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SNAP: Supportive noninvasive ventilation for acute chest syndrome prevention in children with sickle cell disease

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An abstract titled "SNAP: Supportive Non-Invasive Ventilation for ACS Prevention in Children with Sickle Cell Disease" was accepted for publication and platform presentation at the Pediatric Academic Societies Annual Meeting, Philadelphia, PA, May 2, 2020. Due to COVID-19-related conference cancellation, this peer-reviewed abstract was disseminated in April 2020 in the PAS 2020 Meeting Program Guide: https://plan.core-apps.com/pas2020/abstract/15b51e55c72bb23c66b248e2be8c44f9

Abstract

Background: Acute chest syndrome (ACS) is a leading cause of morbidity and mortality among children with sickle cell disease (SCD). Preventing hypoxemia by optimizing lung aeration during sleep remains a challenge.

Objectives: To explore safety, feasibility, and tolerability of noninvasive, bi-level positive airway pressure ventilation (BiPAP) as preventative, supportive care for hospitalized, medically stable children with SCD on a general pediatric inpatient unit.

Methods: Retrospective chart review of patients ≤22 years of age with SCD admitted to the general pediatric inpatient unit from February 1, 2017 to March 1, 2020 for whom BiPAP was recommended as supportive care. Hospitalizations were excluded if patients were admitted to the pediatric intensive care unit (PICU), required BiPAP for respiratory failure, or used BiPAP at home for obstructive sleep apnea.

Results: Twenty-three patients had 53 hospitalizations in which BiPAP was recommended. Fifty-two (98%) hospitalizations included acute SCD pain. Indications for BiPAP included prior ACS (94%), chest or back pain (79%), and/or oxygen desaturation (66%). On 17 occasions, patients already had mild to moderate ACS but were stable when BiPAP was recommended. BiPAP was used successfully during 75% of hospitalizations for a median of two nights. There were no adverse effects associated with BiPAP. PICU transfer for respiratory support occurred during three hospitalizations. In 26 hospitalizations of children at risk for ACS who tolerated BiPAP, 23 (88%) did not develop ACS.

Conclusions: BiPAP is safe, feasible, and well tolerated as supportive care for hospitalized children with SCD. Next steps include an intervention trial to further assess the efficacy of BiPAP on ACS prevention.

KEYWORDS
acute chest syndrome, BiPAP, sickle cell disease

1 | BACKGROUND

Acute chest syndrome (ACS) is the second most common acute complication and number one cause of death in children with sickle cell disease (SCD).[1,2] It is associated with prolonged hospitalizations, blood transfusions, and respiratory failure.[1,2] One episode of ACS in childhood is a risk factor for future episodes,[3–6] and recurrent episodes increase the risk of restrictive lung disease in adulthood.[7,8]

Episodes of ACS often develop in the setting of acute SCD pain,[2–4,9–11] especially when in the chest and back, because of

Abbreviations: ACS, acute chest syndrome; BiPAP, bi-level positive airway pressure; OSA, obstructive sleep apnea; PICU, pediatric intensive care unit; SCD, sickle cell disease

splinting, suboptimal chest wall expansion, and hypoventilation. Additionally, the use of opioids for pain depresses respiratory drive, contributing to hypoventilation, atelectasis,[12] and ultimately, localized and generalized hypoxemia. Incentive spirometry is an important component of ACS prevention and management.[11,13–15] By encouraging patients to breathe with maximal inspiratory capacity, incentive spirometry counteracts the effects of splinting,[11,15] ultimately preventing ACS.[11]

While incentive spirometry has been shown to be effective at preventing ACS in hospitalized children with acute SCD pain,[11] this intervention can only be used during waking hours. An additional strategy is needed to prevent oxygen desaturation and hypoventilation for these patients during sleep.[16] In February 2017, we initiated the use of nocturnal bi-level positive airway pressure ventilation (BiPAP) on the general pediatric inpatient unit as supportive care for medically stable, hospitalized patients at risk for ACS. BiPAP refers to noninvasive ventilation through a mask that provides positive airway pressure during exhalation plus higher pressure "breaths" during inhalation to assist with work of breathing. BiPAP is commonly used in ICU settings[17,18] for patients with acute respiratory failure, often in an attempt to avoid intubation and mechanical ventilation. It is also used chronically for patients with obstructive sleep apnea (OSA) and for patients with chronic hypoventilation due to neuromuscular disease.

