

Novel Therapeutic Trends in Pneumonia: Antibiotics and Mesenchymal Stem Cells

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Abstract:

Pneumonia remains a major cause of morbidity and mortality. With the significant global health burden that pneumonia poses, it is essential to improve therapeutic and management strategies. The increasing emergence of antibiotic-resistant bacterial strains limits options for effective antibiotic use. New antibiotics for the treatment of pneumonia may address deficits in current antimicrobial drugs, with an ability to cover both typical, atypical, and resistant pathogens. Several of these newer drugs also have structural characteristics that allow for a decreased propensity for the development of bacterial resistance. The potential use of stem cell therapies in place of corticosteroid treatments may also offer an improvement in patient outcomes. Human mesenchymal stem cell treatments have shown efficacy and safety in treating COVID-19 induced pneumonia. Combined treatment with both stem cells and antibiotics in pneumonia in a rabbit model has also shown significantly increased efficacy in comparison to antibiotic treatment alone. This presents yet another possible route for a novel strategy in treating pneumonia, though additional future studies are necessary before clinical implementation. While pneumonia remains a major disease of concern, having newer approved antibiotics as well as novel therapies such as stem cell treatments in the pipeline offers clinicians more options in effectively treating pneumonia.

Keywords: community-acquired pneumonia; hospital-acquired pneumonia; antibiotics; mesenchymal stem cells; corticosteroids, COVID-19

Introduction

Pneumonia, defined as an infection of the lung or pulmonary parenchyma by bacteria, viruses, fungi, and/or bacteria-like organisms, is one of the leading causes of morbidity and mortality globally [1-3]. Pneumonia is characterized by symptoms including fever, sweating, shortness of breath, chest pain, fatigue and loss of appetite [1]. The most common pneumonia is community-acquired pneumonia (CAP), which is pneumonia acquired outside of a hospital setting [3]. *S. pneumoniae*, *H. influenzae*, *S. aureus*, and the influenza virus, are the main causative agents of CAP, with *S. pneumoniae* accounting for more than 25% of cases of CAP worldwide [1,3,4]. Hospital-acquired pneumonia (HAP), another common form of pneumonia, is acquired after at least 48 hours of hospitalization for other diseases [1,3]. While HAP can be caused by gram-positive cocci such as *S. aureus* and *S. pneumoniae*, gram-negative bacilli such as *P. aeruginosa*, *K. pneumoniae*, *E. coli*, and Enterobacter are more likely to be involved in HAP [1].

CAP has been shown to greatly increase the risk of long-term morbidity and mortality as well as the rates of all-cause hospitalization, emergency department visits, and CAP-related hospital visits [5]. In 2019,

pneumonia and influenza were the ninth leading cause of death in the United States, accounting for over 49,000 deaths [6]. Pneumonia-related deaths in patients admitted to the intensive care unit (ICU) was approximately 30%, however, with the COVID-19 pandemic caused by the novel Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), mortality has increased to 35-50% [7]. The COVID-19 pandemic has further highlighted the dangers of viral pneumonia, with over 2.7 million deaths worldwide and over 539,000 deaths in the United States as of March 24, 2021 [8,9].

With the significant global health burden that pneumonia poses, it is essential to improve therapeutic and management strategies [10]. Although there are many treatments available, including antibiotics, corticosteroids, breathing treatments, and oxygen therapy, the increasing emergence of antibiotic-resistant bacterial strains limits options for effective antibiotic use [3,10,11]. Furthermore, approximately 14-35% of hospitalized CAP patients die despite appropriate antibiotic treatments [12]. Beyond the problems associated with antibiotics, the use of corticosteroids has been controversial due to their associated adverse side effects, demonstrating the need for other therapeutic options. In this review, we summarize the most updated research and therapeutic

guidelines for treating pneumonia, specifically antibiotics and mesenchymal stem cell therapies.

Novel antibiotic treatments

Although antibiotics remain the primary treatment for bacteria-induced pneumonia, many of the currently available pharmacological agents have limitations, including allergies, antibiotic resistance, inadequate penetration in lung tissues, and adverse side effects [13]. Despite improvements in clinical management of pneumonia, treatment failure rates for pneumonia remain high at 2.4%-31.0% in CAP and 30.0%-62.0% in HAP [14]. Among the many factors that contribute to treatment failures, one major cause is associated with antibacterial therapies. Antibiotic resistance, for example, makes up more than 80% of the cases in bacteria-induced HAP [14]. The acquisition of antibacterial resistance genes by ESKAPE pathogens has increased the disease burden and death rates [15]. ESKAPE pathogens are antibiotic-resistant bacteria including *E. faecium*, *S. aureus*, *K. pneumoniae*, *A. baumannii*, *P. aeruginosa*, and Enterobacter, that have developed resistance mechanisms against many antibiotics, including those that are used as the last line of defense [15,16]. Mechanisms of drug resistance include drug inactivation, modification of

drug binding sites or targets, changes in cell permeability that reduce intracellular drug accumulation, and biofilm formation [17].

