International Journal of Applied Research

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Treatment of bloodstream infections in cancer patients with daptomycin: Our experience

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Abstract
Excessive vancomycin usage has contributed to the emergence of vancomycin-resistant enterococci, and a high vancomycin minimal inhibitory concentration (MIC) >1.0_g/mL has been associated with poor outcome in patients with meticillin-resistant Staphylococcus aureus (MRSA) infection. In view of these limitations, there is a need for an alternative agent. We evaluated the clinical efficacy and safety of daptomycin given as an alternative agent in the treatment of Gram-positive catheter-related bloodstream infections (CRBSIs) in cancer patients. Between June 2013 and March 2015, 40 patients with probable or definite CRBSI caused by Gram-positive organisms were prospectively enrolled to receive daptomycin intravenous 6 mg/kg/day for up to 4 weeks. In addition, 40 historical matched control patients treated with vancomycin were retrospectively identified. The control group was matched based on underlying disease, organism and neutropenic status. The daptomycin group was comparable with the vancomycin group in terms of neutropenia rate, complications, adverse events, length of hospital stay and death. However, more patients in the daptomycin group achieved symptom resolution at 48 h compared with the vancomycin group (76% vs. 53%; P = 0.04). Similarly, more patients in the daptomycin group achieved microbiological eradication at 48 h compared with the vancomycin group (78% vs. 34%; *P*<0.001). Although not significant, nephrotoxicity was almost three-fold lower in the daptomycin group. The overall response was significantly better for daptomycin compared with vancomycin (68% vs. 32%; P = 0.003). In conclusion, compared with vancomycin, daptomycin treatment of Gram-positive CRBSI in cancer patients was significantly associated with earlier clinical and microbiological response as well as improved overall response.

Keywords: Immunocompromised patients, bloodstream infections, central venous catheters, gram-positive infections

Introduction
Malignancy patients stay at generous hazard for creating genuine diseases notwithstanding critical advances in disease treatment and strong consideration [1]. Despite the fact that neutropenia is as yet the most widely recognized pre-arranging factor, usually superimposed on other immunological shortfalls (for example debilitated cell or humoral invulnerability) every one of which is related with a particular range of disease [2]. Bacterial contaminations prevail amid the early periods of a neutropenic scene, while parasitic diseases happen all the more frequently in patients with delayed neutropenia. The range of contamination in disease patients experiences occasional changes and is affected upon by various variables including the idea of antineoplastic treatment, the utilization of chemoprophylaxis, remote therapeutic gadgets and geographic/neighborhood institutional components. Antimicrobial specialists are utilized for numerous signs in malignancy patients. These include: (a) prophylaxis, to avert diseases in high-chance patients, (b) pre-emptive treatment, when past colonization or the nearness of specific markers for contamination make it likely, (c) empiric treatment, when a disease is suspected however not yet reported, (d) directed or explicit treatment, when a disease has been archived and (e) upkeep or suppressive treatment in patients with intermittent contaminations. It is critical to know about the neighborhood the study of disease transmission and weakness/obstruction designs since they will manage the decision of antimicrobial specialists that are utilized at explicit establishments [3]. Substantial antimicrobial utilization especially in high-chance disease patients makes determination weights that lead to the development of safe small scale life forms. For example, numerous disease focuses have announced an expansion in quinolone safe microscopic organisms

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(fundamentally Escherichia coli and Pseudomonas aeruginosa) in patients accepting quinolone prophylaxis [4- 6]. The utilization of very broadspectrum operators, for example, the carbapenems has been related with the determination of Stenotrophomonas maltophilia and multi-sedate safe (MDR) Pseudomonas aeruginosa [7-9]. Expanded and delayed use of vancomycin has prompted the development of vancomycinresistant enterococci (VRE), vancomycin halfway, or vancomycin-safe Staphylococcus aureus secludes (VISA; VRSA) [10, 11]. Quinolone use has additionally been related with flare-ups of Clostridium difficile-related looseness of the bowels (CDAD) by strains which hyperproduce poisons An and B, bringing about progressively extreme sickness [12, 13]. Every one of these living beings are presenting noteworthy difficulties in the administration of contaminations in malignant growth patients. In this study, we evaluated the MRSA, VRSA and other drug resistance strains with the drug daptomycin.

