

PEDIATRIC ACUTE RESPIRATORY DISTRESS SYNDROME

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There is a lack of epidemiological data related to acute respiratory distress syndrome (ARDS) among pediatric patients. The aim of this study was to determine the incidence, comorbidity and outcome in patients with ARDS treated in tertiary level pediatric intensive care unit (PICU). This retrospective cohort study included patients aged 1 month to 18 years treated at PICU during a five-year period (June 2004 to July 2009) that fulfilled all criteria for the diagnosis of ARDS according to the 1994 North American-European Consensus Conference on ARDS criteria. The incidence of ARDS among critically ill children older than 1 month was 5.7 cases per 1.000 patient-years. ARDS usually developed in a clinical framework of sepsis and severe lower respiratory tract infections. ARDS has a high share in mortality of PICU patients aged 1 month to 18 years, with a mortality rate of 25%, accounting for 10.71% of the total number of deaths in this age group. In patients with ARDS, fatal outcome is almost 6 times more frequent comparing to other life-threatened patients.

Descriptors: RESPIRATORY DISTRESS SYNDROME; INFANT; CHILD, PRESCHOOL; CHILD; ADOLESCENT

INTRODUCTION

Acute respiratory distress syndrome (ARDS) manifests with severe respiratory insufficiency, which always occurs within the framework of other conditions such as shock, infection, trauma, aspiration of gastric contents, inhalation of toxic gases, poisoning, etc. and additionally complicate the already severe clinical course. Sir William Osler gave the first description of a disease corresponding to clinical presentation of ARDS in the 19th century (1). However, more than half century later, in 1967, Ashbaugh, Bigelow and Petty published a paper with first clinical and histopathologic description of ARDS. In the decades that followed, a number of vague definitions of ARDS were in use. Unclear criteria for the diagnosis of ARDS made its recogni-

tion very difficult, so it was almost impossible to precisely assess and monitor the incidence of ARDS. Finally, in 1994, an internationally accepted consensus for the definition and diagnostic criteria of ARDS was introduced (North American-European Consensus Conference acute lung injury criteria). According to this consensus, ARDS is defined as acute respiratory failure followed by development of bilateral lung infiltrates of noncardiogenic origin, with $\text{PaO}_2/\text{FiO}_2 \leq 200$ (PaO_2 in mm Hg, FiO_2 as a decimal number). With respect to these diagnostic criteria, several population-based studies, mainly including adult patients, were conducted and they showed great variability in the incidence ranging from 1.5-3.5 per 100.000 through 4.5 per 100.000 in the United Kingdom and up to 50.7-64.3 per 100.000 in the United States (2-4). Epidemiological data on ARDS among pediatric patients are rarely reported in the literature. Search through available electronic databases revealed only two studies that addressed this problem and few more studies that beside patients with ARDS included patients with a milder form of the

disease, acute lung injury (ALI), defined with $200 \leq \text{PaO}_2/\text{FiO}_2 \leq 300$.

OBJECTIVE

To determine the incidence, morbidity and mortality in children with ARDS treated at tertiary level pediatric intensive care unit (PICU).

MATERIAL AND METHODS

This study was conducted at a tertiary level PICU during a 5-year period, in the region of Vojvodina (Serbia), with an estimated population of 370.099 children aged up to 18 years, and around 350.000 children aged 1 month to 18 years (as estimated by Statistical Office of the Republic of Serbia for 2009). PICU is designed as a combined neonatal and pediatric intensive care unit for all patients up to 18 years of age, excluding primarily surgical patients (e.g., trauma, burns and postoperative recovery), hospitalized at other specialized department.

This retrospective cohort study included all patients beyond neonatal period

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(aged 1 month to 18 years), who were treated at PICU during the 5-year period (June 2004 to June 2009). All patients included in the study required noninvasive or invasive respiratory support with additional oxygen in inspired air at concentration $\geq 40\%$. The diagnosis of ARDS was made according to the 1994 North American-European Consensus Conference acute lung injury criteria. Patients were followed up until discharge from the hospital. The methods of descriptive statistics were used on data processing.

