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Practical review of non-invasive ventilation and feeding intolerance in preterm infants

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ABSTRACT

Background. Preterm infants in neonatal intensive care units (NICUs) frequently require respiratory and nutritional support. Non-invasive ventilation (NIV)—including nasal continuous positive airway pressure (nCPAP), non-invasive positive pressure ventilation (NIPPV), and humidified high-flow nasal cannula (HHFNC)—has become the preferred respiratory strategy to reduce chronic lung disease and neurological complications. However, these modes may influence feeding intolerance (FI), a multifactorial condition that affects growth and overall clinical outcomes.
Objective. To review current evidence on the relationship between different modes of NIV and feeding intolerance in preterm infants.
Material and methods. A descriptive review of the literature was conducted to evaluate studies on the physiological mechanisms, definitions, and clinical manifestations of FI across various NIV modalities.
Results. Definitions of FI vary considerably among studies. CPAP and NIPPV, particularly non-synchronised modes, are associated with increased abdominal distension and delayed enteral feeding due to gastric insufflation and impaired swallowing coordination. HHFNC demonstrates comparable FI rates but greater infant

comfort. NIV-NAVA, a synchronised NIV mode driven by diaphragmatic electrical activity, may reduce gastric insufflation, enhance patient comfort, and improve feeding tolerance, although current evidence is limited. Additional interventions such as oral-motor therapy, sensory stimulation, enteral massage, and skin-to-skin care (SSC) have shown benefits in promoting earlier transition to breastfeeding, improving gastrointestinal function, and enhancing physiological stability, thereby supporting integrated strategies to optimise feeding tolerance in preterm infants.

Conclusions. Ventilatory pressures, synchronisation, and gastrointestinal immaturity influence feeding intolerance in preterm infants. Combining synchronised NIV modes with evidence-based interventions such as SSC and oral-motor therapy may enhance feeding outcomes and overall developmental progress.

Introduction

Nutrition and respiratory support are two of the most significant challenges faced by preterm newborns in the neonatal intensive care unit (NICU). Preterm infants have high nutritional needs, making the delivery of adequate nutrition a challenge, particularly via the enteral route. Additionally, many preterm infants require respiratory support due to both respiratory distress syndrome (RDS) in early life and bronchopulmonary dysplasia later in their neonatal stay.

Multiple national and international guidelines for the respiratory care of very preterm infants recommend avoiding intubation after birth, instead providing non-invasive ventilation (NIV) to minimise the risk of chronic lung disease, retinopathy of prematurity and neurological complications. NIV is an umbrella term that includes modes such as noninvasive positive-pressure ventilation (NIPPV), nasal continuous positive airway pressure (nCPAP), and humidified high-flow nasal cannula (HHFNC).

NIV, especially unsynchronised NIPPV, may drive air into the oesophagus and on into the stomach. Therefore, NIV modes, especially those involving higher flow or pressure, may lead to feeding intolerance (FI) [1], which the work of breathing may further exacerbate. FI is an everyday problem seen in preterm infants in the NICU and is often a source of clinical concern in certain situations, where it may be an early sign in patients who may be developing necrotising enterocolitis (NEC), gastric perforation or any other gastrointestinal tract (GI) problems. Recognising and managing FI is likely to be crucial to improving clinical practice, as frequent feeding interruptions negatively impact growth and nutrition.

Current evidence suggests that appropriately tailored nutritional care can accelerate growth and reduce nutritional deficits and complications. While parenteral nutrition (PN) generally meets all nutritional requirements of very preterm infants, enteral nutrition will be the mainstay of nutritional intake for the majority of their neonatal unit stay and is a prerequisite for hospital discharge. Furthermore, long-term PN itself carries risks such as central line infection and PN-associated liver disease.

In the era of minimally invasive interventions in the newborn, NIV is the most commonly used respiratory support, even for extremely preterm infants. In this descriptive review, we will focus on current knowledge of NIV's impact on FI.

This narrative review was based on a literature search of PubMed-indexed articles, covering publications from the 1980s to the present. The search used the key terms feeding intolerance, preterm, neonate, and respiratory support. We included studies focusing on feeding tolerance, swallowing, and respiratory support in neonates, while excluding studies involving adult populations.

