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PERSPECTIVE

The naked emperor: that is the realm of logical fallacy

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ABSTRACT

Bronchiolitis is the most common cause of admission to hospital for infants in high-income countries. Management recommendations, based predominantly on high-quality evidence, state that the mainstays of treatment remain supportive interventions, such as oxygen therapy and hydration only. Despite evidence of no efficacy for salbutamol, adrenaline, glucocorticoids, antibiotics or chest X-ray, and repeated warnings to improve practice being published, substantial variation in practice continues. Evidence suggests use of high-flow oxygen therapy in bronchiolitis does not decrease length of hospitalization and rates of intensive care unit admission or intubation. High-flow oxygen should be limited to rescue therapy after failure of conventional nasal oxygen only in infants who are hypoxic. Reducing the use of inappropriate health interventions is important for minimizing patient harm, maximizing resources, and improving evidence-based health care delivery. Despite international clinical guidelines promoting supportive rather than interventional therapy, universal de-implementation of interventional care in bronchiolitis has not occurred and remains a major challenge.

IMPACT STATEMENT: The article summarizes the main shortcomings of pediatricians facing with children with bronchiolitis.

INTRODUCTION

"Oh! Let us never, never doubt What nobody is sure about!"
(Hilaire Belloc, The Bad Child's book of Beasts, 1896)

In the tale "*The emperor's new clothes*" by Hans Christian Andersen, two swindlers arrive at the capital city of an emperor who spends lavishly on clothing at the expense of state matters. Posing as weavers, they offer to supply him with magnificent clothes that are invisible to stupid people. The emperor hires them, and they set up looms and go to work. A succession of officials, and then the emperor himself, visit them to check their progress. Each sees that the looms are empty but pretends otherwise to avoid being thought a fool. Finally, when the weavers report that the emperor's suit is finished, they mime dressing him and he sets off in a procession through the whole city. The townspeople uncomfortably go along with the pretence, not wanting to appear stupid, until a child blurts out that "the emperor is wearing nothing at all". The people then realize that everyone has been fooled.

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KEY WORDS
Bronchiolitis; oxygen; high-flow nasal cannula.

THE FACTS

The title of the present article relates to logical fallacies and refers to something widely accepted as true or professed as being praiseworthy. It is also a metaphor for anything that smacks of pretentiousness, popular belief, unwillingness to criticize and pluralistic ignorance. Sixty years ago, Reynolds and Cook concluded their iconic article on treatment of bronchiolitis remarking that: "The mainstays of treatment of bronchiolitis remain supportive interventions, such as oxygen therapy. There is little convincing evidence that any other therapy is consistently or even occasionally useful" (1). Since then, several therapies have been investigated, but none has shown clear efficacy. Over the years, numerous guidelines have been published to aid clinicians in the management of bronchiolitis and all of them invariably recommend only supportive care, including oxygen to correct hypoxemia and appropriate fluid replacement to maintain hydration (2). Traditionally, low-flow 100% oxygen (up to 2 L/min) through nasal prongs has been used by physicians to correct hypoxemia in infants with bronchiolitis. Occasionally, a face mask at oxygen flow of up to 15 L/min may be a reasonable option.

High-flow oxygen therapy, in which humidified and heated air is blended with oxygen and delivered via high-flow nasal cannula (HFNC), usually at a flow rate of up to 2-3 L/kg per min, was one of the options evaluated to treat respiratory failure in children with bronchiolitis admitted to intensive care units (ICU), part of a therapeutic armamentarium that includes nasal continuous positive airway pressure (nCPAP), intubation, and invasive mechanical ventilation (IMV). HFNC is thought to work by providing a degree of positive airway pressure that reduces upper airway resistance and washout end-expiratory gases of the nasopharyngeal dead space, thus reducing work of breathing and improving gas exchange (3, 4).

