Acute Respiratory Distress Syndrome in Children: a 10 Year Experience

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Abstract

Background: Acute respiratory distress syndrome is a well-recognized condition resulting in high permeability pulmonary edema associated with a high morbidity.

Objectives: To examine a 10 year experience of predisposing factors, describe the clinical course, and assess predictors of mortality in children with this syndrome.

Methods: The medical records of all admissions to the pediatric intensive care unit over a 10 year period were evaluated to identify children with ARDS[1]. Patients were considered to have ARDS if they met all of the following criteria: acute onset of diffuse bilateral pulmonary infiltrates of non-cardiac origin and severe hypoxemia defined by <200 partial pressure of oxygen during ≥6 cm H_2O positive end-expiratory pressure for a minimum of 24 hours. The medical records were reviewed for demographic, clinical, and physiologic information including PaO_2[2]/forced expiratory O_2, alveolar–arterial O_2 difference, and ventilation index.

Results: We identified 39 children with the adult respiratory distress syndrome. Mean age was 7.4 years (range 50 days to 16 years) and the male:female ratio was 24:15. Predisposing insults included sepsis, pneumonias, malignancy, major trauma, shock, aspiration, near drowning, burns, and envenomation. The mortality rate was 61.5%. Predictors of death included the PaO_2/FIO_2, ventilation index and A-aDO_2[3] on the second day after diagnosis. Nonsurvivors had significantly lower PaO_2/FIO_2 (116±12 vs. 175±8.3, $P<0.001$), and higher A-aDO_2 (368±28.9 vs. 228.0±15.5, $P<0.001$) and ventilation index (43.3±2.9 vs. 53.1±18.0, $P<0.001$) than survivors.

Conclusions: Local mortality outcome for ARDS is comparable to those in tertiary referral institutions in the United States and Western Europe. The PaO_2/FIO_2, A-aDO_2 and ventilation index are valuable for predicting outcome in ARDS by the second day of conventional therapy. The development of a local risk profile may allow early application of innovative therapies in this population.

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Acute respiratory distress syndrome has become a well-recognized condition that results in high permeability pulmonary edema [1–3]. Despite advances in patient care techniques and the presence of trained critical care pediatricians at tertiary centers, the fatality rate in children has remained in excess of 50% [3–5]. This has prompted interest in alternative approaches to providing supportive therapy for these patients, such as extracorporeal membrane oxygenation, perfluorocarbon-associated gas exchange, surfactant replacement, and high frequency ventilation [3–7]. However, with the rising cost of medical care, in particular expensive services such as intensive care, it is essential to determine when to provide limited resources and how to monitor their performance. Furthermore, the health care system in Israel is in the midst of a long process of reform in both concepts and services, focusing on policy making, setting of standards, quality control, and the collection and evaluation of essential data. Thus, the development of unconventional techniques in combination with financial constraints has made systematic evaluation of local medical care imperative.

This retrospective chart review examines predisposing factors, describes the clinical course, and assesses predictors of mortality in children with this syndrome in our pediatric intensive care unit. Identification of such predictors is essential before designing a future local clinical trial of extracorporeal membrane oxygenation or other high risk procedures for pediatric patients with ARDS.

Methods

The medical records of all patients with ARDS, respiratory failure, or respiratory insufficiency admitted to the pediatric intensive care unit at Sheba Medical Center from

1984 to 1994 were examined. Patients were considered to have ARDS if they met both of the following criteria: acute onset of diffuse bilateral pulmonary infiltrates of non-cardiac origin, *and* severe hypoxemia, defined as PaO_2 <200 mmHg during PEEP ≥6 cm H_2O simultaneous with continuous treatment with >0.5 FIO_2 for a minimum of 24 hours. Similar physiologic criteria have been used by other investigators to define ARDS in children [5,8]. Children with chronic respiratory failure (clinical symptoms of respiratory illness for >14 days before ICU admission) were excluded, as were children with respiratory failure due to neuromuscular disease or airway obstruction.

