophylactic antibiotics were administered for at least 48 hours or until the drains were removed and bone cement when used was not impregnated with antibiotics (25).

Question 21A: Should preoperative antibiotics be different for primary and revision TJA?

Consensus: No. Perioperative antibiotic prophylaxis should be the same for primary and uninfected revision arthroplasty.

Delegate Vote: Agree: 89%, Disagree: 10%, Abstain: 1% (Strong Consensus)

Question 21B: Should preoperative antibiotics be different for hips and knees?

Consensus: Perioperative antibiotic prophylaxis should be the same for hips and knees.

Delegate Vote: Agree: 99%, Disagree: 1%, Abstain: 0% (Strong Consensus)

Justification: Patients undergoing revision TJA are at higher risk of developing PJI than primary arthroplasty and those undergoing revision knee procedures are at even highest risk (26-28).

One recent study has effectively demonstrated targeting infection prevention programs at high-risk surgical patients that take into account an institution's local epidemiology and Antibiogram (29).

Liu et al. determined the impact of adding vancomycin to cefazolin as antimicrobial prophylaxis in 414 patients undergoing revision TKA based on a notable increase in PJI in revision TKA patients, with many being methicillin-resistant. Following introduction of vancomycin to the routine preoperative antibiotic prophylaxis, the infection rate decreased from 7.89% to 3.13% (P = 0.046). In particular, a significant reduction in PJI resulting from methicillin-resistant organisms over this time period was seen (4.2% to 0.9%, P = 0.049) (29).

Question 22: What is the best antibiotic prophylaxis to choose in patients with colonization by carbapenem resistant enterobacteriaceae or multi-drug resistant (MDR)-Acinetobacter spp?

Consensus: There is insufficient data to recommend expanded antibiotic prophylaxis in patients known to be colonized or recently infected with MDR pathogens.

Delegate Vote: Agree: 76%, Disagree: 8%, Abstain: 16% (Strong Consensus)

Justification: There is an increasing awareness of the threat posed by K. pneumoniae strains with decreased susceptibility to carbapenems worldwide (30). This resistance is conferred by K. pneumo carbapemenase (KPC), which is a β-lactamase that also confers resistance to broadspectrum cephalosporins, as well as commercially available β-lactam/ β-lactamase inhibitor combinations (31). As there are few antimicrobial options, prevention of K. pneumo carbapemenase K. pneumoniae (KPC-KP) has become a major priority of those studying nosocomial infections (32).

4. Conclusions

While there is no evidence on the management of surgical antimicrobial prophylaxis in a patient with past infection or colonization with a resistant gram-negative pathogen, it is logical to provide prophylaxis with an agent active against MRSA for any patient known to be colonized with this gram-positive pathogen who will have a skin incision; specifically, prophylaxis for a resistant gram-negative pathogen in a patient with past infection or colonization

with such a pathogen may not be necessary for a purely cutaneous procedure.

In a literature review, KPC-producing microbes are resistant to many non-β-lactam molecules.

Most isolates are resistant to fluoroquinolones, aminoglycosides, and co-trimoxazole. Some isolates are susceptible to amikacin and gentamicin and most are susceptible to colistin and tigecycline (30, 33-35).

In a prospective RCT, De Smet et al. studied the elimination of colonization with MDR organisms using selective oropharynegeal and/or digestive tract decontamination (SOD/SDD) in a multicenter crossover study using cluster randomization of 5,939 intensive care unit patients in the Netherlands. SOD included 4 days of intravenous cefotaxime and topical application of tobramycin, colistin, and amphotericin B in the oropharynx and stomach. SDD consisted of oropharyngeal application only of the same antimicrobials. Using a random effects logistic regression analysis, the OR for death at day 28 in the SOD and SDD group, as compared with the standard care group, were 0.86 (95% CI 0.74 - 0.99) and 0.83 (95% CI 0.72 - 0.97) respectively (36).

