© Pediatr Med Rodz 2020, 16 (2), p. 148–153
DOI: 10.15557/PiMR.2020.0028

Received: 06.11.2019
Accepted: 27.11.2019
Published: 30.06.2020

Agnieszka Lipińska-Opałka, Anna Jung

Rational antibiotic therapy of respiratory tract infections in a primary care setting

Racjonalna antybiotykoterapia zakażeń układu oddechowego w gabinecie lekarza POZ

Department of Paediatrics, Paediatric Nephrology and Allergology, Military Institute of Medicine in Warsaw, Warsaw, Poland. Head of the Department: Insitute Professor Bolesław Kalicki, MD, PhD
Correspondence: Agnieszka Lipińska-Opałka, MD, PhD, Department of Paediatrics, Paediatric Nephrology and Allergology, Military Institute of Medicine, Szaserów 128, 04-141 Warsaw, Poland, e-mail: alipinska@wim.mil.pl

Abstract

Respiratory infections are one of the main reasons for visits to general practitioners. The ability to make quick decisions on whether to include antimicrobial treatment in these infections is of key importance. If antibiotic therapy is used, then the choice of appropriate antimicrobial, dose and treatment duration is important. Expert recommendations developed as part of the National Program for Protection of Antibiotics provide guidance for primary care practitioners. The aim of this paper was to discuss the treatment of choice and the management in the case of first-line treatment failure in different community-acquired respiratory tract infections in children and adults. Since a large proportion of these infections are caused by viruses, we remind scores and guidelines developed to facilitate the diagnosis of these cases. If antibiotic therapy is needed, its choice should be based on the current epidemiological situation. *Streptococcus pneumoniae* is still the most common cause of respiratory tract infections. Therefore, despite pneumococcal resistance to penicillin derivatives, amoxicillin will be an optimal option to fight these pathogens if used at appropriately high doses. Amoxicillin-clavulanate or cephalosporins are generally used as second-line treatment, while macrolides are recommended in the case of immediate hypersensitivity to beta-lactams or suspected atypical aetiology of infection.

Keywords: amoxicillin, antibiotics, respiratory tract infection

Streszczenie

Jedną z najczęstszych przyczyn wizyt pacjentów w gabinecie lekarza rodzinnego są zakażenia układu oddechowego. W leczeniu tych chorób kluczowa jest umiejętność szybkiego podjęcia decyzji odnośnie do włączenia bądź zaniechania antybiotykoterapii. Przy antybiotykoterapii natomiast ważny jest dobór odpowiedniego leku, jego dawki i czasu stosowania. Na pomoc lekarzom podstawowej opieki zdrowotnej wychodzą rekomendacje ekspertów przygotowane w ramach Narodowego Programu Ochrony Antybiotyków. Celem niniejszego artykułu jest przybliżenie terapii z wyboru oraz postępowania przy niepowodzeniach leczenia pierwszego rzutu w poszczególnych postaciach pozaszpitalnych zakażeń dróg oddechowych u dzieci i u dorosłych. Duża część tych zakażeń jest powodowana przez wirusy, stąd autorzy przypominają skale i wytyczne, które ułatwiają rozpoznanie tych przypadków. Natomiast w razie konieczności włączenia antybiotykoterapii należy kierować się aktualną sytuacją epidemiologiczną. W przypadku zakażeń układu oddechowego najczęstszym patogenem pozostaje *Streptococcus pneumoniae*. Stąd lekiem pierwszego rzutu będzie na ogół amoksycylina, która pomimo pojawiającej się oporności pneumokoków na pochodne penicyliny stosowana w odpowiednio wysokich dawkach będzie optymalnym wyborem w walce z tymi patogenami. Amoksycylina z kwasem klawulanowym lub cefalosporyny są na ogół lekami drugiego rzutu, a w przypadkach nadwrażliwości natychmiastowej na beta-laktamy lub przy podejrzeniu etiologii atypowej zaleca się makrolidy.

Słowa kluczowe: amoksycylina, antybiotyki, zakażenia dróg oddechowych

INTRODUCTION

Respiratory tract infections are the main reason for visits to general practitioners. They are the leading cause of community-acquired infections (50–60%) and the most common cause of fever in young children. Two groups of patients, i.e. children ≤5 years old (immature immune system) and adults >60 years old (multiple comorbidities and ageing process itself), are at a particular risk of respiratory infections. However, regardless of age, viruses are the main cause of respiratory infections. The most common include rhinoviruses, adenoviruses, coronaviruses, influenza viruses, parainfluenza and respiratory syncytial virus (RSV), which are responsible for the majority of cases of acute pharyngotonsillitis, sinusitis, laryngitis, otitis media and bronchitis[1]. Bacterial aetiology is more varied and depends on factors such as age, comorbidities or the place of contracting the infection. Knowledge of these factors is a basis for the proper choice of medications in a primary practice setting, where additional tests, including microbiology, are difficult to perform and unnecessary.

