World Journal of Pharmaceutical Science and Research
www.wjpsronline.com
Review Article
ISSN: 2583-6579
SJIF Impact Factor: 5.111
Year - 2025
Volume: 4; Issue: 2
Page: 179-193

A REVIEW ON CURRENT PERSPECTIVES IN SINO-PULMONARY DISEASES: CAUSES AND TREATMENT

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Article Received: 16 February 2025 | | ***Article Revised: 05 March 2025*** | | ***Article Accepted: 27 March 2025***

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DOI: https://doi.org/10.5281/zenodo.15112454

How to cite this Article: Aqsa Quazi and Mohamed Hassan Dehghan (2025). A REVIEW ON CURRENT PERSPECTIVES IN SINO-PULMONARY DISEASES: CAUSES AND TREATMENT. World Journal of Pharmaceutical Science and Research, 4(2), 179-193. https://doi.org/10.5281/zenodo.15112454

ABSTRACT

Respiratory diseases, including pneumonia, COPD, and fungal infections, have worsened with the emergence of SARS-CoV-2, leading to increased sino-pulmonary complications. COVID-19 weakens immunity, facilitating secondary infections like aspergillosis and mucormycosis. This review examines major respiratory infections, their causes, and treatment approaches, including antibiotics, antivirals, antifungals, and inhalation therapies. The evolving SARS-CoV-2 variants pose challenges for treatment and vaccine efficacy, highlighting the need for ongoing research and improved therapeutic strategies.

KEYWORDS: Respiratory diseases, SARS-CoV-2, sino-pulmonary infections, antifungals, inhalation therapy.

BACKGROUND

The world is facing new infectious diseases which have mild to lethal effects on pulmonary and extra pulmonary organs. Respiratory diseases vary from Pneumonia, sepsis, acute respiratory distress syndrome, chronic obstructive pulmonary disease (COPD), asthma and cystic fibrosis. Apart from these, the respiratory infections with severe complications are those caused by opportunistic fungi of *Aspergillus*, *Candida* and mucorales species. Figure 1 broadly classifies the pulmonary diseases.

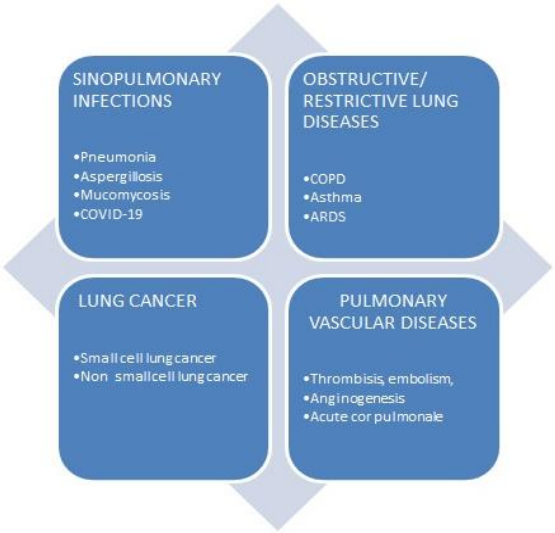

Fig 1: Broad Categorization of pulmonary diseases.

Following the emergence of human coronavirus endemics and pandemics, there has been a notable increase in cases of community-acquired respiratory tract infections. The prevalence of community-acquired pneumonia gained attention starting in 2002 with the outbreak of severe acute respiratory syndrome coronavirus, followed by incidents in 2012 involving the Middle East Respiratory Syndrome coronavirus. More recently, in 2019, the global community faced another surge in community-acquired pneumonia cases due to the emergence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[1]

Studies have indicated that people with neutropenia, immunodeficiencies and antibody deficiency are at a higher risk to suffer with sinopulmonary diseases.[2] The COVID-19 pandemic has substantially added to the respiratory complications. Causing respiratory infection itself SARS-CoV-2 has also paved way for more sinopulmonary infections by weakening the immune system. Recently many of the pulmonary conditions observed were due to post COVID-19 complications.[3]