While most common CAP-causing Enterobacteriaceae are generally susceptible to typical antibiotics, a high prevalence of *S. pneumoniae* strains (20-40%) are resistant to macrolides [18]. Current levels of resistance to fluoroquinolones while still relatively low, continue to increase [18]. Furthermore, fluoroquinolones have been associated with adverse side effects, prompting the United States Food and Drug Administration to suggest that they be reserved for patients with no other treatment options [18,19]. High rates of treatment failure caused by inadequate antibiotic treatments have led to increased mortality and morbidity as well as longer hospital stays, highlighting the need for newer effective antibiotics [11]. These new antibiotics may address deficits in current antimicrobial drugs, with an ability to cover both typical, atypical, and resistant pathogens [7,20]. There are many approaches to antibacterial drug design, such as targeting enzymes that are essential for bacterial survival [21]. While their use in severe CAP is not yet completely understood, these novel antibiotics may offer a potential treatment option for patients with resistant pathogens (Table 1).

Drug Name	FDA Status	Antibiotic Class	Spectrum of Activity	Advantages
Lefamulin	Approval for CAP treatment in August 2019	Pleuromutilin	Gram-positive strains (including vancomycin-resistant Enterococci and MRSA), gram-negative strains, atypical pathogens, pathogens typically associated with CAP (i.e. <i>S. pneumoniae</i> , <i>H. influenzae</i>) [11, 13, 25]	Unaffected by resistance to other antibiotic classes including macrolides, fluoroquinolones, tetracyclines, b-lactam) High specificity for the inhibition of bacterial protein translation with no effect on eukaryotic protein synthesis, resulting in a low propensity for development of bacterial resistance Lack of cross-resistance with antibacterial classes
Delafloxacin	Approval for CAP treatment in November 2019	Fluoroquinolone	MRSA, penicillin-resistant/levofloxacin-resistant <i>S. pneumoniae</i> , <i>S. pyogenes</i> , Enterococci, gram-negative strains (including quinolone-susceptible <i>P. aeruginosa</i>), atypical pathogens (<i>C. pneumoniae</i> , <i>M. pneumoniae</i> , <i>L. pneumophila</i>) [11, 19, 24]	Penetrates well into ELF More potent in vitro activity against most common CAP pathogens Lower mutant prevention concentrations compared to other FQs
Omadacycline	Approval for CAP treatment in October 2018	Tetracycline	MRSA, penicillin-resistant staphylococci, gram-negative bacteria, atypical pathogens [11, 26]	Active against 2 main forms of bacterial resistance to tetracyclines: efflux and ribosomal protection Has higher and sustained concentrations in plasma and ELF
Solithromycin	Rejection in 2017 (safety data required)	Macrolide	MRSA, <i>S. pneumoniae</i> (includes macrolide, penicillin, and quinolone-resistant), <i>H. influenzae</i> , atypical pathogens [11, 27, 28]	Has potent in vitro activity against fluoroquinolone, macrolide, and penicillin-resistant isolates of <i>S. pneumoniae</i>
Imipenem/Cilastatin/Relebactam (IMI-REL)	Approval for HAP/VAP treatment in June 2020	β -lactam (carbapenem)/ β -lactamase inhibitor combination	Gram-negative strains (including multidrug-resistant <i>P. aeruginosa</i> , carbapenem-resistant Enterobacterales, extended-spectrum β -lactamases, <i>K. pneumoniae</i>) [11, 29-31]	Protection against several imipenem-resistant bacteria

MRSA: methicillin-resistant *S. aureus*; **ELF:** epithelial lining fluid **FQ:** fluoroquinolone

Table 1. Characteristics of Novel Antibiotics

Community-acquired pneumonia

Lefamulin

Lefamulin is a pleuromutilin antibiotic that inhibits bacterial growth by binding to the peptidyl transferase center of the 50S ribosome, preventing the binding of tRNA for peptide transfer and inhibiting peptide bond formation [13,20,22]. The binding pocket of the bacterial ribosome closes around the pleuromutilin, causing an induced fit and tightening the binding pocket [13,22-24]. This unique binding mechanism is believed to be the reason for the low potential for the development of bacterial resistance and cross-resistance to other antibiotics [13, 22-24]. Lefamulin exhibits both bactericidal and bacteriostatic activity against gram-positive, fastidious gram-negative, atypical pathogens, and some gram-negative anaerobes [13,25]. It has also been shown to achieve extensive penetration and accumulation in pulmonary epithelial lining fluid [13]. These properties suggest that lefamulin could target several limitations of current existing CAP therapies.

