Quality of Life (2024) 15(1-2):57-66

**DOI:** 10.7251/QOL2401057K **UDC:** 615.33.015.8:579.862.1

*Review*

# Therapeutic Options for the Treatment of Community-Acquired Pneumonia Caused by Streptococcus Pneumoniae

Jasmina Krehić
*Department for Clinical Pharmacology, General hospital "Prim.dr. Abdulah Nakaš" Sarajevo, FBiH, BiH, jasminakrehic@yahoo.com*

**ABSTRACT:** *Streptococcus pneumoniae* is the most common cause of community acquired pneumonia, acute otitis media, meningitis and other infections, asymptomatic colonizing nasopharynx of healthy children and adults. Since late 1970s there has been a steady decline in the susceptibility of *Streptococcus pneumoniae* to various groups of antibiotics.The number of antibiotic-resistant pneumococcal infections has decreased due to the success of the pneumococcal conjugate vaccine. In addition to vaccination, guidelines for treatment of pneumococcal disease are developed by various professional and scientific associations, intending to slow or reverse drug-resistant pneumococcal infections. The aim of this work is to provide a generated information about therapeutic options for the treatment of community-acquired pneumonia caused by *Streptococcus pneumoniae*, based on the recommendations and statements from various guidelines developed by different proffesional and scientific associations but limited on drugs available on the market in Bosnia and Herzegovina.

**Keywords:** pneumonia, *Streptococcus pneumoniae,* guidelines, antibiotics.

## INTRODUCTION

In 1881, the microorganism, later known as *pneumococcus* due to its role in causing pneumonia, was first isolated simultaneously and independently by the American army physician George Sternberg and the French chemist Louis Pasteur.But, for the first time pneumococcus was described by German pathologist Edwin Klebs, who in 1875 observed the pneumonia bacterium under a microscopefrom the pleural fluid of patients with pneumonia (Tukbekova et al, 2019). That is what we now believe to be *Streptococcus pneumoniae*.

*Streptococcus pneumoniae* is a gram-positive, alpha-hemolytic, encapsulated bacteria that grows in chains or pairs (diplococci), with more than 100 known serotypes.It colonizes the nasopharynx of 5-10% healthy adults and 20-40% of healthy children on any single occasion (Fauci et al, 2009). The spread of, often asymptomatic colonized, bacteria from the nasopharynx causesotitis media and sinusitis,aspiration pneumonia andinvasion in normally sterile areas in the body can cause sepsis or meningitis.Other possible infections are endocarditis, septic arthritis, and, rarely, peritonitis.

***Pneumonia is considered the most common clinical manifestation of pneumococcal disease in adults.*** *Streptococcus pneumoniae*(*pneumococcus*) historically hasbeen and still remains the most common cause of pneumonia. It is the most commonly identified bacterial cause of Community - acquired Pneumonia (CAP) requiring hospitalization andis the most common cause of death from pneumonia worldwide (Centers for Disease Control and Prevention - CDC, 2022).

### Prevalence

Previously, in the United States, 5 to 15% of CAP cases were attributed to *pneumococcus*. However, recent quantitative molecular and bacteriological data indicate that this is an underestimate and suggest that nearly 22% of hospitalized cases may be caused by *pneumococcus*as well as in Europe (Musher et al.,

2020; Bjarnason et al., 2018), andeven more, to 30.5% in developing countries (Para et al., 2018).Morbidity and mortality from serious pneumococcal disease is highest in children and elderly people with chronic diseases.

Case fatality rates can be high for invasive pneumococcal disease, ranging up to 20% for sepsis and 50% for meningitis in developing countries (Worl Health Organization - WHO, 2018).Mortality associated with pneumococcal pneumonia in hospitalized patients is high, ranging from18% for adults aged < 65 years and 23% for the older than 65 years (Michelin et al, 2019).In 2008, an estimated 541,000 HIV-negative children under the age of 5 died from pneumococcal disease (WHO, 2018).

Therapeutic options in the treatment of pneumococcal disease are limited. *Streptococcus pneumoniae* was universally susceptible to penicillin until the late 1970s (O'Neill, Gillespie, and Whiting, 1999). Since then, there has been a steady decline in the susceptibility of *Streptococcus pneumoniae* to antibiotics. The bacteria has developed resistance to several antibiotics, including β-lactams, macrolides, tetracyclines, trimethoprim-sulfamethoxazole, vancomycin, and fluoroquinolones (Murphy et al., 2021).

