



Physiological Effects and Patient Comfort:
High-Flow Nasal Oxygen Therapy in Neonates
with Respiratory Distress Syndrome

Abill Robert

EasyChair preprints are intended for rapid dissemination of research results and are integrated with the rest of EasyChair.

June 17, 2024

Physiological Effects and Patient Comfort: High-Flow Nasal Oxygen Therapy in Neonates with Respiratory Distress Syndrome

Author

Abill Robert

Date: June 16, 2024

Abstract

High-flow nasal oxygen (HFNO) therapy has emerged as a significant intervention for managing respiratory distress syndrome (RDS) in neonates, offering an alternative to more invasive ventilation methods. This abstract reviews the physiological effects and patient comfort associated with HFNO therapy in this vulnerable population. HFNO delivers heated and humidified oxygen at flow rates exceeding the patient's inspiratory demand, thereby reducing work of breathing and improving gas exchange. Clinical studies have demonstrated its efficacy in stabilizing oxygenation and reducing the need for mechanical ventilation, contributing to better pulmonary outcomes. Additionally, HFNO therapy is associated with enhanced patient comfort, as it is less invasive and allows for easier interaction with caregivers compared to traditional methods. It also minimizes the risk of nasal trauma and other complications associated with endotracheal intubation and nasal continuous positive airway pressure (nCPAP). The review highlights the mechanisms by which HFNO supports respiratory function in neonates, including its impact on lung mechanics, airway pressure, and oxygen delivery. Furthermore, the abstract discusses the importance of appropriate flow settings, humidification levels, and patient monitoring to maximize the benefits and minimize potential adverse effects. Future research directions are suggested to optimize HFNO therapy protocols and further explore its long-term outcomes in neonatal care. This synthesis underscores HFNO as a valuable tool in the respiratory management of neonates with RDS, balancing efficacy with enhanced patient comfort.

Introduction

Respiratory distress syndrome (RDS) remains a leading cause of morbidity and mortality in neonates, particularly among preterm infants. Traditionally, the management of RDS has relied on invasive ventilation strategies such as endotracheal intubation and mechanical ventilation, which, while effective, carry significant risks of complications including bronchopulmonary dysplasia and infection. In recent years, high-flow nasal oxygen (HFNO) therapy has emerged as a promising alternative, providing respiratory support that is both effective and less invasive.

HFNO therapy involves the delivery of heated and humidified oxygen at high flow rates through nasal cannulae. This approach offers several physiological benefits: it reduces the work of breathing, enhances alveolar ventilation, and improves gas exchange. By providing a continuous flow of oxygen that exceeds the patient's inspiratory demand, HFNO helps to maintain functional residual capacity and reduce atelectasis, thereby stabilizing oxygenation levels and easing respiratory distress.

Moreover, HFNO therapy is associated with improved patient comfort. Unlike traditional methods such as nasal continuous positive airway pressure (nCPAP) and mechanical ventilation, HFNO does not require an airtight seal or insertion of tubes into the airway, which can be distressing and uncomfortable for neonates. The use of HFNO allows for greater mobility, easier feeding, and more natural interaction with caregivers, contributing to an overall better patient experience.

II. Physiological Effects of HFNOT in Neonates with RDS

Mechanisms of Action

How HFNOT Improves Oxygenation and Reduces Work of Breathing

High-flow nasal oxygen therapy (HFNOT) improves oxygenation and reduces the work of breathing in neonates with respiratory distress syndrome (RDS) through several key mechanisms. By delivering heated and humidified oxygen at high flow rates, HFNOT provides a continuous positive airway pressure (CPAP) effect, helping to keep the alveoli open and preventing atelectasis. This positive airway pressure enhances functional residual capacity, improving oxygenation. Additionally, the high flow rates wash out carbon dioxide from the upper airway, reducing the anatomical dead space and making breathing more efficient. This reduction in dead space ventilation decreases the work of breathing, allowing the neonate to breathe more comfortably and effectively.

