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CHAPTER

# 17 CURRENT THERAPEUTICS AND PROPHYLACTIC APPROACHES TO TREAT PNEUMONIA

**A. Krishnamurthy, E. Palombo**

*Swinburne University of Technology, Department of Chemistry and Biotechnology, Faculty of Science, Engineering and Technology, Hawthorn, Victoria, Melbourne, Australia*

## 1 INTRODUCTION

Infections of the lower respiratory tract, such as tuberculosis, pneumonia, exacerbations of chronic obstructive pulmonary disease (COPD), and influenza are the leading infectious disease health problems that result in significant mortality and morbidity in humans. Lower respiratory tract infections (LRTI) are among the most frequent causes of mortality, as stated by the World Health Organisation, with more than three million deaths reported in children due to pneumonia.[1,2] These deaths are caused by both bacterial and viral etiological agents including *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Mycoplasma pneumoniae*, Influenza A or B virus, parainfluenza virus, rhinovirus, respiratory syncytial virus (RSV) and adenovirus.[3,4] Prior to the introduction of the relevant vaccines, bacteria such as *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Staphylococcus aureus,* and *Klebsiella pneumoniae* were identified as major causative agents of bacterial pneumonia.[5]

### 1.1 MICROBIOLOGY AND PATHOGENESIS OF *STREPTOCOCCUS PNEUMONIAE*—THE MAJOR CAUSE OF PNEUMONIA

*S. pneumoniae,* or pneumococcus, is a Gram-positive, nonmotile, facultative anaerobic coccus belonging to the family Streptococceae, and is classified based upon its haemolytic capability and the presence of carbohydrate antigens located in the cell wall using the Lancefield system. The most commonly recognized serotypes of *S. pneumoniae* found in children are serotypes 6, 14, 19, and 23.[6]

The various pneumococcal virulence factors associated with the pathogenesis of *S. pneumoniae* include and are not limited to; pneumolysin, autolysin, capsule and surface adhesins, enzymes and surface proteins such as neuraminidase, SpxB (pyruvate oxidase), and choline-binding proteins.[7] The choline-binding proteins are known to bind to techoic or lipotechoic acid, and function as an anchoring device for most Gram-positive bacteria, including *S. pneumoniae.* It is believed that there are approximately 10–15 different choline-binding proteins including PspA, PspC, and LytA that are encoded by *S. pneumoniae*[8]. After adherence of pneumococcus to a cell surface, further tissue invasion is facilitated by enzymes such as hyaluronidase and neuraminidase. Hyaluronic acid is one of the most abundant

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glycans in the extracellular matrix of connective tissues,[9] while neuraminidase comprising of NanA and NanB, of which NanA is shown to enhance intracellular survival and replication of the bacteria in the lung.[10] Being a nasopharyngeal commensal, *S. pneumoniae* can gain access to the eustachian tube and lungs via the nasopharynx, and can cause middle ear infection and pneumonia, respectively.[11] During this process, there is a massive influx of neutrophils driven by proinflammatory cytokines, such as IL-6, IL-1 and TNF-α. The progression to pneumonia is associated with a viral infection, which can enhance the adherence of *S. pneumoniae* to the respiratory epithelia and is recognized due to the interactions between the phosphorylcholine of the pneumococcus cell wall and platelet-activating factor receptors that are believed to be upregulated upon cytokine stimulation.[12] In addition, various cell wall degradation products such as peptidoglycan, techoic acid, and toxins like pneumolysin are also released following autolysis which can induce inflammatory responses in the host. The various actions of pneumolysin, which include induction of cytokines like TNFα and IL-1β, disruption of the epithelial cell integrity, decreased bactericidal activity, inhibition of neutrophil migration, and inhibition of lymphocyte proliferation and antibody synthesis, highlight its important role in the pathogenesis of *S. pneumoniae.*[13]

### 1.2 BIOLOGY OF PNEUMOCOCCAL PNEUMONIA

The mucosal epithelium of the nasopharynx is a well-recognized primary site of bacterial colonisation including the opaque and transparent phenotypes of the pneumococcus.[14] The pneumococcus can traverse down to the lung upon aspiration and start adhering to the alveolar type II cells to initiate bacterial infection.[15] The progress to pneumonia can occur more rapidly if there is a preexisting respiratory viral infection or increased bacterial adherence facilitated by viruses or cytokines.[16] The different stages of pneumococcal pneumonia are well known. The first stage is characterized by a bulge or engorgement due to the bacterial presence and serous exudate in the alveoli which provides nutrients to the bacteria and facilitates further infection in the lung.[17] The next stage is the intense inflammatory reaction involving leakage of erythrocytes into the alveoli (red hepatisation), followed by the migration of leukocytes into the consolidated area (gray hepatisation), and surface phagocytosis by the leukocytes.[18] Due to the intact immune system of the host, normally the type-specific antibodies and the polymorphonuclear leukocytes phagocytise the pneumococci and the lung returns to its normal state. However, in patients with a compromised immune system having certain complement deficiencies or hypogammaglobulinemia (absence of type-specific antibodies), bacteremia can occur and the pneumococcus with its virulence factors (mostly cell wall components such as peptidoglycan, techoic acid, and proteins such as pneumolysin) induce inflammation causing subsequent tissue damage.[19]

