The Effectiveness of Heated Humidified High-flow Nasal Cannula in Children with Severe Bacterial Pneumonia in the Emergency Department

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ABSTRACT
Aim: The provision of appropriate respiratory support has a great role in outcome of patients presenting to the emergency department (ED) with respiratory distress (RD) associated with severe pneumonia. In recent years, heated humidified high-flow nasal cannula (HHHFNC) therapy has become one of the most popular non-invasive respiratory support modality in all pediatric settings. In this study, we aimed to assess whether the use of HHHFNC therapy is associated with reduced respiratory distress RD and improving hypoxaemia among children with severe bacterial pneumonia (SBP) presenting to the ED.

Materials and Methods: We performed a prospective observational study of patients with SBP admitted to a tertiary children's hospital pediatric ED and received HHHFNC therapy within 2 years study period. The primary outcome was accepted as treatment failure (It was defined as a clinical escalation in respiratory status) and increase in peripheral capillary oxygen saturation (SpO₂). Secondary outcomes covered a decrease of respiratory rate (RR), heart rate (HR), and rates of weaning, intubation and intensive care unit (ICU) admission.

Results: Fifty-six patients were included in the analyses. Treatment failure was 21.5% (12/56). Among this patients, 9 (16%) were intubated and 3 (5.5%) placed on bilevel positive airway pressure. The mean initial RR values were significantly higher in non-responders group than the responder group (p=0.027). Significant variation in the intubation rate or the ICU admission rate was not determined. At the 2nd hour, the falling down of RR (p<0.001), HR (p<0.001), and the increase of SpO₂ (p<0.001) were significantly more evident when compared with the beginning.

Conclusion: HHHFNC therapy reached treatment success in majority of the patients with SBP and provided an earlier effect. Patients with higher respiratory rate responded less to HHHFNC. Further larger studies are needed to assess the impact of HHHFNC compared with other possible therapies.

Keywords: Pediatric emergency departmen, hypoxia, oxygenation, pneumonia, high-flow nasal cannula

Introduction
Severe bacterial pneumonia (SBP) is a common life-threatening disease for pediatric population, and is more common in infants and young children (1). Respiratory distress (RD) due to SBP is one of the most common causes of emergency department (ED) admissions (1-3). Every year, it causes over 500,000 ED visits in the USA and over 1.3 million deaths worldwide (2,3). In the 1980s, World Health Organization (WHO) developed a case management strategy aiming to reduce deaths from pneumonia (4). While it suggests that in severe pneumonia, the cornerstones of management are antibiotic and supportive therapy, the
most important basis for the management strategy was hypoxemia which is common and potentially associated with increased risk of death (4-7). Early detection of hypoxemia, and administration of oxygen therapy also improves the outcome of children with SBP (7). The most effective way to treat hypoxemia is oxygen supplementation (6). Although there are many ways to give oxygen, in recent years, heated humidified high-flow nasal cannula (HHHFNC) therapy successfully has been introduced as a novel alternative method for the management of acute RD due to pneumonia (7).

HHHFNC may be set up easily, is safe and well-known as a non-invasive respiratory support therapy method (8). Even though HHHFNC delivers high flow oxygen, owing to humidification and heating it does not irritate the respiratory mucosa (9). HHHFNC also creates a positive-end expiratory pressure without valve system [Fraction of inspired oxygen (FiO\textsubscript{2}) can be varied between 21% and 100%] (8,9).

HHHFNC therapy has been shown to be more efficient than standard care and to reduce the rate of intubation/invasive ventilation in the management severe pneumonia (10-12). Despite these beneficial effects of HHHFNC, the data is still limited on using this modality in ED setting (8,9).

In childhood, few clinical studies assess the efficacy of HHHFNC for patients with SBP and the most of them were conducted in the intensive care unit (ICU) (13,14). The goal of this prospective clinical study was to evaluate whether the use of HHHFNC therapy is associated with reduced the severity among children with SBP presenting to our ED.

**Materials and Methods**

This prospective observational study was conducted in a pediatric ED between May 2017 and April 2019. The ED is a tertiary-care teaching center and has approximately 80000 visits annually. The study was approved by the local Institutional Review Boards, and the written informed consent was obtained. To maintain patient confidentiality, the forms did not include any data that would have enabled identification of any patients.