The definition of feeding intolerance

There is no consensus about the definition of FI. Variations in the definition of FI are due to differences between NICUs. In the 2021 meta-analysis by Weeks et al., the problem of defining FI [2] was highlighted, as they analysed 100 papers and compared definitions of FI across them. One of the most frequently reported symptoms of feeding intolerance was abdominal distension, observed in 72 of the analysed documents. Gastric residual volume (GRV) was used in 81 studies to define FI, and this measure showed the most remarkable heterogeneity in its description. Vomiting was included in the definition of FI in 55 papers, and thirty-five studies used the clinical sign of blood in stool in their definition of FI. They divided the analysed works into groups based on the FI definition. Gastric residual volume, abdominal distension & GI symptoms group consists of the highest number of studies -57, where FI was recognised using a combination of both GRV and abdominal distension (AD) measurements together with GI symptoms, which included descriptions of vomiting, bilious aspirate or blood in stool. Eveleens reported results similar to those of Weeks in a pediatric population study [3]. The use of GRV to define FI has been questioned, with Parker in 2019 suggesting that it may unnecessarily negatively impact enteral feeding intake [4]. Thomas et al. and Kaur et al. showed that replacing GRV with abdominal circumference measurements leads to fewer feeding interruptions, earlier enteral feeding, and potentially a shorter hospital stay [5,6].

In light of the above, a standardised, clinically practical definition of feeding intolerance (FI) is necessary to support consistent clinical decision-making and improve patient outcomes. A reasonable and applicable definition of FI may be described as a clinical syndrome reflecting an impaired ability to tolerate enteral nutrition, most commonly manifested by progressive abdominal distension, persistent vomiting (particularly if bilious or blood-stained), and/or the presence of blood in the stool. Gastric residual volume (GRV) may be considered in select cases; however, based on current evidence, it should not be used as an isolated diagnostic criterion due to its variability and limited predictive value. An ongoing large randomised controlled trial in the UK seeks to address this evidence gap [7]. This proposed definition prioritises observable and clinically significant signs, thereby facilitating a more uniform approach to diagnosis and management across different care settings while minimising unnecessary interruptions to enteral feeding.

Swallowing and oesophageal sphincter pressure

Coordination of breathing and swallowing is vital. In preterm infants, delayed oral feeding development is associated with more extended hospital stays, poor weight gain, and poorer neurodevelopmental outcomes. The fetus begins swallowing amniotic fluid as early as the 11th–12th week of pregnancy, with sucking movements appearing around the 18th week. By term, the volume of amniotic fluid swallowed by the fetus corresponds to the amount of milk consumed by the neonate. Preterm birth disrupts this process, exposing the neonate to suboptimal extrauterine conditions and morbidities that can delay the development of feeding skills [8].

Preterm neonates are prone to apnea episodes associated with swallowing. The "apnea – swallow – apnea" sequence can lead to bradycardia and oxygen desaturation during oral feeding [8]. There are limited scientific studies on the coordination between breathing and swallowing in human neonates. Research on animal models highlights the importance of non-nutritive swallowing (NNS), which serves as a protective mechanism against pulmonary aspiration of secretions. Disruptions in both nutritive and non-nutritive swallowing can lead to acute, life-threatening events in neonates. NNS can occur at any phase of the respiratory cycle, including both inspiration and expiration, but it is most frequently observed during inspiration [9]. This presents a challenge for clinicians in selecting the appropriate respiratory support method for neonates, ensuring sufficient airway pressure and tidal volumes while preventing air aspiration into the stomach during swallowing.

Observations regarding NIPPV indicate that its impact on NNS frequency is more variable, with increases during active sleep and decreases during quiet wakefulness. CPAP has not been found to interfere with the coordination between respiratory cycle phases and NNS. In preterm lambs, NNS bursts have been reported more frequently than in term-born lambs, particularly during active sleep, when they often coincide with apneas. Studies have shown that CPAP suppresses NNS in newborn lambs, increasing the risk of gastroesophageal regurgitation and subsequent pulmonary aspiration [9]. Air swallowing occurs during NNS while infants are receiving NIV. It is hypothesised that non-invasive neurally adjusted ventilatory assist (NIV-NAVA) may be a beneficial respiratory support method for neonates due to its synchronisation with the patient's breathing. However, the limited number of studies on this topic prevents definitive conclusions (**Table 1**).