Information regarding age and predisposing conditions was obtained from the medical records. In addition to demographic information, daily values for the physiologic and biochemical variables used to manage critically ill children were obtained from the medical records and included: vital signs, arterial blood gas values, PEEP, FIO_2, ventilation rate, mean airway pressure, and ventilation index [6]. The A-aDO_2 gradient was determined for each blood gas measurement by the following formula: A-aDO_2=FIO_2×(barometric pressure–vapor pressure of water)–$PaCO_2$/0.8–PaO_2, with 0.8 representing the respiratory quotient (partial pressure of carbon dioxide, oxygen, in arterial blood) [6]. The ventilation index was determined by the following formula: ventilation index=$PaCO_2$[4] (mmHg)×peak airway pressure (cm H_2O)x respiratory rate (breaths/min)/1,000 [6]. We used the single peak or nadir of each variable for each patient to develop mortality predictors. The successful use of a single worst value system similar to ours was previously reported by Timmons et al. [5,8].

The mechanism whereby each acute disease or injury contributed to the development of ARDS in a patient was categorized as being direct or indirect. The mechanism was considered to be direct if the ARDS was caused by an acute primary pulmonary disease or injury; an indirect mechanism of lung injury was assigned to patients in whom ARDS developed in association with an acute non-pulmonary systemic disease or injury. In addition, all other coexisting conditions were noted for each patient, including the presence of a chronic disease.

Information relating to other organ system functions was extracted from the medical records. These included renal function (urine output, serum creatinine), hepatic function (aspartate aminotransferase, alanine aminotransferase, and total bilirubin levels), coagulation mechanism (prothrombin and partial thromboplastin times), and presence of infection (leukocyte count, fever, positive culture data, and use of antibiotics).

In addition to ARDS, other conditions warranted detailed definitions. Sepsis syndrome was identified by criteria similar to those used by Davis [7]: abnormal temperature (<35.5°C or >38.5°C), tachycardia, tachypnea, clinical evidence of an infection site, and at least one end organ demonstrating inadequate perfusion or dysfunction, as evidenced by altered cerebral function, hypoxemia, increased blood lactate concentration, or oliguria. Pneumonia, infectious or chemical, was defined as new infiltrates on a chest X-ray associated with a deterioration in pulmonary gas exchange. Hypotension was defined as a systolic blood pressure below the 5th percentile for age. Multiple organ failure was defined as the development of both liver failure and kidney failure after the onset of ARDS. Survival was defined as living until discharge from the PICU.

Ventilatory management of children with ARDS was in accordance with established therapeutic practices, as described by Timmons and co-workers [5,8]. Indications for continuous positive pressure ventilation were as follows: need for cardiopulmonary resuscitation, frank pulmonary edema, and respiratory distress or PaO_2 <55 torr after a typical trigger event. Techniques of pressure-limited ventilation with permissive hypercapnia were used occasionally since 1992, but not consistently during the study period. PEEP was applied in response to a low PaO_2 and clinical evidence of poor cardiovascular function (peripheral perfusion, urine output) — the goal being to reach FIO_2 values of <0.5 as quickly as possible. Weaning from the respirator was achieved with intermittent mandatory ventilation. Meticulous attention was directed to all aspects of patient monitoring and care, especially to problems such as infection, fluid overload and nutrition. In the presence of gastrointestinal failure, early parenteral alimentation using glucose, intralipid and amino acids was instituted. Tidal volume and mean airway pressure were not documented at 50% of the time points, hence these values were excluded from the review. During our study period none of the patients received other innovative therapies, such as high frequency ventilation, nitric oxide, or ECMO[5].

Analysis of variance with repeated measures-incomplete design [9] was used for statistical evaluation, and a P value <0.05 indicated statistical significance.

Results

During the study period 39 children met the criteria for the diagnosis of ARDS. The mean age was 7.4 years with a range of 0.2 to 16 years. The overall mortality rate was 61.5%. Figure 1A depicts the Kaplan-Meier 30 day survival curves [10]. Twenty-four patients were male (33.3% mortality rate) and 15 were female (46.7% mortality rate). The median duration of hospitalization was 13.3 days. Examination of the overall PICU course revealed a difference in duration of hospitalization between the outcome groups: Non-survivors were hospitalized for 9.4 days compared with 19.4 days in survivors.