Materials and Methods
Between June 2013 and March 2015, 40 patients with plausible or distinct CRBSI with Gram-positive living beings were tentatively selected to get daptomycin intravenous (i.v.) 6mg/kg/day for up to about a month. These patients were contrasted and 40 verifiable coordinated control patients with CRBSI who were treated with vancomycin. The control gather was coordinated by basic ailment, kind of living being and neutropenic status. Qualified patients were matured ≥18 years, with Gram-positive CRBSI, without a hotspot for the bacteraemia other than the CVC, and something like two indications of sepsis inside 48 h preceding daptomycin treatment. Patients were ineligible in the event that they had any of the accompanying: got treatment with an anti-toxin, for example, vancomycin, linezolid, tigecycline or daptomycin for ≥48 h inside 72 h of study prescription inception; pneumonia or conceivable convoluted CRBSI, (for example, osteomyelitis, endocarditis or septic thrombosis); creatine phosphokinase surpassing multiple times the furthest reaches of ordinary; an expected serum creatinine leeway of <30 mL/min (as per the Cockcroft– Gault recipe); a bilirubin surpassing multiple times the maximum furthest reaches of typical; or a background marked by excessive touchiness to lipopeptides. Patients were not enlisted on the off chance that they had pneumonia. On the off chance that a patient created pneumonia after investigation passage, linezolid or vancomycin was utilized as clinically demonstrated however not in blend with daptomycin. Daptomycin was then stopped however the patient was still pursued per convention exercises. These patients were prohibited from adequacy assessment. The choice whether to evacuate or trade the CVC inside 96 h of the beginning of bacteraemia was left to the carefulness of the essential doctor and the patient. In neutropenic patients where pneumonia couldn't be unquestionably prohibited or in patients who created aspiratory disease after investigation section, an expansive range _-lactam with great infiltration into the lungs could be included. Polymicrobial bacteraemia with Gram-negative creatures was treated with other antimicrobial operators. 2.2. Development and result All patients in the daptomycin arm were assessed amid treatment, toward the finish of treatment and post-treatment at 32±7 days after the last portion of study sedate. The essential endpoints were clinical and microbiological

reaction. Optional endpoints, including late inconvenience, contamination related passing and backslide inside 3 months following the underlying bacteraemia were likewise examined. 2.3. Definitions CRBSI was grouped by the ebb and flow Infectious Diseases Society of America (IDSA) criteria rules [2]. Clinical reaction was characterized as goals of clinical signs and side effects inside 48 h of starting proper investigation anti-infection treatment. Microbiological goals was characterized as annihilation of the microorganism from the circulation system inside 48 h of starting fitting investigation anti-infection treatment. Patients who did not have a recurrent blood culture inside the initial 2 weeks of starting proper investigation anti-infection treatment were prohibited from the examination. Determination was characterized as proceeded with separation of the Grampositive life form from the blood 72 h after inception of suitable anti-toxin treatment. Backslide was characterized as the repeat of bacteraemia inside the initial 3 months. A contamination related difficulty was characterized as the improvement of profound situated disease that was absent or associated at the beginning with bacteraemia however was consequently analyzed following multi week from commencement of concentrate anti-infection treatment. In general reaction was characterized as clinical and microbiological goals inside 72 h of inception of fitting (consider medicate) anti-toxin treatment, without proof of backslide, contamination related inconveniences or disease related mortality. Nephrotoxicity was characterized as an expansion of 0.5 mg/dL or ≥50% from gauge serum creatinine level whenever amid treatment. 2.4. Factual examination _2 test or Fisher's correct test were utilized to look at straight out factors, as suitable. Ceaseless factors were analyzed by Wilcoxon rank whole test attributable to deviation of the information from a typical dispersion. All tests were two-sided and measurable centrality was set at P≤0.05. Measurable examinations were performed utilizing SAS adaptation 9.1.

Results
Between June 2013 and March 2015, 40 patients with likely or clear CRBSI with Gram-positive life forms were tentatively enlisted to get daptomycin intravenous (i.v.) 6mg/kg/day for up to about a month. These patients were contrasted and 40 authentic coordinated control patients with CRBSI who were treated with vancomycin. The control bunch was coordinated by basic ailment, kind of creature and neutropenic status. Qualified patients were matured ≥18 years, with Gram-positive CRBSI, without a hotspot for the bacteraemia other than the CVC, and no less than two indications of sepsis inside 48 h preceding daptomycin treatment. Patients were ineligible on the off chance that they had any of the accompanying: got treatment with an anti-toxin, for example, vancomycin, linezolid, tigecycline or daptomycin for ≥48 h inside 72 h of study drug inception; pneumonia or conceivable entangled CRBSI, (for example, osteomyelitis, endocarditis or septic thrombosis); creatine phosphokinase surpassing multiple times the furthest reaches of typical; an expected serum creatinine freedom of <30 mL/min (as indicated by the Cockcroft– Gault recipe); a bilirubin surpassing multiple times the maximum furthest reaches of ordinary; or a past filled with extreme touchiness to lipopeptides. Patients were not selected on the off chance that they had pneumonia. In the event that a patient created pneumonia after