2 | INTRODUCTION OF BIPAP AS SUPPORTIVE CARE FOR MEDICALLY STABLE, HOSPITALIZED PEDIATRIC PATIENTS WITH SCD

BiPAP was first used as supportive care for a patient with SCD in the 24-bed general pediatric inpatient unit of Boston Medical Center in February 2017. An 11-year-old girl with a history of multiple ACS episodes and mild OSA (not using continuous positive airway pressure [CPAP] or BiPAP at home) presented to the Emergency Department with acute sickle cell pain and oxygen desaturation to 88%. She received intranasal fentanyl, IV morphine, and ketorolac for pain in the Emergency Department. Although her lung exam was clear and she did not exhibit increased work of breathing, her chest radiograph demonstrated a new left lower lobe infiltrate consistent with ACS. She was medically stable, admitted to the general pediatrics inpatient unit, and treated with intravenous opioids, antibiotics, and 2–3 L/min of supplemental oxygen. Her case was complicated by red cell alloimmunization (anti-E and anti-Fy[A]), limiting her ability to receive a blood transfusion. On hospital day (HD) 3, because of an ongoing supplemental oxygen requirement that worsened at night, the consulting pediatric pulmonologist, pediatric hematologist, pediatric hospitalist, and nurse manager of the pediatric inpatient unit agreed to a trial of BiPAP during sleep on the general pediatric inpatient floor with the goals of mitigating hypoventilation and improving oxygenation to prevent respiratory decompensation and the need for pediatric intensive care unit (PICU)-level care. A respiratory therapist and a child life specialist (Molly A. Duggan) assisted the patient during the day with mask fitting and acclimating to BiPAP. She used BiPAP (plus intermittent supplemental oxygen as needed) overnight and during long naps for the next 4 HDs. She tolerated BiPAP easily, her clinical status steadily improved, and she was discharged home 5 days later after a night without BiPAP or supplemental oxygen. We began offering BiPAP to other medically stable, hospitalized patients whom we felt were at increased risk for adverse respiratory outcomes. The nurse manager (Karan Barry) collaborated with colleagues from pediatric pulmonology, hematology, hospitalist medicine, and respiratory therapy to develop a hospital policy for use of noninvasive ventilation on the general pediatric inpatient unit for medically stable patients with SCD at risk for adverse respiratory outcomes (history of prior ACS, ACS present on admission, oxygen desaturation, chest and back pain, etc.). The policy states that BiPAP can be used on the general pediatric unit as a "supportive therapy" for the prevention but not for treatment of respiratory failure. (The hospital policy can be viewed in the on-line supplement.) Settings are generally low to facilitate tolerability (i.e., 10/5–12/6 cm H2O); supplemental oxygen may be used in combination with BiPAP if needed. Since that time, BiPAP has been available as supportive care for hospitalized children with SCD at risk of developing ACS (because of prior ACS episodes, an oxygen requirement, pain in the chest and/or back plus IV opioid use, and risk of oxygen desaturation because of a prior abnormal sleep study) or who were admitted with ACS but not requiring PICU-level care.

BiPAP is not being used as treatment of respiratory failure in this setting; rather, this intervention has the primary goal of preventing ACS and a secondary goal of preventing respiratory decompensation among medically stable children admitted with mild to moderate ACS.

The objective of this study was to evaluate tolerability, feasibility, and safety of using BiPAP among hospitalized children with SCD outside the intensive care unit setting, on a general pediatrics inpatient unit.

3 | METHODS

3.1 | Study design

This was a retrospective chart review of all hospitalizations in which BiPAP was recommended as supportive care for patients with SCD ≤22 years admitted to the 24-bed general pediatric inpatient unit of Boston Medical Center from February 1, 2017 to March 1, 2020. Eligible hospitalizations were determined by first using billing data to generate a list of hospitalizations of pediatric patients with SCD, followed by a detailed review of the electronic medical record to identify hospitalizations in which BiPAP was recommended in an admission note, progress note, or consult note. Hospitalizations were excluded if patients were initially admitted to PICU, if BiPAP was initially initiated for treatment of respiratory failure, or if the patient used BiPAP/CPAP at home for OSA. Hospitalizations for patients who had OSA or non-obstructive nocturnal hypoxemia at baseline but who did not use BiPAP/CPAP at home were included. This study was approved

by the Boston University School of Medicine Institutional Review Board.