Therefore, the decision to include antimicrobial therapy should be based on clear evidence for bacterial aetiology. *Recommendations for the Management of Community-Acquired Respiratory Tract Infections*, which were based on evidence-based medicine (EBM) and are updated every few years, provide guidance in this respect. Current recommendations are dated 2016 and include clear guidelines for the management in different clinical entities[1].

RATIONAL ANTIMICROBIAL THERAPY

The first principles for rational antimicrobial therapy were developed in the United States at the end of the 20th century in a response to the problem of growing bacterial resistance to antibiotics. It can be therefore seen that it was already 50 years after the spectacular success of the first synthetic penicillin that the fight with the growing problem of antibiotic resistance due to antimicrobial abuse was initiated. The problem is particularly acute as no new agent that could replace antimicrobials has been recently developed to address the issue of new mechanisms of drug resistance. This phenomenon has its clinical implications as it was demonstrated that the risk of death due to infection is twice higher if caused by an antibiotic-resistant strain[2].

Antimicrobials are probably a group of agents that are most commonly prescribed in the absence of proper indications, are improperly selected or used in inadequate doses[3]. Overuse of antimicrobials is not limited to Poland. Similar observations have been also made in other regions of the world. Data from the United States show that up to 60% of cases of pharyngitis in the paediatric population are treated with antibiotics despite that bacteria account for only 37% of these cases[4]. However, Dutch researchers observed that antimicrobials were not prescribed in accordance with indications in almost one in two cases of respiratory infections in adult patients (46%)[5]. In India, most patients treated for upper respiratory tract infections (URTIs) received wide-spectrum antimicrobials, such as third generation cephalosporins or fluoroquinolones, against recommendations, during the analysed period of time[6].

Therefore, there is an urgent need for reminding about the principles of rational antimicrobial therapy, which will be done in this paper.

UPPER RESPIRATORY TRACT INFECTIONS

Upper respiratory tract infections include acute pharyngotonsillitis (APT), acute rhinosinusitis (ARS), acute subglottic laryngitis (ASL), and acute otitis media (AOM). The discussion on antibiotic therapy in URTIs will not refer to ASL, which is a viral infection and, according to expert recommendations, the use of antibiotics in this entity is not justified[1].

Viruses are also responsible for most cases of APT (75–80%) and ARS, with the predominance of rhino-, corona- and adenoviruses as well as influenza and parainfluenza viruses. It is estimated that bacterial infections account for only 0.5–2% of cases of paranasal sinus infections, and develop secondary to viral infections. In such cases, *Streptococcus pneumoniae* (26–35% of bacterial infections) and *Haemophilus influenzae* (21–40%), followed by *Moraxella catarrhalis*, *Staphylococcus aureus* and *Streptococcus pyogenes* (in total 20% of cases) are the leading pathogens[1]. *S. pyogenes* plays a major role in bacterial pharyngotonsillitis[7]. AOM seems to have mostly mixed viral/bacterial pathogenesis, and the spontaneous resolution of a large percentage of cases supports the dominant role of viruses. *S. pneumoniae* and *H. influenzae*, which are found in the nasopharynx, are the main bacterial pathogens responsible for AOM[8].

In any case, distinguishing bacterial upper respiratory tract infections is not easy and only partly depends on the physician's experience. It has been demonstrated for instance that the sensitivity and specificity of medical history and physical examination is insufficient to differentiate the aetiology of pharyngitis[9]. Scores and recommendations developed by experts, such as the Centor/McIsaac score for acute pharyngitis, are useful in the differentiation of the aetiology. According to this score, fever above 38°C, absence of cough, anterior cervical lymphadenopathy, tonsillar exudates and swelling, and age between 3 and 14 years are criteria increasing the risk of bacterial pharyngitis. In doubtful cases, rapid testing for *S. pyogenes* or pharyngeal swab culture are recommended[1].

Guidelines developed by European and American expert associations (Tab. 1) are used for the differentiation of acute sinusitis. Despite apparent differences, experts list the same symptoms (severe facial pain, purulent nasal discharge and high fever) as typical for bacterial aetiology, while European guidelines additionally point to elevated inflammatory markers as a helpful differentiation criterion.