According to the American CDC - *Centers for Disease Control and Prevention*, pneumococcal bacteria are resistant to one or more antibiotics in 3 out of every 10 cases.The number of antibiotic-resistant pneumococcal infections has decreased due to the success of the pneumococcal conjugate vaccine.

The use of the pneumococcal vaccines contributed to the reduction of resistance at least through the direct reduction of organisms and strains carrying resistance genes that are specifically targeted by the vaccine, andthrough a secondary effect thanks to the reduction of febrile illnesses that often lead to the use of antibiotics.Besides the vaccination, appropriate antibiotic use can also slow or reverse drug-resistant pneumococcal infections (CDC, 2022).There are different methods of antibiotic administration within the framework of rational (reasonable) administration.To understand the relationship between drug dose and efficacy, pharmacokinetic (PK) and pharmacodynamic (PD) characteristics must be integrated (Jacobs, 2001).There are two main patterns of antimicrobial activity to distinguish:

a) concentration - dependent bactericidal activity which needs maximised antimicrobial concentration (aminoglycozides, quinolones and azalides)

b) time - dependent bactericidal activity which is characteristic of many classes of antibiotics, such as β-lactams and macrolides. By this way, an attempt is made to optimize the duration of exposure of the pathogen to the antimicrobial drug.

When *Streptococcus pneumoniae* is in question, **time - dependent bactericidal activity** is of the greatest interes and the main PK/PD parameter that correlates with the efficacy of time-dependent antimicrobials is the serum concentration present for 40-50% of the dosing interval. This concentration is the sensitivity limit or cut-off point for the dosing regimen used. The best two examples are given by Jacobs in his work from 2001 where he states the use of two different doses of amoxicillin, administered by different dosing shedule.

*Example 1.*

The serum concentration of amoxicillin when 500 mg of this drug is administered orally at 8-hour intervals over a 24-hour period indicates that amoxicillin has an elimination half-life of 30-45 minutes. With this dosing regimen, amoxicillin reaches a concentration of 2 mg/L in 3.3 h of each 8-hour dosing interval (or 9.9 h in a 24-hour day), which is 41% of the dosing interval. Therefore, this regimen achieves an amoxicillin concentration of 2 mg/L for more than 40% of the dosing interval, and should therefore be active against organisms with an MIC ≤2 mg/L (minimal inhibitory concentration).

*Example 2.*

If 875 mg is given at 12-hour intervals, the amoxicillin concentration exceeds 2 mg/L during 4.5 h of each dosing interval (9 h in a 24-hour day). Therefore, this regimen achieves an amoxicillin concentration exceeding 2 mg/L for approximately 40% of the dosing interval.

Thus, both dosing regimens achieve serum concentrations above 2 mg/L for about 40% of the dosing interval.

## Mechanism of resistance

The mechanism of pneumococcal resistance to penicillin and cephalosporins is based on a change in the penicillin-binding protein (PBP). Mutations that alter PBP result in reduced binding affinity for these drugs, making them less effective.This type of resistance can be overcome if the concentration of the antibiotic at the site of infection exceeds the MIC of the organism by 40-50% of the dosing interval(Iyer, 2023). It is important to emphasise the two main virulence factors of *Streptococcus pneumoniae* that are polysaccharide capsule that surrounds the bacteria, and the toxin pneumolysin which is released during *Streptococcus pneumoniae* autolysis (Martner, Dahlgre, Paton & Wold, 2008).

Capsule is mainly composed of polysaccharides, with each capsule type having a different composition and linkage of sugars and other components, resulting in more than 100 different serotypes on the basis of antibody reactions with the capsule. For the pneumolysin it has been shown that it can stimulate the innate immune response including release of the inflammatory cytokine from the host's airway epithelial cells (Küng et al, 2014). In short, capsule inhibits antibody binding, directly inhibits phagocytosis, and prevents capture by neutrophiles, while pneumolysin inhibits neutrophil and oxidative burst, induces neutrophil lysis and inhibits neutrphil chemotaxis. So, these are numerous challenges for antibiotics to be effective against this bacteria, making these two virulence factors main therapeutic targets.

## Mechanisms of action of antibiotics

Based on their *mechanism of action*, antibiotics can be classified in four major groups (Li F., Collins J.G. and Keene F.R., 2015).

