ACUTE RESPIRATORY DISTRESS SYNDROME IN THE TROPICS

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INTRODUCTION

The acute respiratory distress syndrome (ARDS) is a disease with high mortality and is an important cause of admission into intensive care units (ICUs) worldwide (1-6). The initial reports describing ARDS lacked specific criteria that could be used to identify patients with this syndrome systematically. In 1994, the European-American Consensus Conference (7) definition of ARDS was in vogue till recently. The Berlin definition of ARDS (Table 1) (8) is currently being used to define ARDS in the clinical setting as well as in recent clinical studies.

AETIOLOGY

Several conditions can cause ARDS. Of these, sepsis syndrome, polytrauma, obstetric complications, surgery, among others appear to be the most common causes of ARDS in the reports from the developed countries. However, several causes of ARDS not commonly seen in the developed world are sometimes encountered in the tropical countries (Table 2) (1,6). With increased international travel, they constitute an important but rare differential diagnosis of ARDS even in developed countries.

ARDS is a disease with high mortality especially in the tropical countries where facilities for intensive care and assisted ventilation are not widely available. Furthermore, the cost of ICU treatment is beyond the reach of most of the patients in the tropical countries. Since many of the causes of ARDS in the tropics are curable their early recognition and institution of specific treatment can be life saving. Some of the important treatable causes of ARDS in the tropics, their early recognition and therapeutic strategies that are available for their management are summarized below.

TUBERCULOSIS

Clinicians in tropical countries are familiar with the subacute or chronic nature of the clinical presentation of tuberculosis (TB). Acute presentation of TB, especially ARDS due to TB is not widely known even in areas where the disease is highly endemic (9,10). ARDS due to pulmonary and miliary TB has been described (11-13). Clinical presentation of ARDS in patients with TB is similar to that of ARDS due to any other cause. In a study from India (10), prolonged illness, miliary TB, absolute lymphocytopenia and elevated serum alanine aminotransferase were independently associated with the development of ARDS in patients with TB. Simple diagnostic methods such as smear microscopy and mycobacterial culture examination of the sputum, endotracheal aspirate are useful in early diagnosis of TB as the aetiological diagnosis.
In patients with miliary TB, careful physical examination for choroid tubercles, peripheral lymphadenopathy, judicious use of bone marrow aspiration and biopsy; lymph node and liver biopsy can help in confirming the diagnosis of TB (11,13). Institution of specific anti-TB treatment and where indicated, early initiation of mechanical ventilation, have been shown reduce the mortality in patients with ARDS due to TB. In a study from India (10) acute physiological and chronic health evaluation (APACHE II) score, serum sodium and ratio of the arterial oxygen tension and fraction of inspired oxygen (PaO₂/FIO₂) were found to be determinants of outcome in patients with ARDS due to TB.

MALARIA

ARDS is an important complication that has often been described in falciparum malaria and is increasingly being reported form the tropics as well as in returning travelers in developed countries (14-16). ARDS has also been documented in malaria caused by Plasmodium vivax, Plasmodium ovale and Plasmodium malariae (17). Factors, such as, sequestration of parasitized erythrocytes in the capillaries and post-capillary venules, and the production of pro-inflammatory cytokines, complement activation, disseminated intravascular coagulation (DIC), and associated bacterial sepsis are thought to be responsible for the causation of ARDS in malaria (14,17,18).

Development of ARDS itself is considered to be a poor prognostic marker in patients with falciparum malaria. Non-immune status, extremes of age, pregnancy, immunocompromised state, are associated with a poor outcome in patients with ARDS due to malaria.

In areas where malaria is endemic, repeated peripheral blood smear examination, examination of the bone marrow aspirate and use of rapid diagnostic tests such as the quantitative buffy coat examination may help in identifying malaria. Prompt institution of specific antimalarial treatment, in addition to mechanical ventilation can be life saving in these patients. Haemodialysis will be required in patients with acute kidney injury.

