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POST COVID PNEUMONIA: MODERN THERAPEUTIC APPROACH BY PULMONARY DRUG DELIVERY DEVICE

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AUTHORS' CONTRIBUTIONS

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Review Article

ABSTRACT

Streptococcus pneumonia (also known as pneumococcal) is a commensal that colonizes the upper respiratory tract and a pathogen that causes intrusive illnesses like otitis media, pneumonia, sepsis, and meningitis. In India, the Invasive Bacterial Infection Surveillance (IBIS) organization and South Asian Pneumococcal Alliance (SAPNA) have been associated with assortment of significant information in regards to serotype dissemination and antimicrobial obstruction of pneumococcal diseases for over 12 years. COVID 19 Patients are much more prone towards this infection, if untreated at appropriate time. So development of New Device are immense Important which contributes rapid and Proper Drug Delivery to lungs. Research must be carried out in the field of Novel Drug Delivery System for target delivery of Drugs like Antibiotic, Bronchodiator and Corticosteroid to Respiratory Tract. The present Review article focus Different grade of Pneumococcal Infection and Infection associated with Post COVID Condition. The article also highlights new devices which helpful for Pulmonary drug delivery which is vital during COVID Associated Pneumococcal Infection.

Keywords: Pneumonia; antimicrobial; corticosteroid; pathogenesis; pulmonary drug delivery.

1. INTRODUCTION

Streptococcus pneumonia (also known as pneumococcus) is a commensal that colonizes the upper respiratory tract and a pathogen that causes intrusive illnesses like otitis media, pneumonia, sepsis, and meningitis [1]. Pneumococcus is a lancet-shaped, gram-positive bacterium originally isolated in 1881 [2] with 100 distinct serotypes [3]. Pneumococcal infection can be divided into three stages: transmission, colonization, and invasion [4] [Fig. 1].

Streptococcus pneumoniae colonizes the mucosa of the upper respiratory tract (URT). This carriage is the essential for both transmission to others and intrusive disease in the carrier. Carriers can shed S. pneumoniae in nasal secretions and subsequently send the bacterium. Scattering past its specialty along the nasal epithelium, either by aspiration, bacteraemia or local spread, can prompt invasive diseases, like pneumonia, meningitis and otitis media [5].

These contaminations are especially normal in younger children and in older adults and might be partitioned comprehensively into invasive (i.e. bacteremic) and non-invasive disease; the previous alludes to diseases in which the microorganism is disengaged from ordinary sterile body destinations, like the blood or the cerebrospinal fluid [6].

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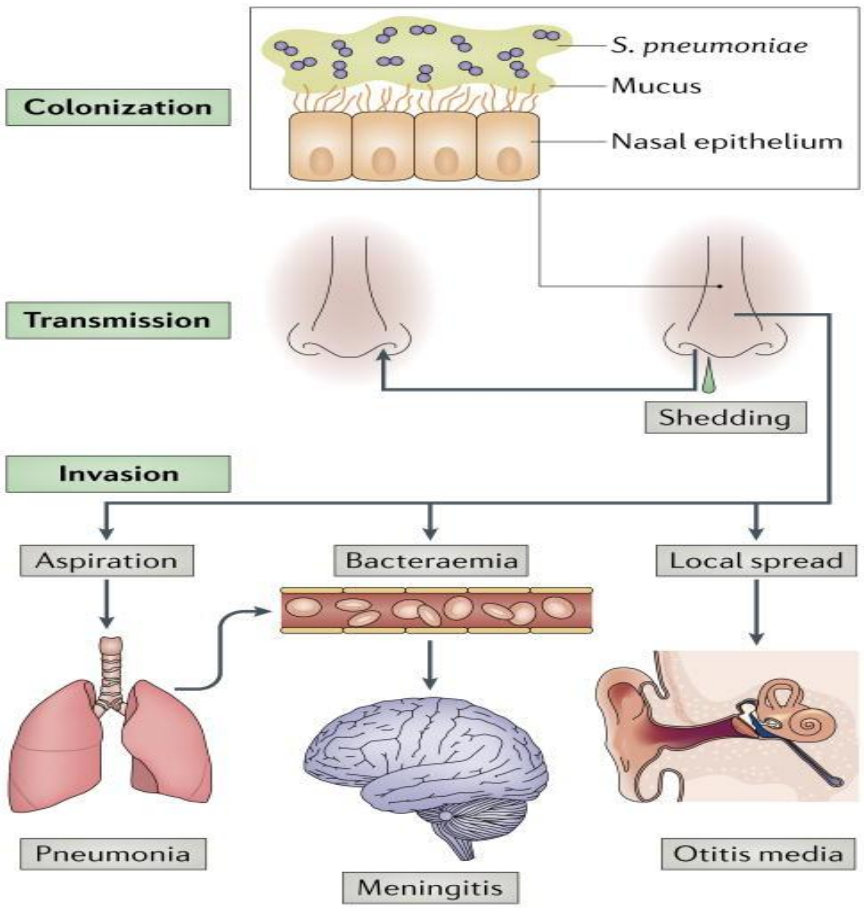

