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Noninvasive pressure-support ventilation in immunocompromised children with ARDS: a feasibility study

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Abstract *Objective:* To verify the feasibility of non-invasive ventilation (NIV) in immunocompromised children affected by ARDS. *Setting:* University Hospital PICU. *Patients:* Twenty-three consecutive immunocompromised children treated with NIV for ARDS. *Interventions:* All consecutive patients received NIV through a face-mask or a helmet. *Results:* No differences were found regarding admission data and severity scores between NIV responders and non-responders. Early and sustained improvement in PaO_2/FiO_2 ratio were observed in 82 and 74% of cases, respectively. 13 out of 23 patients (54.5%) avoided intubation and were discharged from the PICU; ten patients required intubation: two of them survived and eight patients died (two refractory hypoxemia, three septic shock, three multi-organ failure). PICU and intra-hospital mortality was significantly higher for NIV-nonresponders ($P < 0.001$). PICU stay was significantly shorter for NIV responders ($P = 0.03$). NIV responders had significantly lower heart and respiratory rate at the end of treatment ($P < 0.001$ and $P = 0.048$, respectively). *Conclusions:* NIV administration is feasible and well tolerated in immunocompromised children with ARDS. A short NIV trial can be used to verify the usefulness of the technique. A randomized controlled trial is needed to confirm the efficacy of NIV in immunocompromised children requiring ventilatory support for ARDS.

Keywords Noninvasive ventilation · Children · PICU · ARDS

Introduction

In recent years, survival and pediatric intensive-care unit (PICU) admission of children with immunosuppression have increased. The main causes of PICU admission are infection related acute respiratory failure (ARF) and severe sepsis/septic shock, both complicated by high mortality. In the past, these patients have been conventionally treated with endotracheal intubation and mechanical ventilation; this has been associated with a large spectrum of complications and high mortality [1].

Extensive research on non-invasive ventilation (NIV) has been performed in adults and NIV is now regarded as first-line intervention for immunosuppressed patients with hematologic malignancies or solid-organ transplantation complicated by hypoxemic ARF [2–5].

Fewer data are available about NIV use in pediatric patients and the usefulness of this technique seems to be related to the underlying disease causing ARF [6, 7]. Differently from the subset of immunocompetent patients with ARDS for which a recent study reported negative results [6], another study investigated

the application of NIV in immunocompromised children with promising results [8]. To date, no study is available about the use of NIV in immunocompromised children with ARDS.

Because an NIV program with an NIV register has been implemented in the last decade as a reasonable alternative to immediate intubation in our PICU, both for selected hypoxemic and hypercapnic patients, we designed this study to evaluate the feasibility of NIV and its potential usefulness in immunocompromised children with ARDS.

Partial results from this study were presented at the 9th European Pediatric and Neonatal Ventilation Conference (2008) [9].

Methods

Patients

All immunocompromised children presenting with hypoxemic ARF and pulmonary infiltrates, admitted to our six-bed university PICU from January 2006 to May 2008 were eligible for the study. The immunosuppression was caused by:

1 hematologic malignancies:
2 solid tumors needing intensive chemotherapy; or
3 autoimmune diseases.

Patients presenting with these diagnoses were considered immunosuppressed if they had the presence of marked neutropenia (i.e. ANC < 500/mcL); the presence of absolute lymphopenia; or the recent administration of chemotherapy and/or immunosuppressive drugs.

This study was approved by our Institutional Review Board that waived the need for informed consent, because an NIV protocol is routinely used in our PICU and no specific treatment or additional diagnostic procedure was required for the study purposes. All data from NIV-treated children were collected in real time in an NIV register form in our PICU.

To be enrolled children had to fulfil the Consensus Conference Criteria for ARDS diagnosis within 24 h of the PICU admission [10]. Children were excluded if they met at least one of the following criteria:

1 need for cardiopulmonary resuscitation;
2 Glasgow coma score (GCS) of <8;
3 absent cough or gag reflex;
4 hemodynamic instability (defined as systolic arterial BP <fifth centile for age);
5 ECG with evidence of ischemia or arrhythmias;
6 uncorrected bleeding diathesis;
7 recurrent apneas;
8 infants less than one year of age; and
9 major congenital malformations or known chromosomic abnormalities.