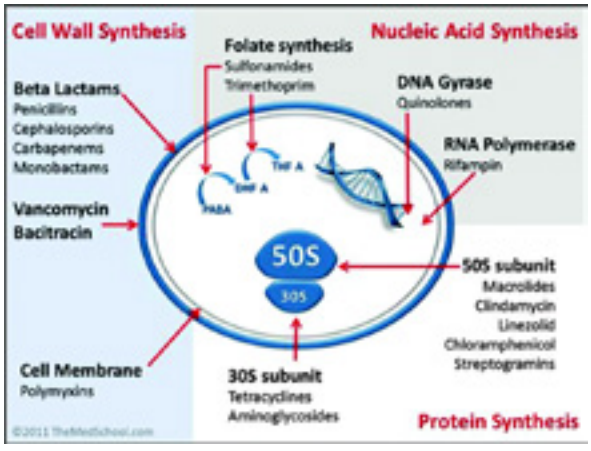


**Figure 1.** Classification of antibiotics by mechanism of action. (Image by Kendrick Johnson: Creative Commons Attribution-Share Alike 3.0 Unported license) in Li et al, 2015.

1. Inhibitors of cell wall synthesis (e.g. penicillins, cephalosporins, carbapenems, monobactams, glycopeptides)
2. Antibiotics that disrupt cell membrane (e.g. polymyxins)

3. Inhibitors of nucleic acid synthesis (e.g. quinolones, rifampicin)
4. Inhibitors of protein synthesis (e.g. tetracyclines, aminoglycosides, macrolides)

According to their mechanism of action antibiotics are classified based on the *effects* that they produce in two major groups:

a) bactericidal (killing the bacteria)

b) bacteriostatic (stopping bacterial growth)

Bactericidal antibiotics are those from group 1., 2. and 3. while bacteriostatic antibiotics are mainly from group 4. as well as inhibitors of folate synthesis. But, some bacteriostatis antibiotics can also act as a bactericidal, depending on their concentration(Fohner A.E., Sparreboom A., Altman R.B. and Klein T.E., 2017). Example is macrolide antibiotic erythromycin, which in low concentrations is classified as bacteriostatic but in high concentrations is classsified as a bactericidal.

***Note:The above is of high importance for understanding the therapeutic options for pneumococcal disease, especially regarding dose levels and dosing regimens used.***

## Therapeutic options for the treatment of Community - acquired pneumonia

Various professional associations and various guidelines agree on therapeutic options for treatment of pneumococcal disease. Our intention is to present the main recommendations from different guidelines developed by respected scientists and professionals, available online *in extenso,* that can be used in Bosnia and Herzegovina, taking into account the drugs that are present on our market. Other drugs will not be included in this work.

In every guideline for the treatment of pneumococcal disease is stated that ***initial antibiotic therapy is empiric***. This empiric therapy varies depending on:disease severity, comorbidities, patient's history of recent antibiotic use, probability of infection with antibiotic-resistant pathogens, simultaneous infection with *Pseudomonas* or *Methicillin-resistant Staphylococcus aureus* (MRSA), allergies or drug intolerance.

## Pneumonia (Comunity - acquired Pneumonia – CAP)

The main recommendations for treatment of ***Community Acquired Pneumonia (CAP)*** are summarized from following guidelines:

- "Diagnosis and Treatment of Adults with Community-acquired Pneumonia. An Official Clinical Practice Guideline of the American Thoracic Society and Infectious Diseases Society of America" (Metlay etal, 2019)
- "ERS/ESICM/ESCMID/ALAT guidelines for the management of severe community-acquired pneumonia"- first international guidelines (Martin-Loeches et al, 2023)
- "Pneumonia (community-acquired): antimicrobial prescribing"(NICE guideline, 2019)
- "Updated Clinical Practice Guidelines for Community-Acquired Pneumonia"(Sucher, Knutsen, Falor & Mahin, 2020)

Considering empiric therapy for CAP, it has to be emphasized that there are different stages of disease severity as well as different patient populations regarding comorbidities, so the way of administration and the dose levels are different for different groups of patients, as follows:

1. Outpatients without comorbidities,
2. Outpatients with comorbidities
3. Hospitalized patients who are not in intensive care unit (ICU)

