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# Bronchoscopic interventions with surfactant and recombinant human deoxyribonuclease for acute respiratory distress syndrome–type respiratory syncytial virus–pneumonia in moderately preterm infants: Case series

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**Abstract**

Atelectases, over-inflation of ventilated regions of the lung, and consecutive pneumothoraces are life-threatening conditions in mechanically ventilated infants with acute respiratory distress syndrome–type respiratory syncytial virus–pneumonia. The accumulation of viscous secretions secondary to impaired mucociliary clearance in the more proximal parts of the bronchial tree is the prerequisite for atelectases and also prevents the delivery of inhaled medications to the more distal parts of the lung. Herein, we describe four moderately premature infants with respiratory failure on mechanical ventilation, displaying a total of 20 radiologically verified new atelectases that were treated by bronchoscopic interventions with consecutive suctioning of secretions, restoration of the surfactant film within the airways, and deposition of recombinant human deoxyribonuclease at the first segment level of the bronchial tree. On 13 occasions (65%), resolution of atelectases was proven by chest X-ray and resulted in improved lung function. We conclude that these bronchoscopic interventions may contribute to the restoration of the gas exchange area in moderately premature infants with acute respiratory distress syndrome–type respiratory syncytial virus–pneumonia.

**Keywords**

Acute respiratory distress syndrome–type respiratory syncytial virus–pneumonia, lower respiratory tract infection, infiltrations, mucociliary clearance, secretions, atelectasis, pneumothorax

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## Introduction

Respiratory syncytial virus (RSV)–induced lower respiratory tract infections (LRTIs) in young infants account for 26,000 hospital admissions per year in Germany.[1] RSV-LRTIs present with obstructive symptoms (bronchiolitis) and/or restrictive symptoms (pneumonia). A small subgroup of essentially premature infants with pronounced restrictive symptoms manifests as an acute respiratory distress syndrome (ARDS)–type pneumonia[2] and needs mechanical ventilation due to the severe deterioration in both gas exchange and compliance of the respiratory system. The combined occurrence of more proximal airway obstruction (lobar atelectasis) and more distal airway obstruction (reduced gas exchange area) frequently results in the over-inflation of adjacent non-atelectatic areas with impending pneumothoraces. Ventilation-associated mortality in RSV-LRTI is in the range of 8%–29%[1,3] and may be even higher in moderately preterm infants with ARDS-type pneumonia, providing a rational behind the search for new therapeutic options.

Respiratory failure following RSV-pneumonia is partly due to the abundance and retention of brittle, thickened

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mucus in the proximal and distal airways. The high viscosity of RSV-mucus accounts for the presence of depolymerized, polyanionic deoxyribonucleic acid (DNA) from apoptotic/necrotic polymorpho-nuclear leukocytes (PMNLs).[4] As the PMNL is the predominant inflammatory cell type in RSV-pneumonia with >80% of cells recovered from the airways,[5] local application of recombinant human deoxyribonuclease (recombinant human deoxyribonuclease (rhDNase), dornase alfa) should transform mucus from its brittle or viscous form to a more liquid consistency.[4] Surfactant film disruption on the hydrophobic airway epithelium by mucus depositions results in reduced mucociliary clearance as cilia become stuck in the hydrophilic liquids and firmly adhere to the epithelial cell membranes.[6] Mucociliary transport may be improved by surfactant replacement onto the epithelial surface.[7] Finally, removal of mucus with firm adherence to the airway epithelium can be efficiently accomplished by bronchoscopic interventions, thus allowing a more homogeneous distribution of drugs by a segment-by-segment approach.

We retrospectively analyzed the following therapeutic approach in four mechanically ventilated moderately preterm infants with ARDS-type RSV-pneumonia in case of radiologically verified lobar atelectases: (1) suctioning of the bronchial tree, (2) broncho-alveolar lavage (BAL) with a diluted surfactant preparation segment-by-segment, and (3) dornase alfa instillation into the two main stem bronchi. We speculated that the combination of targeted mechanical suctioning and homogeneous distribution of surfactant and dornase alfa would be helpful in dissolving atelectases caused by RSV-LRTI in moderately premature infants.

