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When Technology Creates Disease: pulse oximetry and the search for hypoxemia in bronchiolitis

Ricardo A. Quinonez, MD, Eric R. Coon MD, Alan R. Schroeder MD, Virginia A. Moyer, MD, MPH

Section of Pediatric Hospital Medicine, Department of Pediatrics, Baylor College of Medicine, Department of Pediatrics, University of Utah School of Medicine, Department of Pediatrics, Stanford University School of Medicine, American Board of Pediatrics

Corresponding Author: Ricardo A Quinonez, 1102 Bates Street, #FC1860, Houston, Texas, 77030, United States of America, Quinonez@bcm.edu

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Dr. Ricardo A. Quinonez conceptualized the manuscript, developed the initial outline and literature search strategy, drafted the initial manuscript and reviewed, critically revised the manuscript and approved the final manuscript as presented
Dr. Eric R. Coon reviewed, critically revised the manuscript and approved the final manuscript as presented
Dr. Alan R. Schroeder reviewed, critically revised the manuscript and approved the final manuscript as presented
Dr. Virginia A. Moyer conceptualized the manuscript, reviewed, critically revised the manuscript and approved the final manuscript as presented
Summary Box

- **Clinical context** – Hypoxemia as detected by pulse oximetry is a common admission criteria for children with bronchiolitis.

- **Diagnostic change** – The widespread use of pulse oximetry has led to fast and accurate detection of hypoxemia in children with bronchiolitis.

- **Rationale for change** – Pulse oximetry detects hypoxemia that would otherwise not be evident by routine clinical exam.

- **Leap of faith** – Detection of hypoxemia is important to prevent clinical deterioration and negative neurologic sequelae.

- **Evidence for overdiagnosis** – There has been increasing incidence of hospitalization for bronchiolitis coinciding with increases in the widespread use of pulse oximetry without a concomitant increase in mortality. Controlled trials which randomize children to varying probabilities of diagnosis of hypoxemia have not demonstrated improved outcomes with increased detection.

- **Harms of overdiagnosis** – Increased detection of hypoxemia has exposed more children to the dangers of hospitalization and the complications of overtreatment with oxygen.

- **Limitations** – Current studies are underpowered to detect long term benefits of detection of hypoxemia in well-appearing infants.

- **Conclusion** – The increasing use of pulse oximetry to detect hypoxemia in bronchiolitis has led to an increase in hospitalization of children without any evidence of improved outcomes.
BACKGROUND

Karl Matthes, a German physician, is credited with developing the first device to measure oxygen saturation.¹ However, early pulse oximeters were relegated to research or the laboratory due to technical and reliability concerns. In 1972, Japanese engineers developed the first modern pulse oximeter. This device was tested in patients during the 1970’s. Wide-scale commercial use began in the 1980’s with introduction of the first commercial devices.² Since then, pulse oximetry has permeated healthcare to the point that it has been dubbed the “fifth vital sign” and the standard method for non-invasive measurement of oxygenation.³,⁴

Pulse oximetry is widely used to aid in the evaluation of children suffering from bronchiolitis, a lower respiratory tract viral infection that primarily affects children in the first 2 years of life.⁵ Excluding live births, bronchiolitis is the leading cause of hospitalization in infants < 12 months of age in the United States, accounting for 18% of all hospitalizations in this age group. On a yearly basis, nearly 3% of all US infants are hospitalized with bronchiolitis.⁶ Bronchiolitis is a self-limited illness for which most therapeutic interventions have failed to positively impact important outcomes. Treatment, even in hospitalized children, is primarily supportive.⁵,⁷ Respiratory syncytial virus (RSV), the most common agent responsible for bronchiolitis, is a highly common viral pathogen in children with different strains that account for significant differences in disease severity.⁸ However, the trends in temporal variations for the different RSV strains have no direct correlation to a noted significant increase in hospitalization rates for bronchiolitis.⁹,¹⁰ This increase, which coincides with the growing use of pulse oximetry in the 1980’s, has led to a tripling in the number of hospitalizations for bronchiolitis, from 12.9 per 1000 to 31.2 per 1000 children under 1 year of age.¹⁰ Notably, this impressive rise has not been accompanied by increased disease related mortality or morbidity,¹¹ leading several investigators to suggest that overreliance on pulse oximetry and overdiagnosis of hypoxemia are likely explanations.¹²-¹⁴