RESULTS

A total of 420 children aged 1 month to 18 years were hospitalized during the observation period. Inclusion criteria, e. g., criteria for the diagnosis of ARDS, were completely fulfilled in 12/420 (2.86%) patients. ARDS developed within the framework of generalized bacterial infection and lower respiratory tract infection in 4/12 (33.33%) patients each, systemic disease in 1/12 (8.33%) patient, near-drowning in 2/12 (16.66%) patients and heroin overdose in 1/12 (8.33%) patient. Primary lung injury was the cause of ARDS in 6/12 (50%) patients. Synchronized intermittent mechanical ventilation (SIMV) was the mode of ventilatory support most commonly used. Duration of ventilatory support among survivors ranged from 2 to 22 days. Indications for extubation were resolution/stabilization of disease process, spontaneous respirations, hemodynamically stable patient, acceptable ventilator settings ($\text{FiO}_2 < 50\%$, $\text{PEEP} < 8$, $\text{PaO}_2/\text{FiO}_2 > 300$, $\text{pH} > 7.25$). Among ARDS patients, 3/12 (25%) children died, accounting for 10.71% of the total number of deaths ($n=28$, total number of deaths regardless of cause) in the age group observed during follow-up period. In patients with ARDS, fatal outcome was recorded in 3/12 (25%) patients, whereas the mortality in the entire age group was 28/420 or 6.67%, and in patients without ARDS it was 25/408 or 6.13% ($\text{OR}=5.44$ and $\text{RR}=5.92$). The calculated incidence of ARDS among critically ill children older than 1 month, according to our sample was 5.7 cases per 1000 patient-years.

DISCUSSION

Published data on the incidence of ARDS in the general pediatric population

range from 2.2 - 3.2 (1.5 - 6.6) per 100.000 children annually (5, 6). Among PICU patients, the arbitrarily estimated incidence of ARDS is approximately 1% (1). Martin et al. (5) report on the incidence of ARDS among PICU patients of 7.7% and a group of Dutch authors of 7% (7). According to data from an Australian study (8), among PICU patients younger than 16 years the cumulative incidence of ALI and ARDS is 2.2%. The incidence of ARDS in our sample was 2.86%, and the calculated incidence rate was 5.7 per 1.000 patient-years. Low participation of ARDS in the structure of morbidity of vulnerable pediatric patients may be explained in several ways. In a recent article, Schuster (9) points out that the definition of ARDS is still controversial and that the 1994 North American-European Consensus Conference acute lung injury criteria have not provided a uniform and precise algorithm for accurate diagnosis. He suggests that there is no appropriate diagnostic procedure to confirm undoubtedly the diagnosis of ARDS and that the diagnosis of ARDS (ideally) should not be a diagnosis of exclusion but should instead depend on some direct measure of lung injury. Therefore, he proposes correction of definition and criteria for the diagnosis of ARDS. In the study by Rodríguez et al., the North American-European Consensus Conference acute lung injury criteria definition yielded a sensitivity of 80.7% (95% confidence interval 60-92), specificity of 71.4% (95% confidence interval 30-95), positive predictive value of 91.3% (95% confidence interval 70-98), negative predictive value of 50.0% (95% confidence interval 20-78) and likelihood ratio of 2.82. A $\text{PaO}_2/\text{FiO}_2 < 150$ had a slightly higher (but not significantly different) specificity for ARDS than a value < 200 (71% vs. 86%, $P=0.15$) without changing sensitivity. This study suggests the need for further research in a larger number of children to identify an optimal $\text{PaO}_2/\text{FiO}_2$ threshold for identifying ARDS in pediatric population (10). Considering the fact that ARDS in children occurs in settings of serious and dramatic clinical course of diseases, such as generalized bacterial infection, severe infection of other localizations, near-drowning, trauma, etc., the incidence is probably additionally underestimated because a large number of patients are considered under other "more dominant diagnoses". Among our patients, ARDS

