Chapter 6

Advancing in the Direction of Right Solutions: Treating Multidrug-Resistant Pneumonia

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Additional information is available at the end of the chapter

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Abstract

Worldwide, antibiotic resistance is a major contemporary public health threat due to rapid emergence of resistant bacteria and endangering the efficacy of antibiotics. There are significant number of reports on clinical failure of β-lactam and β-lactamase inhibitor combination and even carbapenems due to various carbapenem resistance mechanisms. The increasing rate of the antibiotic resistance and its impact on treatment failure encouraged us to study newly reported concept of antibiotic adjuvant entities (AAEs) by which the increasing failure rate of antibiotics can be controlled. These AAEs have been developed for both Gram-positive and Gram-negative multidrug-resistant (MDR) infections. Elores (ceftriaxone + sulbactam with adjuvant ethylenediaminetetraacetic acid (EDTA)) and Potentox (cefepime + amikacin with adjuvant potassium chloride) are the AAEs for Gram-negative MDR pathogens each catering to a different type of resistance and Vancoplus (ceftriaxone + vancomycin with adjuvant L-arginine), another AAE, can help us to last longer in the war against antibiotic-resistant Gram-positive bugs particularly which cause complicated lower respiratory tract infection (LRTI) leading to pneumonia. These new antibiotic additions (Elores, Potentox, and Vancoplus) to the current armamentarium to treat MDR infections, including pneumonia, can help us combat against antimicrobial resistance more efficiently.

Keywords: antibiotic resistance, pneumonia, Elores, Potentox, Vancoplus

1. Introduction

Pneumonia commonly described as infection of lungs is classified according to where or how it is acquired: community-acquired, healthcare-associated, hospital-acquired, or ventilator-associated pneumonia [1, 2]. According to the area of lung affected, pneumonia can be lobar pneumonia, bronchial pneumonia, and acute interstitial pneumonia [2]. Pneumonia can be

bacterial, viral, and less commonly fungal [3]. In the pediatric age group, pneumonia may additionally be classified as non-severe, severe, or very severe depending on the signs and symptoms [4].

2. Definitions

Hospital-acquired pneumonia (HAP) or nosocomial pneumonia refers to any pneumonia contracted by a patient in a hospital at least 48–72 h after being admitted. Community-acquired pneumonia (CAP) is defined as pneumonia acquired outside a hospital or a long-term care facility. It occurs within 48 h of hospital admission or in a patient presenting with pneumonia who does not have any of the characteristics of healthcare-associated pneumonia. The nosocomial pneumonia, which is associated with mechanical ventilation for a duration of more than 48 h, is termed as ventilator-associated pneumonia (VAP), whereas the healthcare-associated pneumonia is defined as the pneumonia occurring in non-hospitalized patients having contact with the healthcare system.

3. Epidemiology

From 1930s, prior to the discovery of antibiotic, till date pneumonia remains the major cause of death among all age groups accounting for four million deaths annually. The rate of death is highest among children aged less than 5 years worldwide [5]. According to a study conducted by Farooqui et al. [6], 3.6 million (3.3–3.9 million) episodes of severe pneumonia and 0.35 million (0.31–0.40 million) all-cause pneumonia deaths occurred in children younger than 5 years in India. Furthermore, 0.56 million (0.49–0.64 million) severe episodes of pneumococcal pneumonia and 105,000 (92,000–119,000) pneumococcal deaths occurred in India. According to American Thoracic Society/Infectious Diseases Society of America (ATS/IDSA), 2005, HAP had a crude mortality rate of 30–70% with an estimated attributable mortality rate to pneumonia between 27 and 50%. According to some estimates, VAP contributes up to 50–85% of all cases of nosocomial pneumonia [7, 8]. Furthermore, it mainly occurs in intensive care unit (ICU) patients where they most often require ventilator support, amounting to 9–27% of all mechanically ventilated patients [8]. It is estimated that four million cases of CAP occur annually in the United States, of which 20–25% are severe enough to warrant hospitalization [9]. Pneumonia is responsible for about 1.6 million deaths among children aged <5 years in Africa and South-East Asia regions [10, 11]. HAP and VAP are important causes of mortality and morbidity, which continue to baffle the treating physicians in today's era of MDR.

4. Economic burden

Pneumonia is one of the most common causes of economic burden across the globe involving great exploitation of health resources. World Health Organization (WHO) has indicated

that more death of children occurs due to pneumonia than any other diseases. According to a study conducted in India [11], the average cost per patient not put on ventilator is INR 27,123, whereas the cost associated with ventilated patient is almost twice INR 44,812. Ventilator support is the most expensive intervention adding to the cost of care followed by the cost of antibiotics and investigations and still making the patient more prone to complicated infections like biofilm. Thus, the disease adds significantly to the cost of hospital care and to the length of hospital stay. The situation does not seem to improve as antibiotic pipeline is virtually dry and the resistance appears to be further mounting in most parts of the world as per the latest Center for Disease Dynamics, Economics and Policy (CDDEP) reports.

5. Etiology

The etiology of pneumonia in high-income countries is different than in low-income countries [12, 13]. It has been reported that viruses contribute to 30–67% cases of CAP in developed countries and are more frequently identified in children aged less than 1 year than in those aged above 2 years [12]. Bacteria are more frequently identified with increasing age, resulting in mixed infections being less common with age [12].

Respiratory syncytial virus (RSV) is the prime cause of viral pneumonia in children admitted to hospital in developing countries, followed by influenza A and B, parainfluenza, human metapneumovirus, and adenovirus [13]. The bacterial pathogens causing pneumonia include *Pseudomonas aeruginosa, Haemophilus influenza* type b, *Acinetobacter baumannii, Klebsiella pneumoniae, Escherichia coli, Staphylococcus aureus*, methicillin-resistant *S. aureus* (MRSA), and *Streptococcus pneumoniae* [8, 14, 15].