3.2 | Data collection

We recorded demographic information, SCD and respiratory history (SCD type, lifetime ACS episodes, history of PICU admissions, hydroxyurea use, history of asthma and OSA), and hospitalization details (indication(s) for admission, vital signs, respiratory symptoms, pain location, indication(s) for BiPAP). We documented whether the patient tolerated BiPAP, duration of use, and BiPAP settings. BiPAP tolerability was defined as easily tolerated (tolerated on the first attempt), tolerated with mild difficulty (refused once but tolerated during subsequent attempts), moderate difficulty (unable to sleep with BiPAP on >1 night but ultimately tolerated), or never tolerated. A successful night of BiPAP was defined as ≥4 hours of use.[19] Finally, we recorded whether the patient developed ACS or required a blood transfusion or PICU transfer for respiratory issues. ACS was defined as the presence of new lung parenychmal opacity on chest radiograph and respiratory signs or symptoms (tachypnea, retractions, chest pain, and oxygen desaturation). The principal investigator (Robyn T. Cohen) reviewed all chest radiographs to ascertain the presence or absence of a new pulmonary consolidation.

Data were extracted from electronic medical records by two coinvestigators (Cara S. Guenther and Victoria J. Pae) and recorded in a secure REDCap database. For quality assurance, each coinvestigator verified the other's entries. Inconsistencies were adjudicated by the principal investigator (Robyn T. Cohen).

3.3 | Data analysis

The primary outcome was the proportion of hospitalizations in which BiPAP was used successfully for ≥1 night. Secondary outcomes included BiPAP tolerability, adverse effects attributable to BiPAP, and development of ACS or worsening respiratory distress requiring PICU-level care.

Descriptive analyses were performed with SAS 9.3 (Cary, NC).

4 | RESULTS

4.1 | Patient characteristics

We identified 23 patients with 53 hospitalizations during which BiPAP was recommended as supportive care. All patients had hemoglobin SS, and 20 (87%) were taking hydroxyurea at the time of their first included admission. One patient's medical records were unavailable from her country of origin. Twenty (87%) had a history of ACS. Eleven patients (48%) had greater than or equal to one PICU admission for respiratory issues. Of eight patients with a prior sleep study, four had been diagnosed with OSA and two with nocturnal hypoxemia (Table 1).

TABLE 1 Characteristics of the study population ($N = 23$)

	N (%)
Gender	
Male	11 (48)
Female	12 (52)
HbSS SCD type	23 (100.0)
Number of lifetime episodes of ACS before the first episode of BiPAP/CPAP	
0	2 (9)
1	7 (31)
2	4 (17)
3 or more	9 (39)
Unknown	1 (4)
Number of lifetime admissions requiring PICU-level care for respiratory issues before the first episode of BiPAP/CPAP	
0	11 (48)
1	9 (39)
2	2 (9)
Unknown	1 (4)
On SCD-modifying treatment (HU or chronic transfusions)	21 (91)[a]
Ever had a sleep study	8 (35)
Ever diagnosed with obstructive sleep apnea	4 (17)
Ever diagnosed with nocturnal hypoxia	2 (9)
Ever diagnosed with asthma	8 (35)
Number of hospitalizations contributed to the dataset during study period	
1	13 (56)
2–4	7 (30)
6–8	3 (13)

Abbreviations: ACS, acute chest syndrome; BiPAP, bi-level positive airway pressure; CPAP, continuous positive airway pressure; HU, hydroxurea; PICU, pediatric intensive care unit; SCD, sickle cell disease.

[a]Three of 23 patients in our cohort were not on hydroxyurea (HU): one was receiving chronic transfusions, one recently had immigrated to this country and subsequently started HU, and one had sporadically been on and off HU before and after the first admission.

4.2 | Description of 53 hospitalizations during which BiPAP was recommended as supportive care

Median age at the time of admission was 16 years. Fifty-two (98%) hospitalizations included acute SCD pain; 42 (79%) included pain in the chest and/or back. ACS was diagnosed on admission in 15 (28%) hospitalizations; 28 (53%) hospitalizations were preceded by respiratory symptoms.[20,21] Indications for BiPAP included prior ACS ($n = 50$, 94%), chest/back pain ($n = 42$, 79%), oxygen desaturation ($n = 35$, 66%), history of an abnormal sleep study ($n = 15$, 28%), and/or mild to moderate ACS diagnosed at or after admission but not requiring PICU-level care ($n = 20$, 38%) (Table 2).

