ARDS in tropical Infections

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Acute Respiratory Distress Syndrome (ARDS) constitutes a heterogeneous group of disorders characterised by increased permeability of pulmonary capillary endothelial cells and alveolar epithelial cells, leading to hypoxemia that is refractory to usual oxygen therapy. This leads to acute pulmonary insufficiency, leading to respiratory failure with high mortality, even in this era of lung protective ventilation.1 ARDS was first described in 1967 in a series of 12 patients, seven of whom had sustained multiple trauma; one had acute pancreatitis while four had unspecified (possibly viral) pneumonia or drug ingestion.2 The definition of ARDS has evolved over time since its first inception in 1994 by the American-European Consensus Conference (AECC).3 The most recent Berlin Definition of ARDS defines ARDS as "acute onset respiratory failure with PaO2/FiO2 ≤ 300 with PEEP or CPAP ≥5 cm H2O originating within 1 week of a known clinical insult or new or worsening respiratory symptoms, characterised by bilateral opacities – not fully explained by effusions, lobar/lung collapse, or nodules and not fully explained by cardiac failure of fluid overload."4

Lung injury in ARDS occurs due to both direct and indirect mechanisms, arising as a result of several medical, surgical and obstetric disorders. Among these, pulmonary infections and sepsis are the most common. Of particular importance in the tropical regions are the tropical infections, poisoning and inhalational injuries, many of which are unique to this part of the world, as listed in table 1.

Tuberculosis

Tuberculosis (TB) remains a major and global health disease which usually has a subacute or chronic clinical presentation. In India, the annual incidence is 168 per lakh and the prevalence is 249 per lakh population. WHO estimated TB mortality of 23 per lakh population in 2009 in India.5 TB rarely may present with respiratory failure and ARDS; this is more common in advanced tubercular bronchopneumonia and miliary TB. Prolonged illness, absolute lymphocytopenia and elevated transaminases protend higher risk.6 Miliary TB with ARDS has a high mortality ranging between 33 - 90% and duration of miliary TB beyond 20 days tends to markedly increase the risk of ARDS.7,8 In a retrospective study from South Korea, in 90 patients with TB who presented with ARDS, those with miliary TB were younger, required fewer days on mechanical ventilation, were more likely to have extrapulmonary involvement and a lesser incidence of DIC as a complication. The mortality was lower in the group with military TB than those with TB bronchopneumonia (58% vs 68%). The use of corticosteroids predicted higher chances of survival in the bronchopneumonia group but had no effect on prognosis in miliary disease.9"container-title":"The European Respiratory Journal","page":"1625-1630","volume" :"32","issue":"6","source":"NCBI PubMed","abstract":"The aim of the present study was to evaluate the clinical characteristics, prognoses and predictors of mortality of patients with pulmonary tuberculosis (TB

Radiologically, the similarities between tubercular and bacterial bronchopneumonia may delay the diagnosis in ARDS, although the acuteness of clinical presentation may provide a clue.10 Chest X-ray commonly shows bilateral nodular lesions mixed with consolidation or ground glass opacities. HRCT may show miliary or bronchogenic dissemination with diffuse areas of ground glass attenuation. Thus, AFB smear and cultures of the sputum or bronchial secretions should be performed routinely in patients at risk of TB with severe pneumonia, particularly in TB endemic areas. In contrast to bronchopneumonia, miliary TB usually is sputum smear negative and is diagnosed based on the radiological picture and presence of necrotising granulomas in lung biopsy (whenever a fiberoptic bronchoscopy and transbronchial lung biopsy is feasible), or other extrapulmonary sites.

Prompt institution of mechanical ventilation remains the backbone to the management of ARDS due to tuberculosis. Equally crucial is early anti-tuberculous therapy. At present the routine use of corticosteroids for ARDS due to tuberculosis remains controversial with only anecdotal reports showing some benefit, particularly in the subgroup of patients with severe bronchopneumonia and shock.11,12"container-title":"Critical Care Medicine","page":"1594-1603","volume":"37","issue":"5","source":"NCBI PubMed","abstract":"OBJECTIVE: Controversy remains as to whether low-dose corticosteroids can reduce the mortality and morbidity of acute lung injury (ALI In spite of several advancements in intensive care and ventilator support, mortality remains high even in the presence of an effective anti-tubercular treatment.