6. Diagnosis

The outline for the diagnosis of pneumonia is highlighted in WHO/UNICEF Integrated Management of Childhood Illness (IMCI) guidelines. Fever and cough are the most common ones. Fever is present in 65–90% and cough in 75–96% of patients with pneumonia. Other typical respiratory complaints include sputum production, dyspnea, and chest pain [16]. In a hospital, there are numerous investigations available including radiography and microbiological methods to investigate pneumonia.

7. Treatments

The treatment of pneumonia depends on the age, the severity of illness, the likely causative agents, and their resistance patterns. Guidelines recommended the use of third- and fourth-generation cephalosporins, BL + BLI (β-lactam + β-lactamase inhibitor) combinations, and even carbapenems for the management of Gram-negative infections and vancomycin/linezolid for the management of Gram-positive infections.

8. Antibiotic resistance

Worldwide, antibiotic resistance is a major contemporary public health threat due to rapid emergence of resistant bacteria and endangering the efficacy of antibiotics [17]. In 2014, the WHO warned that the antibiotic resistance crisis is becoming extremely serious [18] and is attributed to the overuse and misuse of these medications, as well as a lack of new drug development by the pharmaceutical industry [19]. Different molecular mechanisms are responsible for the development of antimicrobial resistance such as alteration of bacterial cell permeability, acquisition of extended spectrum β-lactamase production (ESBLs), and metallo-β-lactamases (MBLs), bacterial biofilm formation, activation of efflux pump, bacterial conjugation, and curli fiber formation [17, 20–25].

In India, the prevalence of ESBL producing organisms among Gram-negative pathogens was up to 73.5% [26]. Similarly, the prevalence of MBLs is also increasing at an immense rate [27, 28]. Scores of reports highlighting antibiotic resistance because of efflux pump in bacteria is increasing significantly [29]. Outer membrane permeability and β-lactamase are key factor for the resistance of bacteria to antibiotics [30]. The increasing rate of the biofilm problem and its impact on antibiotic resistance triggered us to think new means which could disrupt the biofilm formation by inhibiting bacterial adhesion and curli formation.

There are significant number of reports on the clinical failure of β-lactam and β-lactamase inhibitor combination and even carbapenems due to various carbapenem resistance mechanisms. A number of studies have demonstrated the decreased susceptibility of Enterobacteriaceae to cephalosporins and other drugs [31, 32]. The ESBLs enzyme confers resistance not only to broad-spectrum cephalosporins, including oxymino-β-lactam antibiotics, but also to other commonly used antibiotics, including aminoglycosides and quinolone [33, 34]. Overexpression of efflux pump is often associated with extrusion of most of the β-lactam antibiotics, leading to decreased susceptibility of antibiotics [35].

A decreased susceptibility rates of *P. aeruginosa* and *A. baumannii* to β-lactams including carbapenems has been reported in various countries [36–38]. Failure of vancomycin and linezolid could be attributed to the emergence of VRSA (vancomycin-resistant *S. aureus*), hGISA (heterogeneous glycopeptide intermediate *S. aureus*) [39, 40]. This has raised a huge unmet need in the search for novel resistance-breaking therapies. Besides the above factors, inappropriate selection of empiric broad-spectrum antibiotics stretches the length of treatment and causes emergence of antibiotic resistance.

In view of the above background, the increasing rate of the antibiotic resistance and its impact on treatment failure encouraged us to study newly reported concept of antibiotic adjuvant entity by which the increasing failure rate of antibiotics can be controlled. Adjuvants are commonly used chemical entities which do not possess antibacterial activity of their own but help antibiotic in breaking one or more mechanisms of resistance and accelerate antibiotic effectiveness making AAEs as empiric choice [41]. Information regarding the prevalence of antimicrobial resistance in pathogens can be used for selecting an optional treatment. Earlier studies have supported the combination therapy of two or more drugs in combination with adjuvant (which are usually non-antibiotic in nature) as a suitable approach to reduce the frequency of antibiotic resistance [24].

A few of such synergistic novel antimicrobial adjuvant entities, their mechanisms, and clinical outcomes, which can revolutionize the future, will be discussed in this book chapter. These AAEs have been developed for both Gram-positive and Gram-negative multidrug-resistant infections. Elores (ceftriaxone + sulbactam with adjuvant EDTA) and Potentox (cefepime + amikacin with adjuvant potassium chloride (KCl)) are the AAEs for Gram-negative MDR pathogens each catering to a different type of resistance, and Vancoplus (ceftriaxone + vancomycin with adjuvant L-arginine), another AAE, can help us to last longer in the war against antibiotic-resistant Gram-positive bugs particularly which cause complicated LRTI leading to pneumonia (HAP/CAP/VAP/HCAP).

8.1. CSE1034 (Elores)

CSE1034 is a novel combination of third-generation cephalosporin "ceftriaxone," an irreversible β-lactamase inhibitor "sulbactam," and non-antibiotic adjuvant Antibiotic Resistance Breaker (ARB) "disodium edetate." Due to synergistic action of the inhibition of cell wall by ceftriaxone accompanied by the specific inhibition of β-lactamases by β-lactam component produced by common Gram-negative and Gram-positive pathogens, this drug has been reported to be affective against multiple types of MDR organisms. CSE1034 has proven activity against a wide range of ESBL and MBL producing Gram-negative pathogens and is used as a treatment option for a multitude of bacterial infections.

8.1.1. Mechanism of action

Ceftriaxone acts by binding to penicillin-binding proteins (PBPs) which are transpeptidases that catalyze the cross-linking of the peptidoglycan polymers synthesizing cell wall and subsequently inhibiting bacterial cell wall synthesis. The cell wall of bacteria consists of pentapeptide units attached to a polysaccharide backbone with alternating units of N-acetylglucosamine (NAG) and N-acetylmuramic acid (NAM). PBPs act on a terminal D-alanyl-D-alanine moiety on a pentapeptide unit and catalyze the formation of a peptide bond between the penultimate D-alanine and a glycine unit on an adjacent peptidoglycan strand. The ceftriaxone structure is the mimic of D-alanyl-D-alanine moiety and the PBPs wrongly attack the β-lactam ring in ceftriaxone, which leads to the inactivation of PBPs. As the peptidoglycan synthesis is essential to maintain bacterial cell wall integrity, so the inhibition of PBPs leads to damage and destruction of the cell wall and ultimately in cell lysis.