 DOI: 10.15557/PiMR.2020.0028

2012 EPOS* guidelines, 3 out of 4 are necessary	Guidelines of the Infectious Diseases Society of America, American Academy of Pediatrics
Purulent nasal discharge (mainly unilateral) or purulent discharge in the nasal passages	Symptoms persisting for ≥10 days, no improvement
Severe local pain (with unilateral dominance)	Severe symptoms (fever ≥39°C, purulent nasal discharge and facial pain) persisting for ≥3–4 days since the disease onset
Fever (>39°C)	Recurrent or increased symptoms in the form of fever, headache, nasal discharge
Increased ESR/CRP	
** European position paper on rhinosinusitis and nasal polyps 2012.*	

Tab. 1. Criteria for bacterial ARS[10,11]

The management of AOM is initiated in most cases with watchful waiting, with additional use of analgesic, antipyretic and anti-inflammatory agents. If no improvement is seen after 48–72 hours of watchful waiting, antimicrobial therapy should be included. According to experts, antimicrobial therapy should be immediately included in the following clinical cases of AOM:

- age <6 months;
- high fever (>39°C) accompanied by vomiting and severe earache;
- bilateral otitis media in patients <2 years of age;
- ear discharge;
- accompanying craniofacial defects, Down syndrome, impaired immunity, recurrent otitis[1].

Based on these principles, the diagnosis of bacterial upper respiratory infection should be followed by the inclusion of an antimicrobial active against pathogens most likely to cause infection in a given location, which will effectively penetrate to the affected site, at an appropriate dose and for an appropriate period of time. The treatment of choice in acute bacterial upper respiratory infections is presented in Tab. 2.

In the case of acute bacterial pharyngitis, penicillin at a dose of 100,000–200,000 U/kg/day for children <40 kg and 20–30 million U/day for adults given in two divided doses should be used as first-choice therapy. Its effectiveness is supported by 100% efficacy against *S. pyogenes*, confirmed ability to eradicate the microbe as well as preventing complications in the form of rheumatic fever or purulent complications spreading through continuity. Furthermore, it was shown that penicillin reduces the duration of both symptoms and infectivity, and, at the same time, it has good safety profile and a narrow antimicrobial spectrum. However, penicillin must be used for an appropriately long time in order to meet these assumptions. It was demonstrated that penicillin therapy lasting less than 10 days may fail to eradicate *S. pyogenes*[11]. In the case of first-line therapy failure or a history of delayed hypersensitivity to penicillins, first generation cephalosporins (cefadroxil or cephalexin) are the treatment of choice. It should be noted that the use of higher generation cephalosporins is not justified and may even be harmful due to its excessively wide antibacterial spectrum and effects on the spread of penicillin-resistant pneumococci[12]. Macrolides should be used in the treatment of streptococcal pharyngitis only in the case of immediate hypersensitivity to beta-lactams, and should be preceded by the determination of susceptibility to erythromycin due to a large proportion of streptococci resistant to macrolides. It is worth emphasising that the efficacy of azithromycin is dose-dependent and higher daily doses should be used to eradicate *S. pyogenes* – 12 mg/kg at a single daily dose for 5 days or 20 mg/kg for 3 days in patients <40 kg[1].

A similar treatment is used for acute bacterial sinusitis and AOM. In both cases the antimicrobial should be effective against *S. pneumoniae* and *H. influenzae*, which are the most common aetiology of these infections. Growing pneumococcal resistance to antibiotics, including the emergence of strains with reduced sensitivity to penicillin (penicillin non-susceptible pneumococci, PNSP) and, consequently, to all beta-lactams, is an alarming phenomenon observed in the last decade. Underdosage of β-lactams is one of the reasons. It was demonstrated that almost 30% of pneumococci are insusceptible to amoxicillin at a dose of 40 mg/kg/day for children and 1,500 mg/day for adults[13]. Increasing the dose up to 90 mg/kg/day in children and 3–4 g in adults successfully breaks this resistance, reducing it to 6%[14]. Therefore, amoxicillin remains the first choice therapy for bacterial AOM and ARS, but it must be used at high doses. The optimal duration of antibiotic therapy in AOM

	APT	AOM	ARS
First-choice antimicrobial	Penicillin	Amoxicillin	Amoxicillin
Delayed hypersensitivity to beta-lactams	Cefadroxil/cephalexin	Cefuroxime/ceftriaxone	Cefuroxime
Immediate hypersensitivity to beta-lactams	Erythromycin/clarithromycin/ azithromycin*	Clarithromycin	Clarithromycin/moxifloxacin**/ levofloxacin**
Corrected treatment, recurrence	Cefadroxil/clindamycin	Amoxicillin-clavulanate/ceftriaxone	Amoxicillin-clavulanate
* After determining drug resistance to erythromycin. ** In adults only.			

