Respiratory Syncytial Virus Infection in Children with Neuromuscular Impairment

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Abstract: Clinically obvious reasons why children with neurological impairment (NMI) may be more severely affected in case of a viral respiratory tract infection include reduced vital capacity due to muscular weakness or spastic scoliosis, disturbed clearance of respiratory excretions (weak coughing and dysphagia), inability to comply actively with physiotherapeutic interventions, recurrent micro-aspirations (gastroesophageal reflux disease, vomiting related to coughing), a history of frequent exposure to antibiotics and health care institutions, colonization with resistant pathogens, impaired immunologic defence mechanisms due to severe malnutrition and cachexia, and early clinical deterioration in case of high fever with metabolic acidosis and hypercapnia, and maybe associated seizures or febrile convulsions.

Data from the literature suggests that in all children with NMI, who have to be hospitalized with severe clinical deterioration due to an airway infection, at least one specimen of nasopharyngeal secretions should be sent as soon as possible to a virologic laboratory to detect viral pathogens. Children with severe NMI and those mechanically ventilated for other reasons being hospitalized during the RSV season must be strictly protected against nosocomial RSV infection by means of standard and droplet precautions. Finally, children with severe NMI and age below 24 months of life should receive passive immunization with palivizumab following international recommendations.

INTRODUCTION

Respiratory syncytial virus (RSV) is one of the most frequent causes of lower respiratory tract infection in infants and young children [1]. Most children have been infected at least once by 24 months of age [2], and 1 to 3% require hospitalization. The morbidity and mortality related to RSV infection is greater in prematurely born infants [3], particularly those with chronic lung disease [1, 4, 5] and infants with hemodynamically relevant congenital heart disease [6, 7].

Based on these high risk groups, the American Association of Paediatrics recommended criteria for prophylaxis with the humanized monoclonal antibody palivizumab [8]. For infants born between 32 and 35 weeks of gestation the policy statement referred to 'epidemiologic data' and recommended considering additional risk factors: "child care attendance, school-aged siblings, exposure to environmental air pollutants, congenital abnormalities of the airways, or severe neuromuscular disease" [8].

Clinically obvious reasons why children with neurological impairment (NMI) may be more severely affected in case of a viral respiratory tract infection are given in Table **1** and have been extensively discussed by Panitch [9] and Resch [10]. Sritippayawan *et al.* [11] identified pneumonia as the most important reason for acute respiratory failure and for

the non-elective initiation of mechanical ventilation (69%) in 73 children with NMI. Besides other confirmed environmental and demographic risk factors for RSV lower respiratory tract disease [5] NMI was cited as a risk factor in particular as comorbidity in preterm infants born between 32 and 35 weeks of gestation [12].

DATA ON RSV-INFECTION IN CHILDREN WITH PRE-EXISTING NEUROMUSCULAR IMPAIRMENT

In a subgroup analysis of the Canadian PICNIC RSV-database, Arnold and co-workers [13] compared the outcome of RSV infection in children with CLD with those having other chronic conditions such as NMI, cystic fibrosis and pulmonary malformation. In that study the proportions of patients admitted to the intensive care unit and of those mechanically ventilated were not significantly different between premature infants with CLD and children with NMI, supporting the hypothesis that children with NMI face an increased risk of complications. These results referred only to 6 retrospectively identified patients (NMI subgroup). Five of these 6 children with NMI were older than 12 months.

