Selecting Intermediate Respiratory Support Following Extubation in the Pediatric Intensive Care Unit

Christopher M. Horvat, MD, MHA; Martha A. Q. Curley, RN, PhD; Timothy D. Girard, MD, MSCI

Prolonged invasive mechanical ventilation is associated with considerable morbidity among critically ill children, including secondary infections, exposure to potentially neurotoxic sedatives, and muscle wasting. These adverse outcomes may have detrimental effects on childhood development.1,3

Related article

Children who require invasive mechanical ventilation also pose a unique set of clinical challenges. Short airways require precise endotracheal tube position, lower functional residual capacities potentiating the likelihood of hypoxemia, and episodes of inconsolability may lead to sedation administration. Such factors can impede implementation of intensive care unit liberation bundles, including those designed to promote wakefulness, spontaneous breathing, and ambulation.4

In this complex setting, carefully timed extubation with transition to intermediate respiratory support (such as high-flow nasal cannula [HFNC], continuous positive airway pressure [CPAP], or other noninvasive ventilation modes) offers the advantage of earlier separation from invasive mechanical ventilation while maintaining some degree of respiratory support. In theory, this strategy can promote continued recovery from acute respiratory failure while accelerating overall recovery from critical illness. Evidence, however, is limited regarding the safety and effectiveness of various forms of intermediate respiratory support, and each modality is associated with theoretical and empirical advantages and disadvantages.5,6 Amid this uncertainty, there is variation in the use of postextubation HFNC, CPAP, and other support modalities for patients treated in pediatric intensive care units (PICUs).

In this issue of JAMA, Ramnarayan et al7 provide new evidence for postextubation respiratory support in the PICU. The First-Line Support for Assistance in Breathing in Children (FIRST-ABC) step-down trial was a randomized, pragmatic, unblinded, multicenter, parallel-group, noninferiority clinical trial that examined whether HFNC is noninferior to CPAP when applied following extubation in the PICU. Among 553 children (median age, 3 months) included in the primary analysis, the median time to liberation from respiratory support for at least 48 hours (the primary end point) was 50.5 hours among children who received HFNC vs 42.9 hours among those who received CPAP. The adjusted hazard ratio was 0.83, favoring HFNC, with a 1-sided confidence interval of 0.70, which was below the prespecified noninferiority margin of 0.75. In addition, there were no significant differences between HFNC and CPAP for 5 of 6 prespecified secondary outcomes, including rate of reintubation within 48 hours (13.3% vs 11.5%, respectively), although mortality at 180 days was higher in the HFNC group (5.6%) than the CPAP group (2.4%).

Several key factors distinguish HFNC from CPAP, and these differences likely influence conventional clinical application of each modality. HFNC works predominantly by generating fresh gas flow in excess of peak inspiratory flow, washing out physiologic dead space, facilitating ventilation, and achieving a fraction of inspired oxygen content as high as 1.0. The ratio of extrathoracic dead space volume to body weight is 2- to 3-fold greater in children than adults, starting at up to 3 mL/kg in neonates and becoming similar to adult dead space volume at approximately 6 years of age. This suggests HFNC may be particularly beneficial in younger children. Pharyngeal pressures of 4 to 6 cm H₂O are observed with HFNC, and this intervention is associated with reduced electrical activity of the diaphragm, decreased esophageal pressure swings, and reduced work of breathing.8

By comparison, CPAP has many of the attributes of HFNC but has more established effects on alveolar pressure, restoration of functional residual capacity, and possibly a reduction of work of breathing by overcoming the opening pressure of diseased lungs.9 However, the physiologic benefits of CPAP may be counterbalanced by increased risk of pressure-related skin injury, reduced patient comfort, and the increased attention required by care teams to ensure the therapy is delivered as intended. Balancing these factors and the absence of high-quality data, HFNC has emerged as a common choice for first-line intermediate respiratory support in children.10