In a multicenter randomized control phase III trial (LEAP 1), IV-to-oral lefamulin was non-inferior to IV-to-oral moxifloxacin in early clinical response (87.3% vs. 90.2% respectively, difference -2.9%, 95% CI -8.5 to 2.8) [32]. In a LEAP 2 trial, early clinical response rates were 90.8% for oral lefamulin and 90.8% for oral moxifloxacin (difference 0.1%, 1-sided 97.5% CI, -4.4% to ∞) [32]. The most frequently reported treatment-emergent adverse events were gastrointestinal, (diarrhea 12.2% in lefamulin, 1.1% in moxifloxacin; nausea 5.2% in lefamulin and 1.9% in moxifloxacin) [32]. Both studies showed that lefamulin was non-inferior to moxifloxacin and was safe and well-tolerated [32].

Lefamulin is an effective and well-tolerated agent, with availability in both oral and IV formulations to treat CAP. Patients who may benefit from lefamulin include those at higher risk of adverse events from fluoroquinolone use, those with a history of *C. difficile* infection, or those in settings with high prevalence of community-associated methicillin-resistant *S. aureus* (MRSA) [23].

Delafloxacin

Delafloxacin is an anionic fluoroquinolone with a unique structure that allows for increased intracellular penetration in bacteria, enhancing bactericidal activity in acidic conditions [33]. This property is a unique aspect of delafloxacin, as many other agents including other fluoroquinolones, macrolides, and aminoglycosides typically exhibit decreased antibacterial potency in acidic conditions [33]. Delafloxacin targets both topoisomerase IV and DNA gyrase to inhibit bacterial DNA replication [19,33,34]. This increased intracellular penetration in combination with delafloxacin's unique mechanism gives it a broad spectrum of activity against gram-positive, gram-negative, and atypical organisms, and is approved for the treatment of CAP caused by *S. pneumoniae*, *S. aureus* (methicillin-susceptible isolates only), *K. pneumoniae*, *E. coli*, *P. aeruginosa*, *H. influenzae*, *H. parainfluenzae*, *C. pneumoniae*, *L. pneumophila*, and *M. pneumoniae* [33].

In a multicenter randomized phase III clinical trial (DEFINE-CABP), delafloxacin was shown to be non-inferior to moxifloxacin (88.9% vs. 89.0% respectively, difference -0.2%, 95% CI -4.4% to 4.1%) [35]. Treatment-emergent adverse events occurred in 15.2% of the subjects in the delafloxacin group and 12.6% in the moxifloxacin group, with most events considered mild in severity [35]. Based on baseline MIC₉₀ values, delafloxacin demonstrated 16-fold greater activity compared to moxifloxacin for gram-positive and gram-negative pathogens [35].

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Overall, delafloxacin is non-inferior to moxifloxacin and is effective and generally well-tolerated. In particular, it can be a potential treatment for patients with comorbidities, specifically COPD/asthma, based on improved response in these patients in the DEFINE-CABP trial [33]. Delafloxacin is a promising new antibiotic given its mild side effect profile, including a lack of association with QTc prolongation, a typical side effect of quinolones [19,36].

Omadacycline

Omadacycline is an aminomethylcycline that was created via chemical modification of minocycline and was developed to target *Tet(A)* and other *Tet* efflux genes [26,37]. The chemical modifications to its structure allow it to be active against two forms of bacterial resistance to tetracyclines: efflux and ribosomal protection. Omadacycline remains active and relatively unaffected by the presence of tetracycline efflux pumps (i.e. *TetK*) and ribosomal protection proteins (i.e. *TetM*), as well as other resistance mechanisms to other antibiotic classes [24]. It is active against staphylococci (including methicillin-resistant strains) and streptococci (including tetracycline-resistant strains). Additionally, omadacycline has a higher affinity for the 30S ribosomal subunit than tetracycline, binding to the 30S ribosome to inhibit protein synthesis [24].

In a randomized phase III clinical trial (OPTIC), omadacycline was shown to be non-inferior to moxifloxacin, with clinical success rates of 88.4% for omadacycline compared to 85.2% with moxifloxacin (difference 3.3%, 97.5% CI -2.7 to 9.3) [38]. Both treatments showed high rates of clinical success overall in patients with an identified CAP pathogen, as well as against gram-positive, gram-negative, and atypical pathogens [38]. Furthermore, there was no evidence of decreasing susceptibility to omadacycline during treatment. However, there is also a mortality imbalance in patients with CAP (2% in the omadacycline group compared to 1% in the moxifloxacin group) [38]. As the cause of the mortality imbalance has not yet been established, patients with CAP on omadacycline should be closely monitored [38]. The United States Food and Drug Administration (FDA) has required an additional active-controlled safety study in pediatric patients age 8-17 to further define omadacycline's safety and efficacy in the treatment of CAP [24,39].