Sulbactam is a potent, highly specific inhibitor of a wide variety of β-lactamases including penicillinases and cephalosporinases produced commonly by different strains of bacteria and chromosomally mediated enzymes induced in some strains of *Klebsiella, Enterobacter*, and *Serratia* species to degrade antibiotics. By forming a protein complex with β-lactamases produced by bacterial strains resistant to ceftriaxone, the full potential of ceftriaxone is restored by the addition of sulbactam. Sulbactam not only potentiates the antibacterial activity of ceftriaxone against ESBL-producing pathogens but also exhibits a moderate antibacterial activity.

Disodium edetate is a non-antibiotic adjuvant acts as ARB which chelates the divalent metal ions particularly zinc that functions as a cofactor for carbapenemases. As zinc is necessary for the MBL activity, thus EDTA activity makes MBL-producing organisms susceptible toward Elores [24, 25, 42, 43]. Disodium edetate also chelates divalent metal ions located in the outer

membrane causing destabilization of outer membrane and thus resulting in enhanced penetration of drugs inside the bacterial cells. Moreover, CSE1034 downregulates acrA, acrB, tolC, mexA, and mexB genes in MexA-MexB-OprM efflux pump, which in turn enhances the susceptibility of Gram-negative bacteria (GNB) toward CSE1034 which overexpress this efflux transporter.

8.1.2. Activity spectrum

Elores has a broad spectrum of activity against both Gram-positive and Gram-negative bacteria pathogens. It is reported to be active against both ESBL and MBL producing organisms, including *E. coli, K. pneumoniae, Acinetobacter* spp., and *Pseudomonas* spp. Susceptibility data from various parts of India were collected from various clinical samples (including urine, pus, sputum, bronchoalveolar lavage, and endotracheal fluid); this AAE is very promising. The prevalence of resistance to Elores in ESBL and MBL organisms is reported to be less in various parts of India. The drug has been approved by the Drug Controller General of India (DCGI) for the treatment of various bacterial infections caused by the susceptible isolates of *K. pneumoniae, K. oxytoca, E. coli, P. aeruginosa, Acinetobacter* spp., *S. pneumoniae*, and *S. aureus*. A number of randomized phase 3 comparative trials, prospective, retrospective, and case studies have demonstrated the efficacy of Elores in the treatment of infections pertaining to respiratory tract, skin and skin structure, genitourinary tract, musculoskeletal, and gastrointestinal tract when compared with carbapenems and BL-BLIs showed very promising results [24, 25, 42]. These various published susceptibility reports suggest the use of Elores empirically in HAP and VAP caused due to MDR ESBL and MBL-producing Gram-negative pathogens [44]. A number of studies including randomized phase 3 trials, prospective, retrospective, and case studies validate the safety and efficacy of CSE1034. A phase 3 trial reports published in 2013 showed significantly high improved efficacy of CSE1034 compared to ceftriaxone in LRTI patients [45, 46]. Based on the safety and efficacy data, Elores is recommended as a carbapenem-sparer antibiotic. CSE1034 has shown to be effective and safe in moderate to severe HAP and VAP patients. CSE1034 has shown promising results in sepsis as monotherapy as well as along with colistin [47, 48]. CSE1034 was found to be safe with no serious adverse event was reported in phase 3 trial and post-marketing surveillance studies. Overall, CSE1034 is found to be well tolerated in adult population.

8.2. Potentox

With regard to Potentox for pneumonia, first of all, let's see what this unique AAE offers. Potentox is a synergistic antibiotic combination of cefepime and amikacin and potassium chloride. Cefepime is the fourth-generation broad-spectrum cephalosporin. It is frequently used as first-line empirical therapy for healthcare-associated infections, including those caused by suspected Gram-negative bacteria. Cefepime has relatively low propensity for degradation by ESBLs compared to other cephalosporins. Cefepime also remains active against infections due to AmpC-producing organisms. Amikacin is one of the most commonly used aminoglycosides and it has the highest recommendation from IDSA 2016 for usage in nosocomial pneumonia cases as an empirical antibiotic in the combination protocol against nosocomial pneumonia. Potentox (cefepime + amikacin) is not just the most active combination in vitro [23, 49] but also has demonstrated efficacy in vivo as the most active combination [50, 51].

8.2.1. Mechanism of action

Amikacin, which belongs to aminoglycoside antibiotic group, blocks the production of protein by binding irreversibly to the four nucleotides of 16S rRNA of 30S ribosomal subunit of the pathogenic organism. This region where amikacin binds is known to interact with the wobble base in the anti-codon of tRNA. Thus, amikacin interferes with the tRNA acceptor site and prevents the formation of initiation complex with messenger RNA. This leads to misreading of mRNA so incorrect amino acids are inserted into the polypeptide leading to nonfunctional or toxic peptides and the breakup of polysomes into nonfunctional monosomes.

Cefepime, a fourth-generation cephalosporin, is bactericidal and has the same mode of action as other β-lactam antibiotics. It disrupts the synthesis of the peptidoglycan layer of bacterial cell wall which is important for cell wall structural integrity.

Potassium chloride is a metal halide salt composed of potassium and chloride that is used as an adjuvant in Potentox. Interestingly, Potentox due to adjuvant potassium chloride exhibits activity against Quinolone-resistant Gram-negative pathogens, the prevalence of which is rising alarmingly in developing countries.

8.2.2. Activity spectrum

Both cefepime and amikacin individually have become a victim of high level of resistance [52]. This is where precisely, Potentox is used in combating these multidrug-resistant pathogens as Potentox has demonstrated in vitro and in vivo activity against these resistant isolates to which cefepime and amikacin are resistant individually. Global surveillance studies demonstrate that the actual acquired fluoroquinolone resistance rates are highly variable and are as high as almost 100%, particularly in Asia, whereas resistance rates in Europe and North America range from <10% in rural areas to >30% which is still pretty high. This highlights the importance of Potentox use to target multiple drug resistance effectively which developed both in community and in hospital settings.