NIV application protocol

NIV was applied according to a well established protocol that we had already validated for adult immunocompromised patients and that we adapted to children [11]. In detail, when patients fulfilled ARDS criteria NIV was started and all children were ventilated using a Maquet-Servo-I (Siemens-Elema, Solna, Sweden), with pressure support mode (target tidal volume 6 mL/kg body weight); in selected cases pressure-controlled, time-cycled ventilation was adopted (Fig. 1). Details of NIV management are provided as electronic supplementary material.

The primary end points were the need for endotracheal intubation and mechanical ventilation at any time during the study and the improvement in gas exchange. Improvement in gas exchange was evaluated within 1 h after the study entry (definition: "early response") and over time (definition: "sustained response") and was defined as the ability to increase the PaO_2/FiO_2 ratio above 200 [11].

Predetermined criteria for intubation were:

- the inability to maintain a PaO_2/FiO_2 ratio of 150 during NIV administration;
- the onset of seizures or deterioration of mental status (GCS < 8);
- intolerance of the technique or the inability to manage copious secretions;
- insurgence of hemodynamic instability (systolic BP <fifth centile for age or ECG with signs of ischemia or arrhythmias); or
- the occurrence of apneas.

An high oxygen need, defined as $FiO_2 > 80\%$ 1 h after the initiation of NIV, was also regarded as a major criterion for intubation, because this threshold level has been described as significantly predictive for NIV failure in children [7]. Secondary endpoints were the development of complications, PICU length of stay, and mortality rate in the PICU and in the hospital. We defined as "NIV success" all children who had a sustained response and therefore did not need endotracheal intubation.

The NIV protocol was discussed and approved by the whole critical care team. All children received the standard routine care for ARDS and their basic disease, according to our internal PICU protocols. No change was provided to the remaining clinical assistance because of the NIV treatment. In our PICU, since the first pilot use of NIV in 2001, all nurses have been trained to devote particular care to the prevention and detection of possible complications, as listed above.

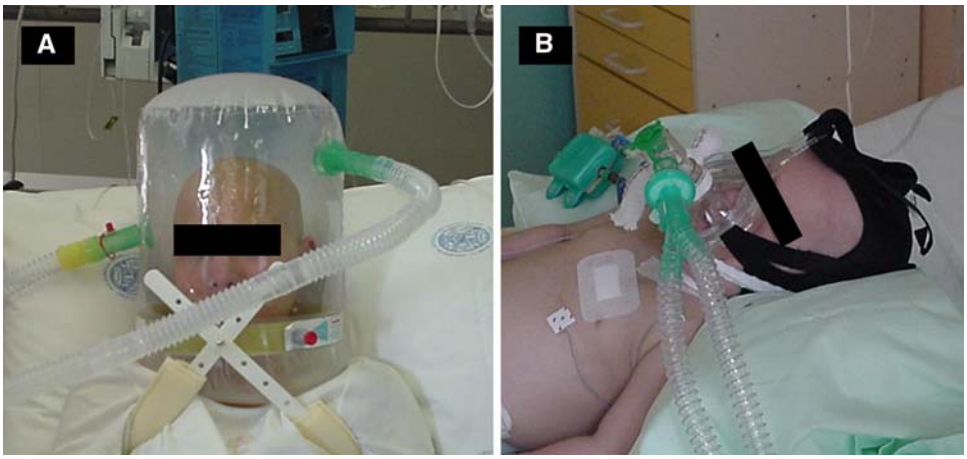

Fig. 1 Helmet (**a**) and face-mask (**b**) use in our patients

Data monitoring and collection

For each patient the following variables were collected in real time in an electronic sheet: demographics, basic diagnosis, Glasgow's coma score, PRISM-III-24 score at PICU admission [12], blood cell count and blood gas data; ventilation data, number of invasive devices, diagnosis of sepsis, number of organ failures, early and sustained improvements, PICU length of stay, and mortality. Ventilator-associated pneumonia (VAP), severe sepsis, septic shock and organ failures were also recorded in accordance with international literature guidelines [13, 14].

Measurements of arterial $PaCO_2$ and pH, respiratory rate (RR), and heart rate (HR), were performed at baseline, after 1 h of treatment ($_{-1\ h}$) and at the end of the treatment ($_{-end}$). Base excess and lactate concentration at admission were also considered. PaO_2/FiO_2 ratio was calculated every 6 h and recorded when it fell below 200 and criteria for ARDS diagnosis were fulfilled. A routinely positioned indwelling peripheral arterial line was used for blood gas analysis.

Skin injuries, claustrophobia, difficulties with ordinary care or with the patient–environment interaction, pain, anxiety, and intolerance of the technique were reported by the nurses and recorded.