Over the past decade, the use of HFNC in bronchiolitis has become progressively more popular worldwide, rapidly moving from the ICU setting to emergency departments and pediatric wards to treat outpatients and inpatients, respectively. Can there be any condition characterized by respiratory distress for which HFNC has not been recommended?

A survey in 97 general and tertiary hospitals in the United Kingdom revealed that use of nCPAP and HFNC was widespread in young children with bronchiolitis; more respondents with access to both modalities (69.8%) would choose HFNC over nCPAP as their first-line treatment option in a deteriorating child with bronchiolitis (5). In a survey of 135 hospitals in France, seventy-two hospitals (53.3%) used HFNC in acute bronchiolitis outside ICU, mostly in pediatric general departments (75%). Pediatricians developed a positive opinion (obviously Class A evidence!) of HFNC and were willing to extend its use to other diseases (6). Another survey describing the practice of HFNC use across pediatric hospitals in North America found that 37/76 sites (48%) used this technique in the ward setting, the commonest indication being for treating bronchiolitis (7). A recent web-based survey of Pediatric Hospital Medicine section chiefs in Canada revealed that approximately half of tertiary children's hospitals currently use HFNC in the ward, with pneumonia and bronchiolitis being the most common conditions requiring such treatment; other centers were considering implementation. Perceived benefits were reduction in ward to ICU transfers and reduced stress for families (8). Finally, a recent study aimed to determine the prevalence of use of HFNC therapy in infants with bronchiolitis presenting to hospital in Australia and New Zealand over four bronchiolitis seasons. Out of 11,715 infants included, 3392 (29.0%) received oxygen therapy, and 1817 of them (53.6%) received HFNC. Use of standard oxygen therapy did not change over the four bronchiolitis seasons, while the proportion receiving HFNC increased from 43.2% in 2014 to 57.8% in 2017 ($p \leq 0.001$) (9). Surprisingly, apart from the enthusiastic (and often uncritical) use of HFNC in general wards as first-line support modality for infants with bronchiolitis, none of these studies addressed the potential higher costs of HFNC over standard oxygen therapy.

The inevitable consequence of the diffuse use of HFNC oxygen therapy was the exponential increase of scientific publications on this subject over the last few years, including a storm of observational studies and some randomized controlled trials (RCT). An open, phase 4, single-center, RCT in Australia compared HFNC at 1 L/kg per min *versus* standard nasal oxygen at up to 2 L/min in 202 children with bronchiolitis and oxygen saturations 90% and above. HFNC therapy had fewer treatment failures (14% *vs.* 33%; $p = 0.0016$), but no statistically significant difference between groups in

length of oxygen treatment (20 h *vs.* 24 h; p = 0.61), length of hospital stay (2.0 *vs.* 2.0 d, p = 0.99) and transfer to ICU (14% *vs.* 12%, p = 0.41) was found. In contrast, the estimated consumable cost of HFNC therapy was 16 times higher than that of standard therapy (10). A large RCT compared HFNC at 2 L/kg per min *versus* standard nasal oxygen at up to 2 L/min in 1472 children with bronchiolitis and oxygen saturations of less than 92-94% (depending on the institution) at 17 hospitals in Australia and New Zealand. Although fewer treatment failures occurred in the HFNC group than the standard oxygen group (12% *vs.* 23%, p < 0.001), no significant differences were observed in the duration of hospital stay (3.12 *vs.* 2.94 d, p = 0.19), the duration of oxygen therapy (1.81 *vs.* 1.87 d, p = 0.61) and transfer to ICU (12% *vs.* 9%, p = 0.08) (11). Noteworthy, in both these studies, more than two-thirds of the patients could be treated successfully with standard oxygen therapy (68% and 77%, respectively), and high flow rescued about 60% of patients in whom treatment with standard oxygen failed. A further trial at 17 French hospitals compared HFNC at 3 L/kg per min *versus* standard nasal oxygen at up to 2 L/min in 268 children with moderate bronchiolitis and oxygen saturation under 95%. There was no statistically significant difference in treatment failure requiring escalation in care (14% *vs.* 20%; p = 0.21). Furthermore, HFNC did not reduce the risk of admission to ICU (15% *vs.* 19%, p = 0.45) (12). In a study conducted in 5 pediatric ICUs in France, increased rates of patient discomfort (43% *vs.* 16%; p = 0.002) was found in the HFNC group with respect to standard oxygen (13). Together, these trials show no difference between HFNC and controls in any important outcome, including length of hospital stay, ICU admission rates or intubation rates. Intervention is safe with adverse events occurring rarely, other than damage to the public purse.