investigation section, linezolid or vancomycin was utilized as clinically demonstrated however not in blend with daptomycin. Daptomycin was then ceased however the patient was still pursued per convention exercises. These patients were prohibited from adequacy assessment. The choice whether to expel or trade the CVC inside 96 h of the beginning of bacteraemia was left to the circumspection of the essential doctor and the patient. In neutropenic patients where pneumonia couldn't be certainly prohibited or in patients who created aspiratory disease after investigation section, a wide range _-lactam with great infiltration into the lungs could be included. Polymicrobial bacteraemia with Gram-negative life forms was treated with other antimicrobial specialists. 2.2. Development and result All patients in the daptomycin arm were assessed amid treatment, toward the finish of treatment and post-treatment at 32±7 days after the last portion of study tranquilize. The essential endpoints were clinical and microbiological reaction. Auxiliary endpoints, including late complexity, contamination related demise and backslide inside 3 months following the underlying bacteraemia were likewise examined. 2.3. Definitions CRBSI was characterized by the flow Infectious Diseases Society of America (IDSA) criteria rules [2]. Clinical reaction was characterized as goals of clinical signs and manifestations inside 48 h of starting suitable investigation anti-infection treatment. Microbiological goals was characterized as destruction of the microorganism from the circulation system inside 48 h

of starting proper examination anti-toxin treatment. Patients who did not have a recurrent blood culture inside the initial 2 weeks of starting suitable examination anti-toxin treatment were barred from the investigation. Ingenuity was characterized as proceeded with seclusion of the Grampositive living being from the blood 72 h after inception of fitting anti-toxin treatment. Backslide was characterized as the repeat of bacteraemia inside the initial 3 months. A disease related complexity was characterized as the improvement of profound situated contamination that was absent or associated at the beginning with bacteraemia yet was in this manner analyzed following multi week from commencement of concentrate anti-infection treatment. Generally speaking reaction was characterized as clinical and microbiological goals inside 72 h of inception of fitting (think about medication) anti-infection treatment, without proof of backslide, contamination related confusions or disease related mortality. Nephrotoxicity was characterized as an expansion of 0.5 mg/dL or ≥50% from benchmark serum creatinine level whenever amid treatment. 2.4. Factual investigation _2 test or Fisher's correct test were utilized to analyze downright factors, as proper. Persistent factors were analyzed by Wilcoxon rank whole test attributable to deviation of the information from a typical circulation. All tests were two-sided and measurable essentialness was set at P≤0.05. Measurable investigations were performed utilizing SAS rendition 9.1.

Table 1: aracteristics of patients in the two study groups: daptomycin versus vancomycin.

haracteristic	Daptomycin (N = 38)		Vancomycin (N = 40)		P-value
Ge (years) [median (range)]	53	(17–81)	61	(16–79)	
Ender (male)	25	(66)	26	(65)	
Ancer type					
Haematological	27	(71)	28	(70)	
Solid tumour	11	(29)	12	(30)	
Epsis at presentation	36	(95)	36	(90)	
Eutropenia (ANC < 500/ L)	17	(45)	19	(48)	0.76
Isk factor: BMT transplant	5	(13)	7	(18)	0.81
Allogeneic	4		5		
Autologous	1		2		
CU admission	4	(11)	2	(5)	0.34
O. of positive cultures [median (range)]	2	(1–14)	2	(1–9)	0.12
Atheter management					0.38
Catheter removed	24	(63)	27	(68)	
Catheter exchanged	10	(26)	6	(15)	
Catheter continued	4	(11)	7	(18)	
Ime to catheter removal or exchange since bacteraemia (days) [median (range)]	4	(3–35)	3	(0–12)	
Uration of antibiotic treatment (days) [median (range)]	8	(3–26)	8	(2–34)	
Ancomycin MIC (g/mL)					
≤0.5	9	(24)	8	(20)	
1–2	26	(68)	32	(80)	
>2	2	(5)	0		
Resistant	1	(3)	0		
Reatinine (mg/dL) [median (range)]					
At baseline	0.85 (0.6–1.9)		0.9 (0.2–2.7)		0.76
At end of therapy	0.9 (0.5–1.8)		0.9 (0.4–3.5)		0.81
Highest level during therapy	0.9 (0.7–2.7)		1.0 (0.6–3.5)		0.34
Ephrotoxicity	3	(8)	9	(23)	0.12

Table 2: Patients in the two study groups: daptomycin versus vancomycin [n (%)].