Defining Hypoxemia

Hypoxemia is defined as a decrease in the partial pressure of oxygen in the blood. Pulse oximetry measures arterial oxygen saturation. The relationship between oxygen saturation of hemoglobin (SaO₂) and the partial pressure of arterial oxygen (PaO₂) represented by the oxyhemoglobin dissociation curve, reveals a steep drop in PaO₂ as SaO₂ falls below 90%.¹⁵ Thus, some believe that tissue oxygenation is compromised once pulse oximetry readings near or fall below 90%. However, despite its prevalent use for monitoring, particularly in the hospital setting, agreed upon
standard definitions of hypoxemia are lacking in guidelines and in clinical practice. As an example, in the United States the American Academy of Pediatrics' (AAP) Clinical Practice Guideline for bronchiolitis proposes an oxygen saturation threshold of 90%, while the British National Institute for Clinical Excellence guideline recommends a threshold of 92%. Additionally, guidelines for asthma and pneumonia from the same British national society set a threshold for hypoxemia at <94% and <92%, respectively. Adding to the difficulty of arriving at a consensus definition for hypoxemia is the fact that the pulse oximeter has a known margin of error of +/− 2% in its readings.

EVIDENCE FOR OVERDIAGNOSIS

Overdiagnosis is defined as the identification of an abnormality where detection will have no net benefit for the patient. Three epidemiologic approaches have historically been used to establish overdiagnosis: 1) randomized controlled trials (RCTs), where patients who are randomly assigned to receive more testing or different thresholds for “disease” have an increased probability of diagnosis but no difference in outcomes; 2) conditions where delayed or missed diagnosis do not cause harm, and 3) epidemiological studies showing increasing incidence of a disease accompanied by an unchanging rate of mortality or morbidity from the specific disease. Recent studies in bronchiolitis utilizing some of these methods suggest overdiagnosis.

Randomized trials affecting the probability of diagnosis of hypoxemia

Three trials have involved randomization of children with bronchiolitis to varying levels of probability of diagnosis of hypoxemia. The Bronchiolitis of Infancy Discharge Study (BIDS) randomized 615 infants hospitalized with bronchiolitis to monitoring with either a standard pulse oximeter or one that had been modified to display a reading that was artificially increased by 4% (to a maximum of 100%). The oxygen saturation threshold for initiating or weaning oxygen was 94%, which represented a saturation of 94% in the true oximetry arm and 90% in the modified oximetry arm. There was no difference in cough resolution, the primary outcome. However, the time on oxygen was 22 hours shorter (P=.002) and the time to discharge was 10 hours shorter (P=.003) in the 90% threshold arm. The need for high-dependency care and readmission to the hospital was no different between groups. Schuh et al similarly randomized children presenting to an emergency department with bronchiolitis to either having accurate oximetry readings versus values artificially increased by 3 percentage points displayed to the treating physician. Independent of clinical appearance, infants with falsely elevated values were significantly less likely to be
hospitalized (25% vs 41%, P=.005), but had no difference in complication or unscheduled visit rates. In a third randomized controlled trial, McCulloh et al assessed the use of continuous pulse oximetry versus intermittent pulse oximetry in hospitalized children with bronchiolitis, with the hypothesis that decreased use of pulse oximetry would lead to less detection of hypoxemia and subsequent oxygen use. The authors conclude that intermittent pulse oximetry use was safe in that there were no escalations of care. Surprisingly, however, there was no difference in length-of-stay (LOS) between groups, perhaps because the intervention was not initiated until children were weaned off oxygen. These three studies suggest that exposing children to less frequent detection of hypoxemia appears to be safe and could also lead to improved outcomes.

Delayed or missed diagnosis of hypoxemia without patient harm

Transient oxygen desaturations occur often in healthy infants, particularly during sleep, leading to the question of whether hypoxemia in children with bronchiolitis is normative or pathologic. Recently, Canadian investigators prospectively studied the frequency and degree of hypoxemia in patients with bronchiolitis managed as outpatients, and analyzed the association between hypoxemia and clinical outcomes. In this study, 118 infants were discharged from the emergency department with pulse oximeters. Oxygen saturations were continuously recorded, but the oxygen threshold alarm and the oxygen saturation display were disabled. After a defined period of time, the information on the oximeters was analyzed and compared to the main study outcome of unscheduled medical visits due to bronchiolitis. The majority (64%) of infants discharged home with bronchiolitis experienced episodes of desaturations, defined as oxygen saturation less than 90% for at least 1 minute, and 29 infants had sustained desaturations to 70% or less, levels that certainly would have triggered hospitalization and supplemental oxygen use under most protocols. These periods of real hypoxemia were effectively missed diagnoses, given that parents and providers were not aware of them. Infants did not receive intervention for these episodes and were no more likely to experience an unscheduled medical visit or re-hospitalization, compared to infants without desaturations.

Increasing detection of hypoxemia without a change in bronchiolitis outcomes

If detection of an abnormality is increasing over time, one would expect the rate of adverse outcomes related to the disease to roughly parallel the disease increase, provided there has been no change in disease severity or treatment efficacy. Increased detection of an abnormality accompanied by unchanged rates of important patient outcomes
suggests less severe forms of disease are being detected and is suggestive of overdiagnosis. Bronchiolitis admissions have nearly tripled since the 1980s, an era that coincides with increasing reliance on pulse oximetry. However, bronchiolitis mortality rates have been completely stable over this same time period. This pattern suggests that children with less severe bronchiolitis are being increasingly hospitalized without measurable benefit, likely driven by overdiagnosis of hypoxemia.