## 2 CHILDHOOD PNEUMONIA

Since the early 1980s, the LRTI caused by *S. pneumoniae* in certain developing countries, such as Ghana and South Africa, have been reported at >60–90% of all cases in children less than 5 years of age, and 100 per 1000 population of adults per year, and has remained at equivalent rates even a decade later.[20–22] The incidence of pneumonia in children less than 5 years of age was higher in regions such as South-East Asia, Africa and Western Pacific countries in comparison with those in the developed countries like the Americas and Europe.[22] More recently, the incidence of childhood pneumonia has been estimated to be >120 million globally, of which ~12% progressed to severe disease with 1%

mortality in children <2 years of age.[23] The risk factors for childhood pneumonia, especially in the developing countries, include nutrition deficiencies, lack of breastfeeding, indoor air pollution due to passive smoking, HIV infection, and substandard housing and living conditions.[24]

The etiological agents causing pneumonia include both bacteria and respiratory viruses. Certain vaccine studies have indicated the predominant bacterial agent causing pneumonia to be *S. pneumoniae* resulting in almost 18–25% severe cases and 30–35% mortality, followed by *H. influenzae* accounting for 4% of severe cases and 16% of deaths. Influenza virus remains the dominant viral etiological agent responsible for 7% of the severe cases and 11% of deaths.[23,25] *S. pneumoniae* is also well-recognized to cause community-acquired pneumonia (CAP) in children with lower fatality rates of 1.5%.[26] In addition to these etiological agents, bacteria such as *Staphylococcus aureus*, *Klebsiella pneumoniae*, and respiratory viruses such as RSV, rhinovirus, human metapneumovirus, human bocavirus and parainfluenza viruses are the other commonly identified agents that contribute to the burden of childhood pneumonia.[25,27]

## 3 ADULT PNEUMONIA AND COMMUNITY-ACQUIRED PNEUMONIA

Community-acquired pneumonia (CAP) is an increasing health problem and the third most common reason for hospitalization for adults, especially the elderly aged >65 years. The prevalence of CAP has been reported as 18–20 cases per 1000 population with an increase from 9% in 65–74 year olds to 17% in 75–84 year olds, and 30% in >85 year olds.[28,29] Several predisposing factors such as impaired immunity and lung function, dysfunctional nasal mucociliary clearance, lung and heart diseases, smoking have been identified as independent predictors for CAP in adults and the elderly.[24]

Certain studies have reported *S. pneumoniae*, *Legionella* species, *H. influenzae*, *Moraxella catarrhalis,* and *S. aureus* as the predominant pathogens in CAP.[30] Although the role of respiratory viruses has been well-recognized in CAP in children and infants, it is not well understood in adults and the elderly. It is still unclear whether a virus by itself can cause pneumonia or whether the virus can act in conjunction with other respiratory pathogens. One study has reported that respiratory viruses such as influenza virus, RSV, adenovirus, and rhinovirus were commonly isolated as part of a co-infection, especially with *S. pneumoniae.*[31] Thus, viral agents in adults with CAP most often seem to be part of a mixed infection, usually with *S. pneumoniae* as the co-pathogen.

## 4 VACCINATION

The World Health Organisation (WHO) recommends routine childhood immunization programs that include vaccines that offer protection from various respiratory disease such as pneumonia, influenza (flu), measles, and pertrussis. The *Haemophilus influenzae* type b (Hib) vaccine and the pneumococcal conjugate vaccines are increasingly available in both developed as well as developing countries, especially the 7- and 13-valent pneumococcal conjugate vaccines which have shown effectiveness in reducing the incidence and severity of pneumonia and other lower respiratory infections in children. Currently, there are three vaccines in the childhood routine immunization schedule; measles, Hib, and the pneumococcal conjugate vaccine that is well-recognized to reduce childhood mortality from and related to pneumonia.