Malaria

Malaria is a parasitic disease caused by one or more of four Plasmodium species: P. falciparum, vivax, ovale, and malariae. Pulmonary manifestations of malaria include cough with or without sputum and dyspnoea occurring as a consequence of bronchitis, pneumonia or bronchopneumonia. These may be complicated by pulmonary oedema and metabolic acidosis, leading to early fatality. Noncardiogenic pulmonary edema is the most significant malaria-induced pulmonary manifestation and occurs most commonly in P. falciparum malaria.13,14 The incidence of pulmonary edema has been reported to be up to 20% in severe malaria, nearly half of whom may fulfil the criteria for ARDS.15,16with (group 1, 12 patients Indian studies report an incidence ranging from 1 to 30%, with up to 5% patients with uncomplicated falciparum malaria and 20% – 30% with severe and complicated malaria going on to develop ARDS.17,18pain abdomen 3.29%, gastroenteritis 5.64%, jaundice 2.58% and bronchitis in 7.50%. We encountered subconjunctival haemorrhages with purpura and/or urticaria in four cases, symptoms suggestive of shock lung in 3, pulmonary oedema in 2, severe anaemia (HB less than 4 g% Furthermore, ARDS is now being increasingly observed even in species which were considered benign, i.e., P. vivax, P. ovale and P. malariae.19,20

Lung injury in malaria occurs as a result of erythrocyte sequestration and destruction, the release of parasite and erythrocyte material into the circulation, and the host response to these events. The rupture of meronts (meronts divide to produce merozoites) release proinflammatory mediators such as TNF- α, IL – 1, IL- 6 and IL - 8. These inflammatory

mediators cause endothelial injury, interstitial oedema, ventilation-perfusion mismatch and impairment of gas exchange.13,21 Secondary bacterial sepsis occurs in 6 - 15% of severe falciparum malaria and significantly affects outcome. 13,15

ARDS in malaria is more commonly associated with cerebral malaria and has a higher propensity to occur in adults and pregnant women. The usual presentation is of abrupt onset dyspnoea, cough, and tightness in the chest that progresses rapidly over a few hours to cause life-threatening hypoxia. Examination may reveal basal crepitation and expiratory wheeze. High level of parasitaemia, acute renal failure, hypoglycaemia, metabolic acidosis, disseminated intravascular coagulation (DIC), and bacterial sepsis usually complicates the clinical course. In a retrospective study of 40 patients with severe malaria, lung involvement was associated with more severe disease, higher simplified acute physiology score (SAPS) on admission and higher rates of occurrence of acute renal failure, unarousable coma, metabolic acidosis, and septic shock.15with (group 1, 12 patients Arterial blood gas analysis may show hypoxemia and chest radiographs reveal bilateral alveolar opacities, increased interstitial markings, or rarely a pleural effusion. Blood counts, peripheral smear examination, blood chemistries, coagulation parameters and cultures are used to guide therapeutic strategies.

Management includes general supportive measures, correction of fluid and electrolyte imbalance. Crystalloids and vasopressors are used to provide adequate tissue perfusion guided by maintaining a CVP of 8-12 mm Hg, although the routine use of pulmonary artery catheter for hemodynamic monitoring is not recommended. Efforts should be made to prevent secondary bacterial and nosocomial infections, gastrointestinal bleeding and pulmonary thromboembolism. Aggressive management of complications such as hypoglycaemia and anemia is recommended.

