

5-1-1997

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S. Sritippayawan

J. Deerojanawong

N. Prapphal

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Recommended Citation

Sritippayawan, S.; Deerojanawong, J.; and Prapphal, N. (1997) "Factors associated with ARDS in childhood pneumonia," *Chulalongkorn Medical Journal*: Vol. 41: Iss. 5, Article 4.

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Factors associated with ARDS in childhood pneumonia.

Suchada Sritippayawan*

Jitladda Deerojanawong* Nuanchan Prapphal*

Sritippayawan S, Deerojanawong J, Prapphal N. Factors associated with ARDS in childhood pneumonia. *Chula Med J* May;41(5): 357-66

Objective : *To identify factors associated with Accute Respiratory Distress Syndrome (ARDS) in childhood pneumonia.*

Design : *Cross-sectional, retrospective study*

Settings : *Department of Pediatrics, Faculty of Medicine, Chulalongkorn University*

Materials and methods : *The medical records of 27 patients with the diagnosis of pneumonia (age 39.9±45.7 months) and developed ARDS during January 1989 - May 1996 were reviewed. Their data concerning history of illness, clinical manifestations and laboratory findings were compared with those of 550 patients (age 38.3±51.3 months) who had pneumonia without respiratory failure during the same period of time.*

The two tailed unpaired T-test, Chi-Square and Fischer Exact test were used for statistical analysis. The factors with p value < 0.05 were considered statistically significant.

Results : *There was statistical difference between pneumonia with ARDS and pneumonia without ARDS group in terms of underlying diseases predisposed to respiratory tract infections (77.8% vs 36%), signs of severe hypoxia such as systolic blood pressures below the 50th percentile for their age (37.3% vs 0%), decreased level of consciousness (66.7% vs 4%), cyanosis in room air (81.5% vs 0%), use of accessory respiratory muscles (92.6% vs 12%) and undetectable abnormal lung sounds (51.6% vs 2%) on admission. Concerning the initial laboratory findings, peripheral white blood cell counts below -2 SD for their age was significantly associated with ARDS in pneumonia patients (25.9% vs 0%)*

Conclusion : *From this study, factors significantly associated with ARDS in childhood pneumonia were the presence of underlying diseases predisposed to respiratory tract infections, systolic blood pressure lower than 50th percentile for their age, decreased level of consciousness, cyanosis in room air, use of accessory respiratory muscles, undetectable abnormal lung sound and peripheral white blood cell counts lower than - 2SD for their age on admission.*

We recommend urgent and appropriate management in the patients with the above mentioned factors are mandatory to decrease their morbidity and mortality due to ARDS.

Key words : *ARDS, Childhood pneumonia.*

Reprint request: Sritippayawan S, Department of Pediatrics, Faculty of Medicine, Chulalongkorn University, Bangkok 10330, Thailand.

Received for publication. March 14, 1997.

สุชาติ ศรียพาวรรณ, จิตลัดดา ตีโรจนวงศ์, นวลจันทร์ ปรามพาล. ปัจจัยสัมพันธ์ต่อการเกิด ARDS ในผู้ป่วยเด็กที่มีปอดอักเสบ . จุฬาลงกรณ์เวชสาร พ.ศ;41(5): 357-66