## 4.1 HIB VACCINE

Vaccination remains the primary preventative strategy for pneumonia, including CAP in the elderly. The Hib vaccine has a proven efficiency of >90% against invasive meningitis and bacteremia and noninvasive pneumonia caused by *H. influenzae* type b.[32,33] This impressive efficiency has resulted in the introduction and addition of the Hib vaccine worldwide into National Immunization Programs, and has resulted in a significant reduction in the vaccination gap between developed and developing countries.[34] A recent review from several randomized controlled trials (from 1970s to 2008) from different developing countries indicated a significant reduction of severe pneumonia by 6%, pneumonia-associated mortality by 7%, and reduction of radiological confirmed cases of pneumonia by 18%.[35] Based on the preventative approach of pneumonia and pneumonia-related mortality with effective vaccination, a certain modeling-based study has estimated that if implemented at present annual rates of increase in developing countries, the vaccine could save up to 51% of pneumonia deaths by 2025 at a cost saving of US$3.8 billion.[36] High coverage of the Hib vaccine immunization in children less than 5 years of age could reduce childhood pneumonia resulting in decreased incidence of severe pneumonia.

## 4.2 PNEUMOCOCCAL VACCINES

The 23-valent polysaccharide vaccine (PPV23) and the 13-valent protein-conjugated polysaccharide vaccine (PCV13) are the two vaccines that offer protection against pneumococcal disease, and have replaced the 7-valent conjugate vaccine (PCV7). As the polysaccharide vaccine (PPV) is T-cell independent, it does not boost immunological memory and the immunity offered may not last for a long time. For this reason, this vaccine is not offered to infants aged <2 years of age, but is provided to children aged >2 years and to elderly people who are at risk (>50 years of age) for developing pneumonia. In contrast, the conjugate vaccines stimulate a T-cell dependent response and are more effective in infants and children <2 years of age.[37]

The different pneumococcal vaccines, serotypes covered, and the conjugate protein used are mentioned in Table 17.1 PCV7 and PCV10 are offered for children aged from 6 weeks to 5 years of age, whereas PCV13 is given to children aged between 6 weeks and 17 years, and to adults aged >50 years of age. Since the introduction of the PCV7 vaccine in 2000, its efficacy against invasive meningitis, pneumonia, and otitis media is well documented.[38–40] The subsequent vaccines, PCV10 and PCV13,

**Table 17.1 Current Pneumococcal Conjugate Vaccines**

| Pneumococcal Vaccine | Serotypes Covered | Conjugate Protein Used | Trade Name |
|---|---|---|---|
| PCV7 | 4, 6B, 9V, 14, 18C, 19F, and 23F | Mutant diphtheria toxoid | Prev(e)nar (Pfizer) |
| PCV10 | 4, 6B, 9V, 14, 18C, 19F, 23F, 1, 5, and 7F | Protein D from nontypeable *H. influenzae*, tetanus toxoid, and diphtheria toxoid | Synflorix (GlaxoSmithKline) |
| PCV13 | 4, 6B, 9V, 14, 18C, 19F, 23F, 1, 5, 7F, 3, 6A, 19A | Mutant diphtheria toxoid | Prev(e)nar-13 (Pfizer) |

*The table shows the currently available pneumococcal vaccines and the conjugate protein used in its making, and the coverage of various serotypes of* S. pneumoniae *by each vaccine.*

have also demonstrated comparable immunogenicity to PCV7 in several clinical trials.[41–43] Although PPV23 covers 23 serotypes of *S. pneumoniae*, and is recommended for adults aged >65 years of age, its effectiveness in reducing invasive pneumococcal disease remains uncertain.[44,45] As PCV13 has equal or greater immunogenicity than PPV23, and has greater immunological memory, the use of PCV13 is now recommended for adults in addition to PPV23, particularly the elderly and high risk individuals. In addition to this, newer PCV's have been shown to reduce the number of healthy carriers of the pathogen in the community because of "herd immunity" where unvaccinated people are protected from the pathogen. Since the introduction of PCV's as a part of "herd immunity", the incidence of invasive pneumococcal diseases was shown to decline by almost 70% among vaccinated children <2 years of age, and by 32% in adults aged 20-39 years, and by 18% in the elderly aged >65 years of age, who were not previously vaccinated.[46]

## 5 CURRENT ANTIINFECTIVE TREATMENTS AGAINST BACTERIAL PATHOGENS

The classification of antibiotics is based on the cellular component that they affect, as well as on whether they can induce cell death (bactericidal) or inhibit cell growth (bacteriostatic). Antibiotic-mediated cell death is a complex process involving physical interaction between a drug molecule and its bacterial-specific target, and/or modulation of the affected bacterium at the biochemical, molecular, and ultrastructural levels.[47] Fig. 17.1 summarizes the different drug targets and mechanism of actions of various antimicrobials such as; inhibition of cell wall synthesis, inhibition of protein synthesis, injury to cytoplasmic membrane, and inhibition of nucleic acid synthesis and replication. DNA synthesis and cell division are well-recognized processes that involve modulation of chromosomal supercoiling through topoisomerase-catalyzed strand breakage and rejoining reactions. Antimicrobials such as quinolone