In addition to its mild side effect profile, omadacycline can be used to treat patients with known hypersensitivity or intolerance to vancomycin and β -lactams, making it another potential option for treatment of CAP [26].

Solithromycin

Solithromycin is a "fourth generation" macrolide and fluoroketolide that has yet to receive FDA approval for treatment of CAP [20,40]. Solithromycin binds the 50S ribosomal subunit near the peptide exit tunnel, prematurely terminating translation and causing frameshift errors in translation [28,41]. This mechanism is considered bactericidal, however, due to its added ability to interfere with the formation of the ribosomal 50S unit, ketolides are considered bacteriostatic [41]. Furthermore, ketolides are less sensitive to macrolide efflux (*mef*), contributing to solithromycin's restored activity against *H. influenzae* [41]. Its structure helps solithromycin to overcome macrolide resistance in addition to problems with adverse events of telithromycin [41]. In particular, solithromycin lacks a pyridine moiety which may reduce hepatic toxicity, and has fluorine at C-2, improving drug binding and enhancing activity [28, 41].

A multicenter double-blind randomized phase II study demonstrated that solithromycin has comparable efficacy and favorable safety compared to

levofloxacin, with an 84.6% efficacy outcome rate of clinical success in the solithromycin group compared to 86.6% in the levofloxacin group, and early response success rates at 72.3% vs. 71.6% respectively [27]. The majority of treatment-emergent adverse events were mild-to-moderate gastrointestinal symptoms (diarrhea 7.8% in solithromycin vs. 5.9% in levofloxacin; nausea 1.6% in solithromycin vs. 10.3% in levofloxacin; vomiting 0% in solithromycin vs. 4.4% in levofloxacin) [27].

Subsequent phase III trials used moxifloxacin as the comparator. A multicenter double-blind randomized phase III trial (SOLITAIRE-ORAL) compared the efficacy and safety of oral solithromycin with oral moxifloxacin and showed that solithromycin was non-inferior to moxifloxacin in the treatment of CAP [42]. Early clinical response was achieved in 78.2% of the solithromycin group compared to the 77.9% in the moxifloxacin group (difference 0.29%, 95% CI -5.5 to 6.1) [42]. Both drugs showed similar safety profiles, with a 10% incidence of treatment-emergent adverse events in the solithromycin group compared to the 13% in the moxifloxacin group [42]. The most common adverse events were mild gastrointestinal symptoms (diarrhea 4% in solithromycin vs. 6% in moxifloxacin; nausea 4% in both groups; vomiting 2% in both groups) and nervous system symptoms (headache 4% in solithromycin vs. 3% in moxifloxacin; dizziness 2% in both groups) [42]. It was noted that overall ALT concentrations of >3 times, >5 times, and >10 times the upper limit of normal were noted in 7.2%, 2.4%, and 0.1% of patients in the solithromycin group in comparison to the 3.6%, 1.0%, and 0.2% in the moxifloxacin group [28, 42].

A second phase III trial (SOLITAIRE-IV) evaluated the safety and efficacy of IV-to-oral solithromycin and moxifloxacin, also supporting prior studies' conclusions that solithromycin was non-inferior to moxifloxacin [43]. Early clinical response was achieved in 79.3% of the solithromycin group compared to the 79.7% in the moxifloxacin group (difference -0.46%, 95% CI -6.1 to 5.2) [43]. Adverse events were comparable between the two groups, though mostly mild/moderate infusion events led to a higher incidence of adverse events in the solithromycin group [43].

Solithromycin is an effective antibiotic regimen that offers additional advantages, including its anti-inflammatory effect and its potent activity against pathogens [40]. However, due to concerns related to hepatotoxicity, the FDA has recommended further clinical studies to assess the safety profile in 9000 patients [20,28].

Hospital-acquired pneumonia

Imipenem/Cilastatin/Relebactam (IMI-REL)

IMI-REL is a new intravenously administered β -lactam (carbapenem)/ β -lactamase inhibitor anti-infective combination antibiotic that recently received FDA approval for use in treating HAP and ventilator-associated pneumonia (VAP) in June 2020 [30]. Imipenem is a carbapenem that inactivates penicillin-binding proteins to inhibit peptidoglycan crosslinking during cell wall synthesis, resulting in bacterial cell lysis and death [30]. It is coadministered with cilastatin, a dehydropeptidase-I

inhibitor that does not have antibacterial activity and simply reduces renal metabolism [29,30]. Relebactam is a novel β -lactamase inhibitor that protects imipenem from degradation by *Pseudomonas*-derived cephalosporins and class A and C β -lactamases, helping to restore imipenem activity against several imipenem-resistant bacteria including *P. aeruginosa* and *Enterobacteriaceae* [29-31]. IMI-REL has a broad spectrum range in vitro, including multidrug-resistant *P. aeruginosa* and carbapenem-resistant Enterobacterales [29-31].