TABLE 2 Characteristics of hospitalizations on the general pediatrics inpatient service during which BiPAP was ordered as supportive care ($N = 53$)

Median age in years during admission (min, max)	**16 (5, 21)**
Median hospital length of stay in days (min, max)	**6 (2, 16)**
Indication(s) for hospital admission, *N* (%)[a]	
SCD pain	52 (98)
ACS	15 (28)
Influenza	2 (4)
Other reason	4 (8)
Had respiratory symptoms in the week prior to admission, *N* (%)	
Yes	28 (53)
No	19 (36)
Unknown	6 (11)
Had chest pain on admission, *N* (%)	26 (49)
Had back pain on admission, *N* (%)	33 (62)
Indication(s) for BiPAP, *N* (%)[b]	
Prior ACS	50 (94)
Chest or back pain	42 (79)
O_2 requirement	35 (66)
Mild to moderate ACS not requiring ICU-level care	20 (38)
Borderline or abnormal sleep study	15 (28)
Other	2 (4)

Abbreviations: ACS, acute chest syndrome; BiPAP, bi-level positive airway pressure; O_2, oxygen.
[a]There can be multiple indications for a single admission.
[b]There can be multiple indications for BiPAP.

4.3 | Tolerability and safety of BiPAP on the general pediatric inpatient unit

BiPAP was used during 40/53 (75%) hospitalizations for a median of two nights. BiPAP was well tolerated with minimal or no difficulty during 34 (64%) hospitalizations. Among the 13 hospitalizations in which BiPAP was ultimately not used, three were for the same patient. We noted variations in tolerability among patients who had multiple hospitalizations during the study period; for some patients, BiPAP was not tolerated during attempts at earlier hospitalizations but was ultimately tolerated in later hospitalizations. For other patients if the initial experience was difficult during an earlier hospitalization, BiPAP was refused during subsequent hospitalizations. The four patients who had previously used BiPAP in the PICU to treat acute respiratory failure tolerated BiPAP easily when it was used as supportive care on the general pediatrics inpatient unit. The most commonly reported reasons for not tolerating BiPAP that were recorded in the medical records included not tolerating the mask (especially a full-face mask) and difficulty breathing with the positive pressure.

CPAP was employed during three hospitalizations: once for a patient who did not tolerate BiPAP during that admission, once for a patient who had a pre-existing ileus, and once for a patient who had not tolerated BiPAP during previous admissions.

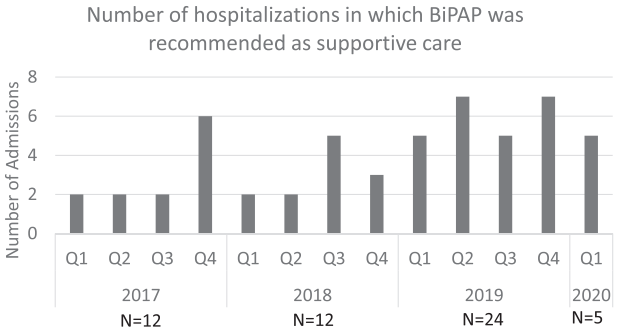

FIGURE 1 Number of hospitalizations, by quarter and year, in which BiPAP was recommended as supportive care for children with sickle cell disease hospitalized on the general pediatrics inpatient unit

Figure 1 shows the increase in attempted BiPAP utilization over time during the study period. It was recommended for supportive care in 12 hospitalizations in 2017 and 2018 and in 24 hospitalizations in 2019. There were no adverse effects attributed to BiPAP/CPAP use (Table 3).

4.4 | Clinical outcomes

Of the 53 hospitalizations, ACS was diagnosed in 17 (32%) in the emergency department or on HD1, prior to starting BiPAP. Radiographically confirmed ACS developed during five additional hospitalizations: four on HD2 and one on HD6. Four of the five had prior episodes of ACS; it is unknown whether the fifth did as well. All had chest radiographs on the day of admission without new opacities. In one case, the patient had used BiPAP the night before ACS was suspected, in two situations patients had acute respiratory symptoms that included a new oxygen requirement - BiPAP was initiated at approximately the same time the radiographic diagnosis was made. In one case, the patient had an ileus and used CPAP instead of BiPAP; ACS was diagnosed on the same day after CPAP had been started. In one case, the patient did not use any positive pressure during the hospitalization.