How current scientific information should be transferred into clinical practice has been recently tackled. First, conventional oxygen therapy works well in most patients with bronchiolitis, and it should therefore remain the first-line modality of respiratory support. Second, early use of HFNC oxygen therapy does not modify the underlying disease process; therefore, there is no real advantage to initiating high flow therapy early rather than postponing it until standard therapy has failed. Third, HFNC increases costs. For all these reasons, high flow oxygen therapy should not be used as a primary treatment modality in bronchiolitis with hypoxemia, but rather as a rescue intervention for children who are not adequately supported by conventional oxygen supplementation. Reasonably, it should be the first option for children admitted to ICUs with severe bronchiolitis (14). The reasons supporting this statement have been confirmed by a further article in the same journal. The author comments that early initiation of HFNC is the inferior choice since it involves providing a costly therapy to many children who will not benefit from it, and it is highly likely that the liberal application of HFNC oxygen in bronchiolitis is doing more harm than good at the population level (15). This view is shared by an Australian Pediatric Research Emergency Department International Collaborative Network (PREDICT); that is, HFNC in patients with bronchiolitis should be limited to use as rescue therapy for infants with hypoxemia in whom standard oxygen therapy has failed (16). It should be remarked that criteria for escalation of care from conventional oxygen to HFNC are not well established and should be defined in further studies (**Infobox 1**).

Infobox 1. *The use of standard and high-flow oxygen therapy in bronchiolitis.*

- Low-flow oxygen therapy has been traditionally used to correct hypoxemia in children.
- High-flow oxygen therapy has become progressively popular over the last 10 years.
- High-flow oxygen therapy does not improve any important outcome with respect to standard oxygen.
- High-flow oxygen therapy greatly increases costs.
- High-flow oxygen therapy should be used only as rescue intervention.

Care patterns for patients with bronchiolitis appear to be shifting, with a rising proportion of ICU admissions and use of non-invasive ventilation (NIV) in the last decade. In accordance with rising use of NIV, reports have indicated a dramatic increase in inflation-adjusted cost of hospitalization for bronchiolitis from $ 449 million in 2003 to $ 734 million in 2016 in the United States (17). In a retrospective cross-sectional study of the Pediatric Health Information Systems database over a 10-year period (2010-2019) in the United States, 203,859 admissions for bronchiolitis were recorded. ICU admissions doubled from 11.7%

in 2010 to 24.5% in 2019 (p < 0.001 for trend), whereas ICU admissions for all children <2 years of age increased from 16.0% to 21.1% during the same period (p < 0.001 for trend). Use of NIV (including HFNC therapy) increased sevenfold from 1.2% in 2010 to 9.5% in 2019 (p < 0.001 for trend). These changes were not associated with changes in the proportion of IMV (3.3% in 2010 to 2.8% in 2019, p = 0.414 for trend) (18). In a population-based cohort study including more than 2.3 million young children from 2004 to 2018 in Ontario, Canada, the bronchiolitis hospitalization, and mortality rates were stable. However, ICU use increased by 130% (from 38.1 to 87.8 per 1000 hospitalizations), as did hospitalization costs from $ 50.000 to $ 59.000 per 1000 person-years. A 1.7-fold increase in the use of IMV (1.6%-2.7%) and an almost 4-fold increase in the use of NIV (0.4%-1.7%) was also reported (19). In their large study in children with bronchiolitis, the PREDICT network found that HFNC use was associated with increases in both hospitals stay (p < 0.001) and ICU admissions (p < 0.001) (20). Finally, a multicenter RCT conducted at 14 metropolitan and tertiary hospitals in Australia and New Zealand, including 1567 children aged 1 to 4 years requiring hospital admission for acute hypoxemic respiratory failure (including some patients with bronchiolitis), found that early high flow oxygen therapy was associated with a significant longer stay in the hospital compared with children who received standard oxygen therapy (1.77 *vs.* 1.50 d; p < 0.001). A greater proportion of children in the high flow oxygen group were admitted to the ICU (12.5% *vs.* 6.9%) and did not tolerate the assigned treatment compared with children in the standard oxygen group (21).