## Case series

Patients: A waiver of consent was obtained by the institutional review committee on ethics of the University Hospital Schleswig-Holstein, Campus Kiel, for the report of this case series. Signed patient consent by all parents was obtained for the use of anonymized data. The four infants were all born moderately premature (30–36 weeks gestational age) and presented in their second month of life (Table 1, patient characteristics). None of the infants had been given palivizumab, in accordance with German guidelines for RSV prophylaxis. The initial symptoms of RSV infection (coughing, nasal secretions, retractions, augmented apnea/bradycardia) appeared only a few days prior to admission to the pediatric intensive care unit (PICU). Infants 1 and 3 were still hospitalized because of apnea of prematurity combined with secondary sinus bradycardia, and inhalation therapy with hypertonic saline and chest physiotherapy for atelectasis (manual vibrations to the chest wall and postural drainage) had been initiated. Infants 2 and 4 presented as soporous upon hospital admission due to acute severe hypercapnia. Intubation and initiation of mechanical ventilation were performed immediately in these two infants and within 3 h following admission for infants 1 and 3 after short trials of continuous positive airway pressure (CPAP) by nasal prongs. Lung protective ventilation strategies such as permissive hypercapnia, limitation of tidal volumes to <8 mL/kg, and fluid restriction are standard practices in our PICU.

### *Methods*

RSV infection was verified by nasopharyngeal secretion testing using multiplex reverse transcriptase polymerase chain reaction (PCR) enzyme-linked immunosorbent assay (ELISA) detection of a panel of 19 common respiratory tract pathogens, thus limiting the likelihood of viral or bacterial coinfection. To prove ARDS-type RSV-pneumonia, we calculated the lung injury score according to Hammer et al.[2] using the following four criteria: alveolar consolidation of lung quadrants affected (scoring points: 1–4); $PaO_2$ (mmHg)/$FiO_2$ (1:225–300, 2:175–225, 3:100–175, 4:<100); positive end-expiratory pressure (PEEP) (cm $H_2O$) (1:5–6, 2:7–8, 3:9–11, 4:≥12); and $C_{dyn}$ (mL/cm $H_2O$/kg) (1:0.75–0.85, 2:0.55–0.75, 3:0.30–0.55, 4:<0.30). The bronchoscopic interventions were carried out in case of newly identified atelectases with regional over-inflation of adjacent aerated parts of the lung. They were performed in deep sedation including muscle paralysis using a pediatric bronchoscope with a 2.8 mm diameter which can be introduced into sized 3.5 and 4.0 mm endotracheal tubes (the latter size was used in one infant because of leakage) while providing uninterrupted mechanical ventilation. Each intervention lasted 25–40 min and included targeted suctioning of secretions (especially from critical branching points of the bronchial tree and from segmental orifices), segmental BAL with a diluted surfactant preparation (20 mL diluted poractant alfa (Curosurf®) in normal saline at a concentration of 6 mg/mL), and instillation of 1.25 mg rhDNase (Pulmozyme®, dornase alfa) in each main stem bronchus.

### *Results*

Within 8 h, resolution of atelectases along with reversal of over-inflation of the ventilated areas was radiologically verified in 4/7 occasions in patient 1, 2/2 occasions in patient 2, 3/7 occasions in patient 3, and 4/4 occasions in patient 4, resulting in an overall success rate of 13/20 (65%). At the same time, $PaO_2/FiO_2$ and dynamic compliance of the respiratory system ($C_{dyn}$, measured by the infant ventilator Dräger Evita Infinity V500 using the single breath least square method by fitting airway flow and tidal volume signals to proximal airway pressure) improved significantly: $PaO_2/FiO_2$ 92 ± 30 → 130 ± 27 mm Hg, $p < 0.001$; $C_{dyn}$ .24 ± .08 → .38 ± .10 mL/cm $H_2O$/kg, $p < 0.001$, paired *t*-test (Figure 1). We did not experience any serious complication in our patients with the bronchoscopic interventions; however, patient 3 presented with stridor one fortnight after demission from the PICU due to subglottic scarring.

