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Antimicrobial therapy in resource-limited settings with high antimicrobial resistance: a case-based approach

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SUMMARY

Choosing antimicrobial therapy in resource-limited settings is challenging because of the lack of advanced diagnostics and limited treatment options. Furthermore, since most international guidelines do not account for settings with high antimicrobial resistance, it is difficult for primary care physicians to choose the right antibiotic. This review, therefore, attempts to summarise the principles of antimicrobial therapy in such settings through six hypothetical case scenarios.

Keywords: multi-drug resistance, antibiotics, antimicrobial stewardship.

INTRODUCTION

The choice of antimicrobial therapy in patients with various infectious diseases requires balancing between an overzealous prescription (leading to antimicrobial resistance, *Clostridium difficile* infection and unintended side effects) and choosing therapy that misses the likely pathogen leading to delay in the microbial killing [1]. Therefore, an excellent clinical judgment guided by the local antibiogram and evidence-based guidelines is crucial for choosing the right therapy [1]. In this article, we discuss the principles of antimicrobial therapy and a stepwise approach to selecting the right antimicrobial therapy in resource-limited settings with a high burden of resistant organisms.

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Construction of the empiric regimen

Broad empirical therapy should be chosen, considering the severity of illness, likely pathogen, and the clinical syndrome [2]. Appropriate dosing and route of administration should be selected according to the situation. Prompt administration of antibiotics is the key, especially in critically ill patients [3]. The therapy should be decided per the resistance patterns and local antibiogram [1]. The national or regional guidelines on syndromic management of infections should be consulted for treatment decisions. The empiric regimen is constructed taking into account the following factors:

1) *Severity at presentation and progression:* The empiric regimen should be broad in individuals with severe disease and cover possible pathogens. The regimen can be de-escalated when the culture results are available [3]. In individuals with stable disease, an escalation approach can be taken. These patients can be started with an antimicrobial that covers the most common pathogen, and escalation, if required, can be based on culture results. Wher-

ever possible, monotherapy is preferred over combination therapy [2]. The severity should guide the route of therapy. The intravenous (IV) route is preferred at the maximum recommended dosage in critically ill patients. The drug's pharmacokinetics should also be considered while administering through the IV route [1]. For example, beta-lactams have time-dependent kinetics. Therefore, after the first loading dose, the subsequent doses should be administered as an infusion over a three to four-hour period [1]. Certain antibiotics may be toxic to the liver or kidneys, and they should be avoided in the presence of pre-existing dysfunction. Other antibiotics may be eliminated via the renal or liver route and, therefore, may require dose adjustment in specific circumstances. In addition, it must be noted that patients with acute kidney injury due to sepsis may have increased non-renal modes of excretion, and these patients may require higher doses of antimicrobials [4]. The number of likely pathogens that can cause a particular syndrome may be higher and/or different in patients with immunosuppression. Also, the disease may be more complex and rapidly progressive in these patients [5]. Therefore, antibiotic choice should be guided by these considerations as well.