The reasons of the observed increase in bronchiolitis ICU admission rates across the globe remain unclear, standing the stable hospital length of stay over most studies. The greater availability and use of NIV including HFNC without high quality evidence to guide its implementation, and the difficulty of the hospital team supervising HFNC in the ward may have at least contributed to this increase. Many protocols for heated HFNC on inpatient units recommend ICU admission based on duration of use, flow rates, and/or fractional inspired oxygen amount. Differences in underlying patient population, local pathogen strains, or variability in ward and ICU capabilities may be other reasons.

Despite management of bronchiolitis being well defined with high quality evidence of no efficacy for salbutamol, adrenaline, glucocorticoids, antibiotics or chest X-ray, and repeated warning to improve practice being addressed (22), substantial variation in practice continues. This (apparently) incomprehensible behavior in the hospital setting is consistent with international comparisons in North America, the United Kingdom and Europe (23) and highlights − once more − the gap between evidence-base and clinical practice in medicine. In a retrospective study conducted in 38 pediatric emergency departments in Canada, USA, Australia/New Zealand, UK/Ireland and Spain/Portugal, full evidence-base medicine (EBM) adherence was achieved in only 1137/2356 (48.3%) infants. There was a marked variation in full EBM intervention between pediatric emergency networks, ranging from 13.2% in Spain/Portugal to 72.3% in UK/Ireland; full EBM delivery was also associated with lower likelihood of hospitalization (24). This study underlines that emergency department-focused de-implementation of erroneous clinical decisions to enhance EBM is urgently needed for the treatment of bronchiolitis.

To better understand factors that influence practice variation in treating bronchiolitis, the uptake of 5 evidence-based guidelines were recently explored by semi-structured interviews with senior and young clinicians in emergency departments and pediatric inpatient areas across Australia and New Zealand. Clinical decisions were mainly influenced by concerns about misdiagnosis, severity of illness, lack of experience (knowledge), lack of confidence in managing infants with bronchiolitis (skills), and parental pressure influencing practice (social influences) (25). Defensive medicine may be also another possible explanation for incorrect, non-evidence based medical care (26) (**Infobox 2**).

Infobox 2. *Possible factors influencing erroneous clinical decisions in bronchiolitis.*

- Concerns about misdiagnosis.
- Severity of illness.
- Lack of scientific learning (knowledge).
- Lack of clinical experience (skills).
- Lack of high-grade supervision (organization).
- Parental pressure (social influences).
- Defensive medicine (legal influences).

For a long time, the simple diffusion and implementation of national guidelines for the management of bronchiolitis was inconsistent as far as regards the required changes in physicians' behavior in the hospital (27). Specific interventions including site-based clinical leads, stakeholder meetings, a train-the-trainer workshop, targeted educational delivery, other educational and promotional materials, and audit and feedback were applied in 26 hospitals in Australia and New Zealand. When data from 3 bronchiolitis seasons (2014-2016) before the implementation period were compared to those collected during the implementation period (2018-2020), compliance with recommendations was 85.1% in intervention hospitals *vs*. 73.0% in control hospitals ($p < 0.001$) (28). Targeted interventions designed to address factors influencing bronchiolitis management can therefore improve the care delivered to infants with this condition and de-implement unnecessary care and should be welcomed in other countries in the future.