Two phase III trials of IMI-REL have been conducted to study its efficacy and safety. In a double-blind randomized phase III trial (RESTORE-IMI 1), the efficacy and safety of IMI-REL were comparable to that of imipenem/cilastatin + colistin for the treatment of hospitalized patients with hospital-acquired/ventilator-associated pneumonia, complicated intraabdominal infection, or complicated urinary tract infection caused by imipenem-nonsusceptible pathogens [44]. A favorable overall response was observed in 71% of the IMI-REL group compared to 70% of the imipenem + colistin group. Serious adverse events occurred in 10% of the IMI-REL group as opposed to 31% in the imipenem + colistin group [44]. The second double-blind randomized control phase III trial (RESTORE-IMI 2) demonstrated noninferiority of IMI-REL compared to piperacillin/tazobactam in patients with HAP/VAP [45]. The favorable early clinical response was 61.0% in the IMI-REL group compared to the 55.8% in the piperacillin/tazobactam group; Day 28 all-cause mortality was 15.9% in the IMI-REL group compared to 21.3% in the piperacillin/tazobactam group (difference -5.3%, 95% CI -3.2 to 13.2) [45]. Serious adverse events occurred in 26.7% of the IMI-REL group vs. 32.0% of the piperacillin/tazobactam group [45]. Common adverse events included anemia, elevated liver enzymes, gastrointestinal symptoms (nausea, vomiting, diarrhea), and headaches [45].

The two studies demonstrate that IMI-REL is generally well-tolerated and is a viable treatment option for gram-negative HAP/VAP, including in critically ill, high-risk patients [44,45].

Corticosteroids

The official clinical practice guideline of the American Thoracic Society (ATS) and Infectious Diseases Society of America (IDTA) for the diagnosis and treatment of CAP recommends corticosteroid treatment only for patients with CAP and refractory septic shock [46]. Corticosteroid use to decrease inflammation in patients with severe CAP has been studied for decades with conflicting results [7,12]. Corticosteroids can be used as adjuvant therapy for acute respiratory distress syndrome, though use in severe viral pneumonia is controversial due to numerous negative side effects associated with it [47]. Potentially, corticosteroids may decrease cytokines to reduce inflammation and help with inadequate adrenal response in critically ill patients [48]. Because antibiotics are largely used to treat bacteria-induced pneumonia, steroids are mainly tested for the treatment of viral-induced pneumonia. Due to the controversies surrounding corticosteroid use in treating CAP, many clinical trials have been performed to evaluate the safety and efficacy of several steroids, particularly in the treatment of SARS-CoV-2 induced pneumonia (Table 2).

	Abd-Elsalam et al. [49], 2020	Dequin et al. [50], 2020	Tomazini et al. [51], 2020	Edalatifard et al. [52], 2020
Patients	194	149	299	68
Study Design	Multicenter, randomized control	Multicenter randomized double-blind sequential	Multicenter, randomized, open-label, clinical	Single-blind, randomized control clinical
Age, yr (mean \pm SD)	40.72 \pm 19.32	62.2	61 \pm 14	58.5 \pm 16.6
Steroid	Hydroxychloroquine	Hydrocortisone	Dexamethasone	Methylprednisolone
Outcomes	Mortality	Rate of treatment failure*	Ventilator-free days	Condition improvement
Treatment Group	6.2%	42.1%	6.6%	94.1%
Control Group	5.2%	50.7%	4.0%	57.1%
Adverse Events	NR	No serious adverse events attributed	Acute MI, DVT, GI perforation, unspecified hyperglycemia, pneumothorax	Fever, dyspnea, GI symptoms, myalgia, headache, cough, weakness
Treatment Group	NR	0%	3.3%	5.8%
Control Group	NR	0%	6.1%	7.1%

*Defined as death or persistent respiratory support with mechanical ventilation or high-flow oxygen therapy
NR: not reported; **MI:** myocardial infarction; **GI:** gastrointestinal; **DVT:** deep vein thrombosis

Table 2. Comparison of Clinical Trials Studying Treatment of Pneumonia with Corticosteroids

Corticosteroid Treatment for COVID-19

In light of the COVID-19 pandemic, several clinical trials have been conducted to determine the efficacy and safety of steroids in treating SARS-CoV-2 induced pneumonia. In a multicenter randomized control study done by Abd-Elsalam et al. evaluating the safety and efficacy of hydroxychloroquine (HCQ) with standard care in patients with COVID-19, the overall mortality did not differ between the control and experimental group (6.2% patients with HCQ + standard care vs. 5.2% patients with standard care alone) [49]. Moreover, patients in the HCQ + standard care group experienced more negatives side effects (i.e. difficulty seeing and hearing, unusual bleeding, irregular heartbeat, etc.) compared to the control group [49].