2) *Community-acquired or hospital-acquired:* An infection is defined as hospital-acquired if the symptoms develop after 48 hours of hospital admission [6]. It is crucial to classify an infection into community-acquired or hospital-acquired as the likely pathogens and resistance pattern differs between the two groups. Hospital-acquired infections tend to be caused by specific drug-resistant organisms such as *Acinetobacter* spp. and *Pseudomonas* spp.
3) *Syndromic diagnosis:* Before initiating antibiotics, it is advisable to make a syndromic diagnosis based on the clinical features and the likely anatomical source. The patients should be categorised into either of the following syndromes: Central Nervous System (CNS) infections, upper respiratory tract infection, lower respiratory tract infection, diarrhoea/dysentery, urinary tract infection, bloodstream infection, skin and soft tissue infection, intra-abdominal infection, febrile neutropenia, acute undifferentiated febrile illness, and sepsis of unknown origin. The used antibiotic should have a good penetration to the affected site [7]. Hydrophilic antibiotics such as beta-lactams or vancomycin have lesser penetration through uninflamed meninges than lipophilic antibiotics such as rifampicin and fluoroquinolone [7]. In cases like bloodstream or CNS infections, bactericidal antibiotics (*e.g.*, beta-lactams, fluoroquinolones, and glycopeptides) are preferred over bacteriostatic antibiotics (tetracyclines, cotrimoxazole and macrolides) [5]. The likely etiologic pathogens based on the syndromic diagnosis should be hypothesised before deciding the choice of antibiotics.
4) *Rapid tests:* Conventional culture-based tests are time-consuming, so early therapy is almost always empiric. Rapid tests can be used in specific scenarios to help tailor the treatment at presentation [8]. However, it should be considered that some of these rapid tests may suffer from poor sensitivity or specificity compared to conventional diagnostics.
5) *Possibility of multi-drug resistant (MDR) organisms:* The likelihood of drug resistance in likely pathogens depends on various local epidemiological factors, including a history of antimicrobial use or stay in hospital and the presence of MDR colonisers [1]. The antibiotics should be tailored according to the possible resistance patterns. In some scenarios, empirical antibiotic therapy may not have enough coverage for the likely drug-resistant organisms. In such a case, combination therapy may enhance the range.

Based on the five principles of empirical antimicrobial therapy discussed above, a few hypothetical case scenarios are put forth (Table 1).

Case 1: A 60-year-old-male patient from South India presented with fever and generalised erythematous rash for four days. He was found to have tachycardia on examination, but his blood pressure was normal. His electrocardiogram (ECG) showed ST-T wave changes, and a rapid test for troponin was positive. His laboratory investigations revealed leukocytosis and elevated C-reactive protein (CRP). A rapid test for malarial antigen was negative.

Approach: This is a case of Acute Febrile Illness (AFI) with myocarditis. This condition is acutely progressive, but the patient is currently stable. Dengue, scrub typhus, leptospirosis and malaria

are the possible differentials. Malaria and dengue are less likely because of the negative rapid test and high CRP/leukocytosis, respectively. Between scrub and leptospirosis, IV or oral doxycycline can be given since the patient is stable, covering both the etiological possibilities.

Table 1 - Case scenario and suggested recommendations for antimicrobial therapy.

	Severity	*Syndrome*	*Likely pathogens*	*Rapid test*	*Local antibiogram*	*Empiric choice*	*Id*	*Sn*	*Final regimen*	*DOT*
1	Acutely progressive but stable	AFI (Com)	Scrub typhus, leptospirosis	Negative for malaria	No data	Doxy (IV/ oral)	Scrub typhus		Doxy (oral)	3 days
2	Acutely progressive, unstable	Necrotising fasciitis (Com)	Strep, *Staph*, Pa, Enterobacteriaceae	Gram stain of exudate- pus cells, no organism seen	*Staph*- Methicillin 45%R, Enterobacteriaceae- Ceftriaxone- 95%R, P/T- 49%R, carbapenems- 15%R	Mero + Van/Teico + Clinda	*Strep dysgalactiae*	S-Pn	Ampi	5-6 days
3	Stable	Complicated UTI (Com)	Enterobacteriaceae	Leukocyte esterase suggests pyuria	Enterobacteriaceae- Ceftriaxone- 95%R, P/T- 22%R, Mero- 8%R	P/T	*E. coli*	S-Nitrofurantoin, cipro, Fosfo, P/T, carbapenems		5-7 days
4	Acutely progressive but stable	PVE (Com)	*S.viridans*, *Staph.*, *E. faecalis*		*Staph.*- Methicillin 45%R *E. faecalis*- Vancomycin 5%R	Vanco + genta + rifampicin	*E. faecalis*	S-Pn, HLAR, V/T, linezolid	Ctx + Ampi or POET trial regime	42 days
5	Acutely progressive, unstable	VAP (Hos)	*Aba*, *Pa*, Enterobacteriaceae	Gram stain- GNB	*Aba.*- C/S- 30%R, carbapenems 60%R. *Pa.*- C/S 30%R, Carbapenem 25%R	C/S + poly	*Aba*	S-tige, poly	Tige+ Poly	8 days
6	Acutely progressive, unstable	Febrile neutropenia (Com)	Enterobacteriaceae, *Pa*, *Staph*	Procalcitonin- >200 ng/ ml	Enterobacteriaceae.- carbapenems 10-20%R, *Pa*- carbapenems 25%R, *Staph*- Methicillin 35%R	Mero + poly + van	*Enterobacter* spp.	S-carbapenems, cefepime, ctx	Cefepime	Afebrile for 72 hours