A chronic disease (existing before the present hospitalization) was present in 13 patients. These included genetic, hepatic, lymphoproliferative disorders, and congenital heart disease. However, the presence of a pre-existing illness had no effect on mortality rate. In 41% of patients ARDS was induced by direct lung injury, in 84.6 and 25.6% respectively of the remaining patients it was associated with indirect or mixed injury. However, there was

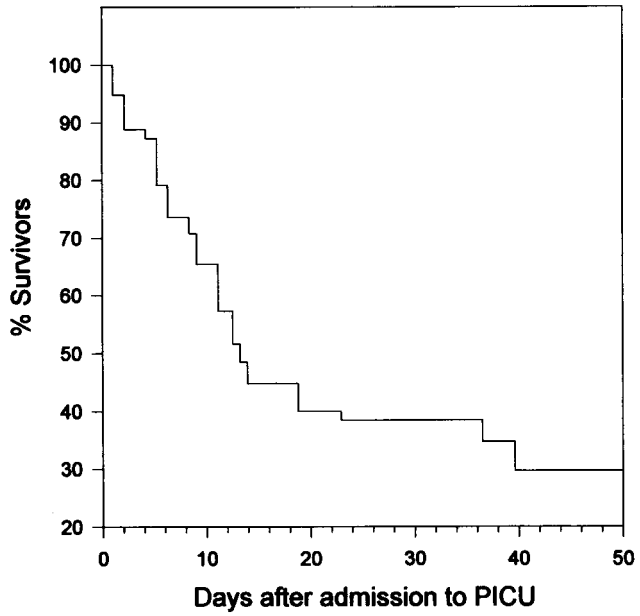

Figure 1A. Kaplan-Meier Plot of survival after admission to the PICU for respiratory failure in 39 patients.

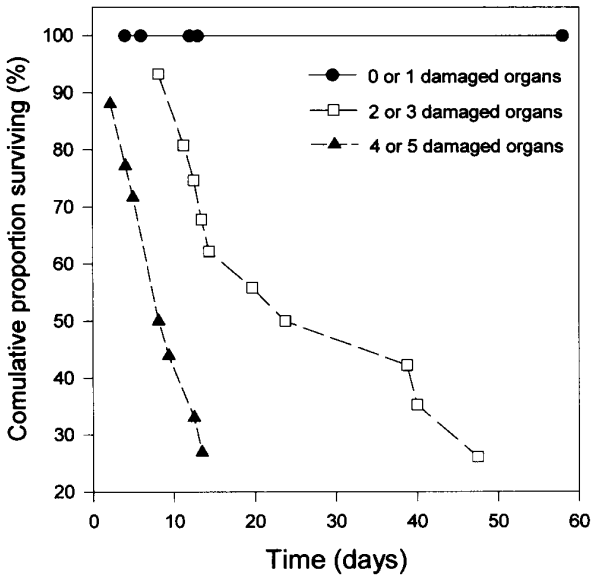

Figure 1B. Cumulative proportion surviving. Diagram shows the percentage mortality in patients with one or more system organ failure designated at enrollment.

no association between mortality rate and any particular mechanism of lung injury.

The acute diseases present in the ARDS patients included sepsis, pneumonias, malignancy, trauma, shock, aspiration, burns, hydrocarbon ingestion, drowning and envenomation [Table 1]. Sepsis syndrome was the most common, occurring in 59% of patients. In those children the most frequent organisms identified were *Pseudomonas aeruginosa, Staphylococcus aureus, Streptococcus* Groups A and D, *Pneumococcus*, *Acinetobacter, Salmonella, Enterobacter,* and *Candida*. When ARDS was triggered by sepsis the mortality rate was as high as 69.6%, compared to 50% in those without sepsis. Infectious pneumonia (25.6%) and malignancy (25.6%) were the next most common diseases in patients who met our definition of ARDS. The mortality rate for children with malignancy complicated by ARDS was significantly higher than in those without malignancy (90% vs. 51.7% respectively, $P<0.03$).

More than half the patients had abnormalities suggesting dysfunction of the kidney, liver, central nervous system, or circulatory system. Only abnormalities of circulation were significantly associated with mortality ($P<0.0004$); there were no significant differences between survivors and non-survivors with regard to any other organ system dysfunction. Nonetheless, non-survivors had significantly more organ systems involved than survivors: non-survivors had at least three organ system failures, compared with two in survivors ($P<0.05$). Furthermore, the time to death varied in the non-survivors, depending on the number of organ systems involved [Figure 1B]. The physiologic variables reflecting pulmonary gas exchange that correlated with outcome included PEEP, peak inspiratory pressure, the A-aDO_2, ventilation index, and PaO_2/FIO_2 from day 2 onward [Figure 2, Table 2]

Table 1. Etiology of acute respiratory distress syndrome in the 39 study children