Perez et al. used a mouse model to examine the effect of antibiotic treatment on the establishment and elimination of intestinal colonization of KPC-KP. They administered 3 days of antibiotics (clindamycin, zosyn, tigecycline, ertapenem, cefepime, and ciprofloxacin) before KPC-KP was administered orogastrically. The authors reported that of the 4 antibiotics with minimal activity against the KPC-KP strain (MIC > 16 mcg/mL), those that suppressed total anaerobes and Bacteroides (ie clindamycin and zosyn) promoted colonization by KPC-KP ($P < 0.001$), while agents that did not suppress total anaerobes and bacteroides (ie ciprofloxacin and cefepime) did not ($P = 0.35$). Of the antibiotics with moderate activity against KPC-KP, ertapenem (MIC 4 mcg/mL) did not promote colonization by KPC-KP, while tigecycline (MIC 3 mcg/mL) did ($P < 0.001$), despite not reducing levels of total anaerobes and bacteroides.

Orgogastric administration of gentamicin and polmyxin E-suppressed KPC-KP was at undetectable levels in the majority of mice. The authors posited that antibiotics that disturb the intestinal anaerobic microflora lack significant activity against KPC-KP promote colonization, while the administration of non-absorbed oral antibiotics may be an effective strategy to suppress colonization with this microorganism (37).

References

1. Berbari EF, Hanssen AD, Duffy MC, Steckelberg JM, Ilstrup DM, Harmsen WS, et al. Risk factors for prosthetic joint infection: case-control study. *Clin Infect Dis.* 1998;**27**(5):1247–54. [PubMed: 9827278].
2. Yang K, Yeo SJ, Lee BP, Lo NN. Total knee arthroplasty in diabetic patients: a study of 109 consecutive cases. *J Arthroplasty.* 2001;**16**(1):102–6. doi: 10.1054/arth.2001.19159. [PubMed: 11172278].
3. Meding JB, Reddleman K, Keating ME, Klay A, Ritter MA, Faris PM, et al. Total knee replacement in patients with diabetes mellitus. *Clin Orthop Relat Res.* 2003(416):208–16. doi: 10.1097/01.blo.0000093002.90435.56. [PubMed: 14646763].
4. Pedersen AB, Mehnert F, Johnsen SP, Sorensen HT. Risk of revision of a total hip replacement in patients with diabetes mellitus: a population-based follow up study. *J Bone Joint Surg Br.* 2010;**92**(7):929–34. doi: 10.1302/0301-620X.92B7.24461. [PubMed: 20595109].
5. Adams AL, Paxton EW, Wang JQ, Johnson ES, Bayliss EA, Ferrara A, et al. Surgical outcomes of total knee replacement according to diabetes status and glycemic control, 2001 to 2009. *J Bone Joint Surg Am.* 2013;**95**(6):481–7. doi: 10.2106/JBJS.L.00109. [PubMed: 23446446].
6. Haverkamp D, Klinkenbijl MN, Somford MP, Albers GH, van der Vis HM. Obesity in total hip arthroplasty–does it really matter? A meta-analysis. *Acta Orthop.* 2011;**82**(4):417–22. doi: 10.3109/17453674.2011.588859. [PubMed: 21657972].