Utcome	Daptomycin (N = 38)	Vancomycin (N = 40)	P-value
Ymptom resolution within 48 h from starting using antibiotica	28/37 (76)	20/38 (53)	0.04
Ymptom resolution within 7 days from starting using antibiotica	33/37 (89)	33/38 (87)	>0.99
Icrobiological resolution within 48 h from starting using antibioticb	29/37 (78)	11/32 (34)	<0.001
Icrobiological resolution within 7 days from starting using antibioticb	34/37 (92)	27/32 (84)	0.46
Ength of hospital stay from date of bacteraemia (days) [median (range)]	8 (2–53)	9 (2–52)	0.68
ate infection-related complications	0 (0)	1 (3)	>0.99
Elapsec	3/37 (8)	0/38 (0)	0.12
Nfection-related deathd	1/38 (3)	1/39 (3)	>0.99
Verall responsee	25/37 (68)	11/34 (32)	0.003

Discussion
In the daptomycin arm, 12 patients experienced a transthoracic echocardiogram (TTE) and 2 patients a transoesophageal echocardiogram. In the vancomycin arm, 13 patients experienced a TTE. Every one of the echocardiograms performed were negative for endocarditis. Four of the eight patients who experienced a venous Doppler ultrasound in the daptomycin arm had proof of thrombophlebitis that happened 1–6 days after the commencement of daptomycin. Three of them had their catheter expelled and one had his catheter traded preceding the analysis of thrombophlebitis. One of the patients who had his catheter evacuated had a backslide scene. In the vancomycin arm, one of the four patients who experienced a venous Doppler ultrasound (three patients) or a venogram (one patient) had proof of thrombophlebitis that happened 5 days after the commencement of vancomycin and had his catheter evacuated on the day that thrombophlebitis was analyzed. These scenes of thrombophlebitis were not considered as a late disease related inconvenience since they happened inside the main seven day stretch of commencement of the anti-toxin. For the three patients who backslid, one patient held his catheter, which was along these lines evacuated after he backslid. This patient did not experience an echocardiogram or a Doppler ultrasound. The second patient had his catheter evacuated however had septic thrombophlebitis that was analyzed 1 day after he was begun on daptomycin; no echocardiogram was acquired. The third patient had his catheter traded; this patient had a negative TEE, yet no venous Doppler ultrasound was acquired. The conceivable relationship of age, bone marrow transplantation and CVC the board with clinical reaction Cancer patients treated with daptomycin accomplished before manifestation goals and microbiological destruction contrasted and patients treated with vancomycin. Moreover, daptomycin was related with an unrivaled in general reaction that incorporated a result free of contamination related confusions, mortality and backslide. There are a few reasons that can represent these discoveries. Initial, a few examinations demonstrated a more noteworthy probability of treatment disappointment when vancomycin was utilized to treat patients contaminated with MRSA strains that had higher MICs to vancomycin (>1_g/mL) [6]. The majority of the Gram-positive living beings causing CRBSI in this present examination had a vancomycin MIC ≥1.0_g/mL. To accomplish better introductory clinical reaction with vancomycin treatment, Hidayat et al. [6] prescribed forceful vancomycin dosing to accomplish trough vancomycin levels >15_g/mL while treating MRSA strains, regardless of the MIC. Nonetheless, notwithstanding accomplishing the objective trough focus, patients with MRSA diseases with a higher MIC (≥2_g/mL) had bring down end-of-treatment

