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Review Article

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Understanding nSARS-CoV-2 and Pneumonia Co-infection-Review

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ABSTRACT

The world is living on the brink.COVID-19, an exciting, outstanding pandemic co-infected with bacterial pneumonia, which demands crucial Public Health Intervention. Covid pandemic created significant economic, social, and medical ambiguity. COVID-19 pneumonia is a severe illness and life-threatening. Coronavirus damages the cells and tissue that line the air sacs of the lungs. The walls of the sacs are thickened and obstruct the diffusion of gases. Bacterial pneumonia is the sixth leading cause of death in the US. Pneumonia can be caused by multifarious bacteria, viruses and fungi in the air we breathe. Bacterial pneumonia disturbs a part, or lobe, of a lung. This condition is described as lobar pneumonia

Key-words: *Pneumococcal pneumonia, Klebsiella pneumonia, Hemophilus influenza, Staphylococcal pneumonia, Atypical pneumonia, legionella pneumonia, Mycoplasma pneumoniae, Chlamydia psittaci*, G-CSF (Granulocyte colony-stimulating factor), TNF (Tumor necrosis factor).

INTRODUCTION

Prolonged mechanical ventilation may expose COVID-19 patients to a higher risk of super pulmonary infection. *A. baumannii* and *S. aureus* co-infection of the respiratory tract in COVID-19 patients admitted to ICU were observed. The nasal microbiome of COVID 19 patients possesses Acinetobacter, and Pseudomonas [1].

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pathogens that cause health care and ventilator-associated pneumonia, including non-fermenting and fermenting gram-negative bacteria (most notably, *A. baumannii*, *P. aeruginosa*, *K. pneumoniae*, *E. coli*, *S. maltophila*) and *S. aureus* [2,3].

Respiratory distress syndrome is complicated by cardiopulmonary and organ failure. Study that sought etiologic agents of infection largely identified nosocomial Postmortem cultures of tissues are susceptible to microbial contamination. Bacterial co-pathogens are commonly identified in viral respiratory tract infections. Bacterial co-infection in patients with severe influenza has been reported with greater severity of illness [4].

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History- Edwin Klebs observed bacteria in the airways of pneumonia patients. The Greek word pneumo meaning is "lung". The symptoms were described by Hippocrates. *S. pneumoniae* and *K. pneumoniae*, was executed by Ehsan *et al.* [4] and Nicholas *et al.* [5]. Langford *et al.* [6] demonstrated pneumonia as an opportunistic bacteria present in the lung. Sir William Osler, described pneumonia as the "captain of the men of death" in 1918, pneumonia had overtaken tuberculosis as one of the leading causes of death.

Pneumonia- Inflammation of lung parenchyma with the accumulation of exudates inflammatory cells and fibrin within the alveolar spaces or alveolar septa. It is characterized by consolidation of the affected part of the lung [7]. Respiratory diseases are caused by several infectious agents including *Streptococcal pneumonia, S. pyogenes, K. pneumonia, H. influenzae, L. pneumophila*, *M. pneumonia, Coxiella burnetii,* and *C. psittaci*. These microbes enter the lungs and cause primary cases of pneumonia [8,9].

Lower respiratory tract microbes- Amniotic fluid filling fetal lungs prenatally was considered sterile. Detectable microbial communities in multiple body sites have been identified in newborns [10]. This premature microbiome has been shown to change design and diversity and mature functionally during the first two to three years of life. Bacterial lung infections are usually categorized as acute or chronic depending upon the rate at which they evolve, but more likely related to the quality they resolve after antibiotic therapy [11]. This approach applies to chronic obstructive pulmonary disease (COPD), where routine culturing is not recommended. Bacterial infections periodically appear in patients with prolonged hospitalization, and *P. aeruginosa*, *Klebsiella* sp., and *S. aureus* were common pathogens [12]. Bacterial co-pathogens are frequently diagnosed in viral respiratory infections and are important causes of morbidity and mortality. Bacterial coinfections occur in less than 5% of patients who are hospitalized with COVID-19 and are usually caused by *S. aureus*, *S. pneumoniae*, and *H. Influenzae* [13,14]. Nosocomial infections are common among patients with prolonged hospitalization for COVID-19, and *P. aeruginosa, Klebsiella* sp. most commonly cause hospital-acquired pneumonia, and *S. aureus* [15].