Abbreviations: Id- Identified organisms, Sn-Sensitivity patterns, DOT-duration of therapy, S-Susceptible, Com- Community acquired, Hos- Hospital acquired, UTI-Urinary tract infection, PVE- prosthetic valve endocarditis, VAP- Ventilator associated pneumonia, *Strep- Streptococcus spp., Staph- Staphylococcus spp., Aba- Acinetobacter baumannii, Pa- Pseudomonas aeruginosa*, GNB- Gram negative bacilli, R-resistance, S- sensitive, doxy- doxycycline (100 mg twice daily), Van- vancomycin (1g twice daily), teico- teicoplanin (400 mg twelfth hourly loading for three doses followed by once daily), genta- gentamicin (80 mg thrice daily), clinda (900 mg thrice daily), C/S- cefoperazone-sulbactam (3g thrice daily), P/T- piperacillin-tazobactam (4.5g thrice daily), poly- polymyxin B (15 lakh units loading followed by 7.5 lakh units twice daily), mero- meropenem (1g thrice daily), tige- tigecycline (200 mg loading followed by 100 mg twice daily), ampi- ampicillin (2g six times daily), ctx-ceftriaxone (2g once daily), cipro- ciprofloxacin, fosfo- fosfomycin., HLAR- high level aminoglycoside resistance.

Case 2: A 45-year-old diabetic male presented with severe pain, redness over his right arm and fever. No history of animal bite or exposure to water was noted. On examination, the patient has tachycardia, tachypnoea, and hypotension. The local examination shows crepitus, blackish skin discolouration and foul-smelling discharge. Aspirate sent for Gram stain shows pus cells but no organisms.
Approach: This is a patient with necrotising fasciitis in shock with a possibility of toxic shock syndrome. The possible organisms are *Streptococcus (*Group A, Group B, beta-haemolytic non-A non-B), *Staphylococcus* spp., *Pseudomonas* spp, and Enterobacteriaceae. Gram stains are helpful but may not always be positive. Because the patient is in shock, all possible pathogens should be covered in the empiric regimen. Carbapenem is given to cover Enterobacteriaceae, *Pseudomonas* spp and anaerobes. It will also work on *Streptococcus* spp. and Methicillin Sensitive *Staphylococcus* spp. (MSS). Because hospital antibiograms show a possibility of Methicillin-Resistant *Staphylococcus* spp. (MRS) as well, vancomycin or teicoplanin is given. Clindamycin is added for its anti-toxin activity. Alternatively, linezolid can be used instead of vancomycin and clindamycin because it has both MRS and anti-toxin activity.
Case 3: A 34-year-old female presented with fever, chills and rigours, urinary frequency, and dysuria. On examination, the vital signs were stable, and the right renal angle was tender. The urine leukocyte esterase test was positive.
Approach: This is a case of complicated urinary tract infection (UTI) with possible pyelonephritis. The leukocyte esterase test is positive, suggesting pyuria. Enterobacteriaceae are the commonest organisms. The local antibiogram suggests that most urinary isolates are Extended-spectrum beta-lactamase (ESBL) and show resistance to 3rd generation cephalosporins (Table 2). Maximum sensitivity is noted for carbapenems followed by piperacillin-tazobactam. In a randomised clinical trial (MERINO trial) that compared piperacillin-tazobactam vs meropenem for ceftriaxone-resistant *E. coli* and *K. pneumoniae*, piperacillin-tazobactam was not found to be non-inferior to meropenem [9]. However, piperacillin-tazobactam can be considered an alternative in stable patients with bacteremia from urinary sources.
Case 4: 45-year-old-male, a known case of rheumatic heart disease with a prosthetic mitral valve, presents with a four-day history of fever and breathlessness. On examination, he has features of heart failure. A trans-thoracic echocardiogram shows 11-mm vegetation on the prosthetic valve.
Approach: This is a case of prosthetic valve infective endocarditis (IE). In most cases, empiric therapy should be avoided, and one should wait for the culture and susceptibility testing. However, in this patient, considering the rapid progression, empiric therapy may be considered after sending blood cultures [10]. The possible organisms include *Streptococcus viridans, Staphylococcus* spp. and *Enterococcus* spp. Because the hospital anti-