reaction rate and a pattern toward a higher contamination related death rate [6]. Besides, nephrotoxicity happens fundamentally more regularly in patients with high vancomycin trough focuses [8]. Jeffres et al. [8] demonstrated that forceful vancomycin dosing to accomplish serum trough fixations ≥15_g/mL is related with a higher danger of nephrotoxicity. Fowler et al. [9] found that daptomycin has a comparative clinical achievement rate contrasted and standard antistaphylococcal antimicrobial treatment, with the dvantage of a fundamentally lower renal brokenness rate when contrasted and standard treatment (11% versus 26%; P = 0.004). Consequently, daptomycin could have a superior security profile contrasted with vancomycin with respect with nephrotoxicity. Despite the fact that the danger of nephrotoxicity was not fundamentally bring down in the daptomycin gathering, it would in general be three-overlap lower than the vancomycin gathering. Second, daptomycin is more quickly bactericidal than vancomycin. Fuchs et al. [10] exhibited in time-kill thinks about that daptomycin is more quickly bactericidal than vancomycin and linezolid. Vancomycin has been appeared to have a lessening bactericidal action against vancomycin-tolerant Gram-positive life forms causing diseases in malignancy patients. Sakoulas et al. [4] demonstrated a relationship between clinical achievement rate and the bactericidal movement of vancomycin. Higher reaction rates were seen when MRSA was slaughtered by 72 h, and higher vancomycin treatment disappointment was seen with decreased executing rates [4]. This improved bactericidal movement of daptomycin may clarify the prior clinical and microbiological goals of the disease related with daptomycin in the flow examine. This is especially vital since the predominant generally speaking reaction related with daptomycin in the present examination was for the most part determined by the before clinical and microbiological reaction to daptomycin. Third, daptomycin is fundamentally more dynamic than vancomycin against Gram-positive living beings inserted in biofilm on a catheter surface [5, 11]. Past examinations have demonstrated that vancomycin has constrained movement against staphylococci installed in biofilm [5, 12]. Roveta et al. [13] demonstrated that daptomycin, at focuses that can be come to amid treatment, can restrain sludge union and incite ooze interruption in beginning and develop biofilms created by various strains of staphylococci. Information from our research center demonstrated that daptomycin is exceptionally powerful in annihilating staphylococci and VRE inserted in biofilm [5, 14]. Essentially, Weiss et al. [11] found that daptomycin is increasingly successful against set up S. aureus biofilms than either linezolid or vancomycin. Gram-positive microorganisms installed in biofilm on the catheter surface are the wellspring of bacteraemia in CRBSI. Consequently, the predominant movement of daptomycin in

destroying Gram-positive microorganisms installed in biofilm may have added to the better generally reaction related with this anti-infection in the present examination. Our information are hence steady with different past distributed investigations that have shown the adequacy of daptomycin in the treatment of bacteraemia caused by different Gram-positive life forms [7, 15]. Segreti *et al*. [7] demonstrated that daptomycin was exceptionally adequate in the treatment of 31 patients with Gram-positive bacteraemia, with a clinical reaction rate of 77%. In like manner, Sakoulas *et al*. [15] found a clinical accomplishment of 89% with the utilization of daptomycin for Gram-positive bacteraemia. Another preferred standpoint of daptomycin is that it is given once day by day and does not require checking of serum levels. Daptomycin pharmacodynamic contemplates confirmed that a once-day by day dosing routine exhibits a decent viability and security profile. Thusly, oncedaily treatment with daptomycin is more convenient and can enhance the nature of consideration for patients with CRBSI contrasted and current standard treatment with vancomycin or different specialists that require various every day i.v. dosing. It may likewise enhance consistence and be increasingly helpful for locally situated treatment. This investigation is liable to a few restrictions. The first is the investigation structure. One a player in the investigation was an imminent associate examination where the patients enlisted were treated with daptomycin. This accomplice was contrasted and a review companion of authentic control patients who were treated with vancomycin. Patients in the vancomycin arm were not on characterized planned clinical conventions, and manifestations and signs were not reliably checked. Sequential blood societies were not constantly accessible amid or after contaminations, and bacteraemia goals was not constantly archived. Thus, we may have thought little of or overestimated the length of genuine bacteraemia and the repeat rate. A second confinement is that the majority of the patients in the daptomycin arm got earlier anti-microbial treatment for <48 h, which could have added to a shorter length to side effect goals and microbiological annihilation.

Conclusions
In disease patients with CRBSI, daptomycin was altogether connected with before clinical and microbiological reaction contrasted and vancomycin. What's more, daptomycin was related with a fundamentally better generally speaking reaction and would in general be related with a lower nephrotoxicity rate. Further planned randomized clinical preliminaries are expected to assess the cost investment funds just as the enhanced personal satisfaction related with the utilization of daptomycin.