- วัตถุประสงค์** : เพื่อหาปัจจัยที่สัมพันธ์ต่อการเกิด ARDS ในผู้ป่วยเด็กที่มีปอดอักเสบ
- สถาบัน** : ภาควิชากุมารเวชศาสตร์ คณะแพทยศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย
- แบบการวิจัย** : การศึกษาแบบย้อนหลังเชิงวิเคราะห์
- การคัดเลือกผู้ป่วย** : ผู้ป่วยเด็กที่ได้รับการวินิจฉัยว่าเป็นปอดอักเสบและมี ARDS ร่วมด้วย ซึ่งเข้ารับการรักษาที่ภาควิชากุมารเวชศาสตร์ โรงพยาบาลจุฬาลงกรณ์ ในระหว่างเดือนมกราคม พ.ศ. 2532 ถึงเดือนพฤษภาคม พ.ศ. 2539 จำนวน 27 คน (อายุเฉลี่ย 39.9 ± 45.7 เดือน) เปรียบเทียบกับผู้ป่วยเด็กที่ได้รับการวินิจฉัยว่าเป็นปอดอักเสบโดยไม่มี ARDS ร่วมด้วย และเข้ารับการรักษาในโรงพยาบาลในช่วงเวลาเดียวกัน จำนวน 50 คน (อายุเฉลี่ย 38.3 ± 51.3 เดือน)
- วิธีการทำวิจัย** : วัดผลและวิเคราะห์ทางสถิติ : รวบรวมข้อมูลจากระเบียนประวัติผู้ป่วย และเปรียบเทียบผู้ป่วยทั้ง 2 กลุ่ม ในแง่ของอายุ, เพศ, ประวัติการเจ็บป่วย, ผลการตรวจร่างกายและการตรวจทางห้องปฏิบัติการตอนแรกเริ่ม วิเคราะห์ทางสถิติโดยใช้ two tailed unpaired T-test, Chi-Square หรือ Fischer Exact test กำหนดช่วงระดับความเชื่อมั่นที่ 95%
- ผลการศึกษา** : พบว่ามีความแตกต่างกันอย่างมีนัยสำคัญทางสถิติระหว่างผู้ป่วยปอดอักเสบที่มี ARDS และไม่มี ARDS ในแง่ของการมีโรคดั้งเดิมซึ่งเสี่ยงต่อการติดเชื้อในระบบหายใจ (77.8% vs 36%), ผลการตรวจร่างกายตอนแรกเริ่ม มีความดันซิสโตลิตต่ำกว่าเปอร์เซนต์ไทล์ที่ 50 เมื่อเทียบตามเกณฑ์อายุ (37.3% vs 0%), ระดับการรูสดีลดลง (66.7% vs 4%), อาการเขียวขณะไม่ได้รับออกซิเจน (81.5% vs 0%), การใช้กล้ามเนื้อช่วยในการหายใจ (92.6% vs 12%) และฟังไม่ได้ยินเสียงหายใจผิดปกติ (51.6% vs 2%) นอกจากนี้ พบจำนวนเม็ดเลือดขาวในกระแสเลือดตอนแรกเริ่มที่ต่ำกว่า $-2SD$ เมื่อเทียบตามเกณฑ์อายุในกลุ่ม ARDS มากกว่ากลุ่มที่ไม่มี ARDS อย่างมีนัยสำคัญทางสถิติ (25.9% vs 0%)

สรุป

: ปัจจัยสัมพันธ์ต่อการเกิด ARDS ในผู้ป่วยเด็กที่มีปอดอักเสบ ได้แก่ การพบว่ามีโรคดั้งเดิมซึ่งเสี่ยงต่อการติดเชื้อในระบบหายใจ, ผลการตรวจร่างกายตอนแรกพบพบว่ามีความดันซิสโตลิตต่ำกว่าเปอร์เซนไทล์ที่ 50 เมื่อเทียบตามเกณฑ์อายุ, ระดับการรู้สติลดลง, อาการเขียวขณะไม่ได้รับออกซิเจน, ใช้กล้ามเนื้อช่วยในการหายใจและฟังไม่ได้ยินเสียงหายใจผิดปกติ, ผลการตรวจทางห้องปฏิบัติการตอนแรกพบพบจำนวนเม็ดเลือดขาวในกระแสเลือดต่ำกว่า $-2SD$ เมื่อเทียบตามเกณฑ์อายุ ดังนั้น ในผู้ป่วยเด็กที่เป็นปอดอักเสบที่มีปัจจัยดังกล่าว ควรได้รับการดูแลรักษาอย่างใกล้ชิด และรักษา underlying disease ตลอดจนภาวะหายใจลำบากอย่างเหมาะสมเพื่อลดอัตราการตายและความพิการอันจะเกิดตามมาได้

Pneumonia is one of the leading causes of death among children in developing countries. In Thailand, it is the second most frequent cause of death in children under 5 years of age,⁽¹⁾ and the most common infectious cause of death among the same age group of children.⁽¹⁾

A number of studies concerning factors associated with respiratory failure or death in childhood pneumonia have been reported. Dr. Suwanjutha and her colleagues reported the results of their study in children under 5 with acute respiratory tract infection between 1986-1987 that underlying heart disease, low birth weight (less than 2,500 grams), prematurity (gestational age below 37 weeks), no antibiotic usage prior to admission and overcrowded family conditions (more than 1 child per family) were the significant risk factors for respiratory failure.⁽²⁾ In addition, the study of Sunakorn P, et al between 1984 - 1991 also showed that significant risk factors of fatal pneumonia in the same age group were underlying congenital heart diseases, severe malnutrition, low socioeconomic status, prolonged periods of respiratory distress (more than 8-14 days), low birth weight and the presence of chest indrawing at the time of admission.⁽³⁾