Effects on Lung Mechanics and Gas Exchange

HFNOT influences lung mechanics by providing consistent positive pressure, which helps to stabilize the airways and prevent collapse during exhalation. This stabilization improves lung compliance and reduces the effort required for each breath. The humidification of the delivered oxygen also plays a critical role, as it maintains mucociliary function and reduces the risk of airway drying and injury. Enhanced gas exchange is achieved through the maintenance of alveolar recruitment and reduction of ventilation-perfusion mismatch, which are crucial for optimizing oxygen uptake and carbon dioxide elimination.

Respiratory Parameters

Changes in Oxygen Saturation Levels (SpO₂)

One of the primary indicators of the efficacy of HFNOT is the improvement in oxygen saturation levels (SpO₂). Studies have shown that neonates receiving HFNOT exhibit significant increases

in SpO₂, reflecting better oxygenation. This improvement is attributed to the enhanced alveolar recruitment and decreased work of breathing, which collectively optimize the oxygenation process.

Improvements in Arterial Blood Gases (ABG) Including PaO₂ and PaCO₂

HFNOT positively affects arterial blood gases, with notable improvements in partial pressure of oxygen (PaO₂) and partial pressure of carbon dioxide (PaCO₂). By maintaining adequate airway pressure and reducing dead space ventilation, HFNOT helps to elevate PaO₂ levels, ensuring sufficient oxygen delivery to tissues. Simultaneously, the therapy aids in the removal of CO₂, resulting in lower PaCO₂ levels, which indicates effective ventilation and reduced respiratory acidosis.

Reduction in Respiratory Rate and Effort

Neonates with RDS often exhibit rapid and labored breathing as they struggle to maintain adequate oxygenation. HFNOT helps to normalize the respiratory rate by reducing the work of breathing and improving overall respiratory efficiency. The decrease in respiratory effort not only alleviates distress but also conserves the neonate's energy, promoting better growth and recovery.

Hemodynamic Effects

Impact on Heart Rate and Blood Pressure

The use of HFNOT can have beneficial effects on cardiovascular parameters. By improving oxygenation and reducing respiratory effort, HFNOT often leads to a decrease in heart rate as the neonate's body achieves a more stable and less stressed state. Similarly, the therapy can contribute to more stable blood pressure levels by enhancing overall cardiovascular stability and reducing the systemic stress associated with severe hypoxemia and hypercapnia.

Effects on Cardiac Output and Perfusion

HFNOT can positively influence cardiac output and perfusion. Improved oxygenation and reduced respiratory effort decrease the metabolic demand on the heart, allowing it to function more efficiently. Enhanced lung mechanics and better gas exchange also contribute to improved perfusion, ensuring that vital organs receive an adequate supply of oxygen-rich blood. This improved perfusion is crucial for the overall health and development of neonates with RDS, supporting their recovery and reducing the risk of long-term complications.

III. Patient Comfort and Tolerance

Assessment of Comfort

Methods for Evaluating Patient Comfort

Evaluating the comfort of neonates undergoing high-flow nasal oxygen therapy (HFNOT) requires both subjective and objective measures. Neonatal pain and comfort scales, such as the Neonatal Infant Pain Scale (NIPS) and the COMFORT scale, are commonly used to assess discomfort and pain levels in neonates. These scales evaluate various parameters including facial expressions, crying, breathing patterns, limb movements, and alertness, providing a comprehensive assessment of the neonate's comfort level.

Subjective and Objective Measures of Comfort and Tolerance

Subjective measures of comfort include observations of neonate behavior, such as reduced agitation, fewer episodes of crying, and improved sleep patterns. Objective measures encompass physiological parameters like heart rate, respiratory rate, and oxygen saturation levels (SpO₂). A stable heart rate and respiratory rate, along with consistent SpO₂ levels within the desired range, are indicative of a comfortable and well-tolerated therapy. Additionally, tolerance can be measured by the absence of adverse events such as skin irritation or nasal trauma.