4. Hospitalized patients in the intensive care unit (ICU)
5. Patients allergic to penicillin

1. **Outpatients without comorbidities** are those with no comorbidities/previously healthy, age < 65 years, no recent use of antibiotics, no risk factors for MRSA or Pseudomonas aeruginosa. The drug of first choice is **amoxicillin 1 g peroral (PO) q8h** (every 8 hours, three times a day), OR, depending on patient's characteristics (allergies, intolerance) azithromycin 500 mg PO one dose, then 250 mg PO daily orclarithromycin 500 mg PO q12h (twice daily) OR clarithromycin extended release 1000 mg PO daily OR doxycycline 100 mg PO q12h.
2. **Outpatients with comorbidities**(e.g. alcoholism, chronic heart/liver/kidney disease, malignancy, asplenia, diabetes mellitus) and who have used antibiotics in the last 3 months. *Preferred*:β-**lactam combination** (**amoxicillin-clavulanate** 500 mg/125 mg PO q8hOR amoxicillin-clavulanate 875 mg/125 mg PO q12h PLUSmacrolides (azithromycin or clarithromycin) OR doxycycline (100 mg PO q12h). *Alternatively*:If there are no contraindications to the use of cephalosporins: cefpodoxime 200 mg PO q12hOR cefuroxime 500 mg PO q12hPLUS macrolide (azithromycin or clarithromycin) OR doxycycline (100 mg PO q12h).

If there are contraindications for β-lactam use: levofloxacin 750 mg PO q.d. (once daily) or moxifloxacin 400 mg PO q.d.

1. **Hospitalized patients who are *not* in intensive careunit** (ICU)

Therapy should be started as soon as CAP is suspected as a diagnosis, ideally within 4 hours of the patient's presentation.Factors determining the antibiotic regimen depend on the likelihood that MRSA or Pseudomonas is present. Risk factors for MRSA or Pseudomonas infection are:known colonization or previous infection with these organisms, especially from a respiratory tract specimen, andrecent hospitalization in the last 3 months, with intravenous (IV) antibiotics.

*a) No suspicion* on MRSA or Pseudomonas

Beta-**lactam combination** (**ampicillin-sulbactam** 1.5-3 g IV (intravenous) q6h (every 6 hours) OR ceftriaxone 1-2 g IV q24h OR cefotaxime 1-2g IV q8hPLUSazithromycin 500 mg IV/PO q24h OR doxycycline 100 mg PO q12h.

If there are contraindications for the above then levofloxacin 750 mg IV or PO q24h OR moxifloxacin 400 mg IV or PO q24h

Many observational studies indicate that macrolide regimens are associated with better clinical outcomes for patients with severe forms of CAP, possibly due to their immunomodulatory effects.

*b) With known colonization or prior infection with* ***Pseudomonas***, recent hospitalization with IV antibiotics, or other strong suspicion of *Pseudomonas* infection

Combination therapy, **antipseudomonal** β**-lactam (piperacillin/tazobactam** 4.5 g IV q6h OR cefepime 2g IV q8h OR ceftazidime 2g IV q8h OR meropenem 1 g IV q8h OR imipenem 500 mg IV q6h-PLUSone**antipseudomonal fluoroquinolone** (ciprofloxacin 400 mg IV q8h OR levofloxacin 750 mg IV q24h).

*c) With known colonization or previous infection* ***with Methicillin-resistant Staphylococcus aureus (MRSA)*** or another ***strong suspicion of MRSA*** infection**Initially add vancomycin** 15 to 20 mg/kg/dose IV q8h to q12h and adjust to therapeutic monitoring (TDM) OR linezolid 600 mg IV q12h.

If there are *contraindications* for macrolides and fluoroquinolones

Beta-**lactam combination** (**ampicillin-sulbactam** 1.5-3 g IV q6 h or ceftriaxone 1-2 g IV q24 h OR cefotaxime 1-2 g IV q8h) PLUSdoxycycline 100 mg q12h.

