Мак Мед Преѓлед 2019; 73(2): 67-72

MMP

Review

PHARMACOEPIDEMIOLOGY AND ANTIMICROBIAL RESISTANCE DATA FOR BACTERIAL INFECTIONS IN HOSPITALIZED CHILDREN

ФАРМАКОЕПИДЕМИОЛОШКИ ПОДАТОЦИ ЗА АНТИМИКРОБНА РЕЗИСТЕНЦИЈА НА БАКТЕРИИ ИЗОЛИРАНИ КАЈ ХОСПИТАЛИЗИРАНИ ДЕЦА

Iskra Pechiareva Sadikarijo[1], Tijana Serafimovska[2], Marija Darkovska Serafimovska[3] and Trajan Balkanov[4]

[1]Macedonian Agency for medicines and medical devices, Republic of North Macedonia, [2]Faculty of Pharmacy, University "Ss. Cyril and Methodius" Skopje, [3]Faculty of Medical Sciences, University "Goce Delchev" Shtip, [4]Institute for preclinical and clinical pharmacology and toxicology, Faculty of Medicine, University "Ss. Cyril and Methodius" Skopje, Republic of North Macedonia

Abstract

Antimicrobial resistance is a global problem that needs an urgent action. The irrational use of antibiotics is widespread and leads to potential usefulness of medicines and negative therapeutic outcome.In April 2016, WHO stated that the problem of antibiotic resistance is a major clinical problem resulting in treatment failures even in a case ofeasy to treat diseases. Resistance to first line medicines results in huge spending on new generation of antibiotics. In some instances resistance to second- and third-line agents is seriously compromising treatment outcome.Seriousness of the situation requires extensive research and constantly monitoring of the spread of bacteria resistance.Another problem regarding bacteria resistance is the lack of new antibiotics reported by the US Center for Control and Prevention of Disease.A systematic literature search of databasesgave us enough information about the use of antibiotics, most often isolated bacteria and resistance to different classes of antibiotics. According to the official data, bacterial resistance is lowest in the countries where guidelines for prescribing and use of antibiotics are consistently implemented, such as Scandinavian countries, The Netherlands, Germany and Great Britain. It is necessary to create a complete database of bacterial resistance and information on whether patients receive medicines appropriate to their clinical conditionin our country.

Keywords: antibiotics, bacterial resistance, multidrug resistance, bacterial pathogens

Correspondence to: Iskra Pechiareva Sadikarijo, Macedonian Agency for medicines and medical devices, Republic of North Macedonia Email: ps_iskra@yahoo.co.uk

Апстракт

Бактериската резистенција претставува голем здравствен проблем за кој е потребно итно делување. Нерационалната употреба на антибиотици е широко распространета и е една од најзначајните причини за зголемување на резистенцијата инегативни терапевтски исходи. Во април 2016 година, СЗО изјави дека проблемот со отпорноста на антибиотици е голем клинички проблем што резултира со неуспех во лекувањето, дури и во случаи кога станува збор за болести кои вообичаено лесно се лекуваат. Отпорноста на лековите од прва линија резултира со зголемување на потрошувачката на новите генерации на антибиотици. Во некои случаи, отпорноста кон антибиотиците од втора и трета линија сериозно го компромитираат исход од третманот. Сериозноста на состојбата во однос на развојот на бактериската резистенција, бара опширно истражување на овој феномен и постојано следење на резистенцијата на бактериите. Во извештајот објавен од страна на американскиот Центар за контрола и превенција на болести се вели дека дополнителна причина за бактериската резистенција е недостигот од нови антибиотици.Систематското пребарување на литературната база на податоци, ни даде доволно информации за употреба на антибиотиците, најчесто изолирани бактерии и нивната отпорност на различни класи на антибиотици. Според официјалните податоци, бактериската резистенција е најниска во земјите во кои насоките за препишување и користење на антибиотици доследно се спроведуваат, како Скандинавските земји, Холандија, Германија и Англија. Во нашата држава неопходно е да се создаде база на податоци по однос на ова прашање и информациите за рационална фармакотерапија.