Major causes of sinopulmonary infections

There can be direct contributors and indirect contributors of sinopuulomary infections

1. Direct factors: A person can contract sino-pulmonary infection due to direct factors like the disease causing pathogen itself or the infection ca be acquired. The direct factors can be-

a. Primary factors

i. Bacteria

ii. Virus

iii. Fungi

iv. Protozoa

b. Secondary factors:

i. Community-acquired

ii. Hospital-acquired

iii. Ventilator-associated

2. Indirect factors: these factors are difficult to determine and can include-

a. Poor air quality

b. Climate changes

c. Life-style related factors

i. Smoking

ii. Occupation related

A brief account of some Sino-pulmonary diseases is as follows

1) Pneumonia

It is a lower respiratory tract infection (LRTI) which can be caused by some bacteria, virus and fungi. Pneumonia can be Commmunity-acquired pneumonia (CAP), Hospital acquired pneumonia (HAP) or ventilator-associated pneumonia (VAP).

My coplasma pneumonia, Chlamydophila pneumonia and *Streptococcus pneumonia* are common causative agents of Bacterial pneumonia while Influenza A, respiratory syncytial virus (RSV) adenovirus and Infuenza B virus are common causes of viral pneumonia.[4]

Infection by SARS-CoV-2 can also cause bronchopneumonia. The novel corona virus damages the wall and the lining of the alveolus and capillaries in the lungs. The damaged air sacs facilitate the influx of liquid which is mostly inflamed cells and protein. Oxygen intake by the lungs is hindered and the fluid build-up leads to pneumonia. Patients can experience shortness of breath, fevers and cough, which can be productive.[5]

Treatment

Bacterial pneumonia: Antibiotics such as oral amoxicilline, injectable penicillin, azithromycin are used as the first-line treatment option. The alternate option is to use doxycycline, and in cases of drug resistance, respiratory fluoroquinolone is used.[6,7,8]

Viral pneumonia: Administration of antivirals such as oseltamivir, zanamivir or peramivir.[4]

Prevention: Pneumococcal conjugated 7-valent vaccine and 13- valent pneumococcal conjugated vaccine have successfully led to decrease in the rate of invasive disease and hospitalisation.[8]

2) COVID-19

Popularly known as COVID-19 the novel corona virus disease is caused by the SARS-CoV-2 virus belonging to the coronaviridae family to which SARS-CoV and, MERS-CoV belonged.[9]

This emerged first in the Wuhan City of China in Dec 2019. The number of patients kept increasing since then in China as well as all over the world giving the disease a pandemic status. On 30 January 2020 the WHO declared a public health emergency of international concern and on 11 March 2020 it was formally declared as a pandemic. As of 10 March 2022, there has been 63,19,35,687 confirmed cases including 65,88,850 deaths of COVID-19 worldwide reported to WHO.[10]

When exposed, the virus can come in contact with the muscous lining of nose, mouth and eyes of the host and enter the body. The ACE2 receptors are the entry point for SARS-CoV-2. The spike protein of the virus contains the receptor binding domain which hooks onto the ACE2 receptor. Though it affects many organs, COVID-19 is mainly known as a respiratory disease or infection. The reason for this can be the large surface area of the lungs which makes them particularly vulnerable to SARS-CoV-2. The upper and lower respiratory tract are first infected irritating the lining and causing inflammation and the infection can reach the alveoli. The virus then uses alveoli as a reservoir for its replication.[11]

Therapeutic management of COVID-19

The manifestations of mild and moderate cases of COVID-19 can be treated merely by over-the-counter drugs, increased fluid intake and proper rest. However, the severe and critical cases require an effective treatment which should be specific for the novel infection. Sadly, no effective and specific treatment of COVID-19 has been established. The virus itself is 'novel' corona virus and the evolved variant forms added more obstacles in devising a specific line of treatment.