4. **Hospitalized patients *in the intensive care unit*** (ICU)

a) *No comorbidities*/previously healthy; age < 65 years; no recent use of antibiotics; *no risk factors for MRSA or Pseudomonas aeruginosa*

Beta-**lactam combination** (**ampicillin-sulbactam** 1.5-3 g IV q6h OR ceftriaxone 1-2 g IV q24h OR cefotaxime 1-2 g OR ertapenem 1 g IV q24h PLUS azithromycin 500 mg IV OR levofloxacin 750 mg IV or PO q24h OR moxifloxacin 400 mg IV or PO q24h.

b) *Present comorbidities* (eg alcoholism, chronic heart/liver/kidney disease, malignancy, asplenia, diabetes mellitus) and who have received antibiotics in the last 3 months *with* ***suspectedPseudomonas***:Combination of **antipseudomonal/antipneumococcal** β**-lactam** and **antipseudomonal fluoroquinolone**:**piperacillin-tazobactam** (4.5 g IV q6h) OR imipenem (500 mg IV q6h) OR meropenem (1 g IV q8h) OR cefepime (2 g IV q8h) OR ceftazidime (2 g q8h; activity against pneumococci is more limited than the above agents)PLUSciprofloxacin (400 mg IV q8h) OR levofloxacin (750 mg IV/PO q24h) The dose of levofloxacin is the same when given intravenously and orally, while the dose of ciprofloxacin is 750 mg orally q12h.

c) *Present comorbidities* (eg alcoholism, chronic heart/liver/kidney disease, malignancy,

asplenia, diabetes mellitus) and who have received antibiotics in the last 3 months with ***suspected MRSA***:**Initially add vancomycin** 15 to 20 mg/kg/dose IV q8h to q12hand adjust to therapeutic monitoring (TDM) OR linezolid 600 mg IV q12h.

Clindamycin 600 mg IV or PO q12his not empiric but directed therapy.

**5. Patients allergic to penicillin**

Approximately 10% of patients who received antibiotic therapy, report being allergic to penicillin, however, up to 90% of these patients do not have an actual allergy. The incidence of an anaphylactic reaction to penicillin is 0.02% to 0.04% and is mediated by a type 1 hypersensitivity reaction. The most commonly reported type of reactions are skin reactions.IgE antibodies decline over time so that,in patients who previously have been tested positive for penicillin allergy, in repeated tests an annual 10% reduction can be expected. Therefore, unless they receive penicillin, 80% to 100% of these patients will have a negative penicillin test 10 years after the first positive one (Patterson and Stankewicz, 2023).

Cross-sensitivity with other penicillin preparations, especially cephalosporins, resulted in the avoidance of its use.Earlier studies may have overestimated the cross-sensitivity between penicillins and cephalosporins, which was attributed to the β-lactam ring. This ring is present in the structure of both groups of these antibiotics.Later research showed that in determining immune reactions, the main determinant is the similarity between the R side chains of the first generation cephalosporins and penicillins, rather than their β-lactam structure(Patterson and Stankewicz, 2023).

Penicillins have one R side chain, while cephalosporins have two. If the penicillin side chain is similar to either of these two in cephalosporins, there is a higher risk of cross-sensitivity.This occurs more often with first and second generation cephalosporins than with third or fourth generation, making them a more attractive treatment choice for patients with proven penicillin allergy.

a) **Outpatients with comorbidities**

If there are *no contraindications for the use of cephalosporins*: cefpodoxime 200 mg PO q12hOR cefuroxime 500 mg q12hPLUS macrolide (azithromycin OR clarithromycin) OR doxycycline (100 mg PO

q12h)

If there are *contraindications for* β-lactam *use*: levofloxacin 750 mg PO q24h or moxifloxacin 400 mg PO q24h

b) **Hospitalized patients with comorbidities**

If there is *no contraindication for the use of cephalosporins:* cefpodoxime 200 mg PO q12hOR cefuroxime 500 mg q12h PLUS macrolide (azithromycin OR clarithromycin) OR doxycycline (100 mg PO q12h)

b) If there are *contraindications for* β-lactam *use*: levofloxacin 750 mg PO q24h OR moxifloxacin 400 mg PO q24h.

***Note: Alternative antibiotics such as doxycycline (tetracycline), clarithromycin (macrolide) and erythromycin as an alternative macrolide in pregnancy, should be used only when there is a clinical reason not to use amoxicillin in patients with mild and moderate CAP.***

These antibiotics have good activity against *Streptococcus pneumoniae*; however, because of their broader spectrum of activity and because some of them have additional safety warnings, the above notice should be kept in mind.