ARDS (Adult Respiratory Distress Syndrome or Acute Respiratory Distress Syndrome) is a symptom complex characterized by dyspnea, tachypnea, cyanosis refractory to oxygen therapy, decreased lung compliance and diffuse alveolar infiltration. It is the result of diffuse alveolocapillary injury due to a variety of predisposing factors

such as sepsis, pneumonia, shock etc.^(4,5,7,8,10-13)

Pneumonia is attributed to approximately 60% of ARDS cases among Thai children⁽⁵⁾ and their mortality rate ranged from 35% to 90%.^(4,5)

The common complications found during treatment were infection, oxygen toxicity, multiple organ dysfunction and barotrauma from positive pressure ventilation. Pulmonary hemorrhage and multiple organ failure were considered to be the more important complications leading to death.^(4,5,8,12)

Moreover, ARDS survivors were reported to have significant pulmonary sequelae such as decreased lung volume and diffusion capacity, airway hyperreactivity, laryngotracheal abnormalities resulting from prolonged mechanical ventilation and pulmonary hypertension.^(4,5,8)

Thus, it is essential to identify the patients at risk and provide appropriate management as early as possible in order to reduce their morbidity and mortality.

Materials and Methods

The medical records of 27 pediatric patients with the diagnosis of pneumonia who were admitted at the Department of Pediatrics of Chulalongkorn Hospital during the period January 1989 to May 1996 and who developed ARDS were reviewed. Their history of illness, clinical characteristics and laboratory findings were compared with those of 50 other patients diagnosed to have pneumonia without respiratory failure or ARDS during the same period of time.

The diagnostic criteria for pneumonia in this study was:⁽⁶⁾

1. Fever
2. Tachypnea
3. Abnormal chest x-ray findings compatible with pneumonia such as lobular, segmental or lobar infiltration.

The diagnostic criteria for ARDS was:^(7,8)

1. Previously normal lungs
2. Exclusion of left heart disease and congestive heart failure.
3. Lung injury scores > 2.5 ^(7,8)

Demographic data (age, sex), history of illness prior to admission, clinical manifestations and laboratory findings were analysed to identify the difference between the ARDS and non-ARDS groups by using the Chi-Square test, Fischer Exact test and two-tailed unpaired T-test where appropriate for statistical analysis (tables 1, 2 and

3). The factors with p-value less than 0.05 were considered statistically significant.

Results

Among the 27 patients who were diagnosed with pneumonia and who developed ARDS were aged between 1 month to 13 years. The mean age was 39.9 ± 45.9 months, and the male : female ratio was 1.25 : 1 while the mean age in the non-ARDS group was 38.3 ± 51.3 months, and the male : female ratio was 0.85 : 1. There was no statistical difference in age and gender between the two groups. The mortality rate in the ARDS group was 66.7% while none of the non-ARDS group died. Seventy seven percent of the ARDS patients (21/27 cases) had associated diseases predisposing them to respiratory infections. This incidence was significantly higher than those of the non-ARDS group (table 1). The most common

Table 1. Age, sex and history of illness.

Variables	Pneumonia with ARDS (n = 27)	Pneumonia without ARDS (n = 50)	p value
- Age (month) ($\bar{X} \pm SD$)	39.9 \pm 45.7	38.3 \pm 51.3	NS*
- Sex (male : female)	15 : 12	23 : 27	NS
- Duration of symptoms (days) ($\bar{X} \pm SD$)	3.5 \pm 3.3	3.3 \pm 2.3	NS
- Previous antibiotic treatment	16(59.3%)	24(48%)	NS
- Underlying diseases	21(77.8%)	18(36%)	0.001
- Past history of pneumonia	4(14.8%)	12(24%)	NS

* NS = no statistical significance

underlying or associated disease was malignancy (13/21 cases). The remainders were HIV disease (4/21 cases), post splenectomy (1/21 case) and Down's syndrome (1/21 case).

Concerning the clinical manifestations at the time of admission, the ARDS group had significantly higher percentages of systolic blood pressure less than 50th percentile for age, decreased

levels of consciousness, cyanosis in room air, use of accessory respiratory muscles and undetectable adventitious lung sound as compared to the non-ARDS group (table 2). There was no statistically significant difference between the two groups in terms of heart rate, respiratory rate, body temperature and body weight.

Table 2. Clinical manifestations.