Клучни зборови: антибиотици, бактериска резис-

тенција, мултирезистенција, патогени бактерии

Introduction

Bacterial resistance is not a new phenomenon butmajor public health concern. It was recognized in the earlier 1950s as a threat to effective treatment outcome. Since the WHO Resolution, many countries have expressed growing concern about the problem of antimicrobial resistance [1,2]. Reporting about bacterial resistance and monitoring the use of antibiotics today is an obligation for all countries.

The most endangered population for acute infectious disease as a result of bacterial resistance are children. Collective accommodation in kindergartens or schools, unhygienic living conditions, insufficiently effective immune system, as well as irrational, empirical and excessive use of antibiotics, especially unjustified in viral infections are the most common reasons for the frequent occurrence of bacterial infections in children [3-5]. Receiving antibiotics for prophylaxis increases the risk of multidrug resistance among recurrent infections [6]. In hospital acquired infections in children, antibiotic resistance is frequently reported in clinical Gram-negative bacteria. The number of available therapeutic options for treatment of these conditions is limiteddue to the lack of novel active antibiotics [7]. At the end of the 20th century, the attention regarding the threat of antibiotic resistance of the scientific and pharmaceutical companies was focused on multidrug resistant Gram-positive bacteria [8].

In order to understand bacterial resistance, there is a huge need to interpret molecular mechanisms of antibiotic resistance, especially to Gram-negative and Gram-positive clinical pathogens [9-11].

Among the diseases that have been declared as "alarming threat" are severe forms of clostridium-induced diarrhea and gonorrhea infections. But, the most serious infections are those coming from enterobacteria that cause relatively new and rare, but deadly infections resistant to carbapenems. For such infections it is stated that they cannot be cured with so-called spare antibiotics, which confirms the fact that no new antibiotic has been synthesized for a long period of time [12,13]. However, we are now faced with the threat of a post-antibiotic era [14,15].

An interesting fact is that bacteria isolated in children younger than 2 years show a higher percentage of antibiotic resistance compared to bacteria isolated in older children [5]. Also, isolated bacteria in the hospitals are more resistant than those isolated in primary health care [16]. The situation is particularly problematic at the University clinics where patients from other regional hospitals who have already received antibacterial therapy come up. That is the possible reason for the occurrence of resistant and multidrug resistant bacterial strains [17].

Bacterial resistance is a global problem that must be resolved locally, having in mind that there are significant geographical variations in the participation of certain resistant strains, as the triggers of bacterial infections. Methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus* (VRE), *Mycobacterium tuberculosis* and *Streptococcus pneumoniae* are the most frequent pathogens who have a significant impact on morbidity and mortality [18].

It is important to highlight that the UN and the WHO organization have developed action plans to reduce antimicrobial resistance in all healthcare settings. They establish the institutional antimicrobial stewardship program as a key intervention to reduce antibiotic consumption in hospitals. The goal was to address high rates of multi-drug-resistant bacteria [19].

Materials and methods

For the purpose of this paper, a systematic literature search of Medline/Pubmed and Embasedatabases was done in order to evaluate the phenomenon of bacterial resistance and multidrug resistance published in the last fifteen years.

A systematic review of Randomized Controlled Trials (RCTs) was made until December 2018 using the following key words: antibiotics, bacterial resistance, multidrug resistance, pharmacoepidemiology. We identified 3287 reports, of which only 32 articleswere subject of evaluation (Figure 1).

Potential analyses, diagnostic criteria, appropriate selection of patients with infections caused by bacteria and therapy were used as criteria for evaluating the study.

In our analysis bacterial strain wasconsidered to be multidrug resistant if it wasresistant to three or more classes of antibioticsat the same time.