had remained unrecognized (i.e. the diagnosis of ARDS was not listed in discharge documentation) in one patient with severe sepsis and two patients with severe lower respiratory tract infection (3/12 or 25%). This percentage is quite high and is in concordance with the findings reported by Martin et al. (5), stating that only 10 (26.9%) of 41 patients who met the criteria for the diagnosis of ARDS were discharged with this diagnosis, whereas the remaining 73.1% of patients were discharged under different diagnoses. ARDS is often excluded from differential diagnosis in patients with primary pulmonary disorders due to overlapping clinical signs and symptoms. This can explain the inaccurate differentiation of radiological changes that are, in these patients, sometimes attributed to the primary pulmonary disease. Interpretation of radiological changes may be difficult in patients with lower respiratory tract infections, especially viral infections, which may give very similar radiological changes as alveolar edema in ARDS, and which, at the same time, are the most common infections of lower respiratory tract in children.

Mortality due to ARDS ranges from 20.4% (5) through 22% (11) to up to 35% in a study conducted by Erickson et al. (8). A somewhat lower mortality rate of 18% is reported by Zimmerman et al. (12), which along to ARDS patients also included "easier cases" with ALI. These figures are approximate to ours (25%). On the basis of our as well as data from the literature, it seems that the mortality in children is significantly lower compared to adult population (41.1%) (13).

The most common conditions that were associated with or preceded the onset of ARDS were generalized bacterial infections and severe lower respiratory tract infection (33%), which is consistent with the findings of other studies (5, 6, 12, 14). Complete structure of the diseases that are commonly associated with ARDS in pediatric patients is shown in Table 1.

We should not neglect that about 50%-75% of pediatric patients who develop ARDS survive the acute illness. In patients who survived ARDS, chronic or delayed sequels may develop. They may be physical and mental. One-year follow-up of adult patients who survived ARDS demonstrated a decrease in the quality of life indicators (QWB scale, Quality of

Tablica 1. Oboljenja povezana s razvojem ARDS-a kod djece i adolescenata hospitaliziranih na odjelima pedijatrijske intenzivne njege, usporedni prikaz rezultata ove studije i rezultata uzetih iz nekoliko stranih studija

Table 1. Diseases associated with development of ARDS in children and adolescents hospitalized in PICU: study results compared with results extracted from other studies

Underlying disease/Osnovna bolest	Reference/Referenca				
	***	Martin et al. ^[5]	Bindl et al. ^[6]	Heidi et al. ^[11] #	Gordon et al. ^[13]
Sepsis/Sepsa	33.33%	19.5%	0	69%	34 %
Lower respiratory tract infection/ Infekcija donjih dišnih puteva	33.33%	58.6%	41.66%	39%	31%
Near-drowning/Utapanje	16.66%	/	0	8%	9%
Systemic disease/Sistemska bolest	8.33%	/	0	0	/
Heroin overdose/Predoziranje heroinom	8.33%	/	0	0	/
Other (aspiration pneumonia, trauma, post CPR, etc.)/Ostalo (aspiracijska pneumonia, politrauma, stanje nakon reanimacije...)	0	21.9 %	58.34%	Trauma/Trauma 21% Aspiration/ Aspiracija 13% Pancreatitis/ Pankreatitis 3%	26 %

Legenda/Legend:

*** - podatci iz ove studije/Data from this study

/ - nema podatka/No data

- Zbroj postotno izraženog sudjelovanja pojedinih bolesti je veća od 100%, jer su autori ove studije prikazali strukturu morbiditeta prema svakoj pojedinačnoj dijagnozi, a ne samo spram jedne (prve) dijagnoze. Prema navodima iz ove studije 49% ispitivanih pacijenata imalo je više od jedne bolesti koja je značila rizik za razvoj ARDS-a/The sum of percentages of certain diseases marked is greater than 100% because the authors of this study showed the structure of morbidity according to each individual diagnosis, not only against the first diagnosis. According to this study, 49% of surveyed patients had more than one disease that represents a risk for the development of ARDS

Well-Being scale) (15). The most frequently observed long-term consequences were locomotor disturbances (muscle weakness, contracture, etc., mostly due to long-term immobilization) (16). In one study that included children, ARDS survivors, after 1- to 4-year period, moderate pulmonary dysfunction, recurrent episodes of effort dyspnea, recurrent cough, and in a few cases development of pulmonary fibrosis were recorded (17). The patients who have survived ARDS are at an increased risk of cognitive and affective disorders, such as impaired memory function, concentration and decreased attention (18), and psychiatric disorders such as depression, posttraumatic stress disorder and anxiety (19), suggesting that children who need long-term follow-up and treatment are recruited from this group of patients.

CONCLUSION

The incidence of ARDS among PICU patients older than 1 month is 5.7 cases per 1.000 patient-years. In patients treated at PICU, ARDS usually accompanied sepsis and severe lower respiratory tract infections. ARDS has a high share (10.71%) in total mortality of life-threat-

ened patients aged 1 month to 18 years. Among patients who developed signs of ARDS the mortality rate is 25%. In patients with ARDS, fatal outcome is almost 6 times more frequent than in other life-threatened patients. The incidence of ARDS in children is significantly lower as compared to adults. Despite low incidence in pediatric population, considering its high mortality and the possible development of long-term sequels, it is clear that ARDS has a significant impact on morbidity and outcome of critically ill children. Considering the significance of ARDS for prognosis, mortality and outcome, it is necessary to implement a wider, multi-level study within more regions to determine the precise epidemiological features of ARDS in pediatric population. It is necessary to animate professional public to reevaluate current and maybe promote new, more specific criteria for the diagnosis of ARDS in children.

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S a ž e t a k

AKUTNI RESPIRATORNI DISTRES SINDROM U PEDIJATRIJI

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U stručnoj literaturi epidemiološki podatci u vezi s akutnim respiratornim distres sindromom (ARDS), pogotovo među pedijatrijskim bolesnicima su malobrojni. Cilj rada je bio da se utvrdi incidencija, komorbiditet i ishod liječenja bolesnika s ARDS-om koji su liječeni na Odjelu intenzivne njege i terapije Instituta za zdravstvenu zaštitu djece i omladine Vojvodine u Novom Sadu. Sprovedena je retrospektivna kohortna studija koja je obuhvatila bolesnike uzrasta od 1 mjeseca do 18 godina, koji su liječeni na OINT-u u petogodišnjem razdoblju (lipanj 2004. – lipanj 2009. godine), a koji su ispunjavali kriterije utvrđene konsezusom (North American-European Consensus Conference acute lung injury criteria, 1994.) za postavljanje dijagnoze ARDS-a. Utvrđena incidencija ARDS-a među vitalno ugroženom djecom uzrasta starijeg od mjesec dana u našem uzorku iznosi 5,7 na 1000 pacijent-godina. ARDS se najčešće razvio u sklopu sepse i teških infekcija donjih respiratornih putova. ARDS visoko sudjeluje u mortalitetu vitalno ugroženih bolesnika u dobi od 1 mjeseca do 18 godina, s mortalitetom od 25%, što čini 10,71% od ukupnog broja umrlih. Kod bolesnika s ARDS-om smrtni ishod je gotovo šest puta češći u odnosu na ostale vitalno ugrožene bolesnike.

Deskriptori: RESPIRATORNI DISTRES SINDROM; NOVOROĐENČE; DIJETE; DIJETE, PREDŠKOLSKO; ADOLESCENT

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