Multi-centric randomized comparative open-labeled phase 3 trial of synergistic antibiotic combination of cefepime and amikacin versus cefepime alone was conducted in nosocomial pneumonia and showed superiority of Potentox in efficacy over cefepime alone.

Potentox and Elores can serve as a true carbapenem sparer as medically important Gram-negative bacteria are developing resistance very fast against this valuable class of antibiotic. In the era of antimicrobial resistance, the judicious use of different antimicrobials in a balanced fashion can help us in preserving these antibiotics for longer duration.

8.3. Vancoplus

While we look for HAP/VAP due to Gram-positive bacteria, methicillin-resistant *S. aureus* is a big concern and empirical antibiotic therapy should cover MRSA whenever factors increase the likelihood of MRSA. Now, MRSA is not confined to western countries only. A network of microbiology laboratories (Indian Network for Surveillance of Antimicrobial Resistance—INSAR) at premier medical colleges and hospitals in India was formed with support from the World Health Organization. In an article published in 2013, INSAR reported that MRSA prevalence in India is to the tune of 40% which shows that MRSA is a significant problem for India too.

Vancoplus is a novel AAE of ceftriaxone and vancomycin along with L-arginine as adjuvant caters to all types of mixed infection especially MRSA, VRSA, VISA, and hGISA [43].

8.3.1. Mechanism of action

The vancomycin plays its bactericidal role primarily through inhibiting cell wall biosynthesis. Specifically, vancomycin forms hydrogen bond interactions with the terminal D-alanyl-D-alanine moieties of the N-acetylmuramic acid- and N-acetylglucosamine-peptide subunits and thus prevents their incorporation into the peptidoglycan matrix, a major component of Gram-positive cell walls. Additionally, vancomycin is known to alter bacterial-cell-membrane permeability and RNA synthesis. No cross-resistance is known to occur between vancomycin and other antibiotics. The mechanism of action of ceftriaxone is already discussed in Elores drug section.

8.3.2. Activity spectrum

Earlier, the natural glycopeptide vancomycin was considered the drug of choice to treat MRSA infections. However, the concerns regarding the efficacy of vancomycin against MRSA including poor bactericidal activity and high recurrence rates are increasing [53]. Stevens and Moise Broder have reported in two studies, published in CID 2004 and 2006, respectively, that MRSA treatment failure rate is associated with higher vancomycin minimum inhibitory concentration (MIC). Higher vancomycin MIC is associated with higher mortality in HAP/VAP due to MRSA. We have started witnessing vancomycin resistance, either in the intermediate range or in the full-resistance range, even in India. Among high-risk MRSA bacteremia patients, Sakoulas et al. [54] documented treatment failure rates of 44% when vancomycin MICs were <0.5 μg/ml and of 90% when vancomycin MICs were 1–2 μg/ml ($p = 0.01$) [54]. Although many other drugs including tigecycline, linezolid, and daptomycin have also been approved and represent alternate antibiotic therapy to vancomycin, no study has reported the superiority in terms of efficacy and safety of these drugs over vancomycin [55]. These clinical challenges necessitate finding alternative effective empirical solutions for the management of MRSA infections and/or mixed infections. It will be prudent to start empirically with an antibiotic which shows MIC in the susceptibility range and works effectively at lower MIC also and that is what Vancoplus offers due to double insult caused by both ceftriaxone and vancomycin. Besides this, Vancoplus effectively helps in preventing and breaking biofilm which is a very frequent problem in intubated nosocomial pneumonia patients [23].

European Antimicrobial Resistance Surveillance Network (EARS-Net) data show that the occurrence of methicillin-resistant *S. aureus* was stabilizing in several European countries; still the percentage of MRSA among all *S. aureus* isolates remained above 25% in seven of the 29 EU/EEA reporting countries. The risk factor in ICU patients increases with an increased length of stay and patients with catheter or other devices. In such cases, Vancoplus is a highly reliable product because it takes care of mixed Gram-negative and Gram-positive infections effectively. Although both these drugs have known incompatibility when given individually and needs infusion line flushing or advised to be given contralaterally, the presence of adjuvant not only potentiates the activity of duo but also makes them compatible [56]. It has

been observed that when two non-compatible drugs are administered due to medical urgency with due precautions, still there exists certain degree of degradation of one of the drug molecules in vivo resulting in lesser efficacy than expected. Vancoplus overcomes this challenge effectively.

Additionally, one of the biggest challenges in the management of *S. aureus* infection including all resistant versions is the management of virulence factors. Panton Valentine Leukocidin (PVL) and δ-toxin, alpha toxins are responsible for cell lysis including human erythrocytes, neutrophils, as well as various mammalian cells. β-Lactams may even induce the production of cytolysins and other virulence-related exoproteins when inadequately used for treating MRSA, which potentially worsens clinical outcomes. In the treatment of meningitis particularly it becomes added taxing issue to prevent neuronal cell damage which is caused by virulence factors generated by pathogens even if treated. Here, Vancoplus offers additional protection by neutralizing toxins secreted by pathogen and reducing sequelae drastically and makes the product highly beneficial for immune-compromised patients [23].

In a nut shell, a number of agencies (Infectious Diseases Society of America/American Thoracic Society, US FDA and SWAB, Asia Pacific Society for Critical Care Medicines, European Society of Intensive Care Medicines, Indian Society of Critical Care Medicines, etc.) have issued guidelines for the treatment of CAP/HAP/HCAP, CUTI/sepsis and the management of other critical ICU infections. The concept of antibiotic adjuvant entity is new and will take time to be a part of these guidelines. The author has tried to share the latest and emerging trends in MDR infection management with proven efficacy and safety in millions of patients across various developing economies. The world has now started talking about adjuvant therapy and soon these therapies will be part of standard critical infection management program. These new antibiotic additions (Elores, Potentox, and Vancoplus) to the current armamentarium to treat MDR infections including pneumonia can help us combat against antimicrobial resistance more efficiently due to presence of ARB as adjuvant.