The committee of the first international guideline for the management of severe CAP (ERS/ESICM/ESCMID/ALAT , 2023)noted that there are no reasonable alternatives to dual therapy in adults who cannot receive penicillin, for example, because of penicillin allergy.The committee discussed the evidence that monotherapy with a fluoroquinolone (levofloxacin or moxifloxacin) was as effective as dual therapy with a β-lactam and a macrolide for people with moderate to severe CAP. However, they noted safety concerns with fluoroquinolones, such as tendon damage and aortic aneurysms. The Committee noted that the license was limited to CAP and agreed that ***fluroquinolones should only be used when other drugs cannot be prescribed or have been ineffective. As a recommendation N$^0$3 they also recommend the addition of macrolides, not fluoroquinolones, to beta-lactams as empiric antibiotic therapy in hospitalized patients with CAP*** (Martin-Loeches et al, 2023).

## NEW ANTIMICROBIAL DRUGS FOR CAP

***Tigecycline*** - glycylcycline class

Tigecycline is effective against multi-resistant strains of *streptococcus, vancomycin-resistant enterococcus (VRE), staphylococcus and methicillin-resistant staphylococcus (MRS), bacteroides, and enterobacteria.* It is also effective against *Acinetobacter,* which today is the cause of severe intrahospital infections. However, tigecycline does not work against *Pseudomonas*. Tigecycline is not the only new drug for CAP but, from this group of antibiotics, is the only one which is on market in Bosnia and Herzegovina.

America Food and Drug Administration - FDA, approved tigecycline in 2009 for adults with CAP caused by *Streptococcus pneumoniae* (penicillin-susceptible isolates), including cases with concurrent bacteriemia. Data from various sources, including PubMed, the European Medicines Agency (EMEA) and the FDA, were evaluated. Tigecycline was found to be non-inferior to levofloxacin in the treatment of patients with bacterial CAP requiring hospitalization.Although tigecycline is indicated for CAP, data from clinical trials indicate a high incidence of adverse effects, especially gastrointestinal, which may limit its use (Ayoade, 2022).

Dosage (adults):Tigecycline 100 mg IV loading dose, then 50 mg IV q12h for 7-14 days

## CORTICOSTEROIDS

The aim of this work is to provide a generated information about antibiotic treatment forCAP, but a short review on corticosteroid use is needed. As use of corticosteroids in patients with severe CAP is limited by their influence on patient's immune system and implies other adverse effects (e.g. hypeglycemia, secondary infections and other), with high doses administered for at least 7 days, and with limited data suggesting benefit in patients with severe CAP, the updated guidelines recommend the following:

- There are *no indications for the routine use* of corticosteroids in adults with mild and moderate CAP
- There are *no indications for the routine use* of corticosteroids in adults with severe CAP
- *May be considered* in patients with refractory septic shock.

## TRANSITION FROM INTRAVENOUS TO ORAL ADMINISTRATION OF ANTIBIOTICS

Patients who initially received parenteral antibiotics can switch to oral administration if:

- are hemodynamically stable;
- are in clinical improvement;
- if they are able to swallow;
- if they have no problems with gastrointestinal tract;
- there is an oral form of antibiotic that they received parenterally or an oral antibiotic from the same group of antibiotics.

## DURATION OF ANTIBIOTIC THERAPY

Before the decision to discontinue the further administration of antibiotics in patients suffering from CAP, it is necessary that the patient is afebrile for 48-72 hours, that there is no more signs of clinical instability for CAP: normalheart and respiratory rate, blood pressure, $O_2$% saturation, body temperature, appetite, mental status. Besides clinical signs, the laboratory findings, especially white blood cell count and C-reactive protein level are of great importance.

Proclacitonin values are useful only in severe cases in order to decide on shortening the duration of antibiotic therapy.

The minimum duration of therapy is 5 days, while, in relation to the degree of severity of the disease and comorbidities, this minimum period can be extended to 14 days. Patients with documented *MRSA* or *Pseudomonas aeruginosa* should receive therapy for at least 7 days. Pneumonia complicated by meningitis, endocarditis, or other deep-seated infection will require a longer duration of therapy.

## CONCLUSION

*Streptococcus pneumoniae*(pneumococcus) still remains the most common cause of community-acquired pneumonia. Since late 1970s there has been a steady decline in the susceptibility of bacteria to various groups of antibiotics and this problem is recognized by professionals and scientist worldwide. Pneumococcal polyvalent vaccine was a great progress but it is used to prevent infection by pneumococcus. Once the patient is infected, antibiotics still remain the main option for the treatment of pneumonia. Various proffesional and scientific associations developed and updated guidelines for the management of adults with CAP, and in every of those guidelines the antibiotic of first choice is β-lactam antibiotic amoxicillin. Also available are combinations of β-lactam antibiotic ampicillin or piperacilin with β-lactamase inhibitors.