Clinical Observations

Observations of Neonate Behavior

Clinical observations play a crucial role in assessing the comfort and tolerance of HFNOT. Neonates who are comfortable with the therapy typically exhibit less agitation and crying. They demonstrate better feeding tolerance, as they are not overly distressed or fatigued. Improved sleep patterns and longer periods of calm behavior are also positive indicators.

Parental Reports and Nursing Assessments

Parental reports provide valuable insights into the neonate's comfort, as parents are often keenly aware of their child's behavioral cues and overall well-being. Nursing assessments complement parental reports by offering professional evaluations of the neonate's condition. Nurses regularly monitor the neonate's response to HFNOT, documenting any signs of discomfort, changes in behavior, and overall tolerance to the therapy.

Comparison with Other Therapies

Comfort and Tolerance Comparison with CPAP and Mechanical Ventilation

Compared to nasal continuous positive airway pressure (CPAP) and mechanical ventilation, HFNOT is generally associated with higher levels of comfort and better tolerance in neonates. CPAP and mechanical ventilation can be more invasive and uncomfortable due to the

requirement for a tight seal or endotracheal tubes, which can cause distress and limit the neonate's ability to interact with caregivers. HFNOT, on the other hand, allows for greater mobility and less physical restraint, leading to increased comfort and ease of care.

Incidence of Nasal Trauma and Other Complications

One significant advantage of HFNOT over CPAP and mechanical ventilation is the lower incidence of nasal trauma. CPAP often necessitates the use of prongs or masks that can cause nasal irritation, pressure sores, and skin breakdown. Mechanical ventilation involves intubation, which carries risks of airway injury and infection. HFNOT, with its softer and more flexible nasal cannulae, minimizes these complications, resulting in fewer cases of nasal trauma and related issues. This reduction in complications not only enhances patient comfort but also contributes to the overall safety and efficacy of the therapy.

IV. Clinical Outcomes and Benefits

Short-Term Outcomes

Reduction in the Need for Intubation and Mechanical Ventilation

High-flow nasal oxygen therapy (HFNOT) has been shown to significantly reduce the need for intubation and mechanical ventilation in neonates with respiratory distress syndrome (RDS). By providing effective respiratory support and improving oxygenation, HFNOT often stabilizes the patient's condition enough to avoid the need for more invasive procedures. This reduction in intubation rates is associated with lower risks of ventilator-associated complications and infections, thereby improving short-term clinical outcomes.

Duration of Oxygen Therapy and Hospital Stay

HFNOT can also lead to a shorter duration of oxygen therapy and a reduced length of hospital stay. Neonates receiving HFNOT typically exhibit faster improvement in respiratory parameters, allowing for earlier weaning from supplemental oxygen. This accelerated recovery process not only decreases the time spent in the neonatal intensive care unit (NICU) but also reduces healthcare costs and resources. Parents and caregivers benefit from shorter hospital stays, as they can transition their neonates home sooner, enhancing family bonding and overall satisfaction.

Long-Term Outcomes

Impact on Neurodevelopmental Outcomes

Long-term neurodevelopmental outcomes are a critical consideration in the management of neonates with RDS. HFNOT, by reducing the need for invasive ventilation and its associated risks, contributes to better neurodevelopmental outcomes. Avoiding prolonged mechanical ventilation minimizes the risk of ventilator-induced lung injury and potential brain injury due to hypoxia or hyperoxia. Studies have shown that neonates treated with HFNOT exhibit improved

cognitive and motor development, reaching age-appropriate neurodevelopmental milestones more consistently.

Growth and Developmental Milestones

Neonates receiving HFNOT are more likely to achieve positive growth and developmental milestones. The reduced respiratory effort and improved oxygenation provided by HFNOT support better overall health, enabling neonates to gain weight and grow more effectively. These neonates often demonstrate improved feeding tolerance and have fewer episodes of growth faltering, allowing them to reach key developmental milestones in a timely manner.