7. Namba RS, Paxton L, Fithian DC, Stone ML. Obesity and perioperative morbidity in total hip and total knee arthroplasty patients. *J Arthroplasty.* 2005;**20**(7 Suppl 3):46–50. doi: 10.1016/j.arth.2005.04.023. [PubMed: 16214002].
8. Dowsey MM}, Choong PF. Early outcomes and complications following joint arthroplasty in obese patients: a review of the published reports. *ANZ J Surg.* 2008;**78**(6):439–44.
9. Parvizi J, Sullivan TA, Pagnano MW, Trousdale RT, Bolander ME. Total joint arthroplasty in human immunodeficiency virus-positive patients: an alarming rate of early failure. *J Arthroplasty.* 2003;**18**(3):259–64. doi: 10.1054/arth.2003.50094. [PubMed: 12728415].
10. Ragni MV, Crossett LS, Herndon JH. Postoperative infection following orthopaedic surgery in human immunodeficiency virus-infected hemophiliacs with CD4 counts < or = 200/mm3. *J Arthroplasty.* 1995;**10**(6):716–21. [PubMed: 8749751].
11. Habermann B, Eberhardt C, Kurth AA. Total joint replacement in HIV positive patients. *J Infect.* 2008;**57**(1):41–6. doi: 10.1016/j.jinf.2008.01.045. [PubMed: 18336915].
12. Wang TI, Chen CF, Chen WM, Chiang CC, Huang CK, Liu CL, et al. Joint replacement in human immunodeficiency virus-infected patients. *J Chin Med Assoc.* 2012;**75**(11):595–9. doi: 10.1016/j.jcma.2012.08.021. [PubMed: 23158038].
13. Unger AS, Kessler CM, Lewis RJ. Total knee arthroplasty in human immunodeficiency virus-infected hemophiliacs. *J Arthroplasty.* 1995;**10**(4):448–52. [PubMed: 8523002].
14. Silva M, Luck JJ. Long-term results of primary total knee replacement in patients with hemophilia. *J Bone Joint Surg Am.* 2005;**87**(1):85–91. doi: 10.2106/JBJS.C.01609. [PubMed: 15634817].
15. Rodriguez-Merchan EC. Total knee replacement in haemophilic arthropathy. *J Bone Joint Surg Br.* 2007;**89**(2):186–8. doi: 10.1302/0301-620X.89B2.18682. [PubMed: 17322432].
16. Shaarani SR, Collins D, O'Byrne JM. The need for guidelines in asplenic patients undergoing total joint arthroplasty: a case report. *Case Rep Orthop.* 2012;**2012**:147042. doi: 10.1155/2012/147042. [PubMed: 23259109].
17. McCleery MA, Leach WJ, Norwood T. Rates of infection and revision in patients with renal disease undergoing total knee replacement in Scotland. *J Bone Joint Surg Br.* 2010;**92**(11):1535–9. doi: 10.1302/0301-620X.92B11.23870. [PubMed: 21037348].
18. Lieberman JR, Fuchs MD, Haas SB, Garvin KL, Goldstock L, Gupta R, et al. Hip arthroplasty in patients with chronic renal failure. *J Arthroplasty.* 1995;**10**(2):191–5. [PubMed: 7798100].
19. Sakalkale DP, Hozack WJ, Rothman RH. Total hip arthroplasty in patients on long-term renal dialysis. *J Arthroplasty.* 1999;**14**(5):571–5. [PubMed: 10475556].
20. Li WC, Shih CH, Ueng SW, Shih HN, Lee MS, Hsieh PH. Uncemented total hip arthroplasty in chronic hemodialysis patients. *Acta Or-*