The diagnosis and the severity of pneumonia were made based on the Pediatric Infectious Diseases Society clinical practice guideline (15). All patients, who were included the study, had fever or fever history, tachypnea, alveolar infiltration or consolidation on chest X-ray and high serum biomarkers values (procalcitonin level >0.25 ng/mL and/or C-reactive protein level >40 mg/L and/or absolute neutrophil count >10,000/mm\textsuperscript{3}) supporting bacterial infection (16-18). Patients who were diagnosed bacterial pneumonia, aged between 0-18 years and had at least one of clinical features of severe pneumonia (1- Moderate to severe respiratory distress [RR >70 breaths/minute for infants, RR >50 breaths/minute for older children, moderate/severe suprasternal, intercostal, or subcostal retractions (<12 months), severe difficulty breathing (≥12 months), grunting, nasal flaring, apnea, significant shortness of breath] 2- Cyanosis 3- Altered mental status 4- Hypoxemia [sustained oxygen saturation <90 percent in room air at sea level] 5- Not feeding [infants] or signs of dehydration [older children] 6- Capillary refill ≥2 seconds) with temperature ≥38.5°C and tachycardia were included to the study. Patients who required immediate invasive ventilation and/or ICU admission on ED presentation; patients with venous PCO\textsubscript{2} greater than 55 prior to HHHFNC initiation; patients who received HHHFNC therapy at some other facility prior to arrival; patients who have coexisting compensated septic shock; and patients who have pneumothorax or nasal trauma were excluded.

After the triage assessment, patients were examined by pediatric emergency medicine specialists for acute life-threatening RD due to bacterial pneumonia. At the same time, the nurse started cardiorespiratory monitoring [SpO\textsubscript{2}, blood pressure, RR, heart rate (HR)], provided vascular access, obtained venous blood gas, and performed nasopharyngeal suction. After confirmation of eligibility and parental consent for study inclusion, the patients were started on HHHFNC therapy. A blend of air/oxygen was delivered via nasal cannula with a flow rate of 2-L/kg/min for the first 10 kg, then 0.5 L/kg/min for every kilogram thereafter. The total flow range was 6-50 L/min. FiO\textsubscript{2} was arranged with minimum value to provide SpO\textsubscript{2} with a range of 94-99% and the humidifier was auto-adjusted at 37°C. Heated and humidified HHHFNC delivery system was Optiflow of Fisher & Paykel Healthcare, Auckland, New Zealand. The optiflow junior nasal cannula (neonatal, infant and pediatric size) and the optiflow nasal cannula (adult size) allowed up to 50 L/min flow rate, was properly used for all participants. The cannula size was selected as not to be wider than half the diameter of the patient’s nares. Sedation was achieved by oral feeding for the majority of patients (breastfeeding was preferred if possible), but if necessary, sedative drugs such as dexmedetomidin or midazolam were administered. All children also received standard management for bacterial pneumonia, including parental antibiotics and supportive care treatment. In addition, if necessary they were given therapy for comorbidities.

The clinical parameters (RR, HR and SpO\textsubscript{2}) were recorded hourly by the nurse and ED physician after HHHFNC.
initiation. At the end of the second hour and during the next follow-up period, providing all of the following criteria was defined as weaning criteria. The criteria were: decreased RR (for infants ≤ 2 months <60 bpm, 2-12 months <50 bpm, 1-5 years <40 bpm and >5 years <20 bpm); absence of dyspnea include accessory muscle use, retractions, nasal flaring, and grunting; SpO₂ reached ≥ %90 with FiO₂ < 30%; no confusion. The ICU admission was considered if the severe RD and/or SpO₂ < %90 with FiO₂ > 50% remained. Patients who were considered HHFNC failure or insufficient response continued to receive HHFNC therapy in the ED critical care room until their transfer to the ICU. If the invasive ventilation modality was required at any stage of observation, it was also provided. The protocol lasted a minimum of 24 h; all study patients were followed-up clinically by recording all their management steps [weaning, restart of HHFNC therapy, requirement another modality of non-invasive ventilation (NIV), intubation].

Treatment failure was described as one or more of the following criteria if observed within 24 h of initiation HHFNC therapy. These criteria were; persistent tachypnea (patients aged 0-12 months with RR >70 bpm and for >12 months >50 bpm); SpO₂ < %90 sustained even if FiO₂ > 50%; PCO₂ remained over 50 mmHg; hypoventilation developed. In these cases, patients received another form of NIV (Bilevel positive airway pressure [BiPAP]) or invasive ventilation. The primary outcome was accepted as treatment failure within 24 h after HHFNC initiation and recovery in SpO₂ (at the end of two hours of the treatment). It was indicated that the highest risk of failure is within the first 24 h of the therapy (9,19). The expected potential benefits of HHFNC therapy are improvement about RR and HR achieving of the weaning, preventing the intubation and ICU admission. Therefore, secondary outcomes were decline of RR, HR, increase of SpO₂, and the rate of weaning, at the end of two hours of the treatment; rates of intubation and ICU admission within the first 24 hours.