Etiology	Total	*Mortality*
Sepsis	23 (59%)	*18 (58.1%)*
Pneumonia	10 (25.6%)	*7 (35%)*
Malignancy	10 (25.6%)	*11 (64.7%)*
Shock	6 (15.3%)	*6 (54.5%)*
Trauma	6 (15.3%)	*4 (57.1%)*
Aspiration	4 (10.2%)	*2 (33.3%)*
Burns	3 (7.6%)	*1 (33.3%)*
Drowning	2 (5.1%)	*0 (0%)*
Hydrocarbon ingestion	2 (5.1%)	*1 (50%)*

Table 2. Pulmonary variables in survivors and non-survivors with severe ARDS

Variable	Survivors (n=24)	Non-survivors (n=15)	P
Maximal PIP (cm H_20)	49.9	60.1*	<0.05
Maximal PEEP (cm H_20)	11.2	14.9*	<0.05
A-aD O_2	368±28.9	228.0±15.5*	<0.001
Ventilation Index	43.3±2.9	53.1±8.0*	<0.001
PaO_2/FIO_2	175.0 ±8.3	116± 12*	<0.001

* Significant differences between survivors and non-survivors ($P<0.05$).
PEEP and PIP values were taken from each patient's maximum level of support during the PICU course.
Ventilation Index, A-a DO_2 and PaO_2/FIO_2 were analyzed by using the single peak of each variable.

All children received antibiotics for proven or suspected bacterial infections: 24 patients received high dose corticosteroid therapy, and 22 were treated with diuretics. Inotropic support was used in all patients: 28, 9, and 17 patients received dopamine, dobutamine and adrenaline respectively.

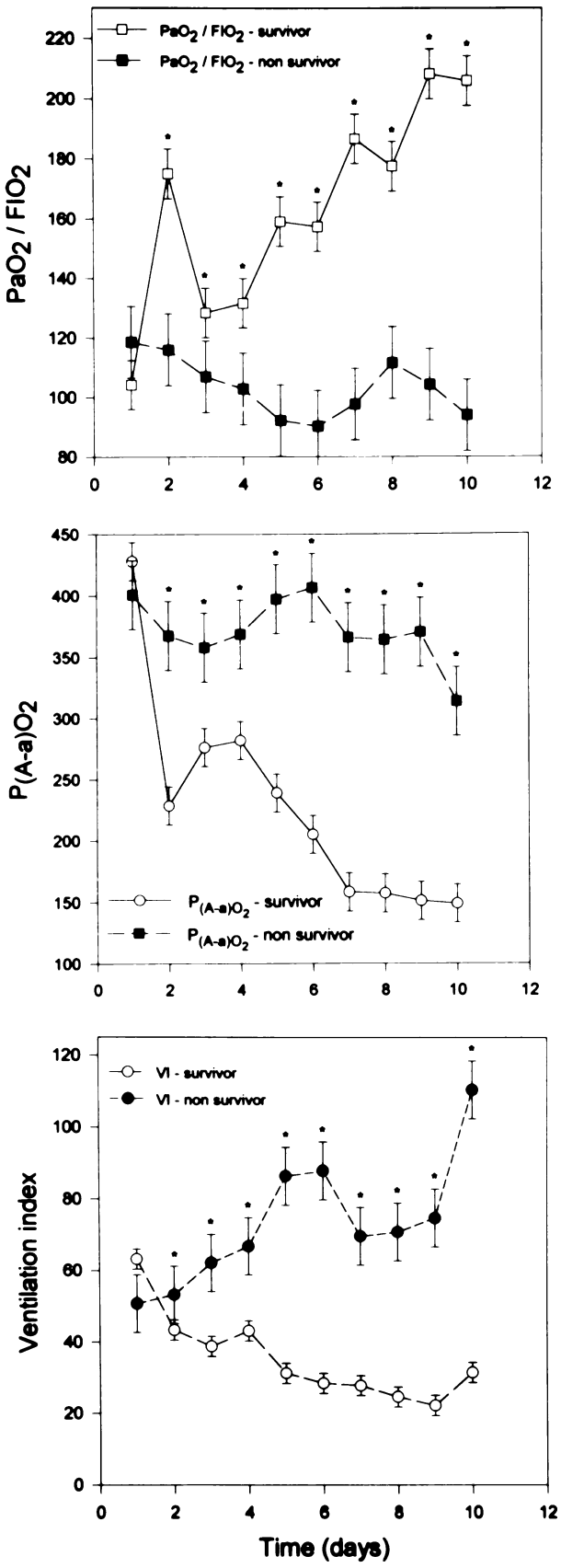

Figure 2. PaO_2/FIO_2 (Panel A), A-aDO_2 (Panel B), and ventilation index (Panel C) vs. study day by survival. Values are mean±SEM. *$P<0.05$