PICU transfer for respiratory support occurred in three (6%) hospitalizations; two transfers occurred in the same patient with a history of severe SCD and recurrent ACS. Patients received blood transfusions during 23 (43%) admissions: 12 for patients with ACS on admission/HD1, four for patients who developed ACS after admission, and seven for patients with a decrease in hemoglobin without ACS (but often with respiratory symptoms). In 26 hospitalizations during which high-risk patients without existing ACS tolerated BiPAP, 23 (88%) did not progress to ACS (Table 3, Figure 2).

5 | DISCUSSION

We have demonstrated that using BiPAP on a general pediatric inpatient unit is safe, feasible, and well tolerated as supportive care for

TABLE 3 Primary and secondary outcomes during hospitalizations when BiPAP[2] was ordered as supportive care for patients with SCD hospitalized on the general pediatrics inpatient service ($N = 53$)

Outcome	*N* (%)
Hospitalizations in which the patient used BiPAP as supportive care on general pediatrics inpatient service, *N* (%)	40 (75)
Ease of BiPAP use, *N* (%)	
Tolerated with no difficulty	26 (49)
Tolerated with minimal difficulty (refused once)	8 (15)
Tolerated with substantial difficulty (refused multiple times)	6 (11)
Did not tolerate, never used BiPAP	13 (25)
Used CPAP only,[a] *N* (%)	3 (6)
Median number of nights BiPAP/CPAP was used (min, max)	2 (0, 9)
ACS present on admission or during HD1	17 (32)
Did not develop ACS during admission (among patients without ACS on HD1)	31/36 (86)
Did not develop ACS during admission (among patients without ACS on HD1 and who tolerated BiPAP for at least 1 night	23/26 (88)
Episodes requiring PICU transfer for respiratory support, *N* (%)	3 (6)
Episodes in which blood transfusion was given during hospital course, *N* (%)	23 (43)
Had ACS on admission or during HD1 (*N*, % of those transfused)	12 (52)
Developed ACS during admission (*N*, % of those transfused)	4 (17)
Decrease in Hb during a sickle cell pain crisis (*N*, % of those transfused)	7 (30)
Episodes requiring transfer to PICU for other reasons, *N* (%)	3 (6)
Episodes with adverse effects attributable to BiPAP/CPAP, *N* (%)	0 (0)

Abbreviations: ACS, acute chest syndrome; BiPAP, bi-level positive airway pressure; CPAP, continuous positive airway pressure; HD, hospital day; PICU, pediatric intensive care unit.

[a]These three episodes were included in the "never used BiPAP" group: one patient did not tolerate BiPAP so CPAP was tried as an alternative, one patient had an ileus and abdominal pain at the time BiPAP was started and was switched to CPAP to avoid exacerbating GI issues, and one patient was never offered BiPAP and only offered CPAP for unclear reasons.

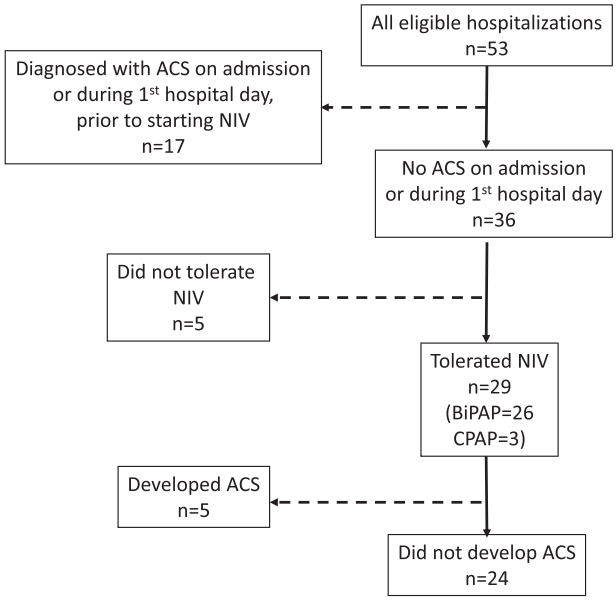

FIGURE 2 Flowchart of outcomes in hospitalizations in which BiPAP was recommended as supportive care for children with sickle cell anemia

hospitalized children with SCD at risk for adverse respiratory outcomes. Notably, despite the presence of multiple potential risk factors (history of recurrent ACS, known OSA, oxygen desaturation, and chest/back pain), hospitalizations only rarely included the development of new ACS or worsening of existing ACS requiring PICU transfer. There were no complications attributable to BiPAP.