Dequin et al. conducted a clinical trial on the efficacy of low-dose hydrocortisone in patients with COVID-19 induced acute respiratory failure and found that there was no significant difference in the rate of death or persistent respiratory support with mechanical ventilation or high-flow oxygen therapy between the group treated with low-dose hydrocortisone and the control group (42.1% in the treatment vs 50.7% in the control) [50].

Tomazini et al. conducted a multicenter randomized open-label clinical trial in 41 ICUs in Brazil to determine if intravenous dexamethasone could treat SAR-CoV-2 induced acute respiratory distress syndrome (ARDS) [51]. Sequential Organ Failure Assessment (SOFA) scores (range, 0-24, with higher scores indicating greater organ dysfunction) were used to evaluate the differences [51]. At 7 days, patients in the dexamethasone treatment group had a mean SOFA score of 6.1 (95% CI, 5.5 to 6.7) in comparison to a 7.5 (95% CI, 6.9 to 8.1) in the standard care group (difference, -1.16; 95% CI, -1.94 to -0.38; P = .004) [51]. However, on day 28, 21.9% in the dexamethasone group compared to the 29.1% in

the standard care group experienced secondary infections, and 3.3% vs 6.1% experienced serious adverse events [51]. This study showed that dexamethasone treatment decreases secondary infections and serious adverse events [51]. Despite its efficacy, however, it is important to note that dexamethasone is associated with many side effects, including mental depression, mood change, headache, and irregular heartbeat.

Lastly, Edalatifard et al. conducted a single-blind randomized controlled clinical trial in Iran to evaluate methylprednisolone's ability to reduce the inflammation of the respiratory system in patients with COVID-19 [52]. There was a higher incidence of improvement in the methylprednisolone treatment group than in the standard care group (94.1% vs. 57.1%) [52]. Furthermore, the mortality rate was significantly lower in the methylprednisolone group (5.9% vs. 42.9%; p < 0.001) [52]. The results of this study suggest that that methylprednisolone could be an efficient therapeutic agent.

Based on the results of the multiple clinical trials conducted, most steroids were not very effective in treating pneumonia. Although some steroids may have shown efficacy in treating pneumonia, they are also associated with many negative adverse events, prompting the ATS/IDTA to recommend against routine corticosteroid use in treating CAP and severe influenza pneumonia [46]. Given these adverse events and recommendations, several studies have been conducted evaluating the use of alternative therapies in place of corticosteroids.

Mesenchymal Stem Cell Treatments

Mesenchymal stem cells (MSCs) are adult multipotent stem cells found in bone marrow and have potent immunomodulatory properties to suppress the pro-inflammatory processes in the lungs, though its mechanism of action is not yet fully understood [53,54]. Recent studies,

however, have identified several mechanisms through which MSC treatments can promote tissue repair, including mitochondrial transfer, exosome transfer, and paracrine secretions. Mitochondrial transfer from MSCs to innate immune cells has been shown to enhance phagocytic activity [53]. Additionally, MSC paracrine activity appear to modulate immune responses and promote cell survival. MSCs secrete several factors that support survival, including growth factors, cytokines, and extracellular matrix, which theoretically can rescue injured cells to reduce tissue damage and accelerate tissue repair [54]. Subsequent release of soluble factors after MSC activation can lead to the differentiation, proliferation, and activation of immune cells including T cells, B cells, macrophages, and mast cells, inhibiting local inflammation [55,56]. Lastly, MSCs have played a role in maintaining tissue homeostasis and in modulating inflammatory disease [57]. Although the mechanisms of MSC treatments are still not yet fully understood, MSC treatments may have a specific therapeutic potential and safety profile in the treatment of pneumonia that may be used in place of corticosteroid therapies [55].

MSC treatment for bacteria-induced pneumonia

The first line of treatment for bacteria-induced pneumonia is the empiric prescription of antibiotics, while stem cell therapies are being considered as a replacement for corticosteroid treatments. Gupta et al. conducted a study using a mouse model of gram-negative pneumonia to evaluate the efficacy of MSCs [58]. MSCs could reduce lung injury and increase survival (55% in the MSC group vs. 8% in the 3T3 control and 0% in the PBS control group). Furthermore, MSCs were noted to enhance bacterial clearance in the alveolar space as early as 4 hours following administration and were still able to retain their classic immunosuppressive properties [58]. Moreover, MSCs significantly upregulated their production of lipocalin 2, an innate immune protein used

to prevent the growth and spread of microorganisms [58,59]. The same research group also conducted a study to test the effect of human MSCs derived from bone marrow on the bacterial growth of gram-negative (*E. coli* and *P. aeruginosa*) and gram-positive (*S. aureus*) bacteria and found that MSCs directly inhibited bacterial growth [59]. While Gupta et. al concluded that MSCs could be beneficial in bacteria-induced pneumonia, it has not yet been clinically tested in humans [58,59]. Clinical trials would be required to determine the efficacy and safety of MSCs in treating bacteria-induced pneumonia in humans.