Another challenge in FI among preterm neonates is oropharyngeal dysphagia, which may affect up to 60% of neonates in the NICU [10]. Immaturity of the oesophageal structures, including its upper and lower sphincters, delays the introduction of full oral feeding and reduces its effectiveness [10]. Additionally, apneic episodes (defined as those lasting over 20 seconds) observed in patients are associated with decreased lower oesophageal sphincter tone, increasing the risk of gastroesophageal reflux [11]. Other studies confirm that the most common cause of gastroesophageal reflux (GER) is transient relaxation of the lower oesophageal sphincter (LES). These relaxation episodes typically last about 10 seconds, occur independently of swallowing, and reach pressures similar to those of intragastric pressure [12]. In the context of positive-pressure ventilation and apnea episodes, relaxation of the LES facilitates the entry of air into the neonate's stomach. For this to occur, the pressure generated during ventilation must exceed the LES pressure. According to a study by Omari et al., oesophageal pressures range from 16.3 to 28.5 cm H_2O before apnea and can decrease to 6.8–10.9 cm H_2O during an apneic episode [13]. Positive airway pressure applied via CPAP is 4–8 cm H_2O, while HFNC provides variable end-expiratory pressures of 2–15 cm H_2O. Both may therefore potentially exceed LES pressure values (**Table 1**).

Table 1. Summary of swallowing development, effects of preterm birth, swallowing characteristics in preterm neonates, the impact of respiratory support modalities, and changes in lower oesophageal sphincter (LES) pressure.

	Summary
Swallowing Development	Begins at 11–12 weeks gestation; sucking starts at 18 weeks; usually mature by term.
Effects of Preterm Birth	Disrupts development of feeding; leads to delayed oral feeding, longer hospital stays, poor weight gain, neurodevelopmental risks.
Swallowing in Preterm Neonates	Prone to apnea during feeding; "apnea–swallow–apnea" pattern may cause bradycardia and oxygen desaturation.
Respiratory Support Impact	– Non-Invasive Positive Pressure Ventilation (NIPPV): Variable effects on swallowing, increases during active sleep. – Continuous Positive Airway Pressure (CPAP): Does not disrupt coordination, but suppresses swallowing in preterm lambs. – Non-invasive Neurally Adjusted Ventilatory Assist (NIV-NAVA): May help due to breathing synchronization; more studies needed.
Lower Esophageal Sphincter (LES) Pressure	– Before apnea: 16.3–28.5 cm HO. – During apnea: 6.8–10.9 cm HO.

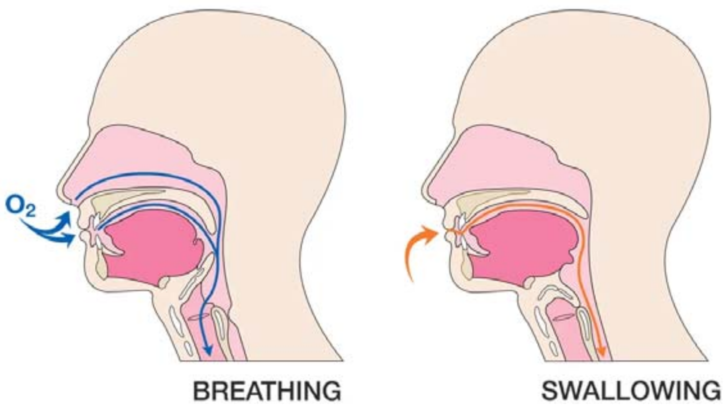

Figure 1. Diagram illustrating the airflow during breathing and the changes that occur during swallowing, demonstrating that it is impossible to swallow and breathe effectively at the same time. Blue lines – airflow during breathing; orange lines – airflow during swallowing.