8.4. Adjuvant therapy to treat secondary bacterial superinfections caused by influenza and other respiratory viruses

Viral influenza is very common in community and is often mistreated with antibiotics. Antibacterial drugs are not meant for viral infections and misuse leads to creation of resistant bacterial species. Viral-bacterial co-infections in humans are well documented. Viral infections often lead to bacterial superinfections. Bacterial superinfections accompanied by influenza and other respiratory virus infections contribute to the significant morbidity and mortality particularly among elderly and young children.

Bacterial infection could be concomitant with influenza viral infection as a result of an enhanced pneumonic illness or may happen soon following influenza virus has been widely cleared from the lungs, when the host seems to be more susceptible to bacterial infection [57, 58].

Morbidity and mortality have been recognized to be greater in cases of influenza-associated bacterial infection in all age groups [59]. The increase in influenza infection during winter is often associated with a rise in cases of community-acquired pneumonia. The most common

causes of CAP are *S. pneumoniae, S. aureus*, and *H. influenzae. S. pneumoniae* is the most frequently isolated pathogen associated with influenza [60], although deaths, especially in children, are also associated with *S. aureus* infection, as highlighted by the recent emergence of community-acquired methicillin-resistant *S. aureus* [61]. Besides influenza, other respiratory viruses, such as coronavirus, adenovirus, and respiratory syncytial virus, are also associated with pneumonia [62].

The mechanisms of superinfection are very complex process. Several reports indicate that changes due to virus in the respiratory tract prime the upper airway and lung make way for subsequent bacterial infection. Super bacterial infections are accompanied by virus-induced cytopathology, leading to immunological impairment, which could be caused in part by the overproduction of inflammatory cytokines [63]. Transformation of the immune response by curtailing the capacity of the host to clear bacteria may contribute to the severity of the resulting infection [64]. Earlier studies on animal model have demonstrated that influenza predisposes to bacterial pneumonia [63, 65, 66]. It has been reported with 7–21 days of lag time for the onset of bacterial infection following seasonal influenza. However, shorter times from onset to death have been noticed in pandemic periods [67–69].

8.5. Antibiotic adjuvants potentiate anti-inflammatory properties of antibiotics

There is limited information on the effectiveness of adjuvant therapy for the treatment of bacterial complications of influenza. In a very recent study [70], explored the adjuvant effect of polyactin (PA), an inactivated trivalent influenza virus (ITIV) with or without PA or MF59 was instilled intranasally once a week in BALB/c mice. Results showed that PA is a novel mucosal adjuvant for intranasal vaccination with the inactivated trivalent influenza vaccine that has safe and effective mucosal adjuvanticity in mice and successfully induces both serum and mucosal antibody responses and a cell-mediated response.

The inflammatory response of viral infections results in the excessive production of reactive oxygen species (ROS) in the cells and tissues, and antioxidant system cannot neutralize them. Imbalance in this protective mechanism can lead to the damage of cellular molecules such as DNA, proteins, and lipids [71]. Moreover, the role of ROS in inflammation has been investigated vigorously by earlier authors [72, 73]. ROS are thought to be key signaling molecules in the progression of inflammatory disorders. It induces inflammation by the induction of COX-2, inflammatory cytokines (TNFα, interleukin 1 (IL-1), and IL-6), chemokines (IL-8 and CXCR4), and pro-inflammatory transcription factors (NF-κB) [74]. Inflammatory cytokines trigger inflammation, causing the immune response to weaken which may help to increase the risk of bacterial infection. This rise in inflammatory markers with infection is a cascade reaction and is not easily broken only by antibiotics. Adjuvants have a major role to play here. Buret [75] reported that some antibiotics, such as the 16-membered macrolide tilmicosin, may generate anti-inflammatory benefits by modulating the production of pro-inflammatory mediators, and by inducing neutrophil apoptosis. Many studies have highlighted that adjuvants co-administered with antibiotics reduce the oxidative stress, which in turn reduce inflammation [76, 77]. Dwivedi et al. [78] reported that AAE used for 21 days, the levels of antioxidant enzymes (superoxidase dismutase, catalase, glutathione reductase, glutathione

peroxidase), along with xanthine oxidase, lipid peroxidation, myeloperoxidase (MPO) levels, hepatic, and renal parameters were significantly improved in plasma and tissues of the AAE-treated group indicating antioxidant or free radical scavenging properties [50].

Osteomyelitis is an infection and inflammation in bone which is primarily caused by *S. aureus* and *S. epidermidis* and the levels of cytokines (TNFα and IL-6) is increased in osteomyelitis [79]. Dwivedi et al. [80] demonstrated that the combination of antibiotic along with adjuvant significantly improved the inflammatory cytokines (TNFα and IL-6), malondialdehyde (MDA), and myeloperoxidase in animal osteomyelitis infection model. From the earlier explanation, it may be concluded that compounds or drugs along with adjuvant generating both antibacterial and anti-inflammatory effects are likely to be most effective at treating bacteria-induced inflammatory syndromes.

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References

[1] American Thoracic Society, Infectious Diseases Society of America. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. American Journal of Respiratory and Critical Care Medicine. 2005;**171**:388-416

[2] Sharma S, Maycher B, Eschun G. Radiological imaging in pneumonia: Recent innovations. Current Opinion in Pulmonary Medicine. 2007;**13**(3):159-169

[3] Dunn L. Pneumonia: Classification, diagnosis and nursing management. Nursing Standard (Royal College of Nursing (Great Britain). 1987, 2005;**19**(42):50-54

[4] World Health Organization. Pocket Book of Hospital Care for Children: Guidelines for the Management of Common Illnesses with Limited Resources. Geneva: World Health Organization; 2005. p. 72

[5] Black RE, Cousens S, Johnson HL, Lawn JE, Rudan I, Bassani DG, et al. Global, regional, and national causes of child mortality in 2008: A systematic analysis. Lancet. 2010; **375**(9730):1969-1987

[6] Farooqui H, Jit M, Heymann D, Zodpey S. Burden of severe pneumonia, pneumococcal pneumonia and pneumonia deaths in Indian states: Modelling based estimates. PLoS One. 2015;**10**(6):e0129191

[7] Hunter JD. Ventilator associated pneumonia. British Medical Journal. 2012;**344**:e3325