Klebsiella pneumonia- *K. pneumonia* is a rare disease with high mortality. The cardinal hvKp virulence genes *rmpA*, *rmpA2*, *iroBCDN*, *iucABCD*, and *peg-344*, which have been recognized as molecular markers for the identification of hvKp that carry a high risk for disseminated and fatal infections [16,17].

Streptococcus pneumonia- *S. pneumoniae* is the first cause of community-acquired pneumonia (CAP) *S. pneumoniae*, K. pneumoniae and *H. influenza* were the most common bacterial co-infections. Bacterial co-infections were dominant in all COVID-19 patients; *S. pneumoniae* was the most common, followed by *K. pneumoniae* and *H. Influenzae* [18]. Bacteria are the most common cause of CAP Invasive Pneumococcal Disease/ COVID-19 confections do not support current recommendations for any of the available pneumococcal vaccines during the COVID-19 pandemic Senior citizens, who had received a 13-valent pneumococcal conjugate vaccine (PCV13) have a lower incidence of COVID-19 deaths [19-21].

Mechanism- After entry into the lungs, bacteria may invade the spaces between cells and between alveoli, where the macrophages and neutrophils inactivate the bacteria [22]. The neutrophils release cytokines and activate the immune system. Finally produce fever, chills, and fatigue similar to bacterial pneumonia [23]. Consolidation on chest X-rays appears as a result of neutrophils, bacteria, and fluid from surrounding blood vessels [24].

Clinical Situation- Co-infections in CAP and hospital-acquired pneumonia (HAP)- Lower respiratory tract infections are major causes of morbidity and mortality and are frequently caused by co-infecting pathogens. Identification of the causative agent and encouragement for vaccination promotes infection [25]. MRSA can be initiated if patients have necrotizing pneumonia, acute respiratory distress. Antimicrobial resistance is increasing because of the overuse and misuse of antibiotics [26]. COVID-19 pandemic is associated with the higher use of antibiotics which in turn lead to antibiotic resistance

Diagnosis of Lower respiratory tract Bacterial infection

Diagnosis of Covid-19 and bacterial confection- The use of diagnostics became an integral part of modern medicine and involves molecular biology and cutting edge bioengineering as well. Stem cells can remain alive

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in human corpses at least 17 days after death, researchers say [27,28]. Gene therapy is viable, available and reliable.

Mucus- The microbiological examination is a practical way for diagnosis, especially sputum culture, However, taking sputum or blood samples from SARS-CoV-2–infected patients may pose a significant risk to biological sample collectors and laboratory technicians as the SARS-CoV-2 does not only spread through respiratory droplets and direct contact but also virus-laden aerosols RT-PCR as a primary diagnostic procedure for detecting SARS-CoV-2 [29,30]. Mucus is the oil in the engine. Without mucous the engine seizes. The immune system sends white blood cells in the nose to fight for infection. They contain a greenish enzyme that sheds the substance yellow or green:

i. White- Viral infection
ii. Rust red- *Pneumococcal*
iii. Full red- TB
iv. Bright red- Pulmonary embolism
v. Dark red currant Jelly with blood and mucus- *Klebsiella*

RT-PCR as a Frontline Diagnostic Method for COVID-19 Diagnosis- For the diagnosis of COVID-19 and bacterial coinfection of this disease, standardized testing of coinfection is still unavailable. Serological based diagnosis can detect different serum antibodies like IgG, IgM, and IgA in an infected patient.PCR based diagnostic procedures are reliable, not cost-effective tests, rapid, and sensitive with accuracy [1,32]. Predominantly identified co-pathogens of SARS-CoV-2 are bacteria such as S*. pneumoniae, S. aureus, K. pneumoniae, H. influenzae, M. pneumoniae, A. baumannii, L. pneumophila* and *C. pneumoniae* followed by viruses including influenza, coronavirus, rhinovirus/enterovirus, parainfluenza, metapneumovirus, influenza B virus, and human immunodeficiency virus [33,34].