For designing an immunomodulatory therapy, care should be taken that an anti-inflammatory therapy should do least damage to the immune function while an immune enhancement therapy should avoid inflammatory rebound as to the maximum degree.

Since the beginning of this pandemic, various classes of drugs have been investigated for the treatment of COVID-19. Many antibacterial, antiviral, antiprotozoal, ACE inhibitors and other categories of drugs were used in COVID-19 positive patients. Apart from administrating drugs, plasma therapy was also used as an approach for treatment where the antibodies in the plasma of patients who got cured of the infection helped new patients to fight the infection.

An account of some of the drugs which were used (and sometimes even withdrawn) for treating COVID-19[12-31] is given in Table 1.

Table 1: Drugs which have been used in COVID-19.

Category	Sub-class	Examples	Mechanism of Action	Comments	Reference
Antiinflammatory drugs	Corticosteriods	Dexamethasone Prednisolone Methylprednisolone	Inhibits release of proinflammatory substances Stabilize the cell membrane and enhance permeability	Classic antiinflammatory drugs due to high potency, ready availability, cost effectiveness	12
	Ta1	Maipuxin Heri	Promotes maturation of T cell Improves ability of dendritic cells to engulf bacteria	Strong immune booster Can be specifically used in COVID induced sepsis	
ACE inhibitors		Ramipril Enalapril Lisinopril	Angiotensin II (ANG II) causes inflammation and various types of tissue injury. ACE I increases the production of ANGII.	Widely used in patients having hypertension, cardiac and renal disorders.	13-15

			ACE inhibitors block the actions of ACE1 and thus reduce the level of ANG II		
Angiotensin receptor blockers (ARBs)		Valsartan Losartan	These drugs have effects similar to those of ACE inhibitors.	Can be used in COVID-19	13-15
Antiviral drugs[13-19]	Blocking virus-cell membrane fusion	Chloroquine (CQ) & Hydroxychloroquine (HCQ)	Interfere with the glycosylation of ACE2 and reduce the binding efficacy of RBD of the virus. Inhibit the viral binding as well as the membrane fusion.	Gained attention in the early stages of COVID-19 therapy designing. Both the drugs have shown to kill SARS-CoV-2 in laboratory dishes.	16-18
	Viral protease inhibitor	Lopinavir Ritonavir	Lopinavir is an HIV type 1 aspartate protease inhibitor. It has in vitro inhibitory activity against SARS-CoV. Its combination with Ritonavir inhibits cytochrome P450 increasing its plasma half-life and so the duration of action.	Due to adverse events such as nausea, diarrhea and hepatotoxicity, Lopinavir–ritonavir treatment was stopped early.	19, 20
	RNA-dependent RNA polymerase inhibitor	Remdisivir	Remdesivir is a nucleotide prodrug of adenosine analogue and causes decrease in viral RNA production.	Remdesivir has shown activity against SARS-CoV-2 in *in vitro* testing	20
		Ivermectin	Ivermectin stimulates of gamma amino butyric acid (GABA)-gated-Cl^- channels and causes hyperpolarization which paralysis the infecting organism.	A study has claimed that ivermectin has an inhibitory concentration 50 (IC50) which was estimated to be ~2 µM against SARS-CoV-2 infected cell cultures[18]	21, 22
		Molnupiravir	It is a prodrug of N-hydroxyytidine (NHC). NHC is phosphorylated to NHC triphosphate. Viral RNA polymerase incorporates NHC triphosphate into the viral RNA. NHC impairs the viral replication by misdirecting RNA polymerase to	Molnupiravir is a small molecule antiviral prodrug given orally. It has shown to reduce hospitalization and death by 50% in COVID-19 patients.	23, 24