Resch and co-workers [14] from Graz/Austria identified 45 prematurely born infants with clinically significant neurologic handicaps in their retrospective single centre cohort study, which included 453 infants with a gestational age at birth of 29-36 weeks of gestation. The NMI rate was 26% in infants born at 29-32 weeks of gestation and 5% in those born at 33-36 weeks. In a multivariate analysis, NMI was confirmed as a significant independent risk factor for rehospitalization (21% *vs.* 9%; OR 2.93; CI95 1.44-5.97;

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Table 1.   Pathogenesis of Complications in Patients with Neurologic Impairment and Viral Respiratory Tract Infection [Adopted from Panitch HB 2004 [9]]

• Reduced vital capacity due to muscular weakness or spastic scoliosis[#]
• Disturbed clearance of respiratory excretions (weak coughing and dysphagia)
• Inability to comply actively with physiotherapeutic interventions.
• Recurrent micro-aspiration (gastroesophageal reflux disease, vomiting related to coughing)
• History of frequent exposure to antibiotics and health care institutions (admissions); Colonization with resistant pathogens (i.e. *Pseudomonas* spp., *Acinetobacter* spp.)
• Impaired immunologic defence mechanisms due to severe malnutrition and cachexia
• Early clinical deterioration in case of high fever with metabolic acidosis and hypercapnia
• Seizures, febrile convulsions
• Rhabdomyolysis /acute myositis triggered by viral infection*

[#] May result in a cor pulmonale in adolescents

* One patient in the NMI group of our study [16] experienced rhabdomyolysis temporally related to the RSV infection. This complication has been reported by others [28].

p<0.001). The same group reported in 2006 the results of an Austrian multicenter observational study, in which 801 premature infants with a gestational age at birth of 29-32 weeks were included [15]. These children represented 60-70% of all infants born in Austria in this age group during the surveillance period (2001-2003). Of all these preterms, 84 (10.5%) had neurologic disease and 30 (3.8%) were classified as suffering from 'severe neurological disease'. Although presence of NMI doubled the risk of rehospitalization in the univariate analysis, the confidence interval (CI95) of the odds ratio in multivariate analysis failed to prove a significant difference (OR 2.16; CI95 0.77-5.25) [15].

The first prospective multicenter study confirming the hypothesis that hospitalized children with clinically relevant NMI run an increased risk for severe RSV-disease, was a study published from our group, in which six consecutive RSV seasons were covered [16]. The surveillance took place in 14 paediatric hospitals in Germany from 1999-2005. In total, 1568 RSV infections were prospectively documented in 1541 paediatric inpatients. Of these, 73 (4.7%) patients displayed a clinically relevant NMI; 41 (56%) NMI patients had at least one additional risk factor for a severe course of the infection (multiple risk factors in some patients; prematurity in 30, congenital heart disease in 19, chronic lung disease 6, and immunodeficiency in 8). Median age at diagnosis was higher in NMI patients (14 mo *vs*. 5 mo), NMI patients had a greater risk of seizures (15.1% *vs*. 1.6%), and a higher proportion in the NMI group had to be mechanically ventilated (9.6% *vs*. 1.9%). Eventually, the attributable mortality was significantly higher in the NMI group (5.5% *vs*. 0.2%; p<0.001 for all). Multivariate logistic regression confirmed that NMI was independently associated with PICU admission (odds ratio 4.94; 95% confidence interval 2.69 to 8.94; p<0.001] and mechanical ventilation (OR 3.85; 1.28 to 10.22; p=0.017). Our study did not document higher rates of pneumonia in children with NMI. This suggests that radiologically confirmed pneumonia is not a prerequisite for respiratory failure in these patients. Even infections of the upper respiratory tract lead to an increase in nasopharyngeal and tracheal secretions, which cannot be cleared by the

patients because of muscle weakness and an impaired cough mechanism [17]. Any acute viral infection, in particular if associated with airway obstruction [18] could aggravate respiratory muscle fatigue and predispose children with NMI to severe hypoxemia and hypercapnia. As shown previously by others [19], even children, who are on prolonged mechanical ventilation for other reasons are at risk for nosocomial RSV infection.