Recent advances- The gene Xisco gene was recently described as a biomarker for PCR based detection of *S. pneumonia* due to low cost and relatively short testing time. EIA serological assays are the most common method of *M. pneumoniae* detection is used in the patient [35].

Breakthrough the treatment- There are currently only a few treatment options available for multidrug-resistant bacteria and the need to develop new antimicrobial therapies to treat co-infections [36]. An early study of antibiotic therapy in critically ill patients with CAP showed a significant reduction in mortality when macrolide was used as part of the treatment [37]. Macrolide therapy has additional benefits such as anti-inflammatory effects and immunomodulatory effects. Combination therapy of beta-lactam and a macrolide is used in hospitalized and severely ill patients with CAP [38].

1- Macrolide should be given before the initiation of beta-lactam therapy.
2- Antibiotic therapy should start as soon as possible after the confirmation of CAP.
3- Fluoroquinolone should be carefully considered to be given to patients in areas with endemic tuberculosis. Areas with endemic Tuberculosis prefer macrolides such as clarithromycin/azithromycin over quinolone/doxycycline as initial empiric therapy in patients with CAP.
4- Once the results of the microbiological testing become available, we can then tailor the appropriate treatment to the findings.

The most promising adjunctive treaty-mentoring appears to be corticosteroids; which in multiple RCTs have shown a significant reduction of morbidity, but not mortality for patients with non-complicated CAP [39,40]. There has been a bit of a debate about hyperglycemia, the side effects of the corticosteroid therapy, and the harm that did not outweigh the benefits [41-43]. Antibiotics for acute exacerbation in patients with chronic pulmonary disease are recommended in two scenarios: firsts to treat an infection associated with an acute exacerbation of COPD and second for prophylaxis. The initial choice should be amoxicillin or amoxicillin-clavulanate, where beta-lactamase production by the H. Influenzae is prevalent or the use of fluoroquinolone. Other medications to consider are cephalosporins cefuroxime or cefpodoxime; macrolide; piperacillin-tazobactam, cefepime, or ciprofloxacin for pseudomonas or other more-resistant organisms [44,45]. Also, there is antibiotic therapy for COPD patients to reduce exacerbation like inhaled corticosteroids, anti-muscarinic agents (long-action), and Phosphodiesterase 4 inhibitors [46,49].

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Title 1: Treatment of choice for typical and atypical Pneumonia

Typical and Atypical pneumonia	Causative Organisms	Treatment of choice - antimicrobials
Typical pneumonia	*H. influenzae*	Intravenous third-generation cephalosporin until antibiotic sensitivities becomes available of intramuscular ceftriaxone when IV administration is not available.
	S. aureus	Combination therapy with penicillinase-resistant penicillin or cephalosporin (in case the organism is methicillin-sensitive *S. aureus* [MSSA]) and clindamycin or fluoroquinolone.
	K. pneumonia	Third-generation cephalosporins, carbapenems, aminoglycosides, and quinolones.
	L. pneumophila	The treatment should have high intracellular concentrations like macrolide, quinolones, ketolides, tetracyclines, and rifampins.
Atypical pneumonias	*M. pneumonia*	The drugs of choice are either azithromycin or clindamycin.
	C. pneumoniae	Tetracyclines and macrolide are the drugs of choice.
	C. psittaci	Tetracycline or doxycycline is the drug of choice. Azithromycin should be considered as the second line of defence.

Haemophilus influenza: Intravenous third-generation cephalosporin until antibiotic sensitivities becomes available of intramuscular ceftriaxone S. *aureus*: combination therapy with penicillinase-resistant penicillin or cephalosporin (and clindamycin a fluoroquinolone [47]. *K. pneumoniae*: Third-generation cephalosporins, carbapenems, aminoglycosides, and quinolones *L. pneumophila*: the treatment should have high intracellular concentrations like macrolide, quinolones, ketolides, tetracyclines, and rifampin [48].