Fig. 1. The life cycle of *Streptococcus pneumoniae* and the pathogenesis of pneumococcal disease

2. THE BURDEN OF PNEUMOCOCCAL DISEASE

Despite progresses in therapeutics and antibodies, the world continues to experience a high burden of the infection, especially in the frail masses which fuse little youths more seasoned grown-ups, and immunocompromised people . In 2017, the World Health Organization published a rundown of antibiotic-resistant "priority pathogens" which included penicillin-nonsusceptible pneumococcus as one of the 12 groups of microorganisms that represent the best danger to human health [7].

Multidrug resistance, (resistance from more than any three antimicrobial specialists of various classes), was seen in 59.3% of disengages from Asian countries [8]. As the issue of pneumococcal protection from anti-microbials declines, the viability of immunizations turns out to be much more important [9].

At present accessible pneumococcal antibodies incorporate the 23-valent pneumococcal polysaccharide immunization (PPSV23) and the 10-valent or 13-valent pneumococcal protein-form immunization (PCV10, PCV13) which supplanted the PCV7. These three immunizations, particularly the PCV, have signifificantly diminished the occurrence of invasive pneumococcal disease, and pneumococcal pneumonia [10,11,12] .

3. CORONA VIRUS DISEASE 2019 (COVID19)

Corona virus disease 2019 (COVID-19) is an infectious disease caused by severe acute respiratory syndrome corona virus 2 (SARS-CoV-2). The illness was first recognized in December 2019 in Wuhan, the capital of China's Hubei territory, and has since spread worldwide, bringing about the continuous 2019-21 Covid pandemic [13]. Corona viruses (CoVs), are enveloped, non-segmented, positive-sense RNA viruses. They are described by club-like spikes that venture from their surface .

The strategy of replication of corona viruses involves a nested set of messenger RNAs with common polyadenylated 30 ends. Only the unique portion of