			incorporate either guanine or adenine		
	Guanosine nucleotide analog	AT-527: Double prodrug AT-511: Intermediate metabolite AT-9010: Ultimate active metabolite	It inhibits the SARS-CoV-2 replications *in-vitro.* The free base AT-511 is found to be effective against several coronaviruses *in-vitro*	It was orally administered and was previously very successful in the treatment of hepatitis (HCV)	25, 26
Antibiotics	Azithromycin		It is a broad-spectrum antibiotic which interfere with protein synthesis of bacterial. Binding to 50S subunit of bacterial ribosomes, it inhibits the translation of mRNA.	It also has anti-inflammatory properties, excellent safety profile and easy availability	27-29
Monoclonal antibodies	Tocilizumab		Tocilizumab is a recombinant humanized monoclonal anti-IL-6 receptor antibody. It binds both soluble and membrane-bound IL-6R to inhibit IL-6-mediated cis- and trans-signalling. This helps to control the autoimmune reactions or the cytokine storm.	The safety and efficacy of tocilizumab has not been prven by well-designed trials. Its use can cause allergic reactions post infusion and it may also alter the liver function tests.	29
Main protease M^{pro} or 3CL protease inhibitor	M^{pro} inhibitor	PF-07321332	PF-07321332 inhibits the enzyme vital for viral replication. SARS-CoV-2 M^{pro} has an important role in virus replication.it cleaves the two polyproteins viz., pp1a & pp1ab to short proteins required for viral replication.	The drug is a small molecule and is also orally bioavailable. It seems a good candidate to treat COVID-19 and has been effective against all beta-coronaviruses as well as alpha-coronaviruses which are known to infect humans.	30

Inhalation therapy for COVID-19

Inhalation therapy has a great potential for successful drug delivery to the nose and lungs and can be used for local as well as systemic treatments. Eedara et al[32] have reviewed the inhaled therapeutics for treatment and prevention of COVID-19 an account of which is illustrated in Figure 2.

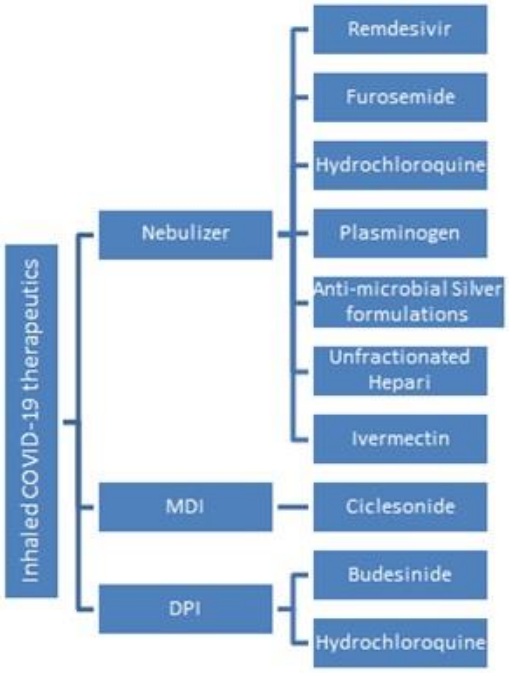

Fig. 2: Inhalation Therapy for COVID-19.

Variants of SARS-CoV-2

The SARS-CoV-2 virus is continuously evolving. New variants of the virus with different mutations are adding up to the challenges for managing COVID-19. Some of the variants of concern are Alpha, Beta, Gamma, Delta and Omicron. The lineage of these variants and their WHO names are tabulated in table 2.

Table 2: Different variants of SARS-CoV-2.

Variant	Other names	Mutation	Country	Initially reported
B.1.1.7 variant	Variant of Concern (VOC) 202012/01 ▪ Alpha variant ▪ 201/501YV1 ▪ UK variant	23 mutations 17 amino acid changes	United Kingdom	December 14, 2020
B.1.351variant	▪ 501YV2 ▪ Beta variant ▪ South Africa variant	23 mutations 17 amino acid changes	South Africa	December 18, 2020
B.1.1.28.1 variant	▪ 501V3 ▪ P.1 ▪ Gamma variant ▪ Brazil variant	35 mutations 17 amino acid changes	Brazil	January 12, 2020
B.1.617.2 variant	▪ Delta variant ▪ Delta Plus variant	E484Q L452R P614R	India	October 2020
B.1.617.2.1 variant	▪ Versions: AY.1. and AY.2.	K147N	India	6 genomes have been reported till June 7, 2021
B.1.1.529 variant	▪ Omicron	▪ In spike protein (S): 30 substitutions: A67V, T95I, Y145D, L212I, G339D, S371L, S373P, S375F, K417N, N440K,	South Africa	November 24, 2021