Thorburn and co-workers [19-21] from the Department of Paediatric Intensive Care, Royal Liverpool Children's Hospital-Alder Hey, have investigated the role of RSV infection in paediatric intensive care unit (PICU) in a sequence of three interesting studies. In the most recently published cohort study comprising all children with severe RSV infection from eight consecutive RSV seasons (1999-2007), the authors included 406 RSV-positive patients admitted to PICU. Of these, 98.5% required mechanical ventilation and 35 children (8,6%) died [median age 5.1 months; interquartile range (IQR) 2.4-13.6)]. The median length of PICU stay in the subgroup with fatal outcome was 16 days (IQR 8-31). The median age in 371 survivors was 2.5 months (IQR 1.2-9) with a corresponding median length of PICU stay of 5 days (IQR 4-9). During the study period 2009 RSV-positive patients were admitted to the children's hospital, giving an overall hospital RSV mortality rate of 1.7%.

Of the deaths, 18 were directly RSV related (RSV bronchiolitis-related mortality PICU 4.4% and hospital 0.9%) as the patients were still RSV positive when they died and 17 children died from non-pneumonitis causes after becoming RSV negative.

All of the RSV deaths had pre-existing medical conditions--chromosomal abnormalities 29%, cardiac lesions 27%, neuromuscular impairment 15%, chronic lung disease 12%, large airway abnormality 9%, and immunodeficiency 9%. Nineteen children (56%) had pre-existing disease in two or more organ systems [relative risk (RR) 4.38]. Predisposing risk factors for death were pre-existing disease (RR 2.36), cardiac anomaly (RR 2.98) and nosocomial/hospital-acquired RSV infection (RR 2.89). An interaction effect was

observed between pre-existing disease, nosocomial RSV infection and mortality (p<0.001). Data on the prior receipt of palivizumab prophylaxis have not been reported considering this population as it was only introduced into clinical practice late in the study period and therefore any impact would be difficult to ascertain.

Von Renesse an co-workers [22] recently focused on the subgroup of patients ventilated for other reasons at the time of the RSV infection. Referring to the risk factors which have been confirmed for severe RSV disease, 60% (n=12) of the patients in the group ventilated mechanically showed at least one additional risk factor for a severe course of the viral respiratory tract infection:

- 50% (n=10) were born prematurely,

- 20% (n=4) had a chronic lung disease with dependence on oxgen supplementation in the last 6 months,

- In 35% (n=7), congenital heart disease had been documented.

The frequency of pneumonia was 40% in the group ventilated mechanically and 20% in the control group. Significantly more patients in the group ventilated mechanically received antibiotic treatment (85% *vs*. 45%, P = 0.008), and attributable mortality was higher in the group ventilated mechanically (15% [n = 3] *vs*. 0% in the control group, P = 0.231). The median length of hospitalization was 31 days in the group ventilated mechanically (range 4–257 days), and 12 days in the control group (range 4–206 days, P=0.05).

Despite existing consensus recommendations, only two of these high risk patients (10%) had received the recommended palivizumab prophylaxis. Children treated by long term mechanical ventilation may acquire RSV infection by transmission by droplets and *via* contact to caregivers and healthcare workers. Fourty percent of all RSV infections in these children were nosocomial RSV infections.

In a landmark study published in JAMA in 2005, Keren and coworkers [23] confirmed a strong association between the presence of NMI and the development of respiratory failure in children with influenza virus infection. This was confirmed by a recent 2003-2004 surveillance study of severe paediatric influenza cases (hospitalization in the PICU or death) in California: 23% (36 of 160) children had a neurologic disorder as an underlying condition [24].

CONCLUSIONS

Taken together, these data from the literature suggests that

- In all children with neuromuscular impairment, who have to be hospitalized with severe clinical deterioration due to an airway infection, at least one specimen of nasopharyngeal secretions should be sent as soon as possible to a virologic laboratory to detect viral pathogens [25, 26].

- Children with severe neuromuscular impairment and those mechanically ventilated for other reasons being hospitalized during the RSV season must be strictly protected against nosocomial RSV infection by means of standard and droplet precautions [19, 20, 27].

- Children with severe neuromuscular disease, in particular those within the first 24 months of life, should receive passive immunization with palivizumab following the actual recommendations [8].

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