MSC treatment for virus-induced pneumonia

MSCs have the potential to treat virus-induced pneumonia. Chen et al. demonstrated that MSC transplantation in treating H7N9 virus-induced acute respiratory distress syndrome (ARDS) was both safe and effective, lowering the mortality rate in the experimental group, compared with the control group (17.6% vs. 54.5%) [60]. Furthermore, 85% of patients showed significant improvement at their 3-month follow-up visit [60]. MSC transplantation also did not show any significant side effects [60]. This study suggests that MSCs significantly improved the survival rate of H7N9-induced ARDS. This evidence of the potential use MSCs in treating virus-induced pneumonia is important, as their mechanisms of action may be similar for many other different types of viral infections.

MSC treatment for SARS-CoV-2-induced pneumonia

A majority of the studies evaluating the efficacy and safety of MSCs have been performed on virus-induced pneumonia. While the efficacy and safety of MSCs in treating bacteria-induced pneumonia have not yet been determined in humans, there have been numerous clinical trials performed to test the safety and efficacy of MSCs in treating virus-induced pneumonia (Table 3).

	Meng et al. [61], 2020	Shi et al. [62], 2021	Shu et al. [63], 2020	Hashemian et al. [64], 2021
Patients	18	100	41	11
Study Design	Parallel, non-randomized, phase I control	Phase II randomized, double-blind, placebo-control	Single-center open-label, individually randomized, standard treatment-control	Phase I, two-center, open-label, single-arm
Age, yr (mean ± SD)	NR	Treatment: 60.72 ± 9.14 Control: 59.94 ± 7.79	58.78 ± 16.26	53.9 ± 10.37
Outcome	Efficacy not evaluated	Change in whole lung lesion volume	Time to clinical improvement*	Survival rate
Treatment Group	N/A	-19.4%	91.67%	6 / 11
Control Group	N/A	-7.30%	51.72%	None
Adverse Events	No serious adverse events attributed	Increased LDH, increased ALT, hypokalaemia, increased AST	No serious adverse events attributed	NR
Treatment Group	0%	55.3%	0%	NR
Control Group	0%	60.0%	0%	NR

*Clinical improvement was defined as a decline of two categories on the modified seven-category ordinal scale of clinical status or hospital discharge
NR: not reported; **LDH:** lactic acid dehydrogenase; **ALT:** alanine aminotransferase; **AST:** aspartate aminotransferase

Table 3. Comparison of Clinical Trials Studying Treatment of Pneumonia with Mesenchymal Stem Cells

Meng et al. conducted a parallel non-randomized phase I clinical trial evaluating the safety of human umbilical cord-derived mesenchymal stem cell (UC-MSCs) infusions on patients with moderate-to-severe COVID-19 pulmonary disease [61]. No serious UC-MSCs infusion-associated adverse events were observed and all patients had recovered and were

discharged, demonstrating that intravenous UC-MSCs infusions are safe [61].

Two individual clinical studies were conducted testing both the efficacy and the safety of UC-MSCs in treating COVID-19-induced pneumonia. Shi et al. demonstrated that the administration of UC-MSCs improved

whole lung lesion volume from baseline to day 28 compared to the placebo group (the median difference -13.31%, 95% CI -29.14% to 2.13%, $P = 0.080$) [62]. UC-MSCs also significantly reduced the proportions of solid component lesion volume (median difference -15.45%; 95% CI -30.82% to 0.39%; $P = 0.043$). Moreover, the incidence of adverse events was similar between the treatment group and the placebo group, indicating that UC-MSCs were not only effective, but also did not have severe side effects and were safe to use [62]. Similarly, Shu et al. found that patients in the UC-MSC had a shorter time to clinical improvement in comparison with the control group (median 9.0 days vs. 14.0 days respectively, $P = 0.006$) [63]. Furthermore, all of the patients in the treatment group had no adverse reactions (rash, allergic reaction, and febrile reaction) [63]. Both studies done by Shi et al. and Shu et al. demonstrate that the administration of UC-MSCs in the treatment of COVID-19 induced pneumonia was effective and safe.