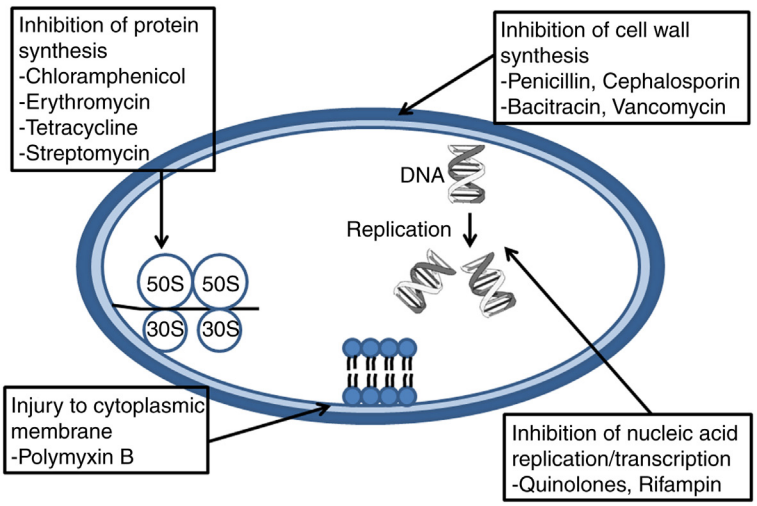


**FIGURE 17.1 Summary of Target and Mechanisms of Actions of Various Antimicrobials**

This figure summarizes the various targets and mechanism of actions of different antimicrobials along with relevant examples of antibiotics.

target enzymes like DNA gyrase (topoisomerase II) and topoisomerase IV (topoIV) that are required for bacterial DNA synthesis and replication, and prevent DNA strand rejoining.[48] Peptidoglycan, a covalently cross-linked polymer matrix composed of peptide-linked β-(1–4)-N-acetyl hexosamine, is the main component of bacterial cell walls that contributes towards the structural integrity of the bacterial cell. The peptidoglycan layer is maintained through the activity of transglycosylase and transpeptidase enzymes, which add disaccharide pentapeptides to extend the glycan strands of existing peptidoglycan molecules and cross-link adjacent peptide strands of immature peptidoglycan units, respectively.[49] β-lactams and glycopeptides are among the classes of antibiotics that interfere with cell wall biosynthesis resulting in changes to bacterial cell shape and size and induction of cellular stress responses that leads to bacterial cell lysis.[50] The process of protein synthesis via mRNA translation involves the ribosome that is composed of two major components, the 50S and 30S subunits. Drugs that inhibit protein synthesis are divided into two subclasses: the 50S inhibitors and 30S inhibitors. The 50S ribosome inhibitors include the macrolide, lincosamide, streptogramin, amphenicol, and oxazolidinone classes of antibiotics.[51] The 30S inhibitors include the tetracycline and aminocyclitol families of antibiotics.[52]

## 5.1 CURRENT ANTIINFECTIVE ANTIMICROBIALS

The mortality caused due to pneumonia can be avoided through cost-effective and life-saving treatment from antibiotics for bacterial pneumonia, thereby significantly increasing the patient's chances of survival. The pneumonia management strategy with the use of appropriate antibiotics and supportive care including oxygen systems remains an effective cornerstone in the treatment and management of children suffering from pneumonia. The WHO Integrated Management of Childhood Illness program has consistently reported a reduction of childhood mortality rates by approximately 20%, while certain community based management strategies have reported a decrease in 70% mortality due to the usage of oral antibiotics such as amoxicillin.[53–55] The four types of antibiotics recommended for children <5 years of age for the treatment of pneumonia are; cotrimoxazole, amoxicillin, cephalosporins, and macrolides, with oral amoxicillin (40 mg/kg/dose) used for 3 days (nonsevere pneumonia) and 5 days for children with severe pneumonia.[56] During severe pneumonia, the first line of treatment is often parenteral ampicillin (penicillin) and gentamicin, followed by ceftriaxone if the first line of treatment is not effective.[56] Various randomized controlled studies from the Cochrane database of Systemic Reviews have shown a multitude of available treatments for pneumonia in children with (1) cefpodoxime proving to be more effective than amoxicillin, (2) amoxicillin more effective than chloramphenicol, (3) amoxicillin being an effective alternative to cotrimoxazole for CAP patients, (4) coamoxyclavulanic acid and cefpodoxime as alternative second-line drugs of choice, and (5) penicillin/ampicillin plus gentamicin more effective than chloramphenicol for children hospitalized with severe CAP.[57] A 3-year pediatric study of the susceptibility of 208 *S. pneumoniae* isolates, including serotype 19A, using antibiotics such as second- and third-generation cephalosporins showed significant efficacy against 60–70% of the isolates, with clindamycin susceptibility of 60–85%, levofloxacin 95%, and ceftriaxone >95%.[58] The American Thoracic Society and the European Respiratory Society recommend that hospitalized patients with CAP are preferably treated with a respiratory fluoroquinolone or combination therapy with a β-lactam and a macrolide.[59] The success rates of incorporating the fluoroquninolone or combination with a macrolide based on the clinical, bacteriological, or radiological examinations ranged from 87–96%.[60] Vancomycin or clindamycin (based on local susceptibility data) should also be provided in addition to β-lactam therapy if clinical, laboratory, or radiological characteristics are