[8] Oliveira MS, Prado GV, Costa SF, Grinbaum RS, Levin AS. Ampicillin/sulbactam compared with polymyxins for the treatment of infections caused by carbapenem-resistant Acinetobacter spp. Journal of Antimicrobial Chemotherapy. 2008;**61**(6):1369-1375

[9] Centers for Disease Control and Prevention Web Site. Pneumonia. Available from: http://www.cdc.gov/nchs/FASTATS/pneumonia.htm [Accessed: February 6, 2010]

[10] Kabra SK, Lodha R, Pandey RM. Antibiotics for community-acquired pneumonia in children. The Cochrane Database of Systematic Reviews. 2013;**4**(6):CD004874

[11] Kateel R, Adhikari P, Rajm S. Cost and antibiotic utilization of pneumonia patients in intensive care unit. Journal of Applied Pharmaceutical Science. 2016;**6**(02):087-090

[12] Harris M, Clark J, Coote N, Fletcher P, Harnden A, McKean M, Thomson A. British Thoracic Society guidelines for the management of community acquired pneumonia in children: Update 2011. Thorax. 2011;**66**(2):ii1-23

[13] Rudan I, Boschi-Pinto C, Bioglay Z, Mulholland K, Campbell H. Epidemiology and etiology of childhood pneumonia. Bulletin of the World Health Organization. 2008;**86**(5):408-416

[14] Moreira MR, Filho PPG. Multidrug-resistant pathogens causing ventilator-associated pneumonia: Risk factors, empirical antimicrobial therapy and outcome of patients in an intensive care unit (ICU) of a Brazilian university hospital. International Journal of Medicine and Medical Sciences. 2012;**4**(9):204-210

[15] Kalanuria AA, Zai W, Mirski M. Ventilator-associated pneumonia in the ICU. Critical Care. 2014;**18**:208

[16] Bochud PY, Moser F, Erard P, Verdon F, Studer JP, Villard G, Cosendai A, Cotting M, Heim F, Tissot J, Strub Y, Pazeller M, Saghafi L, Wenger A, Germann D, Matter L, Bille J, Pfister L, Francioli P. Community-acquired pneumonia. A prospective outpatient study. Medicine (Baltimore). 2001;**80**:75-87

[17] Chaudhary M, Payasi A. Prevalence of heterogeneous glycopeptide intermediate resistance in methicillin-resistant *Staphylococcus aureus*. American Journal of Infectious Diseases. 2013;**9**(3):63-470

[18] Ventola CL. The antibiotic resistance crisis: Part 1: Causes and threats. Pharmacy and Therapeutics. 2015;**40**(4):277-283

[19] Gould IM, Bal AM. New antibiotic agents in the pipeline and how they can help overcome microbial resistance. Virulence. 2013;**4**(2):185-191

[20] Askoura M, Mottawea W, Abujamel T, Taher I. Efflux pump inhibitors (EPIs) as new antimicrobial agents against *Pseudomonas aeruginosa*. Libyan Journal of Medicine. 2011;**13**:6

[21] Chaudhary M, Kumar S, Payasi A. A novel approach to combat acquired multiple resistance in *Escherichia coli* by using EDTA as efflux pump inhibitor. Journal of Microbial and Biochemical Technology. 2012;**4**(6):126-130

[22] Chaudhary M, Payasi A. Sulbactomax prevents antimicrobial resistance development by inhibition of conjugal transfer of F plasmids. International Journal of Drug Development & Research. 2012;**4**(1):337-345

[23] Chaudhary M, Payasi A. Resistance patterns and prevalence of the aminoglycoside modifying enzymes in clinical isolates of gram negative pathogens. Global Journal of Pharmacology. 2014;**8**(1):73-79

[24] Kumar M, Chaudhary S, Makkar MK, Garg N, Chugh S. Comparative antimicrobial efficacy evaluation of a new product Elores against meropenem on Gram-negative isolates. Asian Journal of Pharmaceutical Clinical Research. 2015;**8**:1-4

[25] Arora S, Munshi N. Comparative assessment of antibiotic susceptibility pattern of Gram negative pathogens isolated from intensive care unit patients in Pune. British Microbiology Research Journal. 2015;**10**(2):1-9

[26] Dalela G. Prevalence of extended spectrum β-lactamase (ESBL) producers among Gram negative bacilli from various clinical isolates in a tertiary care hospital at Jhalawar, Rajasthan, India. Journal of Clinical and Diagnostic Research. 2012;**6**:182-187

[27] Bora A, Ahmad G. Detection of NDM-1 in clinical isolates of *Klebsiella pneumoniae* from Northeast India. Journal of Clinical and Diagnostic Research. 2012;**6**:794-800

[28] Uma KR, Srinivasa RR, Suchismita S, Shashikala P, Kanungo R, Jayachandran S, Prashanth K. Phenotypic and genotypic assays for detecting the prevalence of metallo-b-lactamases in the clinical isolates of *Acinetobacter baumannii* from a south Indian tertiary care hospital. Journal of Medical Microbiology. 2009;**58**:430-435

[29] Levy SB. Active efflux mechanisms for antimicrobial resistance. Antimicrobial Agents and Chemotherapy. 1992;**36**:695-703

[30] Hancock REW, Wong PGW. Compounds which increase the permeability of the *Pseudomonas aeruginosa* outer membrane. Antimicrobial Agents and Chemotherapy. 1984;**26**:48-52

[31] Wani KA, Thakur MA, Fayaz AS, Fomdia A, Gulnaz B, Maroof P. Extended spectrum β-lactamase mediated resistance in *Escherichia coli* in a tertiary care hospital. International Journal of Health Sciences. 2009;**3**:155-163

[32] Kibret M, Abera B. Antimicrobial susceptibility patterns of *E. coli* from clinical sources in northeast Ethiopia. African Health Sciences. 2011;**11**:S40–S45

[33] Pitout JD. Infections with extended-spectrum beta-lactamase producing Enterobacteriaceae: Changing epidemiology and drug treatment choices. Drugs. 2010;**70**:313-333