References
1. Rolston KVI. Challenges in the treatment of infections caused by gram-positive and gram-negative bacteria in patients with cancer and neutropenia. Clin Infect Dis. 2005; 40:S246-S252.
2. Rolston KVI, Bodey GP. Infections in patients with cancer. In Cancer Medicine e7, Kufe DW, Bast RC, Jr Hait WN, Hong WK, Pollock RE, Weichselbaum RR, Holland JF, Frei E, III (eds). BC Decker: Hamilton, Ontario, 2006, 2222-2245.
3. Hughes WT, Armstrong D, Bodey GP *et al*. Guidelines for the use of antimicrobial agents in neutropenic patients with cancer. Clin Infect Dis. 2002; 34:730-751.
4. Rolston KV, Jones RN, Coyle EA, Prince RA. Emergence of quinolone resistant *Escherichia coli* at a cancer center. [Abst. #506]. In Programs and Abstracts of the 45th Annual Meeting of the Infectious Diseases Society of America (IDSA). Infectious Diseases Society of America: San Diego, CA, 2007, 4-7.
5. Gomez L, Garau J, Estrada C *et al*. Ciprofloxacin prophylaxis in patients with acute leukemia and granulocytopenia in an area with a high prevalence of ciprofloxacin-resistant *Escherichia coli*. Cancer. 2003; 97:419-424.
6. Cattaneo C, Quaresmini G, Casari S *et al*. Recent changes in bacterial epidemiology and the emergence of fluoroquinolones resistant *Escherichia coli* among patients with haematological malignancies: results of a prospective study on 823 patients at a single institution. J Antimicrob Chemother. 2008; 61:721-728.
7. Ohmagari N, Hanna H, Graviss L *et al*. Risk factors for infections with multidrug-resistant *Pseudomonas aeruginosa* in patients with cancer. Cancer. 2005; 104:205-212.
8. Safdar A, Rolston KV. *Stenotrophomonas maltophilia*: changing pectrum of a serious bacterial pathogen in patients with cancer. Clin Infect Dis. 2007; 45:1602-1609.
9. Hidayat LK, Hsu DI, Quist R, Shriner KA, Wong-Beringer A. High-dose vancomycin therapy for methicillin-resistant *Staphylococcus aureus* infections: efficacy and toxicity. Arch Intern Med. 2006; 166:2138-44.
10. Segreti JA, Crank CW, Finney MS. Daptomycin for the treatment of Gram positive bacteremia and infective endocarditis: A retrospective case series of 31 patients. Pharmacotherapy. 2006; 26:347-52.
11. Jeffres MN, Isakow W, Doherty JA, Micek ST, Kollef MH. A retrospective analysis of possible renal toxicity associated with vancomycin in patients with health care-associated methicillin-resistant *Staphylococcus aureus pneumonia*. Clin Ther. 2007; 29:1107-15.
12. Fowler Jr VG, Boucher HW, Corey GR, Abrutyn E, Karchmer AW, Rupp ME *et al*. *S*. aureus Endocarditis and Bacteremia Study Group. Daptomycin versus standard therapy for bacteremia and endocarditis caused by Staphylococcus aureus. N Engl J Med. 2006; 355:653-65.
13. Fuchs PC, Barry AL, Brown SD. *In vitro* bactericidal activity of daptomycin against *Staphylococci*. J Antimicrob Chemother. 2002; 49:467-70.
14. Weiss EC, Zielinska A, Beenken KE, Spencer HJ, Daily SJ, Smeltzer MS. Impact of sarA on daptomycin susceptibility of *Staphylococcus aureus* biofilms *in vivo*. Antimicrob Agents Chemother. 2009; 53:4096-102.
15. Petersen PJ, Bradford PA, Weiss WJ, Murphy TM, Sum PE, Projan SJ. *In vitro* and *in vivo* activities of tigecycline (GAR-936), daptomycin, and comparative antimicrobial agents against glycopeptide-intermediate *Staphylococcus aureus* and other resistant Gram-positive pathogens. Antimicrob Agents Chemother. 2002; 46:2595-601.

16. Roveta S, Marchese A, Schito GC. Activity of daptomycin on biofilms produced on a plastic support by *Staphylococcus* spp. Int J Antimicrob Agents. 2008; 31:321-8.
17. Raad II, Hanna HA, Boktour M, Chaiban G, Hachem RY, Dvorak T *et al*. Vancomycin-resistant *Enterococcus faecium*: catheter colonization, esp gene, and decreased susceptibility to antibiotics in biofilm. Antimicrob Agents Chemother. 2005; 49:5046-50.
18. Sakoulas G, Golan Y, Lamp KC, Friedrich LV, Russo R. Daptomycin in the treatment of bacteremia. Am J Med. 2007; 120(1):S21-7.