Discussion

Reports of the incidence and subsequent mortality of ARDS has primarily come from the experiences of large tertiary referral centers, particularly in Western Europe and the USA [2–7]. Consequently, very little has been published on the etiology, incidence, management and outcome of ARDS in smaller intensive care units. We used strict criteria for the diagnosis of ARDS, and by using both a 24 hour requirement for severe hypoxemia and a Murray disease severity score greater than 2.5 we ensured that our group consisted only of children with severe ARDS [11]. The acute diseases associated with ARDS in this study were similar to those in previous reports [2–8].

The reported range of mortality for pediatric ARDS during the 1980s and early 1990s was 29–94% [2–5]. For pediatric ARDS resulting from multiple insults, conventional therapy with mechanical ventilation has a reported mortality rate varying from 35 to 90% [2–8]. The case fatality rate of our sample was 61 — comparable to the mortality rate reported in pediatric reviews during the past decade. Recent experience describes a 75% mortality risk for patients with ARDS who required mechanical ventilation with a PEEP of 6 cm H_2O and an FIO_2 of 0.5 [5].

The development of mortality predictors early in the illness, when the lung disease is still reversible, may allow the timely application of new alternative treatment techniques. Furthermore, long-term pulmonary function is generally good in patients who survive, regardless of the severity of their respiratory failure [12,13]. Thus, accurate differentiation of survivors from non-survivors is necessary in order to minimize the risk of new alternative techniques, and to allow early and accurate identification of the child certain to die despite best management. However, predicting mortality in non-neonatal ARDS has been complex, because of the variable institutional experience and varied selection criteria for using the rapidly evolving array of new technologies [8,14,15]. Thus, each institution that uses experimental techniques should review its data to determine local predictors of mortality [8,14,16].

There were no significant differences in the ventilation index and A-aDO_2 between survivors and non-survivors during the initial 24 hour period [Figure 2]. However, outcome groups could be identified as early as the second day by referring to the ventilation index, A-aDO_2, and PaO_2/FIO_2. These findings agree with those of previous studies in adults and children with ARDS [12,13].

Higher mechanical ventilation PIP and PEEP were also associated with poorer outcome [Table 1]. This may be related to the degree of pulmonary injury, with more severely injured lungs requiring higher pressures for gas exchange; or alternatively, higher PIP might cause more barotrauma, stress failure of pulmonary capillaries, and further pulmonary injury [2,18].

The correlation between survival and number of organ dysfunctions in our study is in accordance with previous reports [18]. Examination of the etiology of ARDS re-

vealed that only sepsis was associated with a significant risk of mortality. However, neither the presence of a pre-existing disease nor the mechanism of the lung injury correlated with outcome.

The main limitation of our analysis is that due to the retrospective nature of the study, only limited clinical information was collected during the course of the ICU stay. Because ARDS in children is rare, we required 10 years to investigate 39 patients. Furthermore, we were unable to evaluate the role of specific treatment factors, such as changes in mechanical ventilation techniques, in patient outcome. For example, permissive hypercapnea has been used in our institution since 1992 in only two selected patients. However, the small number of patients and the non-randomization of innovative techniques make it difficult to evaluate the role of these techniques in patient survival.

In conclusion, our data show that our outcomes are comparable to those of large tertiary referral centers, particularly in Western Europe and the U.S. The development of a local risk profile may allow early selective application of innovative therapies in our patient population.

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[1] ARDS = acute respiratory distress syndrome
[2] PaO_2 = partial pressure of oxygen
[3] A-aDO_2 = alveolar–arterial O_2 difference
[4] $PaCO_2$ = partial pressure of carbon dioxide
[5] ECMO = extracorporeal membrane oxygenation

The mind is not a vessel to be filled but a fire to be kindled.

Plutarch

Capsule

Yersinia — multiple threat

Bacterial pathogens can inject target cells with virulence factors. Orth et el. have determined that a virulence factor of *Yersinia pseudotuberculosis,* the YopJ protein, can bind to several members of the mitogen-activated protein kinase (MAPK) superfamily and prevent their phosphorylation and activation. This binding resulted in a specific block in signaling pathways that would otherwise have led to cytokine synthesis and apoptosis, both of which are involved in host defenses against bacterial infection. Proteins related to YopJ are found in many bacteria that are plant and animal pathogens.

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