Statistics

Being a pilot study about feasibility, no sample size was calculated. Data were tested for normality using the Kolmogorov–Smirnov test and then were summarized as mean values ± standard deviation, or median (interquartile range). Proportions were compared by use of the χ^2 test or Fisher's exact test, whereas continuous variables were contrasted by use of the Student *t* test or the Mann–Whitney *U* test, as appropriate.

Repeated measures of PaO_2/FiO_2 ratio during the NIV treatment were analyzed with the ANOVA procedure and the Holm–Sidak test was used as post-hoc correction.

Data were analyzed using SPSS for Windows release 15.0 (SPSS, Chicago, IL, USA) and *P*-values <0.05 were considered to be statistically significant.

Results

In the study period 922 patients were admitted to the PICU and about 65% required a form of mechanical ventilation for respiratory failure. Approximately 10% of our patients had some form of immunodepression. Twenty-three consecutive immunocompromised children with ARDS were enrolled and were treated with NIV using a face-mask (10; 43.5%) or helmet (13; 56.5%). Causes of immunodepression in enrolled patients were hematologic malignancies, solid tumors or autoimmune diseases; these data are detailed in Table 1.

The main characteristics of the whole population are shown in Table 2, together with data on NIV success or failure. Basal data were almost identical between the two groups. The NIV failure group consisted of ten patients who required intubation. Reasons for intubation were: refractory hypoxemia ($n = 4$), hemodynamic failure ($n = 3$), multi-organ system failure ($n = 2$), neurologic deterioration ($n = 1$). No failure because of NIV intolerance was observed.

The NIV success group consisted of the remaining 13 children. We did not notice difficulty with care or with interaction, anxiety, claustrophobia, or intolerance of the technique. The only complaints were pressure-related pain in the nasal region (three children with face mask), and axillary pain because of the armpits straps (two children with helmet): both symptoms were successfully relieved. Eighteen children received sedation with low

Table 1 Underlying diseases for all patients

	Underlying disease	Neutropenia	BMT
1	ALL	Yes	Yes
2	Ependymoma	Yes	
3	ALL		
4	Burkitt's lymphoma		
5	ALL		
6	Non-Hodgkin lymphoma	Yes	Yes
7	ALL		
8	ALL	Yes	
9	Non-Hodgkin lymphoma	Yes	Yes
10	ALL		
11	AML		
12	Hyper-IgD syndrome		
13	Ewing's (Askin) sarcoma	Yes	
14	ALL		
15	ALL	Yes	Yes
16	Seronegative myasthenia		
17	AML		
18	AML		
19	Systemic lupus erythematosus	Yes	
20	AML	Yes	
21	AML	Yes	
22	High grade glioma	Yes	
23	ALL	Yes	Yes

Neutropenia was defined as an absolute polymorphonuclear leukocyte count <500 cells/μL
BMT, bone marrow transplantation; ALL, acute lymphatic leukemia; AML, acute myeloid leukemia

dose midazolam continuous infusion (mean dose 1.2 ± 0.4 mcg/kg per min), no differences between midazolam use were noticed for the failure and success groups (ten NIV failures, eight NIV success, $P = 0.560$). Midazolam was administered for a mean duration of 2.5 ± 1.2 days. All patients started i.v. sedation at the onset of NIV support and midazolam was generally discontinued when the patient became accustomed to the feel of the mask/helmet.

Table 3 reports blood gas analysis, vital data at PICU admission, and PaO_2/FiO_2 ratio at ARDS diagnosis. All these data were almost identical between children who experienced NIV success or failure.

Table 4 shows vital data, clinical data, and outcomes for all children and for the two subgroups (NIV success and failure). For the whole population, NIV response rate was 82 and 74%, for early and sustained improvement, respectively. Early and sustained responses were significantly more frequent in the success group ($P = 0.019$ and $P = 0.003$, respectively). NIV duration was also significantly longer in the success group. Among vital data, both respiratory and heart rate at the end of treatment were significantly lower in the NIV success group ($P = 0.048$ and $P = 0.001$, respectively).