**Table 1.** Patient characteristics.

| Patient | 1 | 2 | 3 | 4 |
|---|---|---|---|---|
| Month of admittance | February | March | April | April |
| RSV acquired at | Hospital | Home | Hospital | Home |
| Gestational age (weeks) | 31 | 36 | 33 | 30 |
| Postconceptional age (weeks) | 37 | 44 | 39 | 38 |
| Weight (g) | 2750 | 4050 | 3220 | 2430 |
| Gender | ♀ | ♂ | ♂ | ♀ |
| Twin | No | Yes | Yes | Yes |
| Clinical symptoms before admittance (d) | 2 | 5 | 3 | 2 |
| Reasons for admittance to PICU | Apnea/bradycardia, paroxysmal hypoxemia | Dyspnea, sopor | Apnea/bradycardia, paroxysmal hypoxemia | Apnea/bradycardia, severe stridor, sopor |
| Initial pH/$PCO_2$/$PO_2$ (mm Hg) | 7.31/49/29 | 6.95/>150/80 | 7.18/90/23 | 7.15/84/33 |
| Initial RR, HR (1/min), BP (mm Hg) | 46/180/75–49 | 52/185/117–59 | ?/188/60–45 | 64/205/83–43 |
| Initial $FiO_2$, $O_2$ saturation (%) | 0.21/99 | 0.50/78 | 0.50/62 | 1.0/100 |
| First blood and gas analysis (pH/$PaCO_2$/$PaO_2$) | 7.12/86/69 | 7.10/119/48 | 7.44/51/48 | 7.36/50/49 |
| OI after start of mechanical ventilation | 5 | 16 | 20 | 9 |
| Chest X-ray characteristics after intubation | Hilar infiltrates | Hilar infiltrates, RUL atelectasis, over-inflation | RUL + LUL atelectasis, herniation | Hilar infiltrates |
| Highest OI (n) on day (n) | 17/4 | 34/4 | 24/4 | 41/5 |
| Highest PEEP (cm $H_2O$) | 7 | 12 | 9 | 10 |
| Lung injury score[a] | 1/1/.5/1 (3.5) | 1/1/1/.75 (3.75) | 1/1/.5/.75 (3.25) | 1/1/.75/1 (3.75) |
| Chest X-rays (n) | 15 | 8 | 9 | 12 |
| Interventional bronchoscopies (n) | 5 | 4 | 3 | 8 |
| Resolution of atelectasis (n) | 4 | 2 | 3 | 4 |
| PMNL percentage of cells in BAL (%)[b] | 84 | 76 | 82 | 89 |
| Days on mechanical ventilation (n) | 12 | 12 | 15 | 17 |
| Additional days on nasal CPAP (n) | 5 | 2 | 4 | 2 |
| Days in PICU (n) | 22 | 15 | 21 | 21 |
| Bacterial colonization of airways upon admission | *Staphylococcus aureus, Haemophilus influenzae* | – | – | – |
| Complications | – | – | Subglottic stenosis due to scarring | – |

RSV: respiratory syncytial virus; RR: respiratory rate; HR: heart rate; BP: blood pressure; OI: oxygenation index ($FiO_2$ × MAP / $PaO_2$); PEEP: positive end-expiratory pressure; PMNL: polymorpho-nuclear leukocyte; BAL: broncho-alveolar lavage; BALF: BAL fluid; RUL/LUL: right/left upper lobe; CPAP: continuous positive airway pressure; PICU: pediatric intensive care unit.

[a]Lung injury score according to Hammer et al.[2] to prove acute respiratory distress syndrome (ARDS)–type RSV-pneumonia; the four criteria are (1) infiltrates on chest radiographs, (2) impairment in oxygenation, (3) PEEP applied, and (4) impairment in compliance of the respiratory system. A score of >2.5 is considered characteristic of ARDS.

[b]Cell differentiation using BALF from the first bronchoscopy.

## Discussion

Atelectasis is a common complication in pneumonia and is a predisposition to over-inflation of ventilated lung areas with impending pneumothorax,[8] which is life threatening in conditions of severely reduced $C_{dyn}$ in ARDS-type RSV-pneumonia. The immediate success rate of our bronchoscopic interventions with diluted surfactant and dornase alfa to restore ventilation in previously atelectatic areas was 65%. In addition, reversal of atelectases allowed us to diagnose infiltrations typical of ARDS and to improve $PaO_2/FiO_2$ and $C_{dyn}$.

Mucociliary transport and clearance are greatly disturbed in diseases with severe mucus production and may be immediately improved by surfactant preparations inserted into the airways,[6] while the complete histological and functional