			G446S, S477N, T478K, E484A, Q493R, G496S, Q498R, N501Y, Y505H, T547K, D614G, H655Y, N679K, P681H, N764K, D796Y, N856K, Q954H, N969K, and L981F) 3 deletions and 1 insertion of three amino acids. ▪ In envelope (E): 1 substitution (T9I) ▪ In membrane (M): 3 substitution(D3G, Q19E, and A63T) ▪ In nucleocapsid (N): 3 substitution and 3 residue deletions		
	Sub variants of omicron	BA.1	▪ 39 mutation common with other subvariants ▪ 20 additional mutations ▪ 13 unique mutations		
		BA.2	▪ 39 mutation common with other subvariants ▪ 27 additional mutations ▪ 10 unique mutations		
		BA.3	▪ 39 mutation common with other subvariants ▪ 13 additional mutations ▪ 1 unique mutation		

Vaccines for COVID-19

As the number of COVID-19 patients was increasing tremendously, some mRNA vaccines received the emergency use authorization. Various vaccines have been developed in countries all around the world for COVID-19. These vaccines use different approaches to harmlessly expose the virus or part of it to the host immune system with so that antibodies can be generated in the host body. The vaccine may be a whole virus (where the virus is attenuated or genetically modified to render it harmless), disabled virus, a part of the virus or just the genetic material of the virus.

Depending on whether they used a whole virus rendered harmless or a part of it these vaccines can be:

- Vaccines with attenuated SARS-CoV-2 virus (e.g., COVI-VAC)
- Vaccines with inactive SARS-CoV-2 virus (e.g., CoronaVac, Covaxin)
- Vaccines based on viral proteins (e.g., Co-VLP)
- Naked DNA vaccines (e.g., Zy-Cov-D)
- mRNA vaccines (e.g., BNT162b2- by Pfizer and BioNtech)
- Vaccines based on viral vectors (e.g., Sputnik-V)

Most of these vaccines are given in two doses[33]

Currently authorised vaccines have not shown impressive effects against the new variants but then manage to control the severity of the infection and death. Also the vaccines are most effective for 6 months after which the neutralising

antibody decline. Immunity after infection or vaccination is comparatively better in the B.1.1.7 variant than for other variants.

Booster doses are also required for better protection in case of some vaccines.[33,34]

Inhaled vaccines

Apart from the intramuscularly given vaccines, researchers are working on inhaled vaccines for COVID-19.[32] AdCOVID, MV-014-212, CoroFlu, Ad5-nCoV, AZD12222, COVI-VAC are all inhaled vaccines undergoing clinical trials after showing good results in pre-clinical studies.

3) Sepsis

Sepsis is a life-threatening organ dysfunction caused when the body's response to infection goes astray. It can be an outcome of any infection bacterial or viral. The sepsis caused by SARS-CoV-2 is quite different from the sepsis induced by bacteria because of the concealed antigenicity of the virus until it is replicated in large number. Sepsis by SARS-CoV-2 has an incubation period while in bacterial sepsis a violent inflammatory response is seen very quickly. The sepsis in COVID-19 has a chronic course. If not controlled in time sepsis can lead to blood clot formation in organs and hence multiorgan damage, septic shock and death.[35]

Treatment

Treatment of sepsis includes the following drugs:

- Corticosteriods
- UTI (a trypsisn inhibitor)
- Ta1[35]