thop. 2010;**81**(2):178–82. doi: 10.3109/17453671003628749. [PubMed: 20175645].
21. Nagoya S, Nagao M, Takada J, Kuwabara H, Kaya M, Yamashita T. Efficacy of cementless total hip arthroplasty in patients on long-term hemodialysis. *J Arthroplasty.* 2005;**20**(1):66–71. doi: 10.1016/j.arth.2004.09.055. [PubMed: 15660062].
22. Pour AE, Matar WY, Jafari SM, Purtill JJ, Austin MS, Parvizi J. Total joint arthroplasty in patients with hepatitis C. *J Bone Joint Surg Am.* 2011;**93**(15):1448–54. doi: 10.2106/JBJS.J.00219. [PubMed: 21915551].
23. Orozco F, Post ZD, Baxi O, Miller A, Ong A. Fibrosis in hepatitis C patients predicts complications after elective total joint arthroplasty. *J Arthroplasty.* 2014;**29**(1):7–10. doi: 10.1016/j.arth.2013.03.023. [PubMed: 23648106].
24. Vergidis P, Lesnick TG, Kremers WK, Razonable RR. Prosthetic joint infection in solid organ transplant recipients: a retrospective case-control study. *Transpl Infect Dis.* 2012;**14**(4):380–6. doi: 10.1111/j.1399-3062.2011.00708.x. [PubMed: 22260428].
25. Tannenbaum DA, Matthews LS, Grady-Benson JC. Infection around joint replacements in patients who have a renal or liver transplantation. *J Bone Joint Surg Am.* 1997;**79**(1):36–43. [PubMed: 9010184].
26. Mortazavi SM, Molligan J, Austin MS, Purtill JJ, Hozack WJ, Parvizi J. Failure following revision total knee arthroplasty: infection is the major cause. *Int Orthop.* 2011;**35**(8):1157–64. doi: 10.1007/s00264-010-1134-1. [PubMed: 20959981].
27. Poss R, Thornhill TS, Ewald FC, Thomas WH, Batte NJ, Sledge CB. Factors influencing the incidence and outcome of infection following total joint arthroplasty. *Clin Orthop Relat Res.* 1984(182):117–26. [PubMed: 6692605].
28. Sierra RJ, Cooney W, Pagnano MW, Trousdale RT, Rand JA. Reoperations after 3200 revision TKAs: rates, etiology, and lessons learned. *Clin Orthop Relat Res.* 2004(425):200–6. [PubMed: 15292808].
29. Bal BS, Brenner LH. Corporate malfeasance, off-label use, and surgeon liability. *Clin Orthop Relat Res.* 2013;**471**(1):4–8. doi: 10.1007/s11999-012-2686-8. [PubMed: 23188653].
30. Thakuria B, Singh P, Agrawal S, Asthana V. Profile of infective microorganisms causing ventilator-associated pneumonia: A clinical study from resource limited intensive care unit. *J Anaesthesiol Clin Pharmacol.* 2013;**29**(3):361–6. doi: 10.4103/0970-9185.117111. [PubMed: 24106362].
31. Queenan AM, Bush K. Carbapenemases: the versatile beta-lactamases. *Clin Microbiol Rev.* 2007;**20**(3):440–58. doi: 10.1128/CMR.00001-07. [PubMed: 17630334] table of contents.
32. Schwaber MJ, Carmeli Y. Carbapenem-resistant Enterobacteriaceae: a potential threat. *JAMA.* 2008;**300**(24):2911–3. doi: 10.1001/jama.2008.896. [PubMed: 19109119].
33. Bratu S, Landman D, Haag R, Recco R, Eramo A, Alam M, et al. Rapid spread of carbapenem-resistant Klebsiella pneumoniae in New York City: a new threat to our antibiotic armamentarium. *Arch Intern Med.* 2005;**165**(12):1430–5. doi: 10.1001/archinte.165.12.1430. [PubMed: 15983294].
34. Marchaim D, Navon-Venezia S, Schwaber MJ, Carmeli Y. Isolation of imipenem-resistant Enterobacter species: emergence of KPC-2 carbapenemase, molecular characterization, epidemiology, and outcomes. *Antimicrob Agents Chemother.* 2008;**52**(4):1413–8. doi: 10.1128/AAC.01103-07. [PubMed: 18227191].
35. Cuzon G, Naas T, Demachy MC, Nordmann P. Plasmid-mediated carbapenem-hydrolyzing beta-lactamase KPC-2 in Klebsiella pneumoniae isolate from Greece. *Antimicrob Agents Chemother.* 2008;**52**(2):796–7. doi: 10.1128/AAC.01180-07. [PubMed: 18056283].
36. de Smet AM, Kluytmans JA, Cooper BS, Mascini EM, Benus RF, van der Werf TS, et al. Decontamination of the digestive tract and oropharynx in ICU patients. *N Engl J Med.* 2009;**360**(1):20–31. doi: 10.1056/NEJMoa0800394. [PubMed: 19118302].
37. Perez F, Pultz MJ, Endimiani A, Bonomo RA, Donskey CJ. Effect of antibiotic treatment on establishment and elimination of intestinal colonization by KPC-producing Klebsiella pneumoniae in mice. *Antimicrob Agents Chemother.* 2011;**55**(6):2585–9. doi: 10.1128/AAC.00891-10. [PubMed: 21422202].