consistent with infection caused by *S. aureus*.[61] Although nonsevere and severe CAP have been managed by many antimicrobials as a result of various studies from developing countries that compared different types of antibiotics, there is need for more studies and larger clinical trials for better management of pneumonia in developed countries. Another major health concern is the continual rise in antibiotic resistance with approximately 30% of the isolates being resistant to macrolides including erythromycin, azithromycin, and clarithromycin.[62]

The introduction and inclusion of the Hib vaccine over the past 25 years has resulted in almost complete elimination of *H. influenzae* in children, therefore it is not considered as a pathogen in CAP. Nontypeable *H. influenzae* is also not considered as a pathogen in pediatric pneumonia unless detected in lung disease or COPD. When detected as a true pathogen in CAP, oral amoxicillin is considered effective against β-lactamase negative strains, and for β-lactamase producing strains, amoxicillin-clavulanate, cefuroxime, cefdinir, cefixime, cefpodoxime are all considered effective therapies, while children allergic to oral β-lactam agents are only given fluoroquinolones.[61]

Although an infrequent cause of CAP, group A *Streptococcus* may cause severe necrotizing pneumonia. Penicillin G at the dosage of 100,000–200,000 U/kg/day in 4–5 divided doses is used to treat patients suffering from CAP due to group A *Streptococcus*. As macrolide resistance is greater in streptococcal infections, along with lower tolerability by tissues, erythromycin and other macrolides are not administered.[63]

*S. aureus* capable of causing pneumonia are usually methicillin-sensitive and are treated with either a β-lactamase stable penicillin (oxacillin or nafcillin) or a first-generation cephalosporin, like cefazolin. Community-associated methicillin-resistant *S. aureus* (MRSA) represents >50–70% of the clinical isolates in some region of the United States,[64] but are shown to be susceptible to vancomycin, clindamycin, and linezolid. However, children intolerant to vancomycin and clindamycin could be treated with linezolid. However, severe adverse effects, including suppression of platelets and neutrophils, nerve injury, mean that this drug should be used with caution.

In situations where *Mycoplasma pneumoniae* and *Chlamydophila pneumoniae* are of significant consideration upon diagnostic evaluation, empiric combination therapy with a macrolide and a β-lactam antibiotic is considered.

## 6 CURRENT ANTIINFECTIVE TREATMENTS AGAINST VIRAL PATHOGENS

Children with moderate to severe CAP consistent with influenza virus infection during widespread local circulation of influenza viruses should be administered with influenza antiviral therapy. The susceptible strains of influenza A virus are commonly treated with adamantanes and neuraminidase inhibitors. As the occurrence of genetic variations is highly substantial among influenza strains, resistance to either class of antiviral agents may develop quickly. However, the dosages of antiviral agents currently recommended for seasonal influenza are developed for fully susceptible strains and evaluated in clinical trials mandating the requirement of treatment within 3 days of the onset of symptoms.[65] Early antiviral treatment has been shown to provide maximal benefit, and treatment should not be delayed until confirmation of positive influenza test results. Negative results of influenza diagnostic tests, especially the rapid antigen tests, do not conclusively exclude influenza disease. Therefore, treatment after 48 h of symptomatic infection may still provide some clinical benefit to those with more severe disease.[61]

The efficacy of ribavirin for the treatment of RSV CAP in infants is debatable, as certain in vitro studies have shown activity of ribavirin against RSV, but its usage for RSV infection is not routinely

recommended in the management of lower respiratory tract disease because of the high cost, aerosol administration, and possible toxic effects among healthcare providers. Palivizumab (Synagis), a humanised murine monoclonal antibody is another effective prophylaxis for RSV infection that is administered intramuscularly.[66]

Although parainfluenza virus, adenovirus, metapneumovirus, rhinovirus, coronavirus, and bocavirus are associated with pediatric CAP, there are no prospective, controlled studies for antiviral therapy against these viruses.