Critical review

Three main points were the subject of our research: use of antibiotics, analysis of isolated bacteria and resistance/ multidrug resistance of the most commonly isolated bacteria.

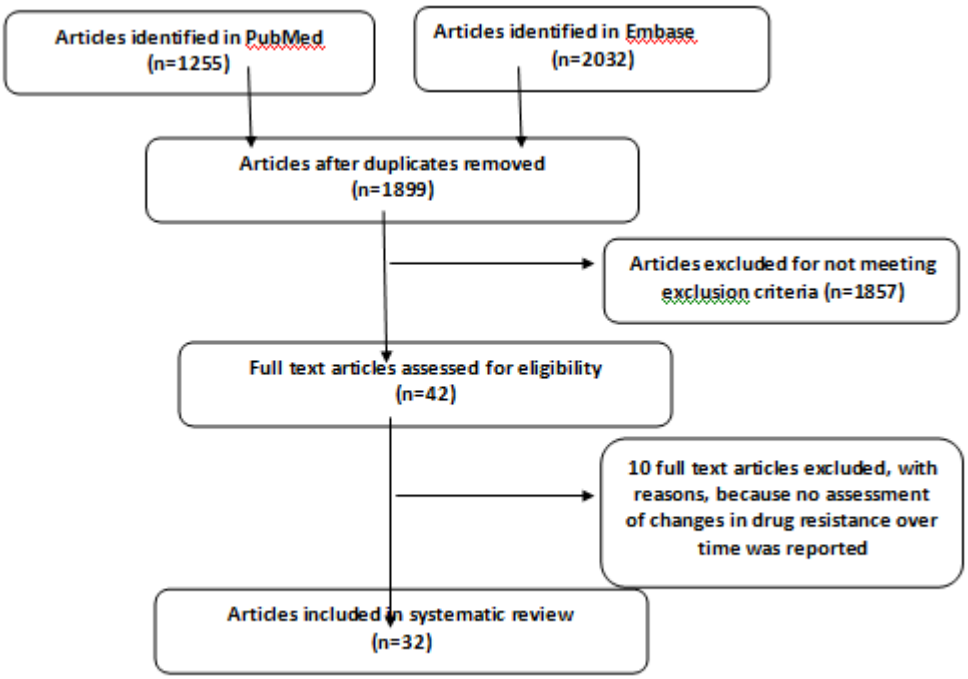

Fig. 1. Flow of Studies Through the Review Process

Use of antibiotics

The analyzed data available from the database for hospitals and general practice within the SACAR project (Specialist Advisory Committee on Antimicrobial Resistance) [20] shows the existence of seasonal variations in prescription of antibiotics. Prescription in the winter period is about 15% higher compared to the summer period. The use of antibiotics was higher in East European countries compared to northern EU countries [20-21].

The use ofpenicillin in hospitals in many European countries is low, although the antimicrobial effect of penicillin is still relatively well preserved [22]. A study conducted at the University of California San Francisco [23] confirms that from 16 classes of antibacterial drugs used, 5 classes are considered safe for pediatric use: beta-lactams+inhibitor, oral and parenteral cephalosporins, macrolides and aminoglycosides. Similar results have also been reportedinone study conducted in China in the period from 2002 to 2006. The most commonly used antibiotics in five children's hospitals in China were amoxicillin+clavulanic acid and parenteral cephalosporins [24]. Penicillins were the most common prescribed in children younger than 5 years in six primary health-care facilities in Burkina Faso, followed by sulfonamides and macrolides [25]. The results of a two-month study [26] conducted at the University Clinic in Bari, Italy, showed that amikacin and a combination of ampicillin + sulbactam were the most used antibiotics in children younger than two years. The most common antibiotics were used for treatment of respiratory infections in children, at the pulmonary departments [5,27]. The results of the multicentric multinational study conducted within the ARPECproject (Antibiotic Resistance and Prescribing in European Children) in September 2011 report a high level of use of antibiotics in the departments for pediatric hematology/oncology. In this one-day data of the use of antibiotics in hospitalized children 73 hospitals worldwide were included [28]. One study conducted in 1992 in three University hospitals in Estonia, Sweden and Spain showed that the use of antibiotics at the surgical departments was 30-50% higher than in other departments [29].