There is increasing awareness of overuse of low-value clinical interventions in health care (29). Reducing the use of inappropriate health interventions is important for minimizing patient harm, maximizing resources, and improving evidence-based health care delivery (30). Cost for oxygen treatment of children with bronchiolitis is of paramount importance. A within-trial economic evaluation from the health service perspective established that mean cost of bronchiolitis treatment, including intervention costs and costs associated with length of stay, was AU$ 420 higher per infant in the early HFNC group compared with the rescue HFNC group (31).

Given the strong suggestion that we are wasting resources with the current use of HFNC, we urgently need prospective research to define the appropriate population in whom to use this therapy. Some studies aimed to identify factors associated with the clinical response to HFNC oxygen therapy and analyze health care-associated economics with different interventions in children with bronchiolitis are in progress. There is preliminary evidence that higher heart rate and oxygen saturation 1 hour after treatment are early factors associated with the success of HFNC therapy (32). One study has also shown that a ratio of oxygen saturation to fraction of inspired oxygen less than 195 after the first hours of treatment is associated with unresponsiveness (33).

FINAL THOUGHTS

Despite two decades of messaging, clinical guidelines, workshops, and thousands of words expended at local and international meetings suggesting that less treatment is better and promoting supportive rather than interventional therapy in bronchiolitis, universal de-implementation of interventional care has not occurred and remains a major challenge. There is no doubt that management approaches in bronchiolitis favor overtreatment, reflecting a perceived need "to do something" (34). But occasionally in medicine – and bronchiolitis is a golden example – "to do less is to do more".

HFNC is the new fashionable hospital treatment of bronchiolitis. Pending the demonstration of better clinical and economic outcomes with the use of such therapy as a substitute for conventional oxygen in most children with bronchiolitis, we caution, like the screaming child in Anderson's tale, against the indiscriminate and uncritical use of HFNC therapy in general wards and suggest using it in children with more severe cases and those who do not respond to conventional oxygen therapy. Strategies to guide appropriate HFNC use in children with bronchiolitis are urgently required. Until criteria for treatment failure of oxygen therapy are established, using standard low-flow oxygen as early intervention and limiting the use of HFNC to rescue therapy is likely to do the best with the least harm. On the other hand, some patients with severe bronchiolitis are admitted to ICU, and anything that can decrease the use of IMV should be welcomed.

The history of medicine is fraught with examples of useless risks and increased costs induced by the latest new techniques without the support of an evidence-based background. There is no magic bullet to guide de-implementation of care in medicine (35), but maintaining critical independence and being more confident with medical ethics when dealing with drug prescription is a cornerstone principle of the art of medicine.

As far as regards the main target of the present article (*i.e.*, the optimal positioning of HFNC oxygen therapy in the armamentarium of interventions in emergency departments and/or hospital wards), there is an urgent need for a more accurate characterization of children with bronchiolitis. International collaborations are essential if progress is to be made. Given our present lack of knowledge, this hope still remains in Pandora's box.

Only Hope remained inside the jar, without passing the mouth, nor did it fly out, because first had put the lid back on the jar at the behest of Zeus who gathers the clouds.
(Esiodo, Teogonia, 8th Century b. C.)

COMPLIANCE WITH ETHICAL STANDARDS

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Author contributions

FMdB conceived and wrote the first draft of the manuscript; ALB and AB reviewed the manuscript for important intellectual content. All Authors approved the final version of the manuscript.

Ethical approval

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N/A.

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N/A.

Data sharing and data accessibility

The data underlying this article are available in the article.

Publication ethics

Plagiarism

The contents of the article are original and any overlaps with other articles are by the Authors themselves and appropriately cited.

Data falsification and fabrication

All the data correspond to the real.

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