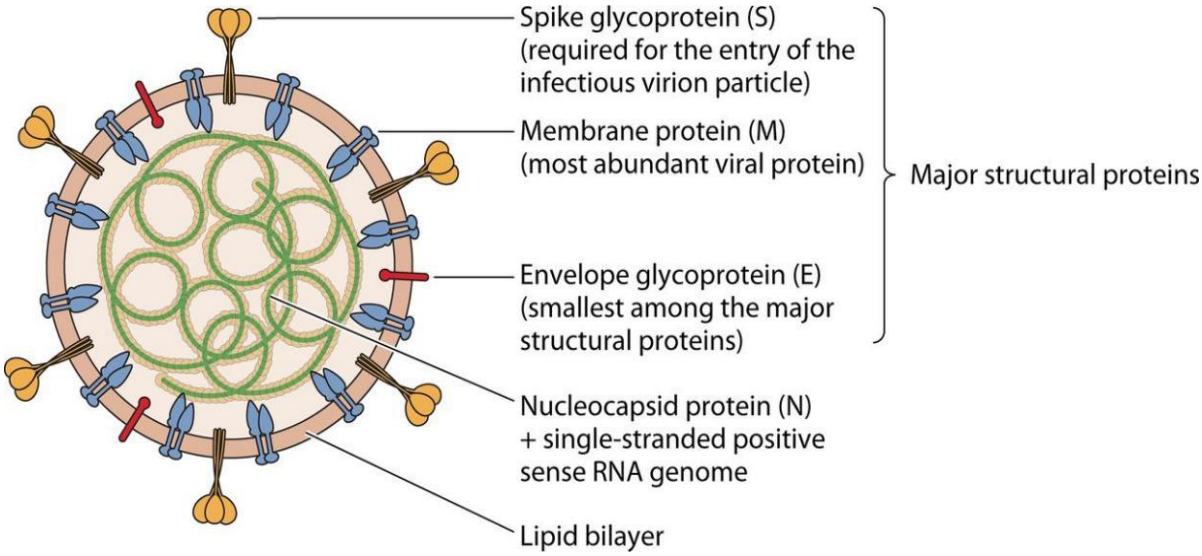

Fig. 2. SARS-CoV-2 virus structure

the 50 end is translated. Mutations are common in nature. In addition, corona viruses are capable of genetic recombination if 2 viruses infect the same cell at the same time [14]. The name corona virus springs from Latin, corona, meaning crown or wreath. Due to characteristic appearance of virions by electron microscopy on the surface of the virus [15] [Fig. 2].

SARS-CoV-2 is genetically similar to other corona viruses in the subgenus Sarbecovirus, a clade of beta corona viruses formed by the corona virus that causes SARS (SARS-CoV) and other SARS-CoV-like corona viruses found in bats. Recombination between corona viruses are common, and SARS-CoV is believed to be a recombinant between bat sarbecorviruses. Interestingly, the whole genome of SARS-CoV-2 is highly similar to that of a bat corona virus detected in 2013 (>96% sequence identity), which suggests that the immediate ancestor of SARS-CoV-2 has been circulating in bats for a minimum of several years.

ACE2 has been identified as a functional receptor for corona viruses, including SARS-CoV and SARS-CoV-2 to enter the cells, the same receptor facilitating SARS-CoV to infect the airway epithelium and alveolar type 2 (AT2) pneumocytes, pulmonary cells that synthesize pulmonary surfactant [16,17]. In general, the spike protein of coronavirus is split into the S1 and S2 domain, within which S1 is liable for receptor binding and S2 domain is liable for cell membrane fusion [18]. Viral S protein priming then requires S protein cleavage of S1 from S2 (and at another S2' site) by the host cell serine protease TMPRSS2. The viral S2 subunit then drives fusion of the viral and host cell membranes [16]. Additionally, cytokine storm triggered by an imbalanced response by type 1 and kind 2 T helper cells and respiratory dysfunction and hypoxemia caused by COVID-19 may end up in damage to myocardial cells [19].

4. COVID-19–RELATED COMPLICATIONS IN NERVOUS SYSTEM

Coronavirus essentially shows with fever, dry cough and weariness. Not many patients have side effects of a stodgy or runny nose, migraine, myalgia, and looseness of the bowels. The vast majority of the basically sick patients foster dyspnea or hypoxia multi week after the beginning of ailment. With quick movement of the disease, acute respiratory distress syndrome (ARDS), septic shock, and metabolic acidosis can develop [20]. Recently, Zhang et al. were the primary to prove that SARS-CoV-2 could directly infect induced pluripotent stem cells–derived human neural progenitor cells, and extensive viral replication and viral particles were detected within the neurospheres and brain organoids with SARS-CoV-2 infection. Additionally, they showed that SARS-CoV-2 could productively infect the human brain [21]. A review case series showed that the neurological side effects incorporate central nervous system (CNS) manifestations or illnesses (migraine, wooziness, disabled cognizance, ataxia, intense cerebrovascular sickness, and epilepsy), peripheral nervous system (PNS) symptoms (hyposmia, hypogeusia, hypopsia, and neuralgia), and skeletal muscle side effects [22] [Fig. 3].