Signs and symptoms	Pneumonia with ARDS (n = 27)	Pneumonia without ARDS (n = 50)	p value
- SP ⁺ <P 50 [#] for age ⁽¹⁴⁾	9(33.3%)	-	<0.001
- HR(/min)($\bar{X} \pm SD$)	148 \pm 19.3	134 \pm 17.9	NS
- RR(/min)($\bar{X} \pm SD$)	68 \pm 12.9	53 \pm 11.6	NS
- BT(^o C)($\bar{X} \pm SD$)	38.2 \pm 1.2	38.2 \pm 0.9	NS
- BW <P50	17(63%)	26(52%)	NS
- Decreased level of consciousness	18(66.7%)	2(4%)	<0.001
- Cyanosis in room air	22(81.5%)	-	<0.001
- Use of accessory respiratory muscles	25(92.6%)	6(12%)	<0.001
- Undetectable abnormal lung sound	14(51.6%)	1(2%)	<0.001

+ SP = systolic blood pressure

P50 = 50th percentile

Peripheral white blood cell counts of less than -2SD for age was the only laboratory finding in the ARDS patients that was significantly different from the non-ARDS group (table 3). All 7 of the cases with decreased white blood cell counts had been treated with chemotherapeutic agents for their malignant diseases.

Hemoculture was positive in 2 cases, or 2.6% of the patients enrolled in this study. Both cases had severe pneumonia and developed ARDS. One of these patient, without underlying disease, grew *Staphylococcus aureus* in both his blood and sputum cultures. The other patient had leukemia and *Klebsiella pneumoniae* in his

Table 3. Initial laboratory investigations.

Lab findings	Pneumonia with ARDS (n = 27)	Pneumonia without ARDS (n = 50)	p value
- Hb <-2SD for age ⁽⁹⁾	13(40.7%)	13(26%)	NS
- WBC			
> +2SD for age ⁽⁹⁾	9(33.3%)	18(36%)	NS
< -2SD for age ⁽⁹⁾	7(25.9%)	-	<0.001
- % neutrophil			
< mean for age ⁽⁹⁾	22(88%)	38(76%)	NS
- Hemoculture +ve	2(7.4%)	-	NS
- Sputum culture +ve	7(25.9%)	15(30%)	NS

hemoculture. None of the non-ARDS group had positive blood cultures. However, this finding was not statistically significant.

Discussion

ARDS is a respiratory syndrome resulting from diffuse alveolocapillary injuries either directly from a number of factors such as pneumonia, chemical pneumonitis, hypovolemic shock etc., or indirectly from mediators which were released from inflamed cells in response to systemic inflammatory reactions found in specific conditions such as sepsis, acute pancreatitis etc.^(4,7,8,10-12)

Diffuse alveolocapillary injuries result in the damage of type II pneumocytes and leakage of proteinaceous fluid into alveolar spaces which reduces the production and enhances the inacti-

vation of surfactant. Loss of surfactant leads to alveolar collapse, reduced FRC (functional residual capacity) and lung compliance and ventilation-perfusion mismatch. These pathophysiologic changes will cause refractory hypoxemia. PEEP (positive end expiratory pressure) is needed in the mechanical ventilation to correct the hypoxemia. As a result of positive pressure ventilation and the high level of PEEP, serious respiratory and cardiovascular complications may occur.

Patients at risk for ARDS are those predisposed to alveolocapillary injuries. Sepsis, pneumonia, shock and trauma are commonly reported predisposing factors of ARDS in children and adults.^(4,5,8,10-12) In children, an increased incidence of ARDS was reported in immune deficient patients such as those with

HIV disease, malignancy and those who were receiving immunosuppressive drugs. These patients were predisposed to severe infections and septic shock unless appropriate and prompt intervention was given.⁽⁴⁾

In our study, the significant factors associated with ARDS in childhood pneumonia were the presence of underlying conditions predisposing to respiratory tract infections, such as immunodeficiency diseases. This finding supported previous reports in children.⁽⁴⁾ In addition, we found that signs of severe hypoxia such as hypotension, cyanosis in room air, decreased levels of consciousness and use of accessory respiratory muscles which were detected at the time of admission were also significant associated factors. Moreover, undetectable adventitious lung sound was also an important sign suggestive of the development of ARDS in children with pneumonia. This may be due to the weakness of the respiratory effort from the more severe illness of the ARDS patients who could not produce enough airflow velocity during the inspiratory and expiratory phases of respiration to create any detectable abnormal lung sound.

In conclusion, the factors associated with ARDS in childhood pneumonia in our study included the presence of underlying diseases which predisposed the patient to respiratory tract infections, systolic blood pressures less than the 50th percentile for age, cyanosis in room air, decreased levels of consciousness, use of accessory respiratory muscles, undetectable adventitious lung

sound and peripheral white blood cell counts of less than -2SD for age.

We recommend urgent and appropriate management, including closed monitoring of respiratory status and blood gas analysis, for those patients with the above mentioned factors in order to decrease their morbidity and mortality.

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