## 7 ANTIBIOTIC RESISTANCE AND ITS IMPACT

Since the introduction of penicillin in 1950s, it has been the first choice for treating pneumococcal pneumonia. During the early 1970s, infants and children were successfully treated with amoxicillin (40–45 mg/kg/day divided into 3 equal doses) because of the susceptible nature of the strains at that time. Resistance to the commonly used antibiotics poses a major problem and concern for health practitioners while choosing an empirical therapy against bacterial pneumonia, and there are large geographical variations indicating different resistance patterns. In the 1990s with the widespread pneumococcal resistance to penicillin, the dosage was increased to ~90 mg/kg/day given twice daily for treating children with acute otitis media.[67] A recent review has highlighted advances in the understanding of the various mechanisms by which bacteria acquire resistance to antibiotics, how they prevent access to different drug targets, and modulate or inactivate antibiotics.[68]

The introduction of pneumococcal conjugate vaccine and the changes in antimicrobial usage have both significantly altered the resistance patterns of *S. pneumoniae*. The decreased degree of penicillin resistance further prompted a decrease in amoxicillin dosage compared to that administered in the prevaccine era.[69] Over the last decade, a certain multicentre clinical trial study has reported a significant decrease in the susceptibility rates of the commonly used antibiotics such as amoxicillin/clavulante, penicillin, and ceftriaxone from 93.8% to 82.7%, 94.7% to 84.1%, and 97.4% to 87.5%, respectively.[70] The susceptibility rates of macrolides such as erythromycin and clindamycin were also reported to be decreased from 82.2% to 60.8% and from 96.2% to 79.1%, respectively. Recently, increasing resistance against macrolides has been reported in several European countries, including the United Kingdom. A 3-year surveillance study involving 1545 clinical isolates reported around 26% and 20% increase in the rates of ampicillin and trimethoprim/sulfamethoxazole resistance against *H. influenzae,* respectively, while antibiotics such as ceftaroline, ceftriaxone, amoxicillin/clavulante, and levofloxacin showed 99–100% susceptibility.[71] This study also showed increasing resistance of penicillin (96.4%) towards *M. catarrhalis*, because of the prevalence of β-lactamase that is known to reduce the susceptibility to penicillins. The resistance to macrolides against *M. pneumoniae* in children and adults with CAP has been increasingly emerging in countries like Japan, France, Denmark, United States, and China, with rates as high as 40% in Japan, 85% in China, and 3–10% in the Europe and the United States.[72,73] Community-acquired MRSA, although primarily associated with skin and soft tissue infections, are now being recognized to cause invasive infections including CAP, with almost 50% mortality rates reported in the United States and Europe.[74,75]

There are certain ways by which resistance to antimicrobials can be minimized, such as: limiting the exposure to any antibiotic, whenever possible; limiting the spectrum of usage of antimicrobials to that specifically required to treat the identified pathogen; using the proper dosage of antimicrobial to

achieve a minimal effective concentration at the site of infection; treatment for the shortest effective duration that will minimize the exposure of both pathogens and normal microbiota to antimicrobials and further minimize the selection for resistance.[61]

## 8 ADVANCES IN ANTIBIOTIC TREATMENT FOR PNEUMONIA

The increasing incidence of antimicrobial resistance remains one of greatest challenges against emerging bacterial infections and has resulted in some bacteria being essentially untreatable with the current available treatment options. As a result, newer antimicrobials with novel modes of action against multidrug resistant strains are being developed. A recent review has highlighted how combinations of drugs can offer synergistic and antagonistic drug interactions, and how these drug interactions can provide opportunities for discovery of newer drugs.[76] In recent years, the availability of new antimicrobials for human consumption has been lower than in the recent past, with no new classes of antimicrobials developed since the introduction of nalidixic acid (1962) and linezolid (2000). The availability of antimicrobials in recent years has mostly been the result of modification of existing molecules. One of the reasons for this is that the development of any new antimicrobial agent is very expensive and time consuming, with research and development of infective drugs taking around 15–20 years, and costing around US$1000 million, with further additional costs for bringing the new drug into the market.[77] There is a strong need for newer unexploited targets and strategies for the next generation of antimicrobial drugs against drug resistant and emerging pathogens. Some of the new antimicrobial agents that are in the clinical development stage are listed in Table 17.2.

**Table 17.2 Newer Antimicrobial Agents Against Bacterial Pneumonia**

| Drug | Class | Year of Approval/Trial | Activity Against |
|---|---|---|---|
| Daptomycin | Lipopeptide | 2003 | Gram+ve bacteria |
| Telithromycin | Ketolide | 2004 | Gram+ve and −ve bacteria |
| Ceftaroline | Cephalosporin | 2010 | Gram+ve bacteria |
| Fidaxomicin | Macrocyclic | 2011 | Gram+ve bacteria |
| Retapamulin | Pleuromutilin | 2007 | Gram+ve bacteria |
| **Under Research and Development** | | | |
| Torezolid | Oxazolidinones | Phase II | Gram+ve bacteria |
| Cethromycin | Ketolides | Phase III | Gram+ve bacteria |
| Oritavancin | Glycopeptides | Phase III | Gram+ve bacteria |
| **Still Needing FDA Approval** | | | |
| Ceftobiprole | Cephalosporin | | Gram+ve bacteria |
| Iclaprim | Dihydrofolatereductase | | Gram+ve bacteria |