Patients who failed NIV had a significantly higher incidence of severe sepsis and septic shock: all these occurred several days after intubation (mean time interval from intubation to diagnosis was 4 ± 1.1 days) and no signs of sepsis-related hemodynamic compromise were present either at PICU admission or at NIV initiation. Post-intubation VAP was diagnosed in four out of ten (40%) NIV failing patients. VAP was confirmed 7 ± 0.5 days after intubation. PICU and intra-hospital mortality in the success group were nil, whereas a significant proportion of failing children died either in the PICU or in the hospital. NIV had an effect on PICU length of stay, significantly ($P = 0.03$) reducing it in the success group. Among patients failing NIV for refractory hypoxemia, two children died. Septic shock and multiorgan failure accounted for the remaining mortality in NIV failure patients. NIV mean duration was longer for non-survivors, although the significance threshold was not reached (10 h ± 2.8 vs. 34.9 ± 45; $P < 0.4$).

Figure 2 shows ANOVA results graphically. We noticed a significant increment of PaO_2/FiO_2 ratio over time for the whole population ($P < 0.001$), for the success group ($P = 0.001$), but not in the failure group ($P = 0.313$). Post-hoc analysis for the success group revealed the improvement to be mainly ascribed to the early response (within 1 h of NIV; $P = 0.003$) whereas

Table 2 Main characteristics of enrolled patients

	All patients (23)	NIV success (13)	NIV failure (10)	*P*
Age (years)	10.2 ± 4.7	11.7 ± 4.7	9.3 ± 4.1	0.22
Weight (kg)	42.3 ± 19.1	40.8 ± 18.5	42.2 ± 22.1	0.87
Males	10 (43.5)	4 (30.7)	6 (60)	0.59
Admission GCS	11.7 ± 2.2	11.6 ± 2.3	12 ± 2.3	0.681
PRISM-III-24	15.9 ± 3.7	15.7 ± 2.6	14.0 ± 2.5	0.407
<2 organ failures	13 (56.5)	8 (61.5)	5 (50)	0.650
>2 organ failures	10 (43.5)	5 (38.5)	5 (50)	0.80
BMT	5 (21.7)	2 (15.4)	3 (30)	0.7
Neutropenia	12 (52.1)	6 (46.1)	6 (60)	0.68

Data are expressed as mean ± SD or number (%). *P*-values are referred to the differences between NIV success and failure group
BMT, bone marrow transplantation. PRISM-III-24 was calculated within the first day from PICU admission

Table 3 Baseline data

	All patients (23)	NIV success (13)	NIV failure (10)	*P*
Arterial pH	7.40 ± 0.1	7.42 ± 0.09	7.37 ± 0.11	0.27
Arterial $PaCO_2$ (mmHg)	32.7 ± 9.5	35.2 ± 11.6	30.8 ± 7.1	0.31
Base excess (mmol/L)	−0.9 ± 2.1	−0.9 ± 0.4	−1.2 ± 0.9	0.599
Lactate (mmol/L)	1.8 ± 1.2	1.8 ± 1.1	1.7 ± 1.2	0.999
RR (breaths/min)	57.8 ± 19.3	61.5 ± 26.3	54 ± 7.4	0.388
HR (beats/min)	143.5 ± 11.6	146 ± 11	138 ± 10	0.131
Mean arterial pressure (mmHg)	70 ± 24	68 ± 22	71 ± 18	0.248
PaO_2/FiO_2 ratio	127.7 ± 51.9	126.3 ± 51.8	129.4 ± 54.9	0.9

Blood gas and vital signs were recorded at PICU admission, and PaO_2/FiO_2 ratio at ARDS diagnosis. Data are expressed as mean ± SD. *P*-values are for differences between the NIV success and failure groups