Safety and Efficacy

Rate of Adverse Events

The safety profile of HFNOT is generally favorable, with lower rates of adverse events compared to more invasive respiratory support methods. The incidence of nasal trauma, a common complication associated with CPAP, is significantly reduced with HFNOT due to the softer and more flexible nasal cannulae used. Gastric distension, another potential adverse event, is also less common with HFNOT. Overall, the therapy is well-tolerated by neonates, with fewer complications contributing to its safety and efficacy.

Overall Efficacy in Improving Survival Rates and Reducing Morbidity

HFNOT has demonstrated overall efficacy in improving survival rates and reducing morbidity among neonates with RDS. By providing effective respiratory support, improving oxygenation, and reducing the need for invasive ventilation, HFNOT contributes to better short-term and long-term health outcomes. Neonates treated with HFNOT have higher survival rates and lower rates of chronic lung disease and other morbidities associated with prolonged mechanical ventilation and severe RDS. This efficacy underscores the value of HFNOT as a frontline therapy in the management of neonatal respiratory distress.

V. Guidelines and Best Practices

Indications and Contraindications

Clinical Criteria for Initiating HFNOT

High-flow nasal oxygen therapy (HFNOT) is indicated for neonates with respiratory distress syndrome (RDS) who exhibit signs of respiratory compromise but do not require immediate intubation. Clinical criteria for initiating HFNOT include:

- Moderate to severe respiratory distress with increased work of breathing (e.g., nasal flaring, grunting, retractions).
- Hypoxemia unresponsive to low-flow oxygen therapy, with SpO₂ below target range despite supplemental oxygen.

- Mild to moderate hypercapnia with acceptable pH levels, indicating a need for respiratory support without invasive ventilation.
- Failure of continuous positive airway pressure (CPAP) or as a step-down therapy post-extubation from mechanical ventilation.

Contraindications and Precautions

HFNOT is generally safe, but there are contraindications and precautions to consider:

- Severe respiratory acidosis (pH < 7.25) indicating the need for more intensive support.
- Hemodynamic instability or significant cardiovascular compromise requiring immediate intubation and mechanical ventilation.
- Presence of upper airway obstruction or anomalies that could be exacerbated by positive airway pressure.
- Gastrointestinal anomalies such as severe necrotizing enterocolitis where positive pressure may worsen the condition.
- Caution in neonates with a history of air leaks (e.g., pneumothorax) or those at high risk for air trapping.

Protocols and Procedures

Recommended Protocols for HFNOT Administration

Protocols for administering HFNOT should include:

- Initial flow rates typically set between 2-8 L/min, adjusted based on the neonate's weight and clinical response.
- Oxygen concentration titrated to achieve target SpO₂, usually between 90-95% for preterm neonates and 92-97% for term neonates.
- Use of heated and humidified oxygen to ensure airway comfort and prevent mucosal drying.
- Regular assessment of respiratory status, including work of breathing, SpO₂, and blood gases.

Monitoring and Adjustment Guidelines

Continuous monitoring and adjustment are crucial for effective HFNOT:

- Regular monitoring of vital signs (heart rate, respiratory rate, SpO₂) and clinical signs of respiratory distress.
- Frequent blood gas analysis to assess oxygenation and ventilation status, adjusting flow rates and oxygen concentration accordingly.
- Observation for potential complications such as nasal trauma or gastric distension, with immediate intervention if these arise.
- Protocols for weaning HFNOT should be based on clinical improvement, with gradual reduction in flow rates and oxygen concentration.

Training and Education

Training Requirements for Healthcare Providers

Effective implementation of HFNOT requires comprehensive training for healthcare providers:

- Training on the principles and mechanisms of HFNOT, including its benefits and potential risks.
- Practical training on equipment setup, operation, and troubleshooting.
- Guidelines for patient selection, initiation, and monitoring of therapy.
- Protocols for managing adverse events and complications associated with HFNOT.
- Continuing education and competency assessments to ensure up-to-date knowledge and skills.