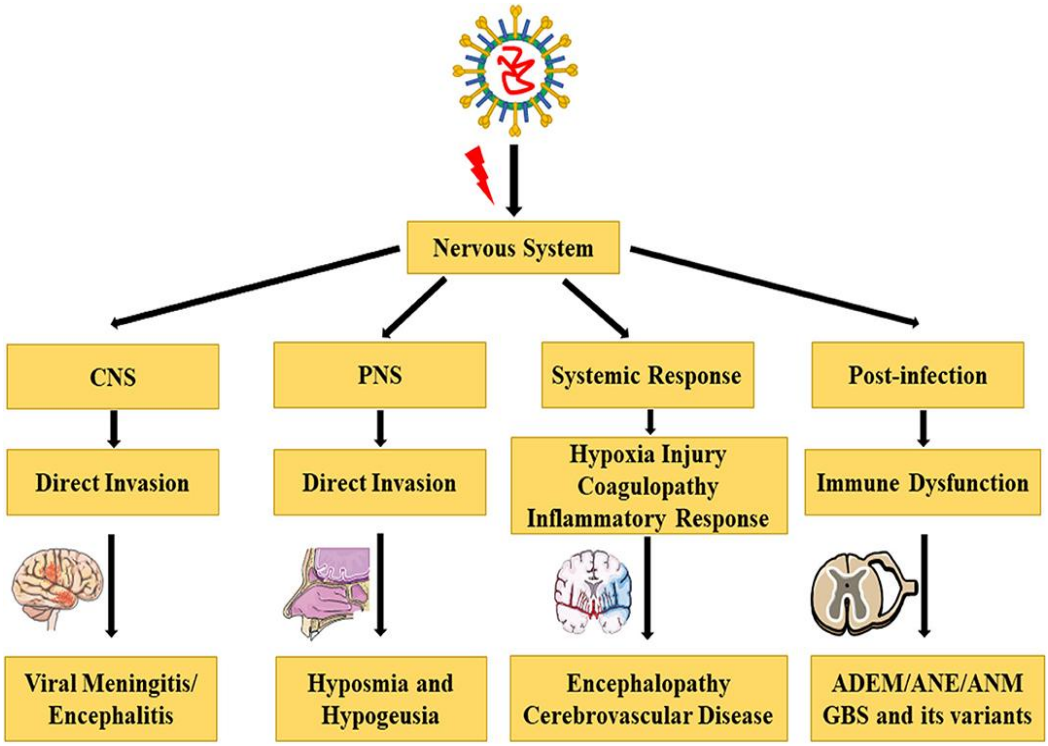

Fig. 3. Complications and pathophysiology of COVID-19 in the nervous system [The illustrations are provided by Servier Medical Art (https://smart.servier.com/) licensed under a Creative Commons Attribution 3.0 Unported License

5. SARS-CoV-2-INDUCED PNEUMONIA

Coronavirus is principally viewed as a viral respiratory ailment as its causative specialist, SARS-CoV-2, overwhelmingly focuses on the respiratory framework.

The pathogenesis of SARS-CoV-2 prompted pneumonia is best clarified by two phases, an early and a late stage. The beginning stage is portrayed by viral replication bringing about direct infection interceded tissue harm, which is trailed by a late stage when the tainted host cells trigger an immune respone with the enrollment of T lymphocytes, monocytes, and neutrophil enlistment which discharges cytokines, for example, tumor necrosis factor-α (TNF α), granulocyte-macrophage colony-stimulating factor (GM-CSF), interleukin-1 (IL-1), interleukin-6 (IL-6),), IL-1β, IL-8, IL-12 and interferon (IFN)-γ. In extreme COVID-19, the the immune system's overactivation brings about a 'cytokine storm' portrayed by the arrival of undeniable degrees of cytokines, particularly IL-6 and TNF-α, into the dissemination, causing a local and systemic inflammatory response [23,24]. The expanded vascular penetrability and resulting improvement of pulmonary edema in patients with extreme COVID-19 are clarified by numerous systems, which incorporates:

1. Endotheliitis because of direct viral injury and perivascular aggravation prompting microvascular and microthrombi deposition
2. Dysregulation of the RAAS because of increased binding of the virus to the ACE2 receptors and
3. Activation of the kallikrein-bradykinin pathway, the enactment of which improves vascular penetrability,
4. Improved epithelial cell contraction causing expanding of cells and unsettling influence of intercellular junctions [25,26,27] .