LEPTOSPIROSIS

Leptospirosis is a zoonotic disease commonly seen in frequent in agricultural labourers, sewage workers (19,20). It is transmitted from animals to humans through contact with contaminated water. In recent years, leptospirosis is increasingly being encountered in town and city dwellers also. Pulmonary manifestations of leptospirosis tend to develop late in the course of the disease
and can develop abruptly (19-25). Leptospirosis and falciparum malaria should be suspected in patients presenting with a short febrile illness, jaundice, renal failure and thrombocytopenia and the patient should be investigated to ascertain these causes. Dark field microscopy, enzyme linked immunosorbent assay (ELISA) and microscopic agglutination test are useful in confirming the diagnosis of leptospirosis. Early institution of antibiotic treatment with crystalline penicillin and doxycycline along with assisted mechanical ventilation can be rewarding (19-25).

**SCRUB TYPHUS**
In recent years, scrub typhus is emerging as an important cause of ARDS in the tropics (26,27). The spectrum of disease ranges from mild inapparent illness to a florid presentation with multiorgan dysfunction syndrome (MODS). Careful examination for the characteristic cutaneous lesion, “eschar” can help in early diagnosis of scrub typhus infection. Rapid diagnosis of scrub typhus can be made by an ELISA test (26,27). Early initiation of treatment with doxycycline can be life-saving.

**ENTERIC FEVER**
Pleuropulmonary complications are the most important extraintestinal manifestations in patients with enteric fever (28,29). ARDS is a rare complication in patients with enteric fever. It usually develops in the first two weeks of the illness and is associated with a high mortality rate (28,29). Blood culture, bone marrow culture confirm the diagnosis. Prompt recognition of the condition, early institution of mechanical ventilatory support and intravenous antibiotic treatment are required in these patients.

**DENGUE FEVER**
Dengue haemorrhagic fever has been implicated as a rare cause of ARDS in some reports from the tropics (30,31). The clinical presentation of ARDS in dengue haemorrhagic fever is similar to that observed in ARDS due to other causes and dengue fever must be suspected in patients presenting in the tropics with ARDS of obscure aetiology. Serological testing for immunoglobulin M (IgM) antibodies to dengue virus confirms the diagnosis (30,31).

**OBSTETRIC CAUSES**
In tropical countries where access to obstetric intensive care is not widely available, ARDS is an underreported cause of morbidity and mortality in pregnant women (5). In obstetric patients, septic abortion, chorioamnionitis, endometritis, amniotic fluid embolism, pregnancy induced
hypertension, haemolysis, elevated liver enzymes, low platelet count (HELLP) syndrome, acute fatty liver of pregnancy, are all associated with occurrence of ARDS (32-35). Less common causes of ARDS in obstetric patients include trophoblastic embolism, obstetric haemorrhage related causes, placental abruption and retained products of conception among others. Aspiration of gastric contents and pyelonephritis also result in ARDS in pregnant women. Prompt recognition and early intervention can be life-saving as ARDS causes high mortality to both the mother and the foetus (32-35).

POISONING AND OVERDOSAGE
Because of their easy availability, and cheap pricing, organophosphorous compound poisoning is a frequent cause of emergency room visit in India. ARDS can develop in these patients, sometimes as a late complication (36,37). Similarly, paraquat poisoning (38), propoxur poisoning (39) have also been implicated as a cause of ARDS.

INHALATION OF FUMES
Inhalation of methyl isocyanate (Bhopal gas tragedy), nitrogen dioxide, paraffin flames, methylene chloride, phosgene gas, chlorine gas inhalation have all been implicated in the causation of ARDS (4,40,41).

HEAT STROKE
ARDS has been described in about one fourth of the patients with heat stroke. This condition is highly fatal and has a mortality exceeding 75% (42). Patients often present with hyperpyrexia and may be unconscious.

OTHER CAUSES
Other important causes of ARDS in the tropics include severe pneumonia, aspiration, drowning, fat embolism, acute pancreatitis, among others (4,6,43). These patients must be monitored for the development of ARDS.

DIAGNOSTIC APPROACH
Patients with ARDS present with abrupt onset respiratory distress and manifest arterial hypoxaemia that is refractory to oxygen therapy. The diagnostic work-up required to confirm the aetiological diagnosis must be promptly initiated especially focusing on the causes prevalent in
the tropics discussed above. When the index of suspicion is high, early diagnosis is likely and will facilitate institution of specific therapy.