Second and third generation cephalosporins are stated as a second line antibiotics,with macrolides, fluoroquinolones, glycopeptide vancomycin for different groups of patients depending on their drug allergy, intolerance, possible or present infection with *Pseudomonas* or *MRSA.* Different antibiotic dose levels, different dosing shedules and different routs of administration are recommended for outpatients and for hospitalized ones. Bosnia and Herzegovina does not have a national treatment guideline for CAP caused by *Streptococcus pneumoniae*, and until one is developed, the recommendations from other guidelines can be used.

**Conflict of interest**
*There are no conflicts of interest.*

**Financial support and sponsorship:** *None*

## REFERENCES

Ayoade, F.O. (2022). Community-Acquired Pneumonia Empiric Therapy. Updated: Jan 03, 2022. https://emedicine.medscape.com/article/2011819-overview

Bjarnason, A., Westin, J., Lindh, M., Andersson, L.M., Kristinsson, K.G., Löve, A., Baldursson, O., Gottfredsson, M. (2018). Incidence, Etiology, and Outcomes of Community-Acquired Pneumonia: A Population-Based Study. Open Forum Infect Dis. 5(2):ofy010. Epub 2018 Feb 8. doi: 10.1093/ofid/ofy010

CDC - Centers for Disease Control and Prevention. Global Pneumococcal Disease and Vaccination Last Reviewed: January 27, (2022). Source: National Center for Immunization and Respiratory Diseases, Division of Bacterial Diseases. Available at https://www.cdc.gov/pneumococcal/global.html

CDC - Centers for Disease Control and Prevention. Pneumococcal Disease, Diagnosis and Treatment. Last Reviewed: September 1, (2020). Source: National Center for Immunization and Respiratory Diseases, Division of Bacterial Diseases. Available at: https://www.cdc.gov/pneumococcal/about/diagnosis-treatment.html

Fauci, A.S., Braunwald, E., Kasper, D.L., Hauser, S.L., Longo, D.L., Jameson, J.L., Loscalzo, J. (2009). Harrison's Manual of Medicine.(17th ed.) Pneumococcal Infections. (Chapter 92) (pp 486 – 489). New York: The McGraw-Hill Companies, Inc.

Fohner, A.E., Sparreboom, A., Altman, R.B., Klein, T.E. (2017). PharmGKB summary: Macrolide antibiotic pathway, pharmacokinetics/pharmacodynamics. Pharmacogenet Genomics. 27(4):164-167. doi: 10.1097/FPC.0000000000000270. PMID: 28146011; PMCID: PMC5346035.

Iyer, U. (2023). Pneumococcal Infections (Streptococcus pneumoniae) Medication. Updated: Jun 08, 2023. Drugs & Diseases > Infectious Diseases. Available at: https://emedicine.medscape.com/article/225811-medication [Accesed: 29 November, 2023]

Jacobs, M.R. (2001). Optimisation of antimicrobial therapy using pharmacokinetic and pharmacodynamic parameters. Clin Microbiol Infect. 7(11):589-96. doi: 10.1046/j.1198-743x.2001.00295.x. PMID: 11737083.

Küng, E., Coward, W.R., Neill, D.R., Malak, H.A., Mühlemann, K., Kadioglu, A., Hilty, M., Hathaway, L.J. (2014). The pneumococcal polysaccharide capsule and pneumolysin differentially affect CXCL8 and IL-6 release from cells of the upper and lower respiratory tract. PLoS One. 9(3):e92355. doi: 10.1371/journal.pone.0092355. PMID: 24664110; PMCID: PMC3963895.

Li, F., Collins, J.G., Keene, F.R. (2015). Ruthenium complexes as antimicrobial agents. Chem Soc Rev. 44(8):2529-42. doi: 10.1039/c4cs00343h. PMID: 25724019.