Other than IL-6 and TNF-α, restricting of SARS-CoV-2 to the Toll-Like Receptor (TLR) prompts the arrival of pro-IL-1β, which is separated into the dynamic develop IL-1β that intercedes lung inflammation, until fibrosis [28].

6. COVID-19 PNEUMONIA IMAGING

In typical cases of COVID-19 pneumonia, the chest X-ray (CXR) shows multiple bilateral peripheral opacities [Fig. 4B-F].

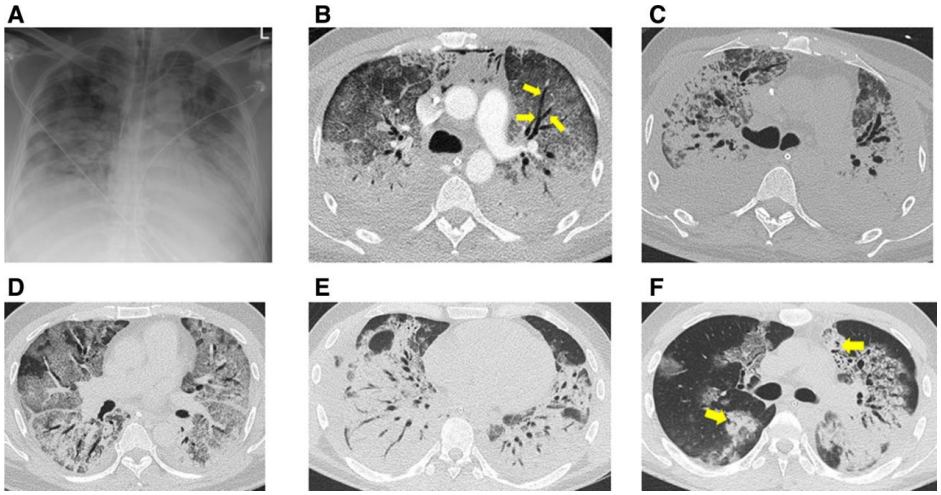

Fig. 4. (A) Plain chest radiograph in a male patient with COVID-19 pneumonia referred for extracorporeal membrane oxygenation support. (B) CT images showing broadly symmetrical air space opacification with dependent dense parenchymal opacification and extensive ground-glass opacification with thickened interlobular and intralobular septa (the 'crazy-paving' pattern) in the non-dependent lung. Note that the airways are conspicuous against the ground-glass opacification but, importantly, taper normally (arrows) and have smooth walls. (C) CT performed 10 days later again showing widespread air space opacification but now with 'varicose' dilatation (non-tapering) of airways in the left upper lobe indicative of developing pulmonary fibrosis. (D) Classical 'crazy-paving' appearance in COVID-19. There is patchy but very extensive ground-glass opacification with superimposed fine thickening of interlobular and intralobular septa throughout both lungs. Relatively limited dense parenchymal opacification is present in the dependent lung bilaterally, likely to reflect variable combinations of the consolidated and atelectatic lung. (E) A patient with COVID- 19-related acute respiratory distress syndrome (ARDS) with image section though the lower zones showing characteristic findings of ARDS with symmetrical air space opacification but with a gradient of increasing density from the ventral to the dorsal lung. (F) Image just below the carina demonstrating foci of non-dependent consolidation (arrows), conceivably denoting areas of organising pneumonia