Among children enrolled in FIRST-ABC, there were no significant differences between the 2 study groups in individual adverse events, such as aspiration, pneumothorax, or nasal, facial, or neck trauma. More than half of the children in each group received sedation while they were receiving noninvasive respiratory support, and there were no differences in sedation depth as assessed by the COMFORT-Behavioral scale. The apparent similarities in safety and tolerance allow focused attention to a key question: Is the primary result of the trial—that postextubation HFNC was not noninferior to postextubation CPAP—clinically meaningful? The estimated absolute difference in time to liberation from respiratory support (7.6 hours) is arguably not large, a finding the authors acknowledge may not have high clinical importance considering the relatively common practice at many institutions of transferring stable children receiving HFNC from the PICU to the general ward. In contrast, CPAP support for deescalation following extubation is commonly confined to a PICU setting.
One potential vulnerability of a noninferiority design is the a priori selection of a margin, which requires both clinical and statistical reasoning. An important attribute of FIRST-ABC was the incorporation of parent perspective in the selection of the noninferiority threshold on the basis of findings from the pilot trial.

The FIRST-ABC trial was both pragmatic and generalizable. For example, patients were randomized both pre- and postextubation, an approach that could have been a major methodologic problem if timing imbalances were apparent between the 2 groups because the primary outcome assessed duration of support between randomization and liberation. However, randomization was distributed comparably between the 2 study groups, indicating the pragmatic timing of randomization is unlikely to have introduced bias. The deferring of written, informed consent from parents or legal guardians may have helped to ensure this balance by facilitating faster enrollment. Notably, the parent-reported stress at the time of consent was low, suggesting this approach may have succeeded in finding the “approachable moment” to discuss the study with parents. An alternative view is that low parental stress may obviate the need to defer consent.

Why did the FIRST-ABC trial surpass its enrollment targets? To start, clinical management may have been influenced by a carefully worded, but not overly regimented, trial protocol. Both the initiation and weaning of postextubation HFNC and CPAP were standardized in a protocol that reads more like a guideline, with crossover allowed per clinical judgment in the setting of treatment failure and algorithm branch points asking clinicians to “consider” specific management strategies. Another boost to enrollment was that nearly 80% of PICUs in the United Kingdom's National Health Service participated in the trial, providing scale across a range of unit sizes, admission volumes, and patient populations and bolstering generalizability of the findings. High-quality randomized trials are scarce in pediatric critical care, and the successful completion of FIRST-ABC and comparable pragmatic studies within the National Health Service are indications that a learning health system approach to care may catalyze new advancements in the field.

Some potential limitations of the study by Ramnarayan et al also should be considered. First, 70 (34%) of 174 respiratory support switch events, such as the decision to change from assigned HFNC to CPAP, did not adhere to study procedures, introducing uncertain practice variation that may have influenced the trial’s results. Second, the simple patient inclusion criteria helped to identify and enroll a heterogeneous patient population in the PICU, but the HFNC cohort included more neonates, more patients requiring invasive ventilation for an “other” reason, and a lower proportion of patients with bronchiolitis. With these case mix differences, it is conceivable that patient heterogeneity may have been a factor in the study findings. Third, the use of clinician determination of the need for intermediate respiratory support may introduce selection bias and limit generalizability to other centers, favoring enrollment at sites with more experience and comfort with postextubation use of HFNC and CPAP.

Do the findings of FIRST-ABC suggest HFNC should be abandoned following extubation in the PICU? In critically ill adults, trials that have examined related study questions have generated conflicting data, with some investigations favoring usual care, some favoring a combination strategy of positive pressure ventilation and HFNC, and some finding that noninvasive positive pressure ventilation causes harm following extubation (when used as a rescue therapy rather than as a preventive intervention). In the PICU, much more work is needed to develop an evidence base that guides individualized respiratory support, including when to apply HFNC, CPAP, other noninvasive modes, or combination approaches, and when to simply continue invasive mechanical ventilation. Higher mortality with HFNC compared with CPAP has been observed among children in other settings, although the reasons are unclear. That HFNC did not meet noninferiority criteria in the FIRST-ABC trial and potentially led to higher 180-day mortality may favor the use of CPAP until more evidence becomes available. The FIRST-ABC trial provides helpful information on preferred approaches to respiratory management in the PICU, although uncertainty still dominates clinical decision-making involving optimal respiratory support following extubation for pediatric patients.