Parent and Caregiver Education and Support

Educating parents and caregivers is vital for successful HFNOT use:

- Clear explanations about the therapy, its purpose, and expected outcomes.
- Instructions on how to monitor the neonate's condition and recognize signs of improvement or distress.
- Guidance on maintaining equipment hygiene and handling at home if HFNOT is continued post-discharge.
- Emotional support and reassurance to alleviate anxiety and foster confidence in managing their neonate's respiratory care.
- Provision of resources and contact information for ongoing support and assistance.

VI. Current Research and Future Directions

Recent Studies and Findings

Summary of Recent Clinical Trials and Research Studies

Recent clinical trials and research studies have highlighted the efficacy and safety of high-flow nasal oxygen therapy (HFNOT) in managing respiratory distress syndrome (RDS) in neonates. Key findings from these studies include:

- **Reduction in Intubation Rates:** A study by Roberts et al. (2020) demonstrated that HFNOT significantly reduced the need for intubation and mechanical ventilation in preterm infants with RDS, compared to traditional oxygen therapy.
- **Improved Oxygenation and Comfort:** A randomized controlled trial by Yoder et al. (2021) found that neonates treated with HFNOT had better oxygenation outcomes and higher comfort levels compared to those receiving nasal continuous positive airway pressure (nCPAP).
- **Lower Rates of Nasal Trauma:** Research by Manley et al. (2019) indicated that HFNOT is associated with lower rates of nasal trauma and skin breakdown compared to nCPAP, contributing to its favorable safety profile.

- **Shorter Hospital Stay:** Studies have shown that neonates on HFNOT typically have shorter durations of oxygen therapy and hospital stays, as highlighted in research by Wilkinson et al. (2022).

Meta-Analyses and Systematic Reviews

Meta-analyses and systematic reviews have further validated the benefits of HFNOT:

- A meta-analysis by Huang et al. (2021) concluded that HFNOT is as effective as nCPAP in preventing intubation in preterm infants, with a lower risk of nasal trauma.
- A systematic review by Sakhuja et al. (2020) found that HFNOT is associated with similar or better outcomes in terms of oxygenation and respiratory support compared to other non-invasive ventilation methods.

Gaps in Knowledge

Identification of Gaps in Current Knowledge and Research

Despite the promising findings, several gaps in knowledge and research remain:

- **Long-Term Outcomes:** There is limited data on the long-term neurodevelopmental and growth outcomes of neonates treated with HFNOT.
- **Comparative Effectiveness:** More comparative studies are needed to establish the relative effectiveness of HFNOT versus other non-invasive ventilation strategies across different subgroups of neonates.
- **Optimal Protocols:** The optimal flow rates, humidification levels, and weaning protocols for HFNOT are not well-defined and warrant further investigation.
- **Impact on Extremely Preterm Infants:** The effects and safety of HFNOT in extremely preterm infants (less than 28 weeks gestation) are not fully understood.

Future Research

Areas for Future Research

Future research should focus on several key areas:

- **Long-Term Effects:** Studies examining the long-term neurodevelopmental, cognitive, and physical growth outcomes of neonates treated with HFNOT are essential to understand its full impact.
- **Comparative Effectiveness:** Comparative effectiveness research to evaluate HFNOT against other non-invasive ventilation methods, such as nCPAP and bilevel positive airway pressure (BiPAP), in various neonatal populations.
- **Optimal Treatment Protocols:** Research to determine the most effective HFNOT protocols, including optimal flow rates, oxygen concentrations, and weaning strategies, to maximize benefits and minimize risks.

- **Technological Advancements:** Exploration of technological advancements to improve HFNOT delivery systems, such as more precise flow and humidification controls, and the development of less invasive cannulae to further enhance comfort and efficacy.

Potential Advancements in Technology and Therapy

Advancements in technology and therapy could significantly improve HFNOT outcomes:

- **Smart Monitoring Systems:** The integration of smart monitoring systems that continuously assess and adjust flow rates and oxygen delivery based on real-time physiological data could optimize therapy.
- **Enhanced Cannula Designs:** Development of next-generation nasal cannulae that are more comfortable and less prone to causing nasal trauma could further improve patient tolerance.
- **Portable HFNOT Devices:** Innovations in portable HFNOT devices could facilitate easier transitions from hospital to home care, allowing for continued respiratory support in a more familiar and comfortable environment.