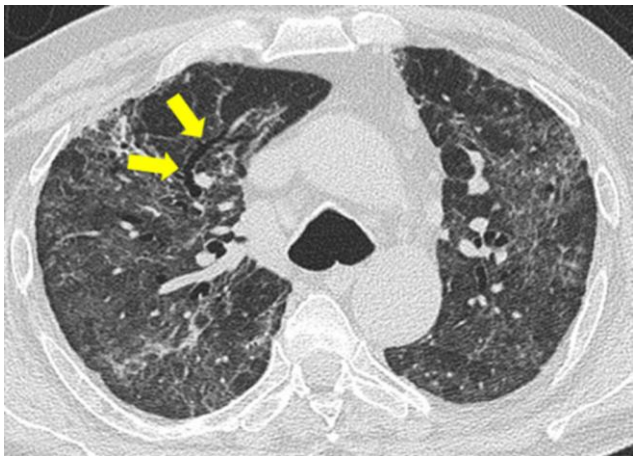

Fig. 5. CT in COVID-19 extubated survivor: a studyperformed during recovery (26 days after onset of COVID-19 pneumonia). Image section at the level of the carina demonstrating widespread groundglass opacification and considerable architectural distortion. There is definite CT evidence of fibrosis—note the varicose dilatation ('traction bronchiectasis') of the anterior segmental bronchus in the right upper lobe (arrows)

In certain patients, the morphological example of lung infection on CT check with districts of ground-glass opacification and union, which dynamically contain foci of oedema, sorting out pneumonia and diffuse

alveolar harm, are not very far taken out from those in patients with an intense inflammatory pneumonitis[Fig:- 4B-F] .

The radiological changes in COVID-19 pneumonia do not appear to resolve fully in all patients and in some, inflammation matures to form residual pulmonary fibrosis [Fig. 5][29]

7. PULMONARY DRUG DELIVERY SYSTEM

Pulmonary delivery of medicines has become a attractive target and of tremendous scientific and biomedical interest within the medical services research area because the lung is capable of absorbing medications either for local deposition or for systemic delivery [30]. The pulmonary route for local and systemic drug delivery is continually being examined to target medications to specific lung cells and for the non-parenteral systemic delivery of macromolecular medications [31]

Pulmonary drug delivery may be a creating innovation where medicine is breathed in or inhaled through the lungs and enters the circulation system through the alveolar epithelium. Pulmonary drug delivery gives a noninvasive, elective strategy to subcutaneous injection, and furthermore intravenous injection [32]. The respiratory epithelial cells play an important role in the regulation of airway tone and the production of airway lining fluid [33].

8. TRANSEPITHELIAL TRANSPORT OF DRUGS

The human respiratory system is a complex organ, where the lung is composed of more than 40 different cells. The airway is further divided into the nasal cavity, and associated sinuses, and the nasopharynx, oropharynx, larynx, trachea, bronchi, and bronchioles. The transepithelial transport of medicines along the respiratory epithelium from these two regions is described by large quantitative differences. The medication transport in the upper airways is limited due to smaller surface areas and lower regional blood flow. this region possesses a high filtering capacity and eliminates up to 90% of conveyed drug particles. inhaled substances deposit on the mucus layer, which coats the walls of the conducting airways. Mucus forms a gel like film consisting of mucin as a major component which is secreted by goblet and submucosal gland cells [30]. Lung will be free from foreign particle by ciliated cells which cause propulsion of mucus upward and out of the lung [33]. In contrast, the smaller airway and alveolar space represents 95% of the lung's surface region and is directly associated with the systemic circulation via the pulmonary circulation. Aside from this, the morphology of the most alveolar epithelial cells, the pulmonary blood-gas barrier system, and size of pores and tight junction depth of alveolar and endothelial cells are presumably reasons that govern the transepithelial drug transport [34].

9. MECHANISMS AND WAYS OF PULMONARY DRUG ADMINATRA-TION

The systemic absorption of a broad range of therapeutic agents after the pulmonary application has been demonstrated in animals also as humans. the medications are often administered by two primary modes through pulmonary routes: first, intranasal administration, which has an anatomical limitation, like narrower airway lumen, second, oral inhalation administration, Oral inhalation administration can further be classified as intratracheal instillation and intratracheal inhalation. By oral inhalation administration, obviously better results can be anticipated as it permits to the administration of very small particles with a concentration loss of only 20% in comparison with 85% by nasal route.

In the intratracheal instillation, through a special syringe, alittle amount of drug solution or dispersion is delivered into the lungs that provide a fast and quantifiable method for medication delivery to the lungs [30].

In preclinical animal studies, the intratracheal installation has frequently been used to assess the pulmonary absorption and systemic bioavailability, particularly as to the exact dosing and effectiveness associated with this method [35]. The medications (drugs) can be deposited by the aerosol system in the pulmonary airway takes place by three mechanisms i.e gravitational sedimentation, inertial impaction, and diffusion.