Table 2 - Antimicrobials for treatment of multi-drug resistant gram-negative infections with most likely susceptibility patterns.

Antimicrobials	*Enterobacteriaceae*					*CRAB*	*CRPA*
	ESBL	*AmpC*	*Carbapenemase*			*Oxa-23/24*	*Porin loss, efflux pump*
			OXA-48	*KPC*	*NDM*		
Ceftriaxone	R	R	R	R	R	R	R
Cefepime	R	S	R	R	R	R	R
Carbapenems	S	S	R	R	R	R	R
Aztreonam	R	R	R	R	S	R	R
Ceftazidime-avibactam	S	S	S	S	R	R	S
Tazobactam combination	S	R	R	R	R	R	Ceftolozane tazobactam S
Sulbactam combination	S	R	R	R	R	S	R
Cefiderocol	S	S	S	S	S	S	S

Abbreviations: S- Most strains sensitive, R- Most strains resistant, ESBL- Extended-spectrum beta-lactamase, AmpC-Ambler Class C beta-lactamase, KPC- *Klebsiella pneumoniae* carbapenemase, oxa- oxacillin carbapenemase, NDM-New Delhi Metallobetalactamase, CRAB- carbapenem-resistant *Acinetobacter baumannii*, CRPA- Carbapenem-resistant *Pseudomonas aeruginosa*.

biogram shows methicillin resistance in *Staphylococcus* spp., vancomycin should be given in an empiric regimen. Teicoplanin reaches only up to the periphery of the vegetation, so it is either avoided or given at a higher dosage. The data on linezolid is scarce. Gentamicin is added for synergistic activity and covers *Enterococcus* spp [10]. Rifampicin is given for its action on biofilms (10).

Case 5: A 60-year-old-female patient presented with intestinal perforation. She could not be weaned off the ventilator after the surgery. Her oxygen requirement on the ventilator was slowly coming down. After four days into the ICU stay, she started to have a fever and increased oxygen requirement. Her secretions increased, and she required frequent suctioning. Routine counts showed neutrophilic leukocytosis, and X-ray showed new infiltrates. Gram stain of endotracheal aspirate showed Gram-negative bacilli.

Approach: The patient presents with ventilator-associated pneumonia (VAP). The most common organisms include *Acinetobacter* spp, *Pseudomonas* spp., and *Enterobacteriaceae*. *Staphylococcus aureus* is possible but unlikely to be present with this Gram stain findings. The hospital's antibiogram shows that *Acinetobacter* spp. is most sensitive to cefoperazone-sulbactam and polymyxins, while its sensitivity for carbapenems is inferior. For *Pseudomonas* spp, carbapenems, cefoperazone-sulbactam and polymyxins have good sensitivity. Infectious Disease Society of America (IDSA) guidelines recommend the addition of another antibiotic if the first choice of antibiotic does not cover 95% of the likely pathogens [11]. Also, it is suggested by most guidelines that both *Pseudomonas* and *Acinetobacter* species require empiric combination therapy. Therefore, in this patient combination of cefoperazone-sulbactam and polymyxin can be used. Newer antibiotics such as cefiderocol can be used as well, as they are active against most MDR strains of *Acinetobacter* and *Pseudomonas* spp (Table 2). They are unaffected by many beta-lactamase enzymes, efflux pumps and porin mutations. However, their availability is limited in low resource settings. Ceftolozane-tazobactam works particularly well with *Pseudomonas* spp but not for *Acinetobacter* spp.