Five primary data collection studies, across the five countries, conducted between 2014-2017 as part of MARVEL (Multi-country economic and epidemiological burden of varicella study), examined empiric data on the appropriate and inappropriate use of antibiotics in the treatment of pediatric varicella patients. In this study 787 patient were included and the proportion of antibiotics prescribed without a probable or confirmed diagnosis of bacterial infection was high (ranged from 45% to 90%) [30].

Analysis of isolated bacteria

Analysis of microbiological isolate along with the antibiogram is one of the preconditions for optimal antibiotic use. For that goal,a sample of patients for microbiological analysis is taken before the start of therapy and the cause of the infection isisolated. The most common samples for bacteriological analysis are blood samples-blood cultures. The most commonly isolated bacteria from the blood cultures are coagulase

negative *Staphylococcus spp.*, which is normally present on the human skin. Therefore, it is very important to properly interpret the bacteriologically positive blood cell finding [31]. A study in England, conducted inneonatal departments in the period from 1992 to 2005, showed an increase of isolated coagulase negative *Staphylococcus spp*. in blood samples, which was partly explained by the increased use of central vascular catheters in these children [18]. In one study conducted in theperiod from 2001 to 2004 inthe Houston Hospital (USA) in respiratory tract samples, a double increase in the number of isolates in which *S. aureus* (771/1562) was reported, were explained by the increased virulence of this bacterium [32]. *E. coli*, the most common cause of urinary tract infections, was the most commonly isolated bacteria from urine samples [33].In urine cultures the most isolated pathogenic gram-negative bacilli are associated with resistance to beta-lactam antibiotics [34].In the samples of the gastrointestinal tract (GIT), *Klebsiella pneumoniae*, *E. coli* (16.5%) and *Pseudomonas aeruginosa* (15.8%) are most often isolated. The results of one retrospective study carried out ina hospital in Caracas (Venezuela) from 1997 to 2003 showed the presence of *Pseudomonas aeruginosa* in 7% of the positive GIT samples [29]. Streptococcus pyogenes was the most commonly isolated bacteria in nasopharyngeal swabs in healthy children (ages of 6 and 7 years) who attended the same primary school. Positive bacterial findings of this pathogenic in healthy carriers are not an indication for antibiotic therapy [35].

Resistance and multidrug resistance of the most commonly isolated bacteria

According to literature data, the level of resistance to bacteria isolated in hospitals is higher comparing tothat in the general practice [36]. Hospitals are often regarded as the focal point for emergence development of resistance and multidrug resistance [37].

E. coli: One-year prospective study conducted in Ankara (Turkey) demonstrated about 30% resistance of*E. coli*, isolated in urinary infections to ceftriaxone. The resistance of ampicillin described in this study was 74.2% [38]. Many authors believe that this high percentage of resistance of *E. coli* is a consequence of irrational, prophylactic and excessive use of antibiotics in general practice [33].

S. aureus: *S. aureus* is usually isolated insamples from the respiratory tract. This bacterium isin a relatively small percentage multidrug resistant (about 10%). Based on the results of five-year retrospective studies conducted in 300 hospitals across the United States, an increase in methicillinresistant *S. aureus* (MRSA) isolated from swabs of the throat was observed [39].

Coagulase negative *Staphylococcus spp.*, according to literature data, is highly resistant and multidrug resistant bacteria, which again is a result ofan inadequate use of antibiotics [40]. Thisbacterium is isolated mainly from blood samples and catheter swabs. The sensitivity of this bacterium remained preserved only on vancomycin and teicoplanin. Regarding fusidic acid it was reported that this bacteriawas almost 30% resistant. Furthermore, isolates from hospital material showed significant resistance to this bacterium tolincosamines and macrolides [41].