In more intensive settings, these pressures may be significantly higher. If ventilatory pressures during NIV exceed LES relaxation phase pressures, air can enter the gastrointestinal tract, leading to gastric distension. Moreover, positive nasal pressure may interfere with the soft palate's ability to elevate, consequently disrupting the closure of the superior pharyngeal valve and further impairing protective mechanisms that prevent air from being swallowed into the stomach [14].

It has been established that during non-synchronized NIPPV with Peak Inspiratory Pressures (PIPs) around 22 cm H_2O, breaths can be administered when the patient closes the glottis, making proper lung ventilation impossible until the neonate initiates spontaneous inspiration [15] (**Figure 1**). It is thought that due to the obstruction caused by closed airways, delivered air volumes may enter the esophagus and, after overcoming LES pressures, reach the stomach, leading to abdominal distention (**Table 1**).

CPAP

One of the most common and widely used respiratory support modalities in the NICU is CPAP, which can cause gastric insufflation [16]. CPAP Belly Syndrome (CBS) was first described in 1992, when infants were noted to have strikingly distended abdomens 4–7 days after initiation of CPAP, with abdominal radiographs demonstrating uniform dilation of small- and large-bowel loops without bowel wall thickening, pneumatosis, or free air. This original study concluded that "CBS is a benign entity and not a contraindication to feeding or to the continued use of nasal CPAP therapy" [17]. Over the years, research has shown that CPAP belly may be a more serious problem than first thought, as it may lead to intubation or mimic NEC [18]. Furthermore, CPAP administration has been shown to shorten gastric emptying time and affect the physiological increase in blood flow velocity in the superior mesenteric artery, potentially slowing bowel motility and leading to FI [16].

In their study on CBS, Gu et al. noted that preterm infants with lower gestational age and birth weight were more likely to develop CBS [19]. Furthermore, the authors highlighted that infants with CBS were more likely to be receiving non-invasive positive-pressure ventilation (NIPPV) than those without (14.6% vs 0%, $p = 0.003$). Infants with CBS were also more likely to be receiving respiratory support with a higher positive end-expiratory pressure (PEEP) than infants without CBS. Interestingly, neonates with CBS had significantly more unnecessary abdominal radiographs, defined as those that did not alter clinical management, and were more likely to be diagnosed with NEC than those without [19].

Comparing CPAP to HHFNC

HHFNC is a high-flow therapy that uses heated, humidified gases. Studies comparing HHFNC with CPAP reported similar times to full enteral feeding and FI rates [20]. Amendolia et al. reported greater weight gain in similar preterm infants during HHFNC therapy compared with CPAP [21]. However, no significant differences were seen in the time required to achieve full enteral feeding or regarding FI [21]. In contrast, Shetty et al. showed that among patients with bronchopulmonary dysplasia (BPD), full enteral feeding was achieved earlier during HHFNC than during CPAP [22].

Cresi et al. compared FI during HHFNC and CPAP therapy, focusing on symptoms of FI such as abdominal distention, significant gastric residual volume, vomiting and/or regurgitation, and associated cardiorespiratory events. They did not notice any significant difference between HHFNC and CPAP [1]. However, reports are indicating higher comfort in preterm infants, as assessed by the EDIN neonatal pain and discomfort score, during HHFNC therapy compared to CPAP [23].

Feeding tolerance during NIPPV

NIPPV is a mode of non-invasive neonatal respiratory support that delivers positive pressure breaths through a nasal interface (such as nasal prongs or a nasal mask) without the need for endotracheal intubation. Current international guidelines recommend early non-invasive respiratory support in neonates with respiratory distress [24,25]. However, standard NIPPV is usually not synchronised with the infant's respiration, meaning that a significant proportion of the delivered gas volume may enter the patient's stomach. This occurs because the ventilator is not synchronised with the patient's glottal opening. Heesters et al. highlighted the problem of ventilation synchronisation during non-invasive ventilation. They found that the majority of the administered breaths, which were not synchronised with the patient's respiratory effort, were administered with the glottis closed [15,26]. Increased gas volume delivered to the gastrointestinal tract and subsequent distension may impair feeding tolerance. Current knowledge on FI during NIPPV therapy is limited. Garland et al reported an association between the use of ventilation via nasal prongs using NIPPV and an increased risk of gastrointestinal perforation because of extreme abdominal distension [27]. Yuan et al., in their 2022 study, reported a higher incidence of abdominal distension in children born before 32 gestational age during nCPAP than during NIPPV [28]. In 2014, Kugelman et al. examined perforation during NIPPV and HHFNC, but they did not observe any perforation in either mode. They also compared the time to achieve full enteral feeding during both respiratory modes, but no statistically significant differences were seen [29]. In 2008, Khorana et al. compared non-synchronised NIPPV with CPAP and found no statistically significant differences in feeding tolerance between the methods [30].