4) Pulmonary fibrosis

Pulmonary fibrosis occurs when the tissue around and in between the lungs becomes scarred and thick. Mostly the cause is unknown in idiopathic pulmonary fibrosis. Many cases of pulmonary fibrosis are seen in COVID-19 patients. As the SARS-CoV-2 virus infects the lungs it causes parenchymatous lesions leading to pulmonary fibrosis. Signs of dyspnoea (i.e., difficulty in breathing) low oxygen saturation, breathlessness and fatigue in post-COVID patients should not be neglected and proper care should be provided as these signs are suggestive of pulmonary fibrosis. Pulmonary fibrosis affects the patients' quality of life and can even be fatal.[36,37]

Treatment

Though the treatment of post-COVID pulmonary fibrosis is yet not established, some of the suggested options are:

- Antivirals- Remdesivir, Lopinavir, Ritonavir, Rubavirin[38]
- Mineralocorticoid Receptor antagonist: Spiranolactone[38]
- Traditional Chinese medicine: Tetrandine, Fuzheng Huayu[38]
- Plasminogen Activation: Urokinase, streptokinase[38]
- Drugs used for Idiopathic pulmonary fibrosis: Pirfenidone, nintedanib[37,38]
- Other: Hyperbaric oxygen, human amniotic fluid.[37]

5) Acute respiratory distress syndrome (ARDS)

Acute respiratory distress syndrome (ARDS) is an acute condition which starts as hypoxemia and dyspnoea and then evolves into respiratory failure. The fluids start leaking into the lungs. It can also be considered as a rapidly progressing non-cardiogenic pulmonary oedema. ARDS can be caused by pulmonary infection, trauma, fat embolism, pulmonary injuries, drowning, sepsis, inhalation of toxic fumes etc. The occurrence of ARDS in severely ill COVID-19 patients is very notable now.[39] About 40% of COVID-19 patients with dyspnoea develop ARDS. SARS-CoV-2 virus can damage the lung cells causing fluid leakage in the lungs making them impermeable to oxygen. Breathing becomes difficult and oxygen levels decrease. The virus also generates a cytokine storm as an immune response. The hypoxia, respiratory failure and CSS lead to ARDS.[40] Thus, ARDS in COVID-19 patients may occur because of the viral infection itself or mainly due to the immune response of the body to the virus. According to Chaomin et.al., old age, hypertension, diabetes, neutrophilia and organ dysfunction are some of the risk factors for ARDS which can cause death in COVID-19.[40]

Mechanical ventilators can save the many lives but in critical COVID-19 patients with ARDS, the mortality rate is as high as 80%. The supportive treatment of ARDS includes:

- Mechanical ventilators starting with low tidal volume[41]
- Treating the underlying cause of lung injury under ventilator support[41]
- Prophylaxis of stress ulcers and venous thromboembolism[41]
- Prone positioning[42]
- Nutritional therapy[41]

The drugs used for ARDS are limited. Use of corticosteroids is controversial but still under further investigation.[43]

6) Pulmonary arterial hypertension

Pulmonary arterial hypertension (PAH) is an elevated level of a potent blood vessel constrictor, endothelin and the arteries in lungs and heart are affected. It causes dyspnea, syncope, chest pain, dizziness, fatigue, and swelling in ankles and legs. Some underlying lung and heart conditions may cause pulmonary arterial hypertension.[44]

Treatment

Treatment of PAH varies from patient to patient. Anticoagulants, calcium channel blockers, diuretics, vasodilators are generally used. Endothelin receptor antagonist like bosentan is also used. Oral delivery of bosentan has limitations such as low boiavalability, systemic hypotension, hepatotoxicity. Inhalation therapy may circumvent such limitations but again it has a short duration of action. Lydia et al have formulated a respirable controlled release polymeric colloid of bosentan which showed a sustained vasodialation effect and improved bioavailability.[44]