*Klebsiella pneumoniae*ismost commonly isolated from samples of the respiratory tractand it is a causative factor for sepsis in neonates. For this bacteriumdata reported from the studies conducted in Asia, Africa and South America shows a high percentage of resistance to many classes of antibiotics: more than 50% tocefotaxime, more than 70% to ampicillin and gentamicin [30]. Isolates of thisbacterium from the blood cultures showed significantly high resistance to aminoglycosides [41]. According to the results of a study conducted in Ankara (Turkey), isolates of *K. pneumoniae* from urinary samples showed about 35% resistance to folate synthesis inhibitors [38].

Penicillin-resistant *Streptococcus pneumoniae* was studied in only one RTC with 35 participants. Before exposure to penicillin, resistance was not significant, but after exposure to amoxicillin the changes in resistance occur and normalized one month after the end of treatment [42].

Pseudomonas aeruginosa is a common cause of hospital infections [43]. It is mostly isolated from samples from the respiratory tract and less from urine and GIT. This bacterium shows 100% resistance to folate synthesis inhibitors and ceftriaxone [44]. It also shows high resistance (about 90%) to antibiotics that are usually prescribed in general practice such as amoxicillin, nitrofurantoin, and cephalexin [45]. 60% of the isolates were sensitive only to quinolones [41].

Acinetobacter spp. has been shown to be highly resistant to most of the includedantibiotics, and appropriate treatment results have been achieved by a combination of a beta-lactam antibiotic and aminoglycoside [46]. Multidrug resistance of Gram-negative bacteria is a major problem in hospitals because it is easily transmitted through contact, and the spread of resistance affects many patients in a small area, especially in immunologically compromised patients [47].

Enterobacter spp. in the developing countries is a common cause of bacteremia and severe complications in newborns. A study analyzing isolates from the respiratory and gastrointestinal tract showed a high percentage of resistance to penicillin and cephalosporins, which is a consequence of the production of beta-lactamase [30]. In Sweden, in adults, this bacterium showed about 20-30% resistance to cefotaxime [48].

Enterococcus spp. takes a more prominent place among the causes of hospital infections [49]. Isolates from urine samples showed the lowest percentage of

multidrug resistance (about 36%), while resistance to GIT, blood and catheter isolates wasmuch higher (around 88%) in all tested classes of antibiotics [50]. According to the results of the international SENTRY project (The SENTRY Antimicrobial Surveillance Program), which included about 70 microbial laboratories around the world, a high percentage of resistance (about 50-65%) has shownthis bacterium to gentamicin [51].

Conclusion

According to the literature data, the highest percentage of antibiotic consumption is at the surgicalclinics. The most commonly used antibiotics in children are parenteral and oral cephalosporins, combinations of beta-lactams+inhibitor (clavulinic acid), macrolides and aminoglycosides. The most commonly isolated bacteria from the samples are *E. coli*, *S. aureus*, coagulase negative *Staphylococcus spp., Klebsiella spp., Pseudomonas spp., Acinetobacter spp., Enterococcus spp.* and *Enterobacter spp*. Multidrug resistance has been confirmed in almost all isolates of *Enterobacter spp*. and *Acinetobacter spp*. In the remaining isolates of *P. aeruginosa*, *Enterococcus spp*., resistance has been confirmed in more than 50% of the isolates. Insignificant multidrug resistance has been identified in isolates of*E. coli* and *S. aureus*.
This data gave us enough information about the use of antibiotics, most often isolated bacteria and resistance to different classes of antibiotics. This will be very helpful in the process of monitoring, completing and comparing data for bacterial resistance in our country.

Conflict of interest statement. None declared.

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