10. APPROACHES IN PULMONARY DRUG DELIVERY SYSTEM

Targeted drug delivery to the lungs has developed to be one of the most widely investigated systemic or local drug delivery approaches.The utilization of medication delivery systems (DDS) for the treatment of pulmonary disorders is increasing as a direct result of their potential for localized topical therapy in the lungs.

Pulmonary drug delivery systems can be classified into 3 types i.e immediate release [e. g. lactose-drug mixtures for dry powder inhaler (DPI) application] and controlled release systems (such as liposomes, micelles, nano- and microparticles based on polymers).

liposomes, microparticles and nanoparticles are examples of Particulate drug carriers have been utilized to improve the therapeutic index of new or established medications by changing medication absorption, reducing metabolism, prolonging biological half-life, or reducing toxicity [36].

11. VARIOUS BIOLOGICAL BARRIERS TO DRUG DELIVERY VIA LUNGS

Various biological and physicochemical barriers are there. These includes mucus barriers and catabolic enzymes in the tracheobronchial region, and macrophages in the alveolar region [37]

12. PULMONARY DRUG DELIVERY DEVICES (PDDS)

Pulmonary drug delivery devices (pdds) are known to be ready to simply deliver the drug to the specified site within the body directly or to other distant sites through the bloodstream. The delivery device in pulmonary administration plays a crucial role within the success of this technique.

In recent years great strides have been made in the development of advanced devices. However, devices are much less explored than powder formulations [38][Table:1]

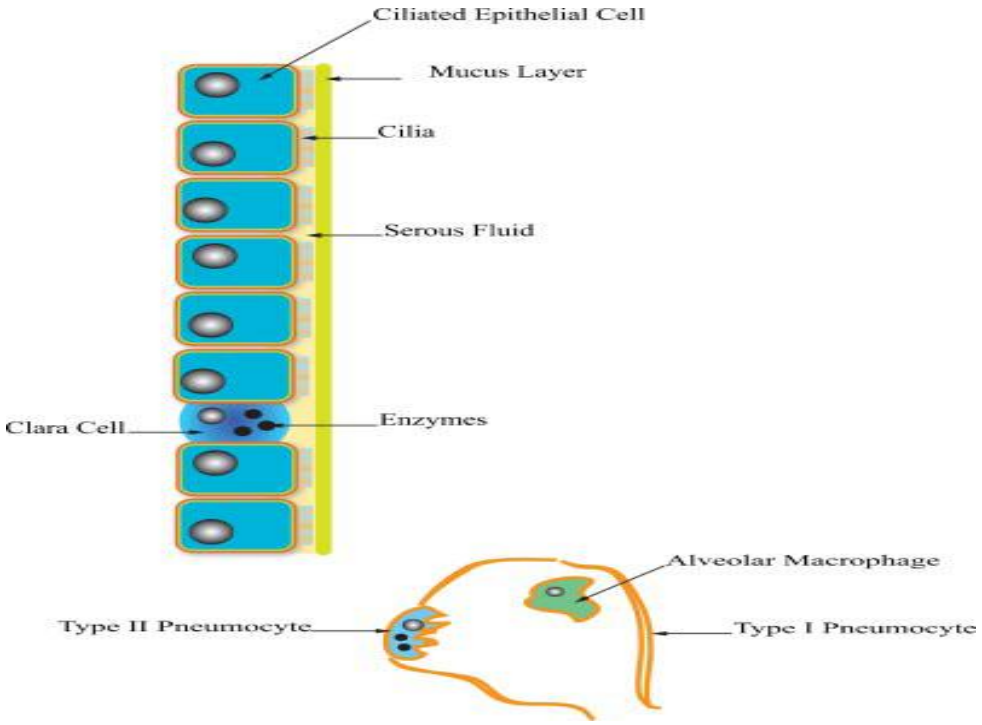

Fig. 6. Various biological barriers to drug delivery via the lung

Table 1.