Early institution of specific antimalarial therapy is the cornerstone in management and should not be delayed in patients with proven or strongly suspected malaria. Parenteral cinchona alkaloids (e.g. quinine and quinidine) or the artemisinin derivatives (e.g. artesunate, artemether and arteether) are the drugs of choice. Doxycycline or clindamycin may be prescribed during follow-up after the patient is able to take orally. The regimen for treatment of complicated malaria as recommended by National Vector Borne Disease Control program is listed in Table-2.

Since there is sparse published data on various ventilatory strategies in ARDS due to malaria, certain generalizations has been made based on observations from ARDS due to other causes. Lung protective ventilation based on the Acute Respiratory Distress Syndrome Network (ARDSNet) study is currently recommended, wherein a low tidal volume of 6 ml/kg predicted body weight, with plateau pressures limited to 30 cm H2O to prevent lung over-distension have shown to improve survival in ARDS of all causes.23,24 The role of permissive hypercapnia in comatose patients with malaria is debatable and may actually be detrimental as it may increase the cerebral blood flow and intracranial tension.13,22yet our knowledge of its pathogenesis and management is limited. Pulmonary edema is the most severe form of lung involvement. Increased alveolar capillary permeability leading to intravascular fluid loss into the lungs is the main pathophysiologic mechanism. This defines malaria as another cause of

acute lung injury (ALI Clinical trials in this area are lacking and further research is required to ascertain the efficacy and safety of various mechanical ventilatory strategies in patients with ARDS due to malaria.

Leptospirosis

Leptospirosis is a zooanthroponosis prevalent in tropical regions, caused by spirochete of the genus Leptospira. Pulmonary involvement in leptospirosis ranges from 20% to 70% and is usually benign, with an uncomplicated recovery. In the severe form, the prototype of which is Weil's disease, the disease may cause fatal pulmonary haemorrhage and respiratory failure, along with high fever, severe transaminitis, intense jaundice, hemorrhagic diathesis, renal dysfunction, neurological alterations, and cardiovascular collapse, with a mortality of upto 5%.23,24,25 Clinically, chest symptoms do not always correlate with the radiographic involvement. Pulmonary examination may be normal or reveal mild basal rales. Alveolar haemorrhage occurs secondary to capillary endothelial damage, resulting in a rapidly fatal outcome within 24 hours. Respiratory failure may also occur due pulmonary edema secondary to myocarditis or hypervolemia as a result of acute renal failure. Severe hemodynamic compromise, raised serum creatinine and hypokalemia are associated with early mortality in severe respiratory failure in leptospirosis.26 Radiographs typically reveal patchy alveolar infiltration that can conglomerate; interstitial infiltration, ground glass opacities, and pleural effusion are, however, uncommon.

The aetiology of ARDS in leptospirosis is unclear, and due to the paucity of neutrophilic inflammation in lung pathology specimens, a mechanism of lung injury by Jarisch–Herxheimer type reaction has been postulated.27 Diagnosis is made by demonstration of leptospira by dark field microcopy in bronchoalveolar lavage and urine or by inoculating in special culture media (Fletcher, Stuart, and Tween 80). Apart from these, serum IgM by ELISA technique and agglutination tests have a high sensitivity and specificity for leptospirosis.

Other Infectious causes of ARDS

Dengue is an important arboviral infection which presents as illness ranging from asymptomatic infection to dengue fever, dengue haemorrhagic fever (DHF), or dengue shock syndrome (DSS). Thrombocytopenia with concurrent hemoconcentration is a distinctive laboratory finding of DHF syndrome. Pulmonary manifestations are uncommon except for pleural effusions which may develop as a part of generalised capillary leak. ARDS in dengue is rarely reported and has good outcome with early initiation of mechanical ventilation and supportive therapy28.

Salmonella causes enteric fever and is widespread in tropical countries. It primarily presents with GI symptoms and fever. Pulmonary manifestations are the most common extra intestinal manifestations and ARDS has been reported in a few case reports.29,30 ARDS, if present, manifests in the early phase of illness and is often fatal. Early recognition and addition of effective antibiotics along with timely institution of ventilatory support may improve survival.