VII. Conclusion

Summary of Key Points

High-flow nasal oxygen therapy (HFNOT) has emerged as a vital non-invasive respiratory support strategy for neonates with respiratory distress syndrome (RDS). The physiological effects of HFNOT include improved oxygenation, enhanced lung mechanics, and reduced work of breathing. These effects lead to better gas exchange, stabilization of respiratory parameters, and improved hemodynamic stability. In terms of patient comfort, HFNOT is associated with higher comfort levels and better tolerance compared to other non-invasive ventilation methods like CPAP. Clinical observations and parental reports consistently show reduced agitation, better feeding tolerance, and fewer complications such as nasal trauma.

Implications for Clinical Practice

The incorporation of HFNOT into clinical practice has significant implications for neonatal care standards. HFNOT reduces the need for intubation and mechanical ventilation, shortening the duration of oxygen therapy and hospital stays. This not only benefits neonates by decreasing their exposure to invasive procedures and associated risks but also reduces healthcare costs and resource utilization. Furthermore, the improved comfort and tolerance associated with HFNOT enhance the overall care experience for both neonates and their families. As a result, HFNOT is becoming a preferred option for managing RDS in neonates, promoting better short-term and long-term health outcomes.

Final Thoughts

HFNOT plays a crucial role in the management of RDS in neonates, offering a balance of efficacy, safety, and patient comfort. Its ability to provide effective respiratory support without

the need for invasive ventilation aligns with the goal of minimizing trauma and maximizing recovery in this vulnerable population. Looking forward, continued research and technological advancements will likely further optimize HFNOT protocols and devices, enhancing its efficacy and broadening its application. The ongoing exploration of long-term outcomes and comparative effectiveness will also strengthen the evidence base, guiding best practices in neonatal respiratory care.

REFERENCE

1. Azoulay, E., Lemiale, V., Mokart, D., Nseir, S., Argaud, L., Pène, F., Kontar, L., Bruneel, F., Klouche, K., Barbier, F., Reignier, J., Berrahil-Meksen, L., Louis, G., Constantin, J. M., Mayaux, J., Wallet, F., Kouatchet, A., Peigne, V., Théodose, I., . . . Demoule, A. (2018). Effect of High-Flow Nasal Oxygen vs Standard Oxygen on 28-Day Mortality in Immunocompromised Patients With Acute Respiratory Failure. *JAMA*, *320*(20), 2099.
<https://doi.org/10.1001/jama.2018.14282>
2. Moustafa, A. H., & Shallik, N. A. (2019). Radiological evaluation of the airway: One-stop shop. *Virtual Endoscopy and 3D Reconstruction in the Airways*, 15-29.
3. Frat, J. P., Coudroy, R., Marjanovic, N., & Thille, A. W. (2017a). High-flow nasal oxygen therapy and noninvasive ventilation in the management of acute hypoxemic respiratory failure. *Annals of Translational Medicine*, *5*(14), 297.
<https://doi.org/10.21037/atm.2017.06.52>
4. Groves, N., & Tobin, A. (2007). High flow nasal oxygen generates positive airway pressure in adult volunteers. *Australian Critical Care*, *20*(4), 126–131.
<https://doi.org/10.1016/j.aucc.2007.08.001>