HR, heart rate; RR, respiratory rate

Table 4 Vital data, clinical data, complications, and outcomes

	All patients (23)	NIV success (13)	NIV failure (10)	*P*
$PaCO_{2\text{-}1h}$	35.8 ± 12.9	32.8 ± 3.5	39.6 ± 18	0.252
$PaCO_{2\text{-}end}$	37.8 ± 12.1	35.7 ± 4.9	40.2 ± 17	0.438
$FiO_2 > 80_{\text{-}1h}$	2 (8.7)	0	2 (20)	0.110
$FiO_2 > 80_{\text{-}end}$	1 (4.3)	0	1 (10)	0.420
$pH_{\text{-}1h}$	7.43 ± 0.09	7.43 ± 0.06	7.39 ± 0.11	0.451
$pH_{\text{-}end}$	7.41 ± 0.08	7.44 ± 0.04	7.38 ± 0.10	0.083
$RR_{\text{-}1h}$	40.0 ± 10.5	39.5 ± 11.3	41.3 ± 10.3	0.710
$RR_{\text{-}end}$	39.1 ± 12.5	34.6 ± 9.0	45.3 ± 13.1	0.048
$HR_{\text{-}1h}$	131.0 ± 13	125.9 ± 12.9	136.0 ± 11.6	0.082
$HR_{\text{-}end}$	127.3 ± 19.3	111.5 ± 8.9	143 ± 12.6	<0.001
Pressure support level (cmH_2O)	12 ± 3.2	12.5 ± 3	13 ± 2.6	0.889
NIV duration (days)	3 ± 2.1	4.1 ± 1.1	2.2 ± 2.2	0.04
Early improvement	19 (82.6)	13 (100)	6 (60)	0.019
Sustained improvement	17 (73.9)	13 (100)	4 (40)	0.003
Severe sepsis/septic shock	7 (30.4)	1 (7.7)	6 (60)	<0.01
PICU length of stay	11.5 ± 7.7	8.3 ± 3.4	15.1 ± 9.8	0.03
PICU mortality	8 (34.7)	0	8 (80)	< 0.001
Hospital mortality	9 (39.1)	0	9 (90)	< 0.001

Data are expressed as mean ± SD or number (%). $_{-1h}$ and $_{-end}$ identify values after 1 h of NIV and at discontinuation of the treatment, respectively. Sepsis/septic shock refers to complications occurring during the PICU stay but were not present at PICU admission or at NIV start

P-values refer to differences between NIV success and failure groups

HR, heart rate; RR, respiratory rate; FiO_2, inspired oxygen fraction; PICU, pediatric intensive-care unit

the difference between 1 h and end of treatment was not statistically significant ($P = 0.90$).

Discussion

Invasive ventilation has been associated with increased morbidity and mortality in adult ICU patients [1]. In immunocompromised patients these risks are higher and VAP is reported to be the most common hospital-acquired infection among patients requiring invasive mechanical ventilation, with relevant impact on outcomes [1, 15]. The usefulness of NIV has been widely demonstrated in immunocompromised adults [2–5]. Yet in 1994, Tognet et al. [16] were able to report a 55% survival rate in immunosuppressed adults responding to NIV, against a 100% mortality rate in invasively ventilated patients.

To date there has been a lack of data about the possibility of performing non-invasive ventilation in immunocompromised children affected by ARDS. Cogliati et al. [17] were the first to report, in 1999, good results for a small series of patients developing ARDS for all-trans retinoic acid (ATRA) syndrome. In this study use of NIV was shown to be feasible; it resulted in improved gas exchange and possibly helped to avoid endo-tracheal intubation in a significant subset of children. Feasibility of NIV in this patient population is particularly relevant,

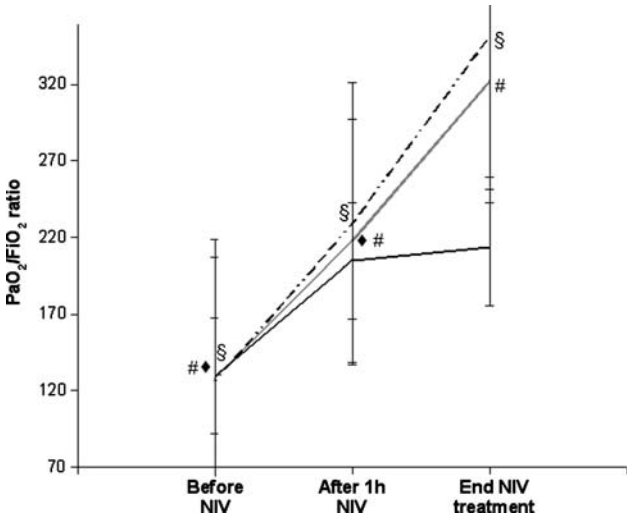

Fig. 2 PaO_2/FiO_2 ratio during treatment: ANOVA results. The *gray line* represents the whole enrolled population whereas the *black full* and *dashed lines* represent the failure and the success group, respectively. There is significant increment of PaO_2/FiO_2 ratio over time for the whole population ($P < 0.001$), for the success group ($P = 0.001$), but not for the failure group ($P = 0.313$). *Symbols* represent results of post-hoc analysis. Whole population: *diamonds*, $P = 0.005$ between baseline and after 1 h; *hash symbols*, $P = 0.001$ between 1 h and end of treatment; between baseline and end of treatment. Success group: *section symbols*, $P = 0.003$ between baseline and 1 h of NIV; between end of treatment and baseline

given their critical status. In general, immunosuppressed patients have been regarded as having a poor outcome, especially when mechanical ventilation for respiratory failure is required [16]. Moreover, the use of NIV in ARDS is still debated [18] and the failure rate of NIV has recently been reported to be higher for children affected by ARDS, although this was reported after one study only [6].