Case 6: A 50-year old male patient was recently diagnosed with acute myeloid leukaemia. He received induction chemotherapy for seven days and consolidation chemotherapy for five days. Post-chemotherapy, the patient reported fever. His vitals were as follows: blood pressure: 80/60, pulse rate: 120/min, respiratory rate: 20/min and oxygen saturation: 82% (room air). He has severe mucositis. His total leucocyte count was 500/µl (Neutrophil- 40%).

Approach: This is a case of febrile neutropenia with hypotension. Since most common organisms in such a case are Gram-negative enteric bacilli, carbapenems are preferred. However, considering the resistance to carbapenem is more than 10% in all the possible microbial etiologies of this case, and the patient's condition is unstable, a case may be made to add polymyxin to cover carbapenemase-producing Enterobacteriaceae. In addition, vancomycin is added to cover for MRSA as the patient is in shock and has severe mucositis. Vancomycin can also be added if there is a central venous catheter in situ.

TAILORING THE ANTIMICROBIAL THERAPY

The empiric regimen should be re-evaluated every 48-72 hours. This could be in the form of a prescriber-led intervention (antimicrobial time-out) or in the form of prospective audit and feedback where trained physicians (not involved in management) review antimicrobial orders and provide recommendations to prescribers.

1) *Clinical improvement with empiric therapy*: The patients should be closely monitored for signs of improvement such as defervescence of fever or improvement of shock or decrease in oxygen improvement. The antimicrobial therapy can be escalated in the absence of significant clinical improvement or deterioration.
2) *Choosing the right bug-drug combination*: Once the microbiological diagnosis is confirmed, the targeted antimicrobial therapy should be initiated. It is essential to differentiate between infection and colonisation in such cases [2]. The decision should be based on the evolution of clinical status and microbiology results to guide the change from empiric to definite therapy.
3) *De-escalation*: The therapy should also be narrowed based on the susceptibility results [1]. Ideally, the narrowest spectrum antimicrobial should be used, as long as the antimicrobial is appropriate for the indication. Whenever possible, intravenous antibiotics should be converted to oral therapy, especially if the antimi-

crobial has high bioavailability (e.g. azithromycin, cotrimoxazole) [2].

4) *Consider side effects*: Antibiotics with a higher potential for certain side effects that can complicate clinical management should be avoided. Likewise, antimicrobials that can increase the risk of *C. difficile* (*e.g.,* fluoroquinolones, clindamycin etc.) should be avoided [2]. In tuberculosis endemic areas, the use of fluoroquinolones should be avoided as much as possible.
5) *Duration of therapy*: The shortest effective duration of therapy should be used based on the available evidence [12]. Clinical improvement and the use of biomarkers such as procalcitonin can guide de-escalation.

Based on the five key principles of tailoring antimicrobial therapy, the same six cases are discussed below after their microbiological reports are available (Table 1).

Case 1 continued: The patient became afebrile in 24 hours. The immunofluorescence assay for scrub typhus was found to be positive.

Approach: This is a case of scrub typhus as evidenced by the defervescence of fever and positive serology. If doxycycline was given in an IV route, it could be changed to oral. The total duration can be as low as three days [13].

Case 2 continued: The patient was improving on treatment. The culture was positive for *Streptococcus dysgalactiae*. In addition, it showed sensitivity to penicillin.

Approach: All three antibiotics can be stopped, and he can be shifted on intravenous penicillin or ampicillin. Carbapenems are not required anymore as no Gram-negative or anaerobic organisms were present. Although it has activity on the isolated organism, the narrowest antibiotic should be chosen instead. Based on recent evidence, clindamycin is not recommended for non-A, non-B betahemolytic streptococcus [14]. In the absence of MRSA growth, vancomycin can be discontinued as well. The duration of therapy can be as low as 5-6 days [12].

Case 3 continued: The patient was improving on treatment. Urine culture grew *Escherichia coli* resistant to ceftriaxone but sensitive to nitrofurantoin, ciprofloxacin, fosfomycin, piperacillin-tazobactam, meropenem and imipenem.