7) Pulmonary Aspergillosis

Aspergillus is a common mold (type of fungus) the spores of which people breathe daily without showing pathological effects. However, when people with lung disease immunocompromised people inhale Aspergillus spores they are at risk of contracting Aspergillosis. It causes dyspnea, fever, and cough as early signs. Chest pain can be seen because of vascular invasion and if it gets disseminated in the Central Nervous System, seizures and stroke may be observed. Though a rare condition, Invasive pulmonary aspergillosis (IPA) can be fatal.[45] As discussed before, an infection of SARS-CoV-2 can develop ARDS, in severe cases this can subsequently lead to pulmonary aspergillosis. This is known

as COVID-19 associated pulmonary aspergillosis (CAPA).[46] Michele Bartoletti and colleagues studied the incidences of invasive pulmonary aspergillosis in patients suffering from critical COVID-19 who were intubated due to their inability to breath. Occurrence of CAPA was seen in around 30% of the total patients included in the study.[47]

Treatment

Treatment of Aspergillosis may include

- Corticosteriods: systemic glucocorticoid such as prednisolone.[48]
- Antifungals: itraconazole, voriconazole, and isavuconazole should be the drug of choice, but as the cases of azole-resistance Aspegillosis[49] are rising, amphotericine B[50] and nystatin[51,52] can be included as a second line of treatment
- Monoclonal antibody: Omalizumab[48]

Treatment of CAPA is complicated due to drug-drug interactions[48]

8) Pulmonary Mucormycosis

Pulmonary mucormycosis is a rare but serious opportunistic fungal infection seen in immunocompromised patients.[53] Chemotherapy for neutropenia weakens the immunity of patients and thus neutropenia imparts high risk of infection.[54] Though the first case of pulmonary mucormycosis was described in 1876[53] and it was relatively uncommon, it has been most prevalent in 2020-21 predominantly seen in post COVID-19 patients. This fact can be associated to the immunosuppressive drugs given in COVID-19 and the opportunistic fungal infection targets such immunocompromised persons.[54]

Pulmonary mucormycosis in neutropenic patients can lead to dissemination. The mortality rate of this infection is about 80%.[55] Though Aspergillosis and mucormycosis both are sinopulmonary infections, there have been many advances in the diagnosis and treatment of apergillosis but such is not the case with mucormycosis. Pulmonary mucormycosis remains to be a devastating and even fatal infection.[53-56]

Treatment

- Debridement surgery at early stage.[53,56]
- Antifungal therapy: Liposomal amphotericin B, Amphotericine B Lipid Complex, combination of amphotericine with an echinocandin or azole.[56]
- Adjuctive therapies: Itraconazol, Posaconazole, iron chelation, cytokine therapy.[56]

CONCLUSION

Current challenges in treatment of sinopulmonary infections

Oral route has the drawback of first-past metabolism and intravenous route gives rise to systemic exposure of the drug, nephrotoxicity and hepatotoxicity in many cases. Hence nasal and pulmonary routes for drug administration are better options for maximum local effect.

However, the nasal and pulmonary routes of drug delivery present some challenges owing to the anatomical features. The drug has to cross various biological barriers like the surfactant layer, the mucus membrane, the basement membrane, capillary endothelium, etc., to reach the luminal surface of the epitilial from where it can be absorbed. The

aerodynamic particles size is of crucial importance so that the particle is neither exhaled out nor phagocytized and is able to reach the site of absorption. The muco-ciliary clearance and the cough- reflex are other challenges that have to be overcome in this kind of delivery.[57,58]

Sinopulmonary infections are mostly observed in non-immunocopetent patients along with some comorbiditites. In such cases drug-drug interactions presents a major challenge in therapy.

The growing resistance to antibiotics is again a significant hurdle in case of infections. Every year, a minimum of 700,000 individuals globally succumb to antibiotic resistance. Reviving old antibiotics which were discared from use due to some of their side-effects is also gaining interest of many reseachers. But again there is a gap in available information of these antibiotics.[59,60]

Lastly there are patient related factors which makes this delivery unpredictable. These include the patient's inhalation flow, clearance rate, presence of any disease condition and their capacity to use a device.

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