Our study suggests the feasibility of NIV in this context and our promising results could be used to design a randomized controlled trial. In fact, we found that 13/23 (56%) of immunocompromised children with ARDS could be successfully managed with NIV in the PICU. Moreover, in this study the main causes of NIV failure were other than hypoxemia in seven out of ten children. This is consistent with the longer mean NIV duration for non-survivors within the failure group: most deaths were caused by septic shock and multiorgan failure, which occurred well after NIV failure. Interestingly, all new septic complications and VAP in the failure group developed and were diagnosed several days after NIV failure and intubation, suggesting a direct role of the intubation in VAP etiology. This could also possibly be related to the higher number of invasive devices required by NIV non-responders after NIV failure, compared with NIV responders (4 ± 0.4 vs. 2.5 ± 0.6; $P < 0.01$). Consistently, for failure patients NIV was performed only for a mean of 2.2 days (Table 4) whereas their mean PICU stay was much longer (15.1 days, Table 4). This is also consistent with available data from other studies [11].

Children successfully ventilated with NIV also had shorter PICU and hospital stays, a lower incidence of septic complications, and lower respiratory and heart rate at the end of treatment, suggesting better hemodynamic and respiratory stability. Of note, our results do not seem to be related to the baseline conditions of patients, because characteristics and severity scores were similar for all children. Moreover, all septic complications, and the resulting increment in the number of invasive devices, occurred after NIV failure. Despite basic data so similar and probably unable to affect our results, we cannot "a priori" exclude the possibility that different ARDS severity affected, at least in part, the response to NIV in our small population.

On the other hand, we should balance these preliminary results with wide literature data revealing very high mortality rate in invasively ventilated immunosuppressed adults [1, 16]. For children undergoing bone marrow transplantation and requiring mechanical ventilation because of pulmonary infection a similar bad outcome has been reported—no survivors if ventilation >48 h [19].

Our findings also indicate a particular trend in improving PaO_2/FiO_2 ratio. In fact, patients who experience NIV success had significant oxygenation improvement during the first hour of NIV application; the difference in PaO_2/FiO_2 ratio from the first hour to the end of treatment also increased, but not to a statistically significant level.

In our series no children required $FiO_2 > 80\%$ at 1 h and, on the other hand, the failure group had significantly shorter NIV duration. Taken together, these data seem to suggest that an NIV trial could be considered in immunocompromised children with early ARDS. This could, theoretically, enable verification of the response to NIV, conversion to endotracheal intubation for unresponsive cases, and, therefore, reduction of possible risks linked to a late intubation. These preliminary findings warrant verification in a prospective controlled study.

Our study is also the first to use different interfaces for NIV in children. It is well accepted that lack of patient compliance (because of poor tolerance) may compromise the rate of NIV success. We did not notice any major problems with the use of either face mask or helmet and minor reported complications were successfully managed. The use of a new interface—the helmet—is interesting because it overcomes the disadvantages of the face mask while keeping the indications and benefits of true pressure-support ventilation. In adults with hypoxemic respiratory failure the helmet has been demonstrated to be as efficient as the face mask but with significantly fewer complications [4, 11, 20] despite a long length of NIV administration. Our current findings are fully consistent

with the positive results described for our first published pediatric series.

We acknowledge several study limitations. First, being a monocentric feasibility study our study lacked a control arm. As stated above, our data should therefore be regarded as a basis for a future randomized, controlled trial to confirm the usefulness of NIV in this population. Second, our results have been obtained in an NIV-oriented PICU with large specific experience. This may impair comparisons with other ICU and affect reproducibility in other settings. Therefore a specific multicenter controlled study is again warranted.

In conclusion, our study, given the absence of large RCT on this topic and the unreliability of historical controls, suggests that NIV is feasible in pediatric immunocompromised patients with ARDS and indicates that trials should be conducted as soon as possible. Because the positive response may be early, a short NIV trial can be used to verify the usefulness of the technique. The objectives of our future work will be further confirmation of the usefulness of NIV and the definition of predictors of its success in a controlled study.

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Conflict of interest statement Authors have no conflict of interest to declare.

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