1. dry powder inhaler	➢ Dry powder inhalation (DPI) devices are versatile devices to which scientists and engineers have devoted many thoughts and ideas. ➢ DPIs are used to treat respiratory diseases such as asthma and COPD, systemic disorders like diabetes, cancer, neurological diseases (including pain), and other pulmonary diseases like CF and pulmonary infectious diseases [39] Ex-ex- Premetered single-dose devices, Capsule-type multiple-dose devices

2. Nebulizers	➢ A nebulizer is a device wont to administer medication to patients within the sort of a mist inhaled into the lungs ➢ It is commonly utilized in treating CF, asthma, and other respiratory diseases. ➢ There are two basic sorts of nebulizers: i.e jet and ultrasonic nebulizers [32]
3. Pressurized metered-dose inhalers	➢ pMDIs are the most popular inhalers to treat local respiratory diseases such as asthma and COPD. ➢ Used to deliver a selected amount of medication to the lungs [40]
4. soft mist inhalers	➢ The inhaler combines the benefits of pMDIs and nebulizers ➢ it's alittle , portable, hand-held inhaler with no need for power supply (like pMDIs) that slowly aerosolizes propellant free-drug solutions as a soft mist (like nebulizers), thus decreasing the chance for oropharyngeal deposition [40]

13. ADVANTAGES AND DISADVANTAGES OF INHALATIONAL DEVICES

Table 2.

1. dry powder inhaler	Advantages- ➢ compact ➢ portable ➢ breath actuated ➢ easy to use	Disadvantages- ➢ humidity may cause powdersto aggregate and capsules to soften most DPI contains Lactose.
2.pMDI	Advantages- ➢ compart ➢ Portable	Disadvantages- ➢ inhalation technique and patient coordination required ➢ high oral deposition
3. Nebuliser	Advantages- ➢ no specific inhalation technique or coordination required ➢ delivers large dose.	Disadvantages- ➢ time-consuming ➢ bulky

14. NANOPRTICLE FORMULATION FOR PULMONARY DRUG DELIVERY SYSTEM (PDDS)

In a 1959 lecture, Feynman proposed that, within the future, small machines are going to be wont to make smaller machines, and these successively are going to be wont to make even smaller machines, all the way down to the atomic level [41].

Advances in nanoscience have moved developments in various logical disciplines, including medication and pharmaceutical formulation.

Nanotechnology has the potential to revolutionize medication and has effectively introduced new regulatory challenges [42,43].

❖ *ADVANTAGES*

Nanoparticle drugs offer a few benefits over formulations containing larger particles, [44]

- Fairly easy preparation.
- Targeted and drug delivery
- Good control over size and size distribution.
- Good protection of the encapsulated drug.
- Retention of drug at the location
- Longer clearance time.
- Increased therapeutic efficacy.
- Increased bioavailability
- Dose proportionality

❖ *DISADVANTAGES*

- Extensive use of polyvinyl alcohol as a detergent –issues with toxicity
- Limited targeting abilities.
- Discontinuation of therapy is not possible.
- Cytotoxicity.
- Pulmonary inflammation and pulmonary carcinogenicity.
- Alveolar inflammation.
- The disturbance of autonomic imbalance by nanoparticles having direct effect on heart and vascular function

15. LATEST DEVELOPMENT OF INHALATIONAL TECHNQUES

- Handihaler
- Technosphere® Insulin (Mankind Corporation)
- GyroHaler
- Aspirair
- AERx system[36].

16. CONCLUSION

The prognosis for patients with streptococcal pneumonia depends on the underlying risk factors, co morbidity, age, the extent of lung involvement, the need for mechanical ventilation and the type of antibiotic. Overall, the pneumonia is associated with high morbidity and mortality. Even those who survive tend to have residual deficits in lung mechanics and recovery is prolonged.COVID 19 Patients are much more prone towards this infection, if untreated at Appropriate time. So Development of New Device are immense Important which contributes rapid and Proper Drug Delivery to lungs. Research must be carried out in the field of Novel Drug Delivery System for target delivery of Drugs like Antibiotic,Bronchodiator and Corticosteroid to Respiratory Tract.

CONSENT AND ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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