Tab. 2. Recommended antibiotic therapy in different bacterial forms of upper respiratory tract infections[1]

DOI: 10.15557/PiMR.2020.0028 PEDIATR MED RODZ Vol. 16 No. 2, p. 148–153

is still under discussion. While a 10-day treatment is still recommended for acute sinusitis, the 2016 recommendations point to the possibility of reducing the treatment time in uncomplicated AOM in adolescents and children >2 years of age to 5 days[1]. The 10-day therapy was shown to be effective in younger patients[15].

In the case of lack of response to first-line antimicrobial treatment or early recurrence (7–10 days after treatment completion), infection with pneumococci highly resistant to penicillins or beta-lactamase-producing *H. influenzae* should be suspected. *S. aureus* and anaerobic bacteria should be also considered in ARS. Amoxicillin-clavulanate, cefuroxime or ceftriaxone are reserved for such cases. However, it should be also emphasised at this point that amoxicillin must be used in high doses[16]. Second and third generation cephalosporins are also recommended in cases of delayed hypersensitivity to amoxicillin. Macrolides are the only group of agents that can be used in children (anti-pneumococcal fluoroquinolones may be additionally used in adults) with immediate hypersensitivity. Macrolides that are not effective against *H. influenzae* include erythromycin, roxithromycin and spiramycin, whereas azithromycin was only shown to be effective after administration of a high single dose[17]; however, this dose is not approved for use in children in Poland. Clarithromycin administered at 15 mg/kg/day in two divided doses in children and 2 × 250–500 mg in adults should be used in the treatment of AOM or ARS in patients with immediate allergic reaction to beta-lactams.

LOWER RESPIRATORY TRACT INFECTIONS

Lower respiratory tract infections managed in an outpatient setting include:

- acute bronchiolitis in infants and children aged ≤2 years;
- acute bronchitis (AB);
- community-acquired pneumonia (CAP);
- infectious exacerbation of chronic obstructive pulmonary disease (COPD) in adults.

Since viruses (RSV, rhinoviruses, influenza and parainfluenza virus, etc.) are the main aetiology of acute bronchiolitis and bronchitis in each age group, routine use of antibiotic therapy in these infections is not recommended. Infection with *Bordetella pertussis* is one of few situations, when the use of antibiotic therapy in acute bronchitis may be beneficial. Pertussis should be suspected in patients with cough persisting for more than 14 days or those with documented exposure to infection. In such cases, the use of antimicrobial treatment will limit the spread of infection if initiated within the first 3 weeks of symptom onset. Causative treatment has no effects on the course of disease. Standard doses of macrolides are recommended for the treatment of pertussis[1].

Administration of antibiotic should be considered in persistent bacterial bronchitis (PBB), i.e. in young children (<5 years of age) with productive cough persisting for more than 4 weeks, without a tendency to subside and after excluding other causes. Then, amoxicillin-clavulanate or a macrolide is administered for 10–14 days[1].

The aetiology of CAP is varied depending on age (Tab. 3), and groups of patients receiving in-hospital treatment for various indications (including children up to 4–6 months of age) were not discussed in this paper.

The younger the patient, the more likely it is that CAP is of viral aetiology; therefore, children aged between 4 months and 4 years who are in good overall condition may be treated symptomatically. At this point, it should be reminded that neither radiology, nor the severity of leukocytosis or acute phase protein levels allow for clear differentiation between viral and bacterial aetiology. Only low levels of C-reactive protein (CRP) and procalcitonin (PCT) reduce the probability of bacterial involvement. When implementing antibiotic therapy in a patient 3 months to 5 years of age, an antimicrobial effective against *S. pneumoniae*, i.e. high-dose amoxicillin (like in AOM), will be the first-line therapy. However, unlike in the treatment of AOM, amoxicillin is used in three divided doses administered at 8-hour intervals in CAP. The duration of antibiotic therapy may be reduced to 5 days in milder cases, whereas 7–10-day therapy is recommended in more severe cases[1].

Since pneumococci and atypical microbes are a common cause of CAP in children aged 5–15 years, there is no clear consensus as to which antimicrobial should be used as first-line therapy. The advantage of amoxicillin over macrolide is argued by a nearly 30% pneumococcal resistance to macrolides and usually a more severe course of pneumonia caused by *S. pneumoniae*. Therefore, the British Thoracic Society guidelines recommend combined use of amoxicillin and macrolide in doubtful situations or moderately severe infections[18]. A retrospective analysis in a cohort of 700 children demonstrated the efficacy of this approach based on reduced failure rates compared to beta-lactam monotherapy[19].