LIMITATIONS OF EVIDENCE

While no investigations, to our knowledge, have been able to demonstrate a measurable benefit to increased pulse oximetry use, such as preventing re-presentation or escalation of care, most studies are underpowered to detect small differences in these important outcomes. Additionally, the potential long term benefits of detecting and treating episodes of mild hypoxemia have not been evaluated rigorously. Associations between mild desaturations into the 90-94% range in certain conditions and future neurodevelopmental delay have been previously described.

Because of this, some investigators have argued that the use of oxygen saturation thresholds in this range in bronchiolitis could lead to adverse cognitive outcomes. However, the desaturations referred to in these studies occurred in children either living at high altitude in South America or with chronic conditions such as congenital heart disease, conditions that are quite distinct from an acute episode of bronchiolitis in an otherwise healthy infant. Additionally, studies on the effects of mild hypoxemia in other chronic conditions such as obstructive sleep apnea and asthma have failed to show any detrimental effect on long term neuro-cognitive outcomes.

EVIDENCE OF HARM

The best-documented harm attributable to widespread use of pulse oximetry in bronchiolitis is its association with unnecessary hospital admission and prolongation of LOS. While the recent RCT by Schuh et al provided convincing proof of the association between pulse oximetry use and hospitalization, earlier evidence came from the epidemiologic study by Shay et al and from a randomized survey of pediatric emergency physicians which demonstrated that lower oxygen saturations had a strong influence on the decision to hospitalize in bronchiolitis. Hospitalization is costly and has the potential for harm. A prospective study of children admitted for bronchiolitis found that preventable adverse events during hospitalization can occur in as many as 10 per 100 admissions. Once hospitalized, the continued use of pulse oximetry has been associated with significant increases in length of stay.
Schroeder et al. demonstrated that a perceived need for oxygen based on pulse oximetry readings led to an increase
LOS of about 1.6 days in a quarter of their patients, while Unger and Cunningham showed that 58% of the patients
in their cohort had increased LOS due to this perceived oxygen need. Cunningham and McMurray also
demonstrated that a pulse oximetry goal of 94% instead of 90% was associated with an increase in the LOS by up to
22 hours in children admitted for bronchiolitis. The Cunningham et al BIDS-RCT found significantly lower LOS
in the group with the lower oxygen saturation target. In contrast to these studies, the RCT by McCulloh et al,
which explored continuous versus intermittent pulse oximetry, did not demonstrate differences in LOS between the
two modalities.

Aside from prolonging LOS by correcting hypoxemia, supplemental oxygen may have other direct harms as well.
While the harms of prolonged oxygen therapy in other clinical entities in pediatrics are well established, it is
unknown whether even low doses of oxygen for short periods are completely safe. In the BIDS-RCT, Cunningham
et al not only demonstrated decreased length of stay with the lower 90% threshold, but also reported two other
outcomes of “time to feed adequately” (≥ 75% of usual) and “time to parental perception of back to normal”. In
both cases the results favored the group with the lower threshold for pulse oximetry with infants in this group
returning to adequate feeding 2.7 hours sooner (95% confidence interval [CI] -0.3 hours – 7 hours) and considered
back to normal 1 day sooner (95% CI 0 to 3 days). While the shorter LOS may explain the more rapid return to
baseline, it is also plausible that direct harms of oxygen therapy (e.g. free radical formation, absorption atelectasis)
may cause delayed clinical resolution in some infants.

An additional concern relating to unnecessary pulse oximetry use is alarm fatigue, an unintended consequence of
patient monitoring and a cumulative threat to patient safety, an issue which has been highlighted as a recent Joint
Commission National Patient Safety Goal. In a secondary analysis of a prior quality improvement project aimed
at reducing time on pulse oximetry for patients with wheezing illness, Schondelmeyer et al found no difference in
overall alarm frequency despite a significant decrease in pulse oximetry utilization. However, this small single-
center study had several limitations, including imbalances of co-morbidities in patients in the intervention group and
the fact that significant reductions in pulse oximetry utilization occurred in both the intervention and control hospital

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Given that monitors cannot alarm when they are off, future studies examining the effects of pulse oximetry reduction should demonstrate an impact on alarm frequency and fatigue.