*The table shows the availability of the newer antimicrobial agents, future promising antiinfective antimicrobials, and those awaiting FDA approval for treating bacterial pneumonia.*

Some of the new antibiotics that have shown promising results in the treatment of pneumonia and CAP are as follows:

Ceftaroline: a fifth generation cephalosporin known to bind to penicillin-binding proteins and preventing synthesis of bacterial cell walls. It is a novel broad-spectrum antibiotic effective against MRSA, penicillin and cephalosporin resistant *S. pneumoniae*, vancomycin-intermediate *S. aureus* (VISA), and vancomycin-resistant *S. aureus* (VRSA).[78] It is also active against many Gram-negative pathogens but inactive against extended-spectrum β-lactamase (ESBL) producing bacteria. It has been approved for the treatment of CAP. Different randomized, double-blind, multicentre trials have demonstrated the efficacy (>82% clinical cure) and safety of ceftaroline (intravenous, 600 mg twice daily) for the treatment of CAP.[79]

Ceftobiprole: another newer cephalosporin that has a broad-spectrum activity against MRSA, penicillin-resistant *S. pneumoniae, P. aeruginosa* and enterococci.[80] A randomized trial consisting of 706 hospitalized adults with severe CAP who were administered ceftobiprole (intravenous, 500 mg over 120 min every 8 h) showed no significant differences between the treatment groups but found adverse events including nausea and vomiting in 36% of the patients.[81]

Telavancin: a semi-synthetic lipoglycopeptide derivative of vancomycin known to disrupt peptidoglycan synthesis and alter cell membrane function. It has been in use for treating complicated skin infections caused by *S. aureus*, and hospital-acquired bacterial pneumonia, including ventilator-associated bacterial pneumonia caused by susceptible isolates of *S. aureus*.[82]

Telithromycin: the first ketolide to enter clinical use for the treatment of CAP, chronic bronchitis and acute sinusitis. Telithromycin is a protein synthesis inhibitor blocking the progression of the growing polypeptide chain by binding to the 50S subunit of the bacterial ribosome. It exhibits 10 times higher affinity to the subunit 50S subunit than erythromycin. In addition, telithromycin strongly binds simultaneously to two domains of 23S subunit of the 50S ribosomal subunit; older macrolides bind to only to one domain and weakly to the second domain. An in vitro study showed activity of telithromycin against *S. pneumoniae* and, compared with clarithromycin and azithromycin, was found to maintain its activity against macrolide-resistant strains of *S. pneumoniae* and *S. pyogenes*.[83] It is formulated as 400 mg tablet for oral administration with good absorption and bioavailability.[84] However, the FDA withdrew its approval in the treatment of CAP in 2007 due to its safety concerns involving hepatotoxicity, myasthenia gravis exacerbation, and visual disturbances.

Cethromycin: a 3-keto,11,12carbamate derivative of erythromycin A with an O-6 linked aromatic ring. It binds strongly to the 50S ribosomal subunit and inhibits bacterial protein synthesis.[85] Cethromycin displays in vitro activity against streptococci, including strains of *S. pneumoniae* that are resistant to penicillins and macrolides.[86] Its activity was greater than telithromycin against macrolide-resistant streptococci and is more potent than macrolides and fluoroquinolones against penicillin-resistant streptococci. It also displays comparable in vitro activity to azithromycin against respiratory Gram-negative organisms including β-lactamase-producing *H. influenzae* and *M. catarrhalis*. It was shown to be more potent than erythromycin and clarithromycin but less potent than fluoroquinolones against β-lactamase-producing *H. influenzae*.[86,87] It showed similar potency against β-lactamase-producing *M. catarrhalis*.

Solithromycin: a new macrolide, and the first fluoroketolide in clinical development, with proven activity against macrolide-resistant bacteria. Solithromycin is being developed in both intravenous and oral formulations for the treatment of CAP, which should allow both oral therapy and i.v.-to-oral step-down therapy in appropriate patients. A recent multicentre, double-blind, randomized phase II study

consisting of 132 patients with moderate to severe CAP administered with oral solithromycin (800-mg loading dose and 400 mg maintenance dose/5 days) showed efficacy comparable to that of levofloxacin in the treatment of CAP, with a favorable safety and tolerability profile.[88]

Nemonoxacin: a novel nonfluorinated quinolone with proven in vitro and in vivo activity against CAP pathogens including multidrug resistant *S. pneumoniae*. A randomized multicentre trial consisting of 265 CAP patients treated with an oral administration of nemonoxacin (750 and 500 mg/7 days) showed a remarkable 80–85% clinical and bacteriological success rate, which was comparable tolevofloxacin therapy.[89] A recent comprehensive review has well documented all the data available on the pharmacodynamics, the pharmacokinetics, and the clinical treatment studies of this antimicrobial agent.[90]