Limited data suggest that BiPAP is safe, well tolerated, and efficacious as *treatment* for ACS in the pediatric ICU setting. Heilbronner et al. found that BiPAP was very well tolerated in the PICU setting as an early treatment modality for ACS.[18] Padman and Henry found that BiPAP was tolerated in the PICU in 25 episodes of ACS and was associated with increased oxygenation and improved work of breathing.[17] While a single-center randomized trial in adults with ACS without respiratory failure found lower satisfaction and compliance rates with BiPAP compared to routine care,[22] there were greater improvements in respiratory rate and oxygenation in the BiPAP group compared to the control group.[22] The younger age of our patients and collaboration between physicians, nursing, respiratory therapy, child life specialists, and families likely played a role in facilitating success of implementing this intervention in a non-ICU setting at our institution.

ACS often arises during hospitalization for acute SCD pain.[4] The National Acute Chest Syndrome Study Group found in almost half of the 671 episodes of ACS, patients had initially been hospitalized for other reasons, most commonly pain, and subsequently developed ACS in the first 3 days of hospitalization.[2] Similarly, a single-center prospective cohort study demonstrated that nearly 75% of ACS cases were preceded by an acute pain episode.[9] While the development of ACS is multifactorial, splinting from pain, hypoventilation from opioids, impaired oxygenation from air space disease, and V/Q mismatch are important factors.[1,2,9] Optimizing alveolar recruitment and oxygenation in children with pain crisis is integral to preventing ACS and its associated adverse outcomes.[11]

Multidisciplinary collaboration was crucial to the successful implementation of BiPAP in a non-ICU setting. The nurse manager of the pediatric inpatient unit (Karan Barry) created an official policy for the use of BiPAP on the pediatric unit, which provided clear steps for communicating the plan of care to staff who were initially unfamiliar with this novel indication; provider utilization increased over the 3 years since we introduced this modality into the care model. Various factors have contributed to the improved uptake and utilization of BiPAP since this intervention was introduced. Consultation with

respiratory therapy and child life therapy is recommended as early in the day as possible on the evening BiPAP will be started, with goals of preparation, mask fitting, and acclimation to the equipment. Several patients have indicated a preference for a nasal mask over a full-face mask to improve tolerability. BiPAP is provided to hospitalized patients during sleep until they consistently maintain oxygen saturations ≥95% on room air during the day and/or until chest/back pain and/or IV opioid requirements are at a minimum. An important lesson learned was to remain vigilant about monitoring the respiratory status of these higher risk patients and to use BiPAP only as a preventive measure and not for treatment of respiratory decompensation in this setting. On one occasion, one of our patients with recurrent, rapid-onset ACS was diagnosed with ACS in the emergency department but was felt to be stable for the general floor. There was an intention to provide him with BiPAP during sleep that evening. Shortly after arriving on the inpatient floor prior to the initiation of BiPAP, he developed progressively increased work of breathing and was transferred to the PICU. In this instance, the inpatient team identified worsening of his clinical status and appropriately transferred him to the ICU where he used BiPAP for *management* of his respiratory decompensation, under much closer monitoring. It would have been inappropriate to implement BiPAP on the floor for that patient.

The retrospective, single-center nature of our study limits the inferences we can draw from our results. Without a control group, we cannot yet make assertions about the efficacy of BiPAP in preventing ACS and severe adverse respiratory outcomes. Important next steps include a pilot feasibility trial and ultimately a large multicenter randomized trial to evaluate both the efficacy and ease of implementation of BiPAP across a broad range of institutions.

In conclusion, our study demonstrates that BiPAP is well tolerated, feasible, and safe as supportive care for hospitalized children with SCD in a non-ICU setting. Future research is needed to determine the impact of implementing BiPAP on ACS prevention among hospitalized children with SCD.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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