Finally, given its frequency, bronchiolitis is a costly disease with at least one study in children estimating the direct cost in the US at $652 million annually. While not extensively studied, overdiagnosis of hypoxemia and overtreatment with oxygen could play a significant role. In an economic analysis of their BIDS-RCT, Cunningham et al found a decreased cost of £290 per patient in the group with lower oxygen saturations and £321 per patient when other variables such as travel and time off from work are factored in. The cost savings from preventing overdiagnosis could prove significant, both for individual patients, and at a societal level.

**HOW TO DO BETTER**

The current body of evidence suggests that we should challenge assumptions regarding the detection of hypoxemia in bronchiolitis and the notion that it should be aggressively pursued (see below Table). In 2013, as part of its participation in the American Board of Internal Medicine Foundation’s Choosing Wisely® campaign, the Society of Hospital Medicine (SHM) published a list of 5 therapies or tests to avoid that lead to overuse of health care resources in hospitalized children. One of the 5 recommendations was to avoid the use of continuous pulse oximetry in children admitted for respiratory illness who are not on supplemental oxygen. A key driver behind this recommendation was to avoid overdiagnosis of hypoxemia. Since then, the updated AAP clinical practice guideline on bronchiolitis has also recommended against the use of continuous pulse oximetry in bronchiolitis. Separately, a single center quality improvement project inspired by SHM’s Choosing Wisely® recommendation used a standardized protocol to discontinue pulse oximetry in children admitted for bronchiolitis meeting defined criteria. Their intervention appeared to be safe and resulted in significant reductions in time on pulse oximetry for patients (10.3 hours pre-intervention to 3.1 hours post-intervention) once specific criteria were met. Similar to the RCT by McCulloh et al, the intervention did not occur until after subjects were weaned off oxygen and was not associated with a reduction in LOS. Because overdiagnosis of hypoxemia can also occur in infants on oxygen, future investigations evaluating intermittent pulse oximetry use over the duration of the hospitalization will be informative. At least one such trial is currently underway (clinicaltrials.gov NCT01646606).
The most impactful intervention may be to decrease overdependence on pulse oximetry as a major decision point for admission in children with bronchiolitis. Schuh et al showed the unequivocal and unique influence of pulse oximetry values on admission, and convincingly demonstrated the ubiquity and lack of influence on outcomes of desaturation in children with bronchiolitis treated as outpatients.\textsuperscript{25,29} Standardized protocols with admission criteria that use pulse oximetry sparingly and judiciously are needed and justified given this groundbreaking work.

A redefinition of hypoxemia is also likely warranted. The variability in oxygen saturation thresholds in various national guidelines suggests opportunities for standardization. The AAP’s Clinical Practice Guideline for bronchiolitis has set thresholds for hypoxemia at the lower target of 90%.\textsuperscript{7} Cunningham et al’s work has demonstrated this definition is safe and associated with better outcomes than higher targets.\textsuperscript{24} However, given that oxygen desaturations to well below 90% are common in infants with and without bronchiolitis, and are not associated with adverse acute outcomes in these studies, even this lower target may result in substantial overdiagnosis of hypoxemia. Since most guidelines do not have rigid thresholds for other vital signs such as respiratory rate, heart rate or temperature, future work might explore whether defined oxygen saturation thresholds are even necessary in routine bronchiolitis care.

**TABLE: Challenging Assumptions for the Detection of Hypoxemia in Bronchiolitis**

Pulse oximetry is the 5th vital sign and all infants with bronchiolitis should have their oxygen saturation assessed.

- Small, clinically irrelevant differences in measured oxygen saturation prompt physicians to escalate medical care (often in the form of hospitalization) without improving patient outcomes.\textsuperscript{25,29}
- Both the American Academy of Pediatrics and the Society of Hospital Medicine’s Choosing Wisely campaign have recommended reduced use of pulse oximetry in the setting of bronchiolitis.\textsuperscript{7,46}

A rigid cutoff threshold for treating hypoxemia is needed to guide medical providers.

- There are not strict thresholds for other vital signs in bronchiolitis.\textsuperscript{7}
- Recurrent and sustained desaturations are common among infants with and without bronchiolitis and are not associated with worse outcomes.\textsuperscript{27,29}
Continuous oximetry is safer than intermittent oximetry measurements.

- The only trial to investigate this statement found equivalent risk for need of escalation of care between infants randomized to intermittent vs. continuous pulse oximetry.\(^{26}\)
- A quality improvement project similarly demonstrated that a reduction in continuous pulse oximetry use did not lead to any adverse events.\(^{42}\)

CONCLUSION

Pulse oximetry as a technology represents a major and significant advance in medicine. Its prevalent use in the care of the critically-ill patient with respiratory illness is undoubtedly justified. Its availability in the operating room as a monitoring tool for the anesthetized patient has helped make some previously dangerous surgical interventions safe and routine. However, its increasing and widespread use for children with bronchiolitis, a self-limited disease with a generally benign course, has led to overdiagnosis of hypoxemia and the technological creation of disease.
References