Zabofloxacin: is being developed as a new fluoroquinolone antibiotic that is a potent and selective inhibitor of the essential bacterial type II topoisomerases and topoisomerase IV and is indicated for community-acquired respiratory infections due to Gram-positive bacteria. Two dosing regimens of zabofloxacin (zabofloxacin hydrochloride 400 mg capsule andzabofloxacin aspartate 488 mg tablet) were well-tolerated with no adverse effects.[91]

JNJ-Q2 and KPI-10: two novel fluoroquinolones that are being developed for the treatment of bacterial pathogens responsible for respiratory infections including CAP, and other skin infections. Both agents have demonstrated increased potency when compared with the marketed fluoroquinolones, thus encouraging further clinical development.[92,93]

BC-3781: a recent semisynthetic pleuromutilin antibiotic with excellent antibacterial activity against skin pathogens such as *S. aureus*, β-haemolytic streptococci, viridans streptococci, and *Enterococcus faecium* as well as against respiratory pathogens. Its activity against respiratory pathogens has also been confirmed in various murine models of infection using *S. pneumoniae*, *H. influenzae*, *S. aureus,* and MRSA (nosocomial and community-associated), with better drug penetration, strongly supporting its potential use in the treatment of bacterial respiratory tract infections.[94]

## 9 NEWER TARGETS FOR THE NEXT GENERATION ANTIMICROBIALS FOR COMBATING DRUG RESISTANCE

Although there are a wide variety of clinically efficacious antibiotics in use today, the development of bacterial resistance has rendered them less effective, with most being bacteriostatic, and acting by either protein or cell wall synthesis inhibition. Further research is needed in the design of novel antibacterial agents with new targets.

### 9.1 TARGETING BACTERIAL PROTEINS

One approach could be to design antibiotics that can be used against novel drug targets such as the bacterial enzymes β-ketoacyl-acyl-carrier-protein synthase I/II which are required for fatty acid biosynthesis. Platensimycin is one such drug undergoing preclinical trials and is known to block these enzymes that are involved in the biosynthesis of essential fatty acids by Gram-positive bacteria.[95] It has potent antibacterial activity against Gram-positive bacteria including multidrug resistant staphylococci and enterococci.

### 9.2 COMBINING β-LACTAMASE ENZYME WITH β-LACTAM ANTIBACTERIAL DRUGS

Another approach worth investigating could be to combine β-lactam antibiotics with naturally occurring β-lactamase enzymes in the gastrointestinal microbiota. These enzymes are shown to hydrolyse various antibiotics including penicillin, ampicillin, and piperacillin. P1A protein (29 kDa) is one such example of having both structural and functional similarities to the β-lactamase enzyme. The emergence of resistant microbes can be significantly reduced by taking advantage of combining this naturally occurring hydrolysis of the antibacterial drug with currently available β-lactam drugs. A Phase II trial for the treatment of serious respiratory infections which incorporated treatment with P1A (β-lactamase product) and ampicillin showed only a 20% change in gut microbiota compared to 50% change in patients treated with ampicillin alone.[96]

### 9.3 IMMUNOMODULATORY STRATEGIES

Apart from antimicrobials, strategies involving immunomodulation of inflammatory responses (targeting pattern recognition receptor signaling, corticosteroids, complement inhibitors etc.), improving pulmonary barrier function (using adrenomedullin, angiopoietin etc.) during pneumonia and its associated complications could add a new dimension in providing better therapeutics for patients.[97]

## 10 CONCLUSIONS AND FUTURE PERSPECTIVES

Despite great advances in management and preventative approaches, pneumonia still remains a major burden of mortality and morbidity in young children and the elderly, especially in the developing and under-developed countries. Prevention by means of vaccination is critical for reducing pneumonia mortality in children <5 years of age, and an effective antibiotic therapy is important for the elderly. The widespread emergence of antimicrobial resistance is a well-recognized cause of the ineffectiveness of the large number of the currently used antimicrobials. Although numerous efforts have been made to combat this, newer targets need to be identified for the generation of the next level of effective antimicrobials. In addition, a complete understanding of the various aspects of drug resistance in microbes is essential to assist us in designing better targets and help us discover new antibacterial drugs. In the near future, the next challenge will be to identify newer agents for the treatment of multidrug resistant pathogens which are emerging at a rapid rate. The constant and unpredictable nature of pneumococcal pathogens can outpace technological and drug development strategies. Therefore, it is critical for researchers, pharmaceutical companies, and governments and other funding bodies to continue making progress in developing new strategies and antimicrobials towards respiratory infections, including pneumonia.

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