Approach: Although it is sensitive to both piperacillin-tazobactam and meropenem, ideally, the patients should be de-escalated to oral antibiotics. Oral ciprofloxacin has good oral bioavailability and can be used for ESBL organisms. However, because of its propensity to cause CDI and increased resistance in TB, some clinicians prefer to avoid it. Although IDSA guidelines suggest avoiding nitrofurantoin and fosfomycin in upper UTI, a recent non-inferiority RCT suggests that fosfomycin was non-inferior to ciprofloxacin for de-escalation in febrile UTI (15). The duration of therapy can be as low as 5-7 days [12].

Case 4 continued: The patient underwent surgery and became afebrile on antibiotics. His breathlessness improved. Three sets of blood cultures grew *Enterococcus faecalis* sensitive to penicillin, but high-level aminoglycoside resistance (HLAR) was detected.

Approach: Rifampicin need not be given in patients with prosthetic IE due to *E. faecalis*. Because the isolate is susceptible to penicillin, vancomycin is not required in this case, and it can be de-escalated. In the presence of HLAR, gentamicin cannot be used. Ampicillin plus ceftriaxone would be a suitable option [16]. In the landmark trial on partial IV vs oral therapy for patients with left-sided IE (POET trial), oral therapy after initial IV therapy was non-inferior to prolonged IV therapy (17). In this trial, combination therapy was used for *E. faecalis* from the following four options: amoxicillin, linezolid, moxifloxacin and rifampicin. Based on the results of this trial, oral combination therapy is an acceptable option here as well. A six-week duration of antimicrobial is recommended [10].

Case 5 continued: The patient worsened on empiric therapy. Culture results showed *Acinetobacter* spp. that was sensitive to only polymyxin, tigecycline and minocycline.

Approach: Because cefoperazone-sulbactam is resistant, tigecycline or minocycline should be added to polymyxins. Alternatively, high dose ampicillin-sulbactam can be used instead of polymyxin, even if the isolate is resistant (Table 2). Tigecycline dose should be higher in patients with VAP (IV 200 mg loading followed by 100 mg IV q12th hourly). It is recommended to give combination antibiotic therapy for VAP caused by *Acinetobacter* spp. There is no single agent with sufficient activity [18]. The maximum duration of therapy in VAP is eight days or lesser [12, 19].

Case 6: The culture grew *Enterobacter cloacae* sen-

sitive to ceftriaxone, cefepime and carbapenems. *Approach*: All antibiotics should be stopped, and the patient can be shifted on cefepime. Since ceftriaxone can induce Ambler Class C (AmpC) production in *E. cloacae*, its use should be avoided even with a narrower spectrum (Table 2). Between carbapenems and cefepime, cefepime is preferred because it is carbapenem-sparing, narrower spectrum, and non-inferior to other commonly used drugs [20].

In conclusion, choosing antimicrobial therapy should not be driven by instincts and biases. It is not an art but an evidence-based multi-step process that requires strong support from scientific literature, knowledge of antimicrobials, local antibiogram, clinical judgement and a good microbiology laboratory.

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None to declare.