[34] Endimiani A, Paterson DL. Optimizing therapy for infections caused by Enterobacteriaceae producing extended-spectrum β-lactamases. Seminars in Respiratory and Critical Care Medicine. 2007;**28**:646-655

[35] Yu EW, Aires JR, Nikaido H. AcrB multidrug efflux pump of *Escherichia coli*: Composite substrate-binding cavity of exceptional flexibility generates its extremely wide substrate specificity. Journal of Bacteriology. 2003;**85**:5657-5664

[36] Owlia P, Azimi L, Gholami A, Asghari B, Lari AR. ESBL and MBL mediated resistance in *Acinetobacter baumannii*: A global threat to burn patients. Infez Med. 2012;**20**:182-187

[37] Mansoor T, Musani MA, Khalid G, Kamal M. *Pseudomonas aeruginosa* in chronic suppurative otitis media: Sensitivity spectrum against various antibiotics in Karachi. Journal of Ayub Medical College. 2009;**21**:120-123

[38] Tripathi P, Banerjee G, Saxena S, Gupta M K, Ramteke PW. Antibiotic resistance pattern of *Pseudomonas aeruginosa* isolated from patients of lower respiratory tract infection. African Journal of Microbiology Research. 2011;**5**:2955-2959

[39] Kirby A, Graham R, Williams NJ, Wootton M, Broughton CM, Alanazi M, et al. *Staphylococcus aureus* with reduced glycopeptide susceptibility in Liverpool, UK. Antimicrobial Chemotherapy. 2010;**65**:721-724

[40] Chaudhary M, Payasi A. Changing trends of commonly used intensive care unit antibiotics due to differential membrane permeability in resistant *Escherichia coli* collected in EASE programme. Journal of Microbial and Biochemical Technology. 2013;**5**:084-087

[41] Beranal P, Molina-Santiago C, Daddaoua A, Llamas MA. Antibiotic adjuvants identification and clinical use. Microbial Biotechnology. 2013;**6**(5):445-449

[42] Sahu M, Sanjith S, Bhalekar P, Keny D. Waging war against extended spectrum beta lactamase and metallobetalactamase producing pathogens—novel adjuvant antimicrobial agent CSE1034—an extended hope. Journal of Clinical and Diagnostic Research. 2014;**8**(6):DC20–DC23

[43] Chaudhary M, Patnaik SK, Payasi A. Inhibition of Panton Valentine Leukocidin toxin indeed neutrophil cell lysis by Vancoplus in methicillin-resistant *Staphylococcus aureus* infections. American Journal of Infectious Diseases. 2014;**10**(4):154-163

[44] Bhatia P, Mir MA. A new fixed dose combination of ceftriaxone + sulbactam + disodium edetate for definitive treatment of infections due to piperacillin/tazobactam resistant bacteria: A retrospective efficacy and pharmacoeconomic study. British Journal of Medicine and Medical Research. 2016;**15**(4):1-14

[45] Chaudhary M, Payasi A. A randomized, open label, prospective, multicenter phase III clinical trial of Elores in lower respiratory tract and urinary tract infections. Journal of Pharmacy Research. 2013;**6**:409-413

[46] Chaudhary M, Payasi A. Clinical, microbial efficacy and tolerability of Elores, a novel antibiotic adjuvant entity in ESBL producing pathogens: Prospective randomized controlled clinical trial. Journal of Pharmacy Research. 2013;**7**:275-280

[47] Verma S. A retrospective study to evaluate the efficacy of a new antibiotic adjuvant entity (β-lactam/β-lactamase inhibitor/adjuvant disodium edetate combination) for management of sepsis. Research Journal of Infectious Diseases. 2015;**3**:1-7

[48] Agarwal VK, Bansal A, Pujani M, Jawa M, Mahajan P, Jain A. A retrospective comparative study to evaluate the use of a new betalactam + betalactamase inhibitor (ceftriaxone + sulbactam + disodium edetate) in comparison to meropenem in the management of Gram-negative bacterial sepsis. Tropical Journal of Medical Research. 2016;**19**(1):5-10

[49] Chaudhary M, Payasi A. A solution to combat aminoglycoside and quinolone resistant gram negative organisms. International Journal of Current Research. 2015;**7**(6):17006-17011

[50] Dwivedi VK, Soni A, Chaudhary M, Singh CP, Shrivastava SM. Fixed-dose combination of cefepime plus amikacin (Potentox) inhibits pneumonia infection. Experimental Lung Research. 2009;**35**(7):621-629

[51] Dwivedi VK, Soni A, Payasi A, Ahmed A, Singh SP, Chaudhary M. Potentox reduces biochemical and inflammatory response in osteomyelites infection. International Journal of Osteoporosis and Metabolic Disorders. 2011;**4**(1):26-36

[52] Shahid M, Malik A. Resistance due to aminoglycoside modifying enzymes in *Pseudomonas aeruginosa* isolates from burns patients. Indian Journal of Medical Research. 2005;**122**:324-332

[53] Liu C, Bayer A, Cosgrove SE, Daum RS, Fridkin SK, Gorwitz RJ, Kaplan SL, Karchmer AW, Levine DP, Murray BE. Clinical practice guidelines by the Infectious Diseases Society of America for the treatment of methicillin-resistant *Staphylococcus aureus* infections in adults and children. Clinical Infectious Diseases. 2011;**52**:e18-e55

[54] Sakoulas G, Moise-Broder PA, Schentag J, Forrest A, Moellering RC Jr, Eliopoulos GM. Relationship of MIC and bactericidal activity to efficacy of vancomycin for treatment of methicillin-resistant *Staphylococcus aureus* bacteremia. Journal of Clinical Microbiology. 2004;**42**:2398-2402

[55] Wunderink RG, Mendelson MH, Somero MS, Fabian TC, May AK, Bhattacharyya H, Leeper KV Jr, Solomkin JS. Early microbiological response to linezolid vs vancomycin in ventilator-associated pneumonia due to methicillin-resistant *Staphylococcus aureus*. Chest. 2008;**134**(6):1200-1207