Non-Invasive Neurally Adjusted Ventilatory Assist

Non-invasive Neurally Adjusted Ventilatory Assist (NIV-NAVA) is a type of NIPPV that is synchronised with the electrical activity of the diaphragm (Edi) of the spontaneously breathing patient. Based on the Edi, the ventilator delivers a pressure that is synchronised and proportional to the patient's needs. The Edi signal, detected by sensing electrodes on a specially built nasogastric tube, allows patients to determine the peak inspiratory pressure (PIP), mean airway pressure, tidal volume, and inspiratory time [31]. Given that with appropriate synchronisation, patients would avoid receiving PIP during swallowing or when the glottis is closed whilst on NIV-NAVA, it might be expected that this mode of support is associated with less FI. However, the impact of NIV-NAVA on FI remains poorly investigated. One of the few papers that examines nutrition during NIV-NAVA respiratory support is the study by Benn et al., in which the authors noted an increased z-score for discharge weight with NIV-NAVA compared to conventional respiratory support[32]. Another study was that of Rong et al., in which the authors observed no difference in weight gain between NIV-NAVA and NIPPV [33]. There is a need for randomised controlled trials (RCTs) on the effect of NIV-NAVA on feeding tolerance in preterm infants (**Table 2**).

NIV-NAVA vs NIPPV

Recent studies comparing NIPPV and NIV-NAVA in preterm infants consistently demonstrate that NIV-NAVA delivers lower PIP while maintaining mean airway pressures equal to or higher than those with NIPPV, thereby enhancing patient-ventilator synchrony and potentially reducing the risk of lung injury at similar PIP settings. NIV-NAVA has been shown to provide lower tidal volumes, which may minimise volutrauma [34]. Critically,

Table 2. Comparison of NIPPV and NIV-NAVA across key clinical and ventilatory parameters, including pressure settings, tidal volume, work of breathing, patient–ventilator synchrony, feeding tolerance, and clinical outcomes.

Parameter	Non-Invasive Positive Pressure Ventilation (NIPPV)	Non-invasive Neurally Adjusted Ventilatory Assist (NIV-NAV)
Peak Inspiratory Pressure (PIP)	Higher	Lower
Mean Airway Pressure (MAP)	Lower or equal	Equal or higher
Tidal Volume	Higher	Lower
Work of Breathing (WOB)	Higher (higher Edi, asynchrony)	Lower (lower Edi, better synchrony)
Patient-Ventilator Synchrony	Less synchronous	Better synchronous
Feeding Tolerance	Variable	Potentially improved
Clinical Outcomes	Variable; similar extubation failure rates	Reduced extubation failure rates (in some studies)

NIV-NAVA significantly reduces work of breathing (WOB) as measured by electrical activity of the diaphragm (Edi), indicating better unloading of the respiratory muscles through synchronisation with the infant's neural respiratory drive. Additionally, NIV-NAVA may have a positive impact on feeding tolerance compared to NIPPV, likely due to lower PIP, improved patient comfort and reduced respiratory effort, though data are still emerging. The majority of evidence supports improved respiratory mechanics and patient comfort with NIV-NAVA, as evidenced by asynchrony index and EDI levels [35]. These physiological benefits correlate with clinical outcomes, including reduced extubation failure and lower reintubation rates in some studies. Nevertheless, larger randomised controlled trials are needed to confirm these advantