2011;29(15):1971-9.

7. Bejar R, Stevenson K, Abdel-Wahab O, Galili N, Nilsson B, Garcia-Manero G, et al. Clinical effect of point mutations in myelodysplastic syndromes. N Engl J Med. 2011;364(26):2496-506.

8. Fernandez-Mercado M, Burns A, Pellagatti A, Giagounidis A, GermingU, Agirre X, et al. Targeted re-sequencing analysis of 25 genes commonly mutated in myeloid disorders in del(5q) myelodysplastic syndromes. Haematologica. 2013;98(12):1856-64.

9. Bejar R, Stevenson KE, Caughey BA, Abdel-Wahab O, Steensma DP, Galili N, et al. Validation of aprognostic model and the impact of mutations in patients with lower-riskmyelodysplastic syndromes. J Clin Oncol. 2012;30(27):3376-82.

10. Mallo M, Del Rey M, Ibáñez M, Calasanz MJ, Arenillas L, Larráyoz MJ, et al. Response to lenalidomide in myelodysplastic syndromes with del(5q): influence of cytogenetics and mutations. Br J Haematol. 2013;162(1):74-86.

11. Sebaa A, Ades L, Baran-Marzack F, Mozziconacci MJ, Penther D, Dobbelstein S, et al. Incidence of 17p deletions and TP53 mutation in myelodysplastic syndrome and acute myeloid leukemia with 5q deletion. Genes Chromosomes Cancer. 2012;51(12):1086-92.

12. Greenberg PL, Tuechler H, Schanz J, Sanz G, Garcia-Manero G, SoléF,et al. Revised International Prognostic Scoring System for myelodysplastic syndromes. Blood. 2012;120(12):2454-65.

13. Schanz J, Tüchler H, Solé F, Mallo M, Luño E, Cervera J, et al. New comprehensive cytogenetic scoring system for primary myelodysplastic syndromes (MDS) and oligoblastic acute myeloid leukemia after MDS derived from an international database merge. J Clin Oncol. 2012;30(8):820-9.

14. Katsanis SH, Katsanis N. Molecular genetic testing and the future of clinical genomics. Nat Rev Genet. 2013;14(6):415-26.

15. Rehm HL. Disease-targeted sequencing: a cornerstone in the clinic. Nat Rev Genet. 2013;14(4):295-300.

The role of antibiotic stewardship in limiting antibacterial resistance among hematology patients

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Haematologica has published European guidelines for empirical and targeted antibacterial therapy for febrile neutropenic patients in the era of emerging resistance (ECIL-4). Indeed, collateral damage by broad-spectrum antibiotic therapy includes selection of multidrug resistant pathogens, and increased predisposition to infection by fungi and *Clostridium difficile*. Antibiotic resistance has become a major public health concern, with fears expressed that we will soon run out of antibiotics.[1]

This is critically important for the management of hematologic cancer patients who receive consecutive courses of immunosuppressive treatments, resulting in varying degrees and durations of neutropenia. During immunosuppressive therapy, many patients will develop fever and are prescribed antibiotics for prevention or treatment of infection.

Several recent studies have shown an increasing prevalence of multidrug-resistance among Gram-negative pathogens in hematology patients. In one recent prospective observational study, the only independent risk factors for the acquisition of multiresistant pathogens were prior antibiotic exposure (OR 3.57; 95%CI: 1.63-7.80) and urinary catheterization (OR 2.41; 95%CI: 1.01-5.74).[2]

The use of broad-spectrum antibiotics also is a well-known risk factor for invasive fungal infection in hematology patients. Chronic disseminated candidiasis in patients with acute leukemia and/or bone marrow transplantation has been independently associated with the use of quinolone antibiotics in particular,[3] and a recent observational study showed that 92% of patients with candidemia had received broad-spectrum antibiotics.[4] Important risk factors for *C. difficile*-associated disease in hematology patients include the number and duration of antibiotics

received, with particular risk attached to certain classes, such as cephalosporins.[5]

For all these reasons, it is becoming more and more necessary to optimize antibiotic use in hematology patients, and to deploy antimicrobial stewardship strategies that have shown benefit in other categories of patients. Key components of stewardship include: i) de-escalation of broad empirical regimens once the pathogen is identified; ii) dose optimization in critically-ill patients;[6] and iii) the long tradition of prudent antibiotic use in Northern European countries which is reflected in their low resistance rates, as shown in, for example, the European Antimicrobial Resistance Surveillance Network EARS-Net.[7]

Antimicrobial stewardship aims to limit the unnecessary use of broad-spectrum antibiotics and involves a continuous effort by healthcare institutions to optimize antimicrobial use in hospitalized patients. Its targets are to improve outcomes, ensure cost-effective therapy, and to reduce adverse effects of antimicrobial use, including resistance.[8] Control of infection is closely related to antimicrobial stewardship programs, as it aims to prevent the spread of the resistant organisms, when these are selected locally or introduced *via* patient transfers. The successful implementation of antimicrobial stewardship and infection control programs complement each other in limiting the number of infections caused by multidrug-resistant organisms.

Infection control strategies found their way into hematology many years ago, and guidelines in this field are published elsewhere.[9] The most important measures in hematology are: i) enforcement of hand hygiene by using alcohol-based hand-rubs; ii) standard barrier precautions; iii) enforcement of isolation criteria for patients colonized or

infected with multidrug-resistant organisms, e.g. methicillin-resistant *Staphylococcus aureus* (MRSA) or Extended-Spectrum Beta-lactamase (ESBL)-producing organisms; iv) cohorting of infected patients; v) the use of single rooms for hematologic stem cell transplant (HSCT) recipients; and vi) High-Efficiency Particulate Air (HEPA) filtration for allogeneic HSCT recipients.[10] Antisepsis with alcohol-based hand-rubs is the single most effective hygienic measure in healthcare institutions and has led to a reduction in overall nosocomial (hospital-acquired) infection and MRSA transmission.[11]

There are several key aspects to implementing antimicrobial stewardship for hematologic cancer patients. These require collaboration between the hematologist/oncologist, the microbiology laboratory, hospital pharmacy and an infectious diseases (ID) consultation service.

1) Local surveillance of antibiotic resistance, antibiotic consumption and patient outcomes, including monitoring reports.

Local surveillance in hematology/oncology centers should be carried out, with a review of the situation twice yearly. It includes data on the identity and resistance patterns of blood isolates. Indicator organisms, or a 'top 10' list of relevant pathogens should be defined. These are likely to include the Gram-negative bacteria, *Escherichia coli, Klebsiella, Pseudomonas aeruginosa, Enterobacter, Serratia* and *Acinetobacter*, and the Gram-positives *S. aureus*, coagulase-negative staphylococci, *Enterococcus* and alpha-

hemolytic streptococci. In addition, antibiotic consumption should be monitored, preferentially as Defined Daily Doses (DDD)/100 patient days or Days on Therapy (DOT) to allow for comparisons with other centers.[12] The DOT unit is particularly useful for pediatric populations.

Policy decisions need also to be made: i) whether or not to use antibiotic prophylaxis in certain categories of patients; ii) the need and frequency of surveillance cultures to detect colonization, especially when antibiotic prophylaxis is used.[10] Good surveillance data allow for fast and targeted adaptation of empirical regimens and/or prophylaxis.[13] Resistance patterns of colonizing microorganisms are often, but not always, indicative of the resistance patterns of subsequent blood isolates in these patients. Microbiological investigation of likely infections should always be carried out, irrespective of what is known or suspected from previous surveillance cultures. In addition, outcome data for bacteremic patients (ICU stay, total length of stay, total and attributable mortality) of the hematology unit should also be collected to determine and review the coverage and adequacy of the local empirical antibiotic regimens. Colonization with resistant organisms should impact the choice of empirical therapy regimens only if these organisms have caused significant morbidity and mortality in previous hematology patients.

2. Multidisciplinary protocols and algorithms on the diagnosis, prevention and treatment of infections should be developed in col-

Table 1. Principles of antimicrobial stewardship for hematology patients.

– The initiation of empirical antibiotic treatment should be prompted by fever and clinical signs, and not by C-reactive protein or other biomarkers, as studies of these have shown inconsistent results;[10] antibiotics should not be initiated on the basis of colonization by resistant organisms.

– Empirical antibiotic treatment should never be started or changed before taking at least two blood cultures, along with relevant specimens from the clinically-suspected sites of infection

– Risk stratification (low/high risk) for infection should be undertaken according to the Multinational Association for Supportive Care in Cancer (MASCC) score,[14] and should be considered in the empirical therapy algorithm[10]

– The spectrum of initial empirical therapy should, at the very least, cover common virulent Enterobacteriaceae (*Escherichia coli* and *Klebsiella pneumoniae*), also *Pseudomonas aeruginosa*, and, depending on the setting, and/or prophylaxis strategies, *S. aureus* including MRSA, but not coagulase-negative staphylococci.

– Individualized risk assessment for multi-resistant pathogens should guide the development of the management algorithms.[2]

– Strategies to reassess empirical antibiotic therapy after 2-3 days (i.e. once microbiology results are available) should be implemented, with de-escalation if possible.

– The algorithms should guide treatment duration, as outlined in point 2.

– Individualized risk assessments for infection can be undertaken, e.g. identifying clinical parameters that have been associated in the literature with a risk for secondary infection after a first episode of fever and neutropenia.[15]

Table 2. Summary of antimicrobial stewardship recommendations for hematology patients.

1. Produce epidemiological data on blood isolates and colonization cultures (especially if prophylaxis is used) on a regular basis.

2. Record infection-related outcome data (length of stay, infection-related mortality).

3. Discuss microbiology, antibiotic use and outcome data in a local multidisciplinary working group/policy committee consisting of hematologists/ ID physicians/microbiologists/ID pharmacists.

4. Develop multidisciplinary protocols and algorithms on diagnosis, treatment and prophylaxis of fever during neutropenia, including on duration of therapy for the inpatient as well as outpatient management.

5. Provide ID training for hematologists and clinical hematology training for ID physicians/microbiologists and pharmacists.

laboration with ID specialists and medical microbiologists and updated to reflect changes in bacterial antimicrobial susceptibilities in the unit.

Once the local surveillance data are available, they should be used to develop or adapt local protocols and algorithms. A few important principles to be considered are listed in Table 1.

3. Swift reporting of positive clinical cultures and implementation of rapid techniques for bacterial identification and resistance patterns by the microbiology laboratory to control the duration of treatment and to facilitate re-assessment of the antibiotic therapy.

The speed of communicating microbiological results to the clinicians by the laboratory is paramount for prompt adaptation of antimicrobial regimens.[16] Re-assessment of empirical antimicrobial therapy with the help of the microbiological results after 2-3 days allows for de-escalation to targeted, narrower-spectrum antibiotics appropriate to the susceptibilities of the pathogens isolated. A clinical example of de-escalation strategy is shown in the Appendix and illustrates how de-escalation works in an individual patient. For details and background of the prophylaxis strategy in this example, see the method section of the publication by Slobbe *et al.*[17,18]

Experience in the Netherlands has shown that broad-spectrum empirical therapy in neutropenic fever can also be replaced by narrower-spectrum oral agents, mitigating selection for resistance. De Marie *et al.* and Cornelissen *et al.* reported that intravenous (i.v.) antibiotics could be discontinued early in febrile patients with persistent neutropenia who received decontamination or oral regimens (neomycin/polymyxin B or co-trimoxazole or ciprofloxacin and an antifungal drug).[19,20] Fifteen years later, Slobbe *et al.* showed that, for the same category of high-risk patients, it was safe to discontinue empirical imipenem for fever after 72 h if, following a standardized protocol, no infectious eti-

ology was documented.[17] In the ECIL-4 guideline on empirical therapy, the suggested duration of antimicrobial therapy is 72 h in stable patients who are afebrile for more than 48 h and have no microbiological or clinical documentation of infection (see Averbuch *et al.* in this issue of Haematologica[21]).

It should be stressed that, in the series described by Slobbe *et al.*, empirical antibiotics were stopped after 72 h for patients on fluoroquinolone prophylaxis with meticulous clinical and microbiological follow up, including twice-weekly surveillance cultures and protective isolation with alternative prophylactic oral antibiotics if surveillance cultures detected ciprofloxacin-resistant Gram-negative bacteria.[17] Although prophylaxis with quinolones exerts a significant selection pressure for colonization and infection by fluoroquinolone-resistant organisms, a recent Cochrane review confirmed earlier meta-analyses that the reduction in mortality and infection rates in high-risk patients still outweighs the risk of resistance, the costs and occasional adverse events.[22] Nevertheless, quinolone prophylaxis should be employed only in selected high-risk patients, not in all neutropenic patients.[12,17]

4. Optimization of dosing regimens using pharmacodynamic principles.

Individualization of antibiotic regimens according to: i) minimal inhibitory concentration (MIC) data for the causative pathogen in the individual or on local surveillance data; and ii) patients' characteristics, can optimize treatment outcomes. This should benefit neutropenic patients who have a malfunctioning immune system, and particularly high-risk patients and those whose pathogens have only borderline antibiotic susceptibility.[23] Several pharmacological issues should be taken into consideration.[24] In particular, high-risk hematologic patients have large volumes of distribution and/or capillary leak syndrome and/or a more rapid

Appendix

Case

A 26-year old woman with acute myeloid leukemia has been treated with 2 remission-induction courses of chemotherapy. There has been no microbiologically or clinically documented infection during the induction phase, only fever of unknown origin. She is currently in complete remission and has been hospitalized for consolidation therapy with high-dose cytarabine.

Today is Day 7 after the start of chemotherapy following which she is expected to be neutropenic (< 0.1x10⁹/L) for at least ten days.

On Day -5 she was started on prophylactic ciprofloxacin 500 mg q12h, colistin 200 mg q6h and fluconazole 400 mg q24h orally. Colonization cultures ten days after the start of prophylaxis showed no ciprofloxacin-resistant Gram-negative bacteria and no growth of S. aureus*.*

This morning at 7:30 am she has developed watery diarrhea. She experiences chills and rigors, and her body temperature quickly rises from 37.5°C at 8:00 am to 39.8°C at 10:00 am. She has no respiratory complaints, no obnubilation, and is not oliguric. On clinical examination, she has painful oral mucositis grade II, multiple petechiae on the legs, and her blood pressure has dropped from 130/80 mmHg to 100/60 mmHg. She has a tunneled subclavia catheter; the insertion site and tunnel are unremarkable. Her abdomen is distended but normal bowel sounds are heard at auscultation and palpation is only slightly painful. The diagnosis of febrile neutropenia is made.

Hemoglobin is 9.3 g/dL; hematocrit 27.7%; neutrophil count less than 0.1x10⁹/L and platelets 23x10⁹/L. The rest of the laboratory tests and a chest X-ray are unremarkable. According to the ward protocol, 1 set of blood cultures is drawn from the catheter, 2 sets of blood cultures are drawn by venipuncture and urine is collected for culture.

Piperacillin/tazobactam 4.5 g q8h iv is started.

The next day, the patient has clinically improved, but she is still febrile (38.5°C). The microbiology laboratory reports growth of Gram-positive cocci (presumably streptococci) from 5 out of 6 blood culture bottles drawn on Day 7. The day after (Day 9), the laboratory reports further identification of the isolates: viridans streptococci, susceptible to penicillin. Piperacillin/tazobactam is stopped. Benzylpenicillin (penicillin G), 2MU q4h i.v. is administered and ciprofloxacin and fluconazole prophylaxis is continued. All antimicrobial agents are stopped after ten days when the neutrophil count has risen to more than 0.5x10⁹/L.

clearance of certain drugs. In general, higher doses are needed to obtain adequate serum concentrations, and individual pharmacokinetic variability is high. For some classes of antibiotics, few pharmacokinetic data are available for patients with fever and neutropenia. However, dosing regimens may be predicted from other categories of patients with large volumes of distribution such as ICU patients with critical illness.[24]

Three patterns of antibiotic activity are important to consider when defining the optimal dosage of different antibiotic classes:[25]

- concentration-dependent killing is seen for aminoglycosides, with a considerable post-antibiotic effect;

- beta-lactam antibiotics display time-dependent killing with little or no post-antibiotic effect;

- quinolones and vancomycin have activity related to the Area Under the time Concentration Curve (AUC):MIC ratio, reflecting both the serum peak and the time above MIC.

In the case of beta-lactams with short half-life, optimization of dosing may be obtained by extending the infusion time prolonging the period that the free-drug levels remain above the MIC. Recent retrospective studies support this optimized dosing in critically-ill patients,[26,27] with relevant data available for piperacillin-tazobactam, ceftazidime, cefepime and meropenem.[23] The choice of continuous versus extended infusion of beta-lactams should be guided by the stability of the drug at room temperature.[23]

Aminoglycoside dosing is optimized via the administration of large (once daily) doses up to 7 mg/kg for gentamicin and tobramycin and up to 20 mg/kg for amikacin, aiming at a serum peak/MIC ratio of 8-12 (individual MIC or local data), which also minimizes nephrotoxicity.[28] Active therapeutic drug monitoring[29] should be performed to avoid toxic drug levels arising via accumulation. Optimization of vancomycin dosing is achieved by using a loading dose (up to 35 mg/kg) and ensuring optimal trough levels of approximately 15 mg/L, either by twice-daily administration or continuous infusion, in order to achieve an $(AUC)_{0-24}$: MIC ratio of more than 400, which correlates with positive outcomes in patients with MRSA bacteremia.[30] Nephrotoxicity of vancomycin, which mainly occurs if they are combined with other nephrotoxic drugs, should be monitored.[31]

5. Frequent multidisciplinary rounds.

Clinical rounds, including discussion of patient histories and interactive, bedside education on antimicrobial drug use and infection control, are recommended. A summary of recommendations is presented in Table 2.

In conclusion, antimicrobial stewardship is crucial in the era of growing microbial resistance. Although not yet broadly introduced in hematology centers, it is warranted by the resistance crisis and the scarce development of new antibiotics, in particular those with new targets or mechanisms of action or with activity *versus* Gram-negative pathogens. Already, resistance developments are jeopardizing the improved outcomes for hematology patients that have been achieved by medical advances over the last decade. Antimicrobial stewardship aims to diminish unnecessary antibiotic exposure and to minimize collateral damage by broad-spectrum antibiotics. Infection control measures are complementary, to prevent the spread of resistant

pathogens. De-escalation strategies have been successfully used in other areas of medicine, including the ICU, to decrease selection pressure by prolonged unnecessary regimens of broad-spectrum antibiotics. Their multidisciplinary implementation in hematology is much to be welcomed.

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References

1. Livermore DM. Has the era of untreatable infections arrived? J Antimicrob Chemother. 2009;6(Suppl 1):i29-36.
2. Gudiol C, Tubau F, Calatayud L, Garcia-Vidal C, Cisnal M, Sanchez-Ortega I, et al. Bacteraemia due to multidrug-resistant Gram-negative bacilli in cancer patients: risk factors, antibiotic therapy and outcomes. J Antimicrob Chemother. 2011;66(3):657-63.
3. Sallah S, Wan JY, Nguyen NP, Vos P, Sigounas G. Analysis of factors related to the occurrence of chronic disseminated candidiasis in patients with acute leukemia in a non-bone marrow transplant setting: a follow-up study. Cancer 2001;92(6):1349-53.
4. Das I, Nightingale P, Patel M, Jumaa P. Epidemiology, clinical characteristics, and outcome of candidemia: experience in a tertiary referral center in the UK. Int J Infect Dis. 2011;15(11):e759-63.
5. Gifford AH, Kirkland KB. Risk factors for Clostridium difficile-associated diarrhea on an adult hematology-oncology ward. Eur J Clin Microbiol Infect Dis. 2006;25(12):751-5.
6. Kaki R, Elligsen M, Walker S, Simor A, Palmay L, Daneman N. Impact of antimicrobial stewardship in critical care: a systematic review. J Antimicrob Chemother. 2011;66(6):1223-30.
7. European Centre for Disease Prevention and Control. EARS-Net Database. Available from: http://ecdc.europa.eu/en/activities/surveillance/EARS-Net/Pages/Database.aspx
8. MacDougall C, Polk RE. Antimicrobial stewardship programs in health care systems. Clin Microbiol Rev. 2005;18(4):638-56.
9. Siegel JD, Rhinehart E, Jackson M, Chiarello L; Health Care Infection Control Practices Advisory Committee. Am J Infect Control. 2007;35(10 Suppl 2):S65-164.
10. Freifeld AG, Bow EJ, Sepkowitz KA, Boeckh MJ, Ito JI, Mullen CA, et al. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the Infectious Diseases Society of America. Clin Infect Dis. 2011;52(4):e56-93.
11. Pittet D, Hugonnet S, Harbarth S, Mourouga P, Sauvan V, Touveneau S, et al. Effectiveness of a hospital-wide programme to improve compliance with hand hygiene. Infection Control Programme. Lancet. 2000;356(9238):1307-12.
12. Polk RE, Fox C, Mahoney A, Letcavage J, MacDougall C. Measurement of adult antibacterial drug use in 130 US hospitals: comparison of defined daily dose and days of therapy. Clin Infect Dis. 2007;44(5):664-70.
13. Vos MC, Endtz HP, Horst-Kreft D, Doorduijn J, Lugtenburg E, Verbrugh HA, et al. Candida krusei transmission among hematology patients resolved by adapted antifungal prophylaxis and infection control measures. J Clin Microbiol. 2006;44(3):1111-4.
14. Klastersky J, Paesmans M, Rubenstein EB, Boyer M, Elting L, Feld R, et al. The Multinational Association for Supportive Care in Cancer risk index: A multinational scoring system for identifying low-risk febrile neutropenic cancer patients. J Clin Oncol. 2000;18(16):3038-51.

15. Akova M, Paesmans M, Calandra T, Viscoli C. A European Organization for Research and Treatment of Cancer-International Antimicrobial Therapy Group Study of secondary infections in febrile, neutropenic patients with cancer. Clin Infect Dis. 2005;40(2):239-45.

16. Kerremans JJ, Verboom P, Stijnen T, Hakkaart-van Roijen L, Goessens W, Verbrugh HA, et al. Rapid identification and antimicrobial susceptibility testing reduce antibiotic use and accelerate pathogen-directed antibiotic use. J Antimicrob Chemother. 2008;61(2):428-35.

17. Slobbe L, Waal L, Jongman LR, Lugtenburg PJ, Rijnders BJ. Three-day treatment with imipenem for unexplained fever during prolonged neutropaenia in haematology patients receiving fluoroquinolone and fluconazole prophylaxis: a prospective observational safety study. Eur J Cancer. 2009;45(16):2810-7.

18. Prentice HG, Hann IM, Nazareth B, Paterson P, Bhamra A, Kibbler CC. Oral ciprofloxacin plus colistin: prophylaxis against bacterial infection in neutropenic patients. A strategy for the prevention of emergence of antimicrobial resistance. Br J Haematol. 2001;115(1):46-52.

19. de Marie S. Diseases and drug-related interventions affecting host defence. Eur J Clin Microbiol Infect Dis. 1993;1(Suppl 1):S36-41.

20. Cornelissen JJ, Rozenberg-Arska M, Dekker AW. Discontinuation of intravenous antibiotic therapy during persistent neutropenia in patients receiving oral ciprofloxacin. Clin Infect Dis. 1995;21(5):1300-2.

21. Averbuch D, Orasch C, Cordonnier C, Livermore DM, Mikulska M, Viscoli C, et al.; on behalf of ECIL4, a joint venture of EBMT, EORTC, ICHS, ESGICH/ESCMID and EL. European guidelines for empirical antibacterial therapy for febrile neutropenic patients in the era of growing resistance: summary of the 2011 4th European Conference on Infections in Leukemia. Haematologica 2013;98(12):1826-35.

22. Gafter-Gvili A, Fraser A, Paul M, Vidal L, Lawrie TA, van de Wetering MD, et al. Antibiotic prophylaxis for bacterial infections in afebrile neutropenic patients following chemotherapy. Cochrane Database Syst Rev. 2012 1:CD004386.

23. Abbott IJ, Roberts JA. Infusional beta-lactam antibiotics in febrile neutropenia: has the time come? Curr Opin Infect Dis. 2012;25(6):619-25

24. Lortholary O, Lefort A, Tod M, Chomat AM, Darras-Joly C, Cordonnier C. Pharmacodynamics and pharmacokinetics of antibacterial drugs in the management of febrile neutropenia. Lancet Infect Dis. 2008;8(10):612-20.

25. Roberts JA, Norris R, Paterson DL, Martin JH. Therapeutic drug monitoring of antimicrobials. Br J Clin Pharmacol. 2011;73(1):27-36.

26. Roberts JA, Ulldemolins M, Roberts MS, McWhinney B, Ungerer J, Paterson DL, et al. Therapeutic drug monitoring of beta-lactams in critically ill patients: proof of concept. Int J Antimicrob Agents. 2010;36(4):332-9.

27. Blondiaux N, Wallet F, Favory R, Onimus T, Nseir S, Courcol RJ, et al. Daily serum piperacillin monitoring is advisable in critically ill patients. Int J Antimicrob Agents. 2010;35(5):500-3.

28. Buijk SE, Mouton JW, Gyssens IC, Verbrugh HA, Bruining HA. Experience with a once-daily dosing program of aminoglycosides in critically ill patients. Intensive Care Med. 2002;28(7):936-42.

29. van Lent-Evers NA, Mathot RA, Geus WP, van Hout BA, Vinks AA. Impact of goal-oriented and model-based clinical pharmacokinetic dosing of aminoglycosides on clinical outcome: a cost-effectiveness analysis. Ther Drug Monit. 1999;21(1):63-73.

30. Kullar R, Davis SL, Levine DP, Rybak MJ. Impact of vancomycin exposure on outcomes in patients with methicillin-resistant Staphylococcus aureus bacteremia: support for consensus guidelines suggested targets. Clin Infect Dis. 2011;52(8):975-81.

31. Rybak MJ, Lomaestro BM, Rotschafer JC, Moellering RC, Craig WA, Billeter M, et al. Vancomycin therapeutic guidelines: a summary of consensus recommendations from the infectious diseases Society of America, the American Society of Health-System Pharmacists, and the Society of Infectious Diseases Pharmacists. Clin Infect Dis. 2009;49(3):325-7.