Hashemian et al. also conducted a clinical trial to evaluate the safety, feasibility, and tolerability of the multiple infusions of high dose MSCs derived from the placenta and umbilical cord in treating COVID-19 induced pneumonia [64]. No serious adverse events were reported within 24-48 hours of cell infusions, and reduced dyspnea and increased oxygen saturation (SpO₂) levels were observed within 48-96 hours after the first infusion in 7 out of 11 patients [64]. Overall, six patients survived with significant reductions in serum levels of tumor necrosis factor- α (TNF- α ; $P < 0.01$), IL-8 ($P < 0.05$), and C-reactive protein (CRP) ($P < 0.01$) [64]. Moreover, none of these patients had complaints of dyspnea on day 60 post-infusion, and lung computed tomography (CT) scans showed remarkable signs of recovery from COVID-19 [64]. Hashemian et al. concluded that multiple infusions of high-dose allogeneic prenatal MSCs were safe and effective [64].

In summary, MSC treatments are safe and effective in treating COVID-19 induced pneumonia, making them an ideal potential replacement for corticosteroid treatments for COVID-19 patients. Recently, the FDA has given conditional approval for use of stem cell treatments on severe COVID-19 patients under “expanded access compassionate use” [61,62]. However, further clinical trials may be necessary to further the establish efficacy and safety of MSC treatments, not only in treating COVID-19 patients but also in treating other virus-induced pneumonia, especially if they are to be considered a replacement for corticosteroids.

Combined stem cell and antibiotic treatments

Because both MSCs and novel antibiotics are promising therapies for the treatment of pneumonia respectively, a few studies have been conducted to determine the efficacy and safety of combined stem cell and antibiotic treatments.

Kong et al. conducted a study testing the combined treatment of antibiotic linezolid and human MSCs (hUMSCs) on a rabbit model with MRSA-infected pneumonia [65]. Linezolid monotherapy (50 mg/kg for two times/day) resulted in improvement of body weight, chest imaging, bronchoscopic manifestations, histological parameters, and IL-10 concentration in plasma ($P < 0.01$), decreasing pulmonary auscultation, and reduction of IL-8, IL-6, CRP, and TNF- α concentrations in plasma ($P < 0.01$) when compared with the pneumonia model group at 48 and 168 hrs [65]. Coadministration of linezolid and hUMSCs (1×10^6 /kg for two times at 6 and 72 hrs. after MRSA instillation) and further increased the body weight ($P < 0.05$) and significant reduction of lung inflammation on CT scans [65].

Combination treatment with both stem cells and linezolid showed significantly improved therapeutic effects in comparison to linezolid treatment alone [65]. Further clinical trials, however, are needed to show that this combination treatment is also effective and safe in treating pneumonia in humans.

MSC availability, costs, and regulation

Although MSCs can be isolated from a variety of sources, like bone marrow, adipose tissue, umbilical cord, dental pulp stem cells, and endometrial MSCs, the availability of MSCs for the treatment of disease is still very low [66]. The eligibility requirements to donate MSCs are limited based on gender, BMI, donor site, age, and diseases [66]. Furthermore, the isolation procedures of MSCs are also very challenging. Even after successful isolation, the number of cells from the primary culture is often insufficient for clinical application, requiring cell expansion [66]. Due to the challenging manufacturing processes and limited availability of MSCs, the current cost of MSCs is quite expensive, varying from \$15,000 to \$30,000 per 1–5 million cGMP-MSCs per kilogram [66]. Improvements in cell expansion technologies to make MSC treatments more readily available and cost-effective need to continue to develop for MSC treatments to become a viable treatment option for pneumonia [67].

Conclusions

Pneumonia continues to remain an important infection due to its impact on patient outcomes, especially amongst young children, the elderly, and immunocompromised patients. The availability of new antibiotics offers an opportunity for the treatment of antibiotic-resistant pathogens associated with both CAP and HAP. These new drugs have a broad spectrum of activity against pathogens, including multidrug-resistant strains that pose a major threat to clinical practice given the limited therapeutic options. Moreover, in addition to having similar safety and efficacy profiles as older drugs, several of these newer drugs have structural characteristics that allow for a decreased propensity in the development of bacterial resistance.

In addition to novel antibiotics, the potential use of stem cell therapies in place of corticosteroid treatments may offer an improvement in patient outcomes. Novel stem cell therapies, especially human UC-MSCs, showed efficacy and safety on COVID-19 induced pneumonia. However, further research and clinical trials are needed to demonstrate the efficacy and safety of UC-MSCs in the treatment of other virus-induced pneumonia beyond COVID-19.

The combined treatment of both stem cells and antibiotics in pneumonia in a rabbit model showed significantly increased efficacy in comparison to antibiotic treatment alone, presenting a possible route for a novel strategy in treating pneumonia, though additional future studies are necessary before clinical implementation.

While pneumonia remains a major disease of concern, having newer approved antibiotics as well as novel therapies such as stem cell treatments in the pipeline offers clinicians more options to effectively treat pneumonia.

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