H1N1 Infection: Since the first documentation of the novel **influenza A virus (H1N1)** during the **Swine Flu** pandemic, its association with severe ARDS have been published in numerous case series from around the world.31–34. H1N1 can rapidly progress to acute respiratory distress syndrome, more commonly in younger patients and pregnant women, including those without co - morbidities, and is associated with a high mortality rate. The sensitivity of rapid antigen testing for influenza is low, so a high degree of suspicion is critical and should prompt empiric antiviral therapy along with lung protective ventilation. The use of Extracorporeal Membrane Oxygenation for refractory hypoxemia in severe ARDS has been shown to improve outcome in recent studies.35,36

Strongyloidosis is a nematodal infection prevalent in the tropics and causes minimal clinical manifestations in an immunocompetent host. However it may cause hyper infection in immunocompromised host and can be life-threatening. Pulmonary strongyloidiasis presents with cough, dyspnoea, wheezing, hemoptysis, and peripheral blood eosinophilia.37 ARDS is associated with hyper infection and mortality remains very high. Administration of antiparasitic agents may itself aggravate ARDS due to intrapulmonary destruction of a large number of larvae.38

Bacterial, viral and fungal pneumonias may present with ARDS which may be indistinguishable from the causes listed above. Apart from these, numerous other infections have also been associated with pulmonary involvement and ARDS, albeit uncommonly. Scrub typhus may present with dyspnoea and cough and progress to ARDS rapidly if appropriate antibiotics are not started on time.39 Similarly, acute pancreatitis and sepsis with multiorgan dysfunction from any cause may progress to ARDS. Drowning, poisoning with organophosphates and paraquat, toxic fume inhalation and heat stroke are all common non-infectious causes of ARDS In the tropics. Finally, extensive burn injury, chest trauma and severe musculoskeletal trauma may cause ARDS, and may develop superimposed infectious complications thereafter.

Conclusion

Infective causes of ARDS in the tropical zone are distinct compared to the temperate countries. Infections such as malaria, dengue and TB are encountered far more commonly. Since most patients are not proven by biochemical or microbiological methods, awareness of the complication with early recognition and prompt institution of directed therapy helps in limiting morbidity and mortality. With expanding respiratory critical care practice and the availability of intensive support including high-end ventilators and well equipped ICU's, the mortality due to these killer diseases is expected to decrease. Research should be directed at optimization of supportive treatment and ventilator strategies for ARDS due to these infections.

Table 1: Common causes of ARDS in the tropics.

Infections Tuberculosis Malaria Leptospirosis Scrub typhus Enteric fever Dengue haemorrhagic fever	**Inhalation of toxic fumes** Chlorine Methyl isocyanate Nitrogen dioxide Paraffin flames Methylene chloride	**Others** Severe pneumonia Aspiration Drowning Fat embolism Acute pancreatitis
Poisoning and Toxins Organophosphours compounds Paraquat	**Obstetric causes** **Heat stroke**	

Table 2: Recommended treatment for Complicated Malaria

Initial parenteral treatment for at least 48 hours: **ONE** of following four options	**Follow-up treatmen**t, when patient can take oral medication following parenteral treatment
QUININE: 20 mg quinine salt/kg body weight on admission (IV infusion or divided IM injection) followed by maintenance dose of 10 mg/kg 8 hourly; infusion rate should not exceed 5 mg/kg per hour. Loading dose of 20mg/kg should not be given if the patient has already received quinine.	**QUININE** 10 mg/kg three times a day **with** **DOXYCYCLINE** 100 mg once a day or **CLINDAMYCIN** in pregnant women and children under 8 years of age, - To complete 7 days of treatment.
ARTESUNATE: 2.4 mg/kg i.v. or i.m. given on admission (time=0), 12 hour, 24 hour, then once a day.	
ARTEMETHER: 3.2 mg/kg i.m. given on admission, followed by 1.6 mg/kg per day.	
ARTEETHER: 150 mg daily i.m for 3 days in adults only (not recommended for children).	

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