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REFERENCES

[1] Gandhi TN, DePestel DD, Collins CD, Nagel J, Washer LL. Managing antimicrobial resistance in intensive care units. *Crit Care Med*. 2010; 38 (8 Suppl.), S315-23.
[2] Cunha CB. Antimicrobial Stewardship Programs: Principles and Practice. *Med Clin North Am.* 2018; 102 (5), 797-803.
[3] Dugar S, Choudhary C, Duggal A. Sepsis and septic shock: Guideline-based management. *Cleve Clin J Med*. 2020; 87 (1), 53-64.
[4] Lewis SJ, Mueller BA. Antibiotic Dosing in Patients With Acute Kidney Injury: "Enough But Not Too Much." *J Intensive Care Med*. 2016; 31 (3), 164-76.
[5] Abbo LM, Ariza-Heredia EJ. Antimicrobial stewardship in immunocompromised hosts. *Infect Dis Clin North Am*. 2014; 28 (2), 263-79.
[6] Liu J-Y, Dickter JK. Nosocomial infections: a history of hospital-acquired infections. *Gastrointest Endosc Clin N Am*. 2020; 30 (4), 637-52.
[7] Tessier JM, Scheld WM. Principles of antimicrobial therapy. *Handb Clin Neurol*. 2010; 96, 17, 29.
[8] Gupta N, Joylin S, Ravindra P, et al. A Diagnostic randomised controlled trial to study the impact of Rapid diagnostic tests in patients with Acute febrile illness when compared to Conventional diagnostics (DRACO study). *J Infect*. 2021 82 (6), e6-e8. Apr 7; doi: 10.1016/j.jinf.2021.04.001.
[9] Harris PNA, Tambyah PA, Lye DC, et al. Effect of piperacillin-tazobactam vs meropenem on 30-day mortality for patients with E coli or *Klebsiella pneumoniae* bloodstream infection and ceftriaxone resistance: a randomised clinical trial. *JAMA.* 2018; 320 (10), 984-94.
[10] Gould FK, Denning DW, Elliott TSJ, et al. Guidelines for the diagnosis and antibiotic treatment of endocarditis in adults: a report of the Working Party of the British Society for Antimicrobial Chemotherapy. *J Antimicrob Chemother*. 2012; 67 (2), 269-89.
[11] Kalil AC, Metersky ML, Klompas M, et al. Management of adults with Hospital-acquired and Ventilator-associated Pneumonia: 2016 Clinical Practice Guidelines by the Infectious Diseases Society of America and the American Thoracic Society. *Clin Infect Dis*. 2016; 63 (5), e61-111.
[12] Spellberg B. The Maturing Antibiotic Mantra: "Shorter Is Still Better." *J Hosp Med.* 2018; 13 (5), 361-2.
[13] Song JH, Lee C, Chang WH, et al. Short-course doxycycline treatment versus conventional tetracycline therapy for scrub typhus: a multicenter randomised trial. *Clin Infect Dis*. 1995; 21 (3), 506-10.
[14] Babiker A, Li X, Lai YL, et al. Effectiveness of adjunctive clindamycin in β-lactam antibiotic-treated patients with invasive β-haemolytic streptococcal infections in US hospitals: a retrospective multicentre cohort study. *Lancet Infect Dis*. 2021; 21 (5), 697-710.
[15] Ten Doesschate T, Kuiper S, van Nieuwkoop C, et al. Fosfomycin versus ciprofloxacin as oral stepdown treatment for Escherichia coli febrile urinary tract infection in women: a randomised, placebo-controlled, double blind, multicenter trial. *Clin Infect Dis*. 2021; 16, ciab934.
[16] El Rafei A, DeSimone DC, Narichania AD, Sohail MR, Vikram HR, Li Z, et al. Comparison of Dual β-Lactam therapy to penicillin-aminoglycoside combination in treatment of Enterococcus faecalis infective endocarditis. *J Infect*. 2018; 77 (5), 398-404.
[17] Iversen K, Ihlemann N, Gill SU, et al. Partial Oral versus Intravenous Antibiotic Treatment of Endocarditis. *N Engl J Med*. 2019; 380 (5), 415-24.
[18] Piperaki E-T, Tzouvelekis LS, Miriagou V, Daikos GL. Carbapenem-resistant Acinetobacter baumannii: in pursuit of an effective treatment. *Clin Microbiol Infect.* 2019; 25 (8), 951-7.
[19] Esposito S, Esposito I., Leone S.Considerations of antibiotic therapy duration in community- and hospital-acquired bacterial infections. *J Antimicrob Chemother*. 2012; 67, 11, 2570-75.
[20] Siedner MJ, Galar A, Guzmán-Suarez BB, Kubiak DW, Baghdady N, Ferraro MJ, et al. Cefepime vs other antibacterial agents for the treatment of Enterobacter species bacteremia. *Clin Infect Dis.* 2014; 58 (11), 1554-63.