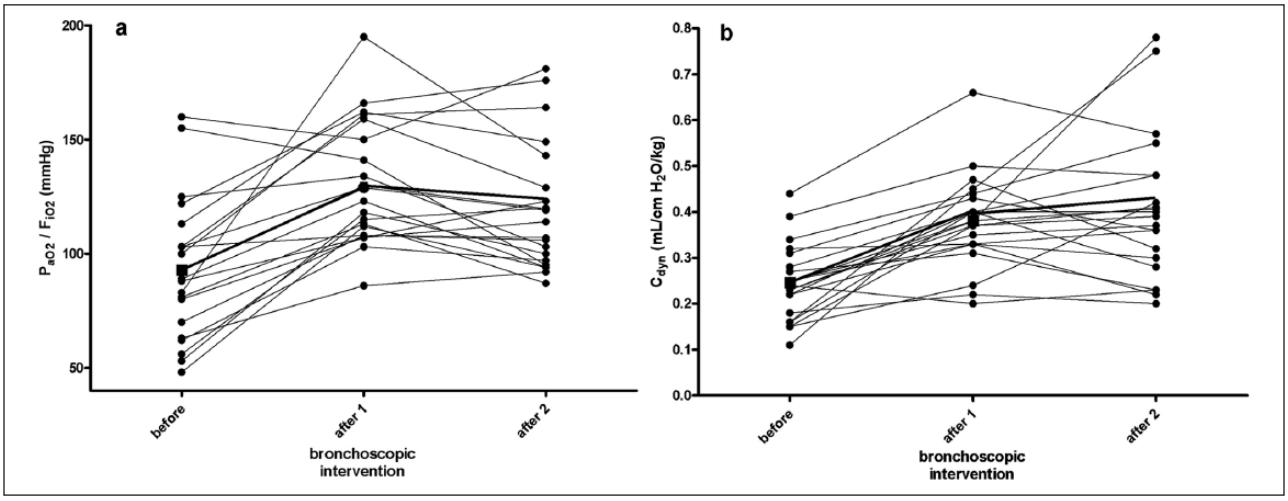


**Figure 1.** (a) $PaO_2/FiO_2$ and (b) dynamic compliance of the respiratory system ($C_{dyn}$) before and after bronchoscopic intervention. $PaO_2/FiO_2$ was determined immediately before and 69 ± 22 min (after 1) and 509 ± 119 min (after 2) after bronchoscopic intervention, and $C_{dyn}$ was determined immediately before and 72 ± 50 / 525 ± 110 min after intervention.
Mean values are displayed by rectangles and fat lines; $p < 0.001$ for both panels (before vs after 1, paired *t*-test).

recovery of the ciliated epithelium takes approximately 13–17 weeks following an acute infection in infants.[9] Two randomized clinical studies including a total of 59 mechanically ventilated infants with RSV-pneumonia demonstrated mildly improved gas exchange and lung mechanics, as well as reduced length of mechanical ventilation in the surfactant treated groups.[10,11] In these studies, surfactant was applied via the endotracheal tube connector without previously checking for airway obstruction by secretions. It is well known that surfactant production and function in the premature lung may not be as robust as it is in the mature infant,[12] and genetic predispositions such as surfactant protein C (SFTPC) single nucleotide polymorphism (SNP) make preterm infants more vulnerable to RSV pneumonia.[13]

PMNLs are the predominant cells in the secretions of RSV-LRTI, which was proven in our patients (Table 1).[5] In addition, the viability of PMNLs is increased, whereas the percentage of apoptotic and necrotic cells is decreased.[14] Because of high-viscosity secretions by RSV infection that cause multilocular airway obstructions, the presence of PMNLs, their adherence to epithelial cells, the abundance of cellular debris, and the sloughing of epithelial cells support the intervention with dornase alfa, providing the patency of airways. Nebulized dornase alfa was investigated in two randomized studies with spontaneously breathing infants with bronchiolitis-type RSV infection and yielded equivocal results: significant improvements in chest X-ray (CXR) scores assessing perihilar markings, hyperinflation, atelectasis, and focal/general opacities were found in a study including 75 infants,[15] whereas no differences in the length of hospital stay or the duration of supplemental oxygen were observed in 225 oxygen-dependent spontaneously breathing infants.[16] Essentially, these finding comply with the authors' conclusions of a recent Cochrane review on nebulized dornase alfa for viral bronchiolitis in children younger than 24 months.[17] However, improvements in lung function could be found in 3/4 mechanically ventilated infants with end-stage respiratory failure and atelectasis.[18] Probably, unfavorable conditions such as non-cooperative infants, small airways, hyperinflation of the lungs, and especially regional airway obstruction by secretions did not allow dornase alfa to be transported into the more distal regions of the lungs.

Our approach to prevent and to treat the loss of gas exchange area by atelectases has two limitations: (1) repeated compilation of CXRs contributes to a significant amount of radiation and (2) bronchoscopic interventions present an additional risk of the infant such as the need for additional sedation and short periods of hypoxemia. Therefore, these risks appear to be only justified in cases of ARDS-type RSV-pneumonia with high oxygenation indices (range: 17–41) and high lung injury scores (range: 3.25–3.75) when the loss of the gas exchange area and impending pneumothoraces, which are life-threatening complications, make an escalation of medical interventions necessary. Finally, the retrospective character of this case series and the lack of a control group make it impossible to determine whether the infants did better or worse than they would have with an alternative or no intervention.

## Conclusion

None of the three interventions used in our report (bronchoscopic removal of secretions, instillation of poractant alfa and dornase alfa into the airways) has been sufficiently studied in mechanically ventilated infants suffering from ARDS-type RSV-pneumonia to come up with an unequivocal result to shorten mechanical ventilation and to reduce the risk of atelectasis and secondary pneumothorax. In four moderately premature infants, this combined approach, however, enabled

reopening of radiologically verified lobar atelectases on 13/20 occasions and supports our speculation that targeted mechanical suctioning and homogeneous distribution of surfactant and dornase alfa may be a superior approach.

## Declaration of conflicting interests

The authors declare that there is no conflict of interest.

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