**PRINCIPLES OF MANAGEMENT**

Patients with ARDS should be managed in an ICU setting. Treatment of the primary cause of ARDS is of paramount importance. Attention should be paid to haemodynamic stabilization, fluid and electrolyte management, and ensuring adequate nutrition. When patients do not improve with oxygen administration, assisted ventilation may be required. Early initiation of mechanical ventilation can be life-saving.

**FUTURE DIRECTIONS**

The clinical presentation of ARDS in the tropics can be atypical and hence the diagnosis can be delayed. Early diagnosis of aetiologicla cause of ARDS is important because, timely institution of specific treatment can be life-saving. The need for developing rapid diagnostic tests for these neglected tropical diseases and making them available where they are most required at an affordable price needs to be addressed. Further, there is a need for capacity building in terms of providing intensive care that is accessible and affordable to every one.

**REFERENCES**


Table 1
ARDS: Berlin definition

<table>
<thead>
<tr>
<th>Variable</th>
<th>Acute respiratory distress syndrome</th>
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</thead>
<tbody>
<tr>
<td>Timing</td>
<td>Timing Within 1 week of a known clinical insult or new or worsening respiratory symptoms</td>
</tr>
<tr>
<td>Chest imaging*</td>
<td>Bilateral opacities not fully explained by effusions, lobar/lung collapse, or nodules</td>
</tr>
<tr>
<td>Origin of oedema</td>
<td>Respiratory failure not fully explained by cardiac failure or fluid overload</td>
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<td></td>
<td>Need objective assessment (e.g. echocardiography) to exclude hydrostatic oedema if no risk factor present</td>
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<tr>
<td>Oxygenation†</td>
<td>Mild: $200 \text{ mm Hg} &lt; \frac{\text{PaO}_2}{\text{FiO}_2} \leq 300 \text{ mm Hg}$ with PEEP or CPAP $\geq 5 \text{ cm } \text{H}_2\text{O}$†</td>
</tr>
<tr>
<td></td>
<td>Moderate: $100 \text{ mm Hg} &lt; \frac{\text{PaO}_2}{\text{FiO}_2} \leq 200 \text{ mm Hg}$ with PEEP $\geq 5 \text{ cm } \text{H}_2\text{O}$</td>
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<tr>
<td></td>
<td>Severe: $\frac{\text{PaO}_2}{\text{FiO}_2} &lt; 100 \text{ mm Hg}$ with PEEP $\geq 5 \text{ cm } \text{H}_2\text{O}$</td>
</tr>
</tbody>
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* Chest radiograph or computed tomography
† If altitude is higher than 1000 m, the correction factor should be calculated as follows: $\left[ \frac{\text{PaO}_2}{\text{FiO}_2} \times \left( \frac{\text{barometric pressure}}{760} \right) \right]$
‡ This may be delivered noninvasively in the mild acute respiratory distress syndrome group
PaO$_2$ = arterial oxygen tension; PaCO$_2$ = arterial carbon dioxide tension; FiO$_2$ = fraction of inspired oxygen; PEEP = positive end-expiratory pressure

Source: reference 8
<table>
<thead>
<tr>
<th>Infections</th>
<th>Poisoning and Toxins</th>
<th>Obstetric causes*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tuberculosis</td>
<td>Organophosphorous compounds</td>
<td>Heat stroke</td>
</tr>
<tr>
<td>Malaria</td>
<td>Paraquat</td>
<td>Others</td>
</tr>
<tr>
<td>Leptospirosis</td>
<td>Propoxur</td>
<td>Severe pneumonia</td>
</tr>
<tr>
<td>Scrub typhus</td>
<td>Inhalation of toxic fumes</td>
<td>Aspiration</td>
</tr>
<tr>
<td>Enteric fever</td>
<td>Chlorine</td>
<td>Drowning</td>
</tr>
<tr>
<td>Dengue haemorrhagic fever</td>
<td>Methyl isocyanate</td>
<td>Fat embolism</td>
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<tr>
<td></td>
<td>Nitrogen dioxide</td>
<td>Acute pancreatitis</td>
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<td></td>
<td>Paraffin flames</td>
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<td></td>
<td>Methylene chloride</td>
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* See text for details