Martin-Loeches, I., Torres, A., Nagavci, B., Aliberti, S., Antonelli, M., Bassetti, M., Bos, L.D., Chalmers, J.D., Derde, L., de Waele, J., Garnacho-Montero, J., Kollef, M., Luna, C.M., Menendez, R., Niederman, M.S., Ponomarev, D., Restrepo, M.I., Rigau, D., Schultz, M.J., Weiss, E., Welte, T., Wunderink, R. (2023). ERS/ESICM/ESCMID/ALAT guidelines for the management of severe community-acquired pneumonia. Intensive Care Med. 49(6):615-632. doi: 10.1007/s00134-023-07033-8. Erratum in: Intensive Care Med. 2023 May 17;: PMID: 37012484; PMCID: PMC10069946.

Martner, A., Dahlgren, C., Paton, J.C., Wold, A.E. (2008). Pneumolysin released during Streptococcus pneumoniae autolysis is a potent activator of intracellular oxygen radical production in neutrophils. Infect Immun. 76(9):4079-87. doi: 10.1128/IAI.01747-07. PMID: 18559434; PMCID: PMC2519426.

Metlay, J.P., Waterer, G.W., Long, A.C., Anzueto, A., Brozek, J., Crothers, K., et al. (2019). Diagnosis and Treatment of Adults with Community-acquired Pneumonia. An Official Clinical Practice Guideline of the American Thoracic Society and Infectious Diseases Society of America. Am J RespirCrit Care Med. 200 (7):e45-e67.

Michelin, L., Weber, F.M., Scolari, B.W., Menezes, B.K., Gullo, M.C. (2019). Mortality and costs of pneumococcal pneumonia in adults: a cross-sectional study. J Bras Pneumol. 45(6):e20180374. doi: 10.1590/1806-3713/e20180374. PMID: 31644703; PMCID: PMC8653114.

Murphy, M.E., Powell, E., Courter, J., Mortensen, J.E. (2021). Predicting oral beta-lactam susceptibilities against *Streptococcus pneumoniae.* BMC Infect Dis. 21(1):679. doi:10.1186/s12879-021-06341-y

Musher, D.M., Jesudasen, S.S., Barwatt, J.W., Cohen, D.N., Moss, B.J., Rodriguez-Barradas, M.C. (2020). Normal Respiratory Flora as a Cause of Community-Acquired Pneumonia.Open Forum Infect Dis. 7(9):ofaa307. Epub 2020 Sep 15. doi: 10.1093/ofid/ofaa307

National Institute for Health and Care Excellence, Public Health England "Pneumonia (community-acquired): antimicrobial prescribing"

NICE guideline (2019). Available at: www.nice.org.uk/guidance/ng138

O'Neill, A.M., Gillespie, S.H., Whiting, G.C. (1999). Detection of penicillin susceptibility in Streptococcus pneumoniae by pbp2b PCR-restriction fragment length polymorphism analysis. J Clin Microbiol. 37(1):157-60. doi: 10.1128/JCM.37.1.157-160.1999. PMID: 9854082; PMCID: PMC84195.

Para, R.A., Fomda, B.A., Jan, R.A., Shah, S., Koul, P.A. (2018). Microbial etiology in hospitalized North Indian adults with community-acquired pneumonia. Lung India. 35(2):108. doi: 10.4103/lungindia.lungindia_288_17

Patterson, R.A., Stankewicz, H.A. (2023). Penicillin Allergy. 2023 Jun 20. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; PMID: 29083777. Available at https://www.ncbi.nlm.nih.gov/books/NBK459320/[Accesed: 1 December, 2023]

Sucher, A., Knutsen, S., Falor, C., Mahin, T. (2020). Updated Clinical Practice Guidelines for Community-Acquired Pneumonia, US Pharm. 45(4):16-20.

Tukbekova, B. T., Kizatova, S. T., Zhanpeissova, A. A., Dyussenova, S. B., Serikova, G.B., Isaeva, A.A., Tlegenova, K.S., Kiryanova, T.A. (2019). Causes of delayed immunization with pneumococcal vaccine and aetiological patterns of pneumonia in young children. Revista Latinoamericana de Hipertensión. Vol. 14 - Nº 3, 337-345

World Health Organization – WHO. Pneumococcus: Vaccine Preventable Diseases Surveillance Standards. Last updated: September 5, (2018). Available at: https://cdn.who.int/media/docs/default-source/immunization/vpd_surveillance/vpd-surveillance-standards-publication/who-surveillancevaccinepreventable-17-pneumococcus-r2.pdf?sfvrsn=5de986bf_10&download=true [Accessed: 16 November, 2023]

*Recived: December 23, 2023*
*Accepted: January 19, 2024*