Before starting the study, the ED nurses and physicians were all trained about the HHFNC therapy process by the investigators.

This study was approved by Ethics Board of Ege University (approval number:17-4/6). All of the parents of the patients gave their informed consent prior to their child’s inclusion in the study.

Statistical Analysis

All analyses that included all children were performed with SPSS for Windows (ver. 22.0 SPSS Inc., IL, USA). Comparison of the changes in RR, HR, SpO₂ and the rate of weaning after 2 hours of the therapy were performed using Wilcoxon’s test. Differences of the baseline characteristics of responder and non-responders groups (sex, age, comorbidity, admitted season, the beginning values of RR, HR, SpO₂, pH, PO₂, and PCO₂) were analyzed with Chi-squared test, Student’s t-test and Mann–Whitney U test as appropriate and were presented as mean differences with 95% confidence intervals (CIs) and P values. A two-tailed probability value (p) of less than 0.05 was considered significant.

Results

During the study period 92 patients presented to the ED with a diagnosis of SBP and 56 of them (61%) assessed eligible for final analysis (Figure 1). The mean age was 45.3±41.2 (2-168) months, and 55.4% (n=31) was male. In the study group 30 (53%) patients had chronic illnesses; 11 (20%) neuromuscular diseases, 8 (14%) chronic lung diseases, 5 (9%) chronic cardiac disease, 4 (7%) immunodeficiency, 1 (2%) malignancie and 1 (2%) malnutrition. The mean initial RR values of non-responders group were significantly higher than the responder group (p=0.027). Another baseline demographic and physiological characteristics of the patients were comparable in the responder and non-responders groups (Table 1).

Among 12 (21.4%) patients who had treatment failure, 9 (16%) underwent orotracheal intubation. The remaining

![Figure 1. Flowchart of the study population and the primary outcomes](image-url)
3 patients were successfully treated with Bilevel positive airway pressure (BiPAP). A total of 12 (21.5%) patients transferred to the ICU. Treatment failure, the intubation rate and ICU admission rate were not statistically different between patients have chronic illnesses and others.

While at the second hours of the therapy, 21 (37.5%) patients received the weaning protocol, HHHFNC therapy continued in 23 patients (41%). The reductions in RR (p<0.001), and in HR (p<0.001), and the increase in SpO\textsubscript{2} (p<0.001) were significantly higher at the second hours of evaluation when compared with the baseline (Table 2).

No child died and therapy-related side effects such as pneumothorax or pressure injuries were not developed within 24 hours.

**Discussion**

In this prospective observational study, we investigated the effectiveness of HHHFNC therapy and affecting factors

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<thead>
<tr>
<th>Table I. Comparison of patient characteristics at admission between responder and non-responder groups</th>
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<tr>
<td><strong>Responder group (HFNC therapy success) (N=44)</strong></td>
</tr>
<tr>
<td>Sex</td>
</tr>
<tr>
<td>Male (%)</td>
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<tr>
<td>Mean age (months) (± SD)</td>
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<tr>
<td>Prematurity (&lt;37 weeks)</td>
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<tr>
<td>Chronic illnesses</td>
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<td>Admitted season</td>
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<tr>
<td>Winter</td>
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<td>Spring</td>
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<td>Autumn</td>
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<tr>
<td>Summer</td>
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<tr>
<td>Initial respiratory rate (breath/min)</td>
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<td>Initial heart rate (beat/min)</td>
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<tr>
<td>Initial SpO\textsubscript{2} (%)</td>
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<tr>
<td>Initial venous PCO\textsubscript{2} (mmHg)</td>
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<td>Initial venous PO\textsubscript{2} (mmHg)</td>
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<td>Initial venous pH</td>
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Values are mean (SD) or n (%) and (min-max).
HFNC: High-flow nasal cannula, PCO\textsubscript{2}: Partial carbon dioxide, PO\textsubscript{2}: Partial oxygen, SpO\textsubscript{2}: Peripheral capillary oxygen saturation.