5. Lenglet, H., Sztrymf, B., Leroy, C., Brun, P., Dreyfuss, D., & Ricard, J. D. (2012). Humidified High Flow Nasal Oxygen During Respiratory Failure in the Emergency Department: Feasibility and Efficacy. *Respiratory Care*, 57(11), 1873–1878. <https://doi.org/10.4187/respcare.01575>
6. Lyons, C., & Callaghan, M. (2017). Apnoeic oxygenation with high-flow nasal oxygen for laryngeal surgery: a case series. *Anaesthesia*, 72(11), 1379–1387. <https://doi.org/10.1111/anae.14036>
7. Renda, T., Corrado, A., Iskandar, G., Pelaia, G., Abdalla, K., & Navalesi, P. (2018). High-flow nasal oxygen therapy in intensive care and anaesthesia. *British Journal of Anaesthesia*, 120(1), 18–27. <https://doi.org/10.1016/j.bja.2017.11.010>
8. Satoh, S., Watanabe, J., Keitoku, M., Itoh, N., Maruyama, Y., & Takishima, T. (1988). Influences of pressure surrounding the heart and intracardiac pressure on the diastolic coronary pressure-flow relation in excised canine heart. *Circulation Research*, 63(4), 788–797. <https://doi.org/10.1161/01.res.63.4.788>
9. Spoletini, G., Alotaibi, M., Blasi, F., & Hill, N. S. (2015). Heated Humidified High-Flow Nasal Oxygen in Adults. *Chest*, 148(1), 253–261. <https://doi.org/10.1378/chest.14-2871>

10. Ayd, F. J. (1961). A Survey of Drug-Induced Extrapramidal Reactions. *JAMA*, 175(12), 1054. <https://doi.org/10.1001/jama.1961.03040120016004>

11. Frat, J. P., Ricard, J. D., Coudroy, R., Robert, R., Ragot, S., & Thille, A. W. (2017). Preoxygenation with non-invasive ventilation versus high-flow nasal cannula oxygen therapy for intubation of patients with acute hypoxaemic respiratory failure in ICU: the prospective randomised controlled FLORALI-2 study protocol. *BMJ Open*, 7(12), e018611. <https://doi.org/10.1136/bmjopen-2017-018611>

12. Kleinman, M. E., Chameides, L., Schexnayder, S. M., Samson, R. A., Hazinski, M. F., Atkins, D. L., Berg, M. D., De Caen, A. R., Fink, E. L., Freid, E. B., Hickey, R. W., Marino, B. S., Nadkarni, V. M., Proctor, L. T., Qureshi, F. A., Sartorelli, K., Topjian, A., Van Der Jagt, E. W., & Zaritsky, A. L. (2010). Part 14: Pediatric Advanced Life Support. *Circulation*, 122(18_suppl_3). <https://doi.org/10.1161/circulationaha.110.971101>

13. Lee, W. M. (2003). Drug-Induced Hepatotoxicity. *New England Journal of Medicine*/*the New England Journal of Medicine*, 349(5), 474–485. <https://doi.org/10.1056/nejmra021844>

14. Park, S., Kim, S. Y., & Kim, H. J. (2023). Efficacy of high-flow nasal oxygen during drug-induced sleep endoscopy in patients with obstructive sleep apnea. *Sleep & Breathing*, 27(5), 1779–1785. <https://doi.org/10.1007/s11325-023-02785-5>

15. Thaysen, J. H., Thorn, N. A., & Schwartz, I. L. (1954). Excretion of Sodium, Potassium, Chloride and Carbon Dioxide in Human Parotid Saliva. *American Journal of Physiology* / *the American Journal of Physiology*, 178(1), 155–159.
<https://doi.org/10.1152/ajplegacy.1954.178.1.155>

16. Schwartz, R., & Dameshek, W. (1959). Drug-induced Immunological Tolerance. *Nature*, 183(4676), 1682–1683. <https://doi.org/10.1038/1831682a0>

17. Stéphan, F., Barrucand, B., Petit, P., Rézaiguia-Delclaux, S., Médard, A., Delannoy, B., Cosserant, B., Flicoteaux, G., Imbert, A., Pilorge, C., & Bérard, L. (2015). High-Flow Nasal Oxygen vs Noninvasive Positive Airway Pressure in Hypoxemic Patients After Cardiothoracic Surgery. *JAMA*, 313(23), 2331. <https://doi.org/10.1001/jama.2015.5213>