[56] Chaudhary A, Kumar S, Bansal R, Payasi A. Synergy of a novel antibiotic adjuvant entity against multi drug resistant methicillin-resistant *Staphylococcus aureus* and heterogeneous glycopeptide-intermediate Staphylococcus aureus. Journal of Pharmacy Research. 2013;**7**:781–e786

[57] Small C-L, Shaler CR, McCormick S, Jeyanathan M, Damjanovic D, Brown EG, Arck P, Jordana M, Kaushik C, Ashkar AA, Xing Z. Influenza infection leads to increased susceptibility to subsequent bacterial superinfection by impairing NK cell responses in the lung. Journal of Immunology. 2010;**184**:2048-2056

[58] Hament JM, Kimpen JL, Fleer A, Wolfs TF. Respiratory viral infection predisposing for bacterial disease: A concise review. FEMS Immunology and Medical Microbiology. 1999;**26**:189-195

[59] Seki M, Kosai K, Yanagihara K, Higashiyama Y, Kurithara S, Izumikawa K, Miyazaki Y, Hirakata Y, Tashiro T, Hohno S. Disease severity in patients with simultaneous influenza and bacterial pneumonia. Internal Medicine. 2007;**46**:953-958

[60] Brundage JF. Interactions between influenza and bacterial respiratory pathogens: Implications for pandemic preparedness. The Lancet Infectious Diseases. 2006;**6**:303-312

[61] Finelli L, Fiore A, Dhara R, Brammer L, Shay DK, Kamimoto L, Fry A, Hageman J, Gorwitz R, Bresee J, Uyeki T. Influenza-associated pediatric mortality in the United States: Increase of *Staphylococcus aureus* coinfection. Pediatrics. 2008;**122**:805-811

[62] Pavia AT. What is the role of respiratory viruses in community acquired pneumonia; what is the best therapy for influenza and other viral causes of CAP? Infectious Disease Clinics of North America. 2013;**27**:157-175

[63] Beadling C, Slifka MK. How do viral infections predispose patients to bacterial infections? Current Opinion in Infectious Diseases. 2004;**17**:185-191

[64] McCullers JA. Insights into the interaction between influenza virus and pneumococcus. Clinical Microbiology Reviews. 2006;**19**:571-582

[65] Loving CL, Brockmeier SL, Vincent AL, Palmer MV, Sacco RE, Nicholson TL. Influenza virus coinfection with bordetella bronchiseptica enhances bacterial colonization and host responses exacerbating pulmonary lesions. Microbial Pathogens. 2010;**49**:237-245

[66] Diavatopoulos DA, Short KR, Price JT, Wilksch JJ, Brown LE, Briles DE, Strugnell R, Wijburg OL. Influenza A virus facilitates *Streptococcus pneumoniae* transmission and disease. FASEB Journal. 2010;**24**:1789-1798

[67] Grabowska K, Hogberg L, Penttinen P, Svensson A, Ekdahl K. Occurrence of invasive pneumococcal disease and number of excess cases due to influenza. BMC Infectious Diseases. 2006;**6**:58

[68] Sachedina N, Donaldson LJ. Paediatric mortality related to pandemic influenza A H1N1 infection in England: An observational population based study. The Lancet. 2010;**376**:1846-1852

[69] Lee EH, Wu C, Lee EU et al. Fatalities associated with the 2009 H1N1 influenza a virus in New York City. Clinical Infectious Diseases. 2010;**50**:1498-1504

[70] Ren S-T, Zhang X-M, Sun P-F, Sun L-J, Guo X, Tian T, Zhang J, Guo Q-Y, Li X, Guo L-J, Che J, Wang B, Zhang H. Intranasal immunization using mannatide as a novel adjuvant for an inactivated influenza vaccine and its adjuvant effect compared with MF59. PLoS One. 2017;**12**(1):e0169501

[71] Ďuračková Z. Some current insights into oxidative stress. Physiological Research. 2010;**59**:459-469

[72] Mittal M, Siddiqui MR, Tran K, Reddy SP, Malik AB. Reactive oxygen species in inflammation and tissue injury. Antioxidants & Redox Signaling. 2014;**20**(7):1126-1167

[73] Berlett BS, Stadtman ER. Protein oxidation in aging, disease, and oxidative stress. Journal of Biological Chemistry. 1997;**272**:20313-20316

[74] Gupta SC, Hevia D, Patchva S, Park B, Koh W, Aggarwal BB. Upsides and downsides of reactive oxygen species for cancer: The roles of reactive oxygen species in tumorigenesis, prevention, and therapy. Antioxidants & Redox Signaling. 2012;**16**:1295-322

[75] Buret AG. Immuno-modulation and anti-inflammatory benefits of antibiotics: The example of tilmicosin. Canadian Journal of Veterinary Research. 2010;**74**(1):1-10

[76] Dwivedi VK, P. Kumar, Chaudhary M. Comparative study of CSE 1034 and ceftriaxone in pneumonia induced rat. Clinical and Experimental Pharmacology. 2012;**2**:1

[77] Kaulmann A, Bohn T. Bioactivity of polyphenols: Preventive and adjuvant strategies toward reducing inflammatory bowel diseases—promises, perspectives, and pitfalls. Oxidative Medicine and Cellular Longevity. 2016;**2016**:29

[78] Dwivedi VK, Bhatnagar A, Chaudhary M. Protective role of ceftriaxone plus sulbactam with VRP1034 on oxidative stress, hematological and enzymatic parameters in cadmium toxicity induced rat model. Interdisciplinary Toxicology. 2012;**5**(4):192-200

[79] Kopf M, Baumann H, Freer G, Freudenberg M, Lamers M, Kishimoto T, Zinkernazel R, Bleuthmann H, Kohler G. Impaired immune and acute phase responses in IL-6 deficiency mice. Nature. 1994;**368**:339-342

[80] Dwivedi VK, Soni A, Payasi A, Ahmad A, Shambhu PS, Chaudhary M. Potentox Reduces Biochemical and Inflammatory Response in Osteomyelitis Infection. International Journal of Osteoporosis and Metabolic Disorders. 2011;**4**: 26-36