<table>
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<th>Table II. Secondary outcomes in the study cohort</th>
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<tr>
<td><strong>Initial values</strong></td>
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<td>Reduction in RR\textsuperscript{1}</td>
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<td>Reduction in HR\textsuperscript{1}</td>
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<td>Rise in SpO\textsubscript{2}\textsuperscript{*}</td>
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Ranges in parentheses are SDs. Values are mean. HFNC=high-flow nasal cannula. \textsuperscript{1}Respiratory rate (breath/min). \textsuperscript{1}Heart rate (beat/min). \textsuperscript{*}Peripheral capillary oxygen saturation.
in children with RD due to SBP in a tertiary care academic pediatric ED. The results of our study have shown that HHHFNC was a safe and effective form of noninvasive respiratory support method for patients with SBP. HHHFNC therapy was significantly efficient in RR, HR and SpO2 at the second hours of the therapy, whereas the treatment success was achieved in 78.5% of the patients. Therapy failure was more common in patients with higher respiratory rate. Although, appropriate antibiotics and supportive care treatment are indispensable for children with pneumonia, it is stated that, hypoxemia is one of the most important risk factor for mortality and morbidity in these patients (6,20). As shown in meta-analysis hypoxemia which is defined with a cut-off for SpO2 below 90% is associated with significant increased odds of death from acute lower respiratory infections (OR 5.47, 95% CI 3.93 to 7.63) children (21). Previously published data indicates that delays in diagnosis or management of hypoxemia due to pneumonia may be the main cause of these high rates in low-income countries (22,23). As expected NIV methods such as HHHFNC use are limited in these countries (23). Since our results indicate early and significant improvement in hypoxemia due to pneumonia, we can conclude that good outcomes are associated with HHHFNC use. If HHFNC had been used in the low-income countries, death and disability would have been prevented (24).

In recent years, HHHFNC has been used widely for patients with RD in all pediatric units of hospitals in many places across the World (9,25). However, there are still limited studies, conducted in the ED setting on using HHHFNC as a respiratory support method for children with pneumonia (8,9). Although the majority of patients included in these studies were infants with acute bronchiolitis, it has been reported that HHHHFCN is also effective in children with pneumonia (10-12). In a unique, randomized controlled study, included only children with severe pneumonia, conducted in the ICU, compared HHHFNC with nasal continuous positive airway pressure (nCPAP), Chisti et al, have determined that, no difference in treatment failure and intubation rate between nCPAP group and HHHFNC group (24). In another study, Er et al. have evaluated 64 children aged 0-18 years with bacterial pneumonia receiving HHHFNC in the ED and found that the therapy success was 80% (26). Our findings are similar to the results of these studies.

It is very important to predict determining factors of HHHFNC therapy failure in children with RD (13,14). That will enable us to identify patients who would not respond, and thus other treatment options would not be delayed. In our study group, nonresponders had higher respiratory rate at the beginning than responders which were consistent with previous studies (12,27). This is may be an explanation why HHFNC should not be selected in children with more severe RD.

Earlier response to HHHFNC is essential when treating a patient with RD and it also can be used a predictor for the main outcomes. A decrease in RR and in HR were frequently chosen as early signs of a good response to HHHFNC (10,28). Davison et al. have found that the surrogate markers (HR and RR) of RD decreased significantly from the first hour of HHHFNC treatment (29). Similarly, we found that, there was manifest improvement in the RR and in HR between initial values and the second hour of the therapy.

Since it has been reported that HFNC reduced the rate of intubation and ICU admission in children with RD, it has become increasingly popular in all pediatric setting (25). Our findings showed that the intubation rate for the present cohort was 16%. In a large study conducted with children with RD in the ED, Wing et al, have showed that, there was an 83% reduction in the odds of intubation in patients receiving HFNC compared with patients did not get HHFNC (11). In a prospective pilot study has been shown that PICU admission is four times less likely in children receiving HHFNC than the standard treatment group (30). In the study of Chisti et al., a total of 79 patients with severe pneumonia were treated with HHHFNC and it has been found that among this patients the rate of intubation was 13% (24).

Study Limitations
This study had some limitations. First, since it was a single center small study, its findings might not be generalizable to other settings. Second, we considered that the study was conducted in the ED; that is why following up the patients 24 hours is enough. However, this decision may have caused us to lose some data. Third, due to time limitations, we could not evaluate possible confounding variables such as antibiotics, supportive care. The last one, the study was not a comparative study, hence the efficacy of HFNC therapy versus other treatment options could not be interpreted.

Conclusion
This study showed that HHHFNC therapy was clinically effective and well tolerated and ensured earlier impact in patients with SBP in the ED. Treatment failure was higher in patients with higher respiratory rate. Multicenter, randomized controlled large studies are needed to confirm...
efficacy of this therapy more accurately for children with pneumonia.

Ethics

Ethics Committee Approval: This study was approved by Ethics Board of Ege University (approval number:17-4/6).

Informed Consent: All of the parents of the patients gave their informed consent prior to their child’s inclusion in the study.

Authorship Contributions


Conflict of Interest: None of the authors had conflict of interest.

Financial Disclosure: The authors declared that this study received no financial support.

References

27. Abboud PA, Roj PJ, Skiles CL, Stolfi A, Rowin ME. Predictors of failure in infants with viral bronchiolitis treated with high-flow,