Since lack of improvement after first-line therapy or complications are usually an indication for hospitalisation, revised treatment of pneumonia will not be discussed in this paper.

Adult patients with mild pneumonia may be treated on an outpatient basis and require no bacteriological testing. However, unlike in children, the diagnosis should be always

Age	Aetiology
4 months – 4 years	RSV, influenza and parainfluenza viruses, adenoviruses, rhinoviruses, *Streptococcus pneumoniae, Haemophilus influenzae, Mycoplasma pneumoniae*
5–15 years	*Streptococcus pneumoniae, Mycoplasma pneumoniae, Chlamydophila pneumoniae*
Adults	*Streptococcus pneumoniae, Klebsiella pneumoniae, Mycoplasma pneumoniae, Chlamydophila pneumoniae, Haemophilus influenzae*

Tab. 3. Aetiology of CAP depending on age[1]

 DOI: 10.15557/PiMR.2020.0028

	4 months – 4 years	4 months – 4 years	Adults
First-choice antimicrobial	None/amoxicillin	Amoxicillin/ampicillin/macrolide	Amoxicillin/ampicillin/macrolide
More severe cases		Beta-lactam + macrolide	Amoxicillin-clavulanate
Type 3 hypersensitivity to beta-lactams	Cefuroxime, ceftriaxone, cefotaxime	Macrolide	Cefotaxime/ceftriaxone
Type 1 hypersensitivity to beta-lactams	Vancomycin, teicoplanin, linezolid	Macrolide	Macrolide

Tab. 4. Antimicrobial therapy in CAP depending on age

based on chest radiography due to the high sensitivity of this method in the differentiation between pneumonia and bronchitis[20]. The choice of empirical therapy should be based on the knowledge of the most common aetiology of CAP in adults, i.e. *S. pneumoniae*, like in children. Amoxicillin is the most effective antimicrobial against pneumococci (93%), followed by ceftriaxone (80%)[21]. Therefore, amoxicillin is once again first-choice antimicrobial in the treatment of respiratory infection, this time CAP in adults, and it should be used at a high dose – 3 × 1 g/day. The use of cefuroxime, cotrimoxazole and doxycycline is not recommended due to the low effectiveness of these antibiotics against *S. pneumoniae* (78%, 64% and 70%, respectively)[1]. Macrolide may be considered as first-line therapy in young adults with no comorbidities and a mild course of disease, when atypical aetiology is suspected. There is no consensus on whether combination therapy with beta-lactam and macrolide is superior to beta-lactam monotherapy[22,23]. Therapy duration should be 10–14 days in the case of suspected atypical aetiology, whereas amoxicillin may be discontinued already after 3 days of evident improvement or 7 days after treatment onset[1]. The treatment of choice for bacterial CAP is shown in Tab. 4.

Antibiotic therapy should not always be used in the treatment of COPD exacerbations as research outcomes on the efficacy of this type of management are inconclusive[24]. The choice of antibiotic therapy should be always based on the clinical picture, and microbiological testing is not necessary in most cases. Infection caused by *Pseudomonas aeruginosa* is an exception and should be suspected if one of the following risk factors is present: severe obstruction (FEV1 <50% of predicted value), at least 4 antibiotic therapies in the past 12 months, hospital stay in the past 90 days or chronic glucocorticoid therapy. Beta-lactams (amoxicillin, amoxicillin-clavulanate) and, in the case of type 1 resistance to amoxicillin, macrolides or anti-pneumococcal fluoroquinolones (levofloxacin or moxifloxacin), are first-line antimicrobials in empirical therapy[1].

CONCLUSIONS

Knowledge of the principles of rational antibiotic therapy in community-acquired respiratory infections is crucial for effective treatment of patients in a primary care setting and, at the same time, it eliminates the risk of developing antibiotic-resistant strains. Following the guidelines allows for successful treatment of many diseases without unnecessary tests or hospital says. The choice of antimicrobials targeting the most common pathogens allows to avoid the incorrect use of antibiotics with excessively wide spectrum of action, and thus protect the patients against the unnecessary exposure to adverse effects of the therapy. The choice of dose and treatment duration is as important as the choice of the antimicrobial itself as it may help reduce the growing antibiotic resistance.

Conflict of interest

The authors do not declare any financial or personal links with other persons or organisations that might adversely affect the content of the publication or claim any right to the publication.

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