Cytokine storm- COVID-19 patients had prominent pro-inflammatory cytokines and chemokines, indicating a cytokine storm. Serum ferritin blood test identifies a cytokine storm. The FDA approved the interleukin-6 receptor antagonist and its effectiveness on COVID-19 [53] Tocilizumab increase serum IL-6 levels across the blood-brain barrier Lenzilumab increase GM-CSF secreting T cells in hospitalized patients with COVID-19 [49-51].

Why is the problem significant in research?- With the outbreak of COVID-19, the world is facing provocation in our lifetime. Apart from adverse health, COVID-19 affected people's social, psychological, and economic loss [52].

Research program for the next generation world- Chest CT scans can provide lung consolidation in COVID-19-positive patients. It helps to enable them to provide care management. Chest CT scans can pinpoint which patients could die in the hospital from the virus [53]. The use of radiation therapy evaluates the impact of the amount of lung involvement. The scan and the therapy help in assessing the risk of in-hospital mortality and percentage of lung involvement by consolidations [54].

Present key findings concerning central research questions- The mechanisms of fatal co-infections are complex. Impaired mucociliary clearance, and host immune responses caused by the virus, promotes bacterial growth. Primary pneumonia caused by *S. pneumoniae* is the most common type of primary pneumonia [55]. Other bacteria which may cause primary pneumonia include *S. pyogenes, S. pyogenes, K. pneumonia, H. influenzae, L. pneumophila* and small bacteria such as *M. pneumonia, C. burnetii, C. psittaci.* Anaerobic organisms include *A. israeli,* are rare causes of primary pneumonia [56]. In secondary pneumonia, *H. influenzae* and some types of *S. pneumoniae* and certain of the bacteria forming the flora of the upper respiratory tract and mouth are the organisms most frequently cultured from sputum [57].

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Research on the development of Lower respiratory tract microbes- The use of antibiotics has increased presently underway SARS-Cov-2 pandemic, increases the risk for resistance to antibiotics [58].

Perspectives on potential future new research work- It is time to generate viable, reliable, cheap, more accessible testing for SARS-CoV-2. A brisk way of developing to identify antibodies that neutralize the virus. More than 100 different vaccines for SARS-CoV-2 are at various stages of development has initiated. The substantial challenge is to determine which vaccine is perfect. There is an immediate need to evaluate evidence in deciding how to treat patients [59]. A combination of drugs that work well should be analysed. Vicky *et al.* [60] has generated hope. It may prove to be a magic bullet. Patients with diseases like cancer, diabetes, renal failure, CAD and pregnant women need special awareness.

Delays have dangerous ends- We are living under the microbial world. Pollution is one foot in the grave. It is green around the gills. The pathogens through polluted air cause respiratory diseases and kill at least nine million people and costs trillions of dollars every year [61]. There is continuous emergence of new and complex infectious pathogens and hence and hence early diagnosis provides ease in disease management recently use of nanotechnology, enzyme-based diagnostics became popular and shown satisfactory results.

CONCLUSIONS

In December 2019 in Wuhan, China the outbreak of nSARS-CoV2 had resulted in a global pandemic and still underway. The virus primarily infects respiratory epithelial cells via ACE2 receptor and internalized them. It has been demonstrated through several findings high viral titer trigger a massive immune response as "cytokine storm" is responsible for the collapse of the respiratory system. There has been an emphasis since the beginning that other respiratory pathogen/s may participate in co-infection. Pneumonia caused by a virus and or a bacteria (*P. pneumonia)* affect respiratory physiology via immune invasion. The nSARS-CoV2 as a virus and *P. pneumonia* as bacteria both are respiratory pathogens and hence a higher percentage in co-infection. It has been previously reported that Flu and influenza pose an additive effect during co-infection as infected cells/tissue remain associated with impaired immunity.

In the case of nSARS-CoV2 a massive immune response due to the release of inflammatory mediators weakens host immunity and hence *P. pneumonia* finds an appropriate habitat to colonize and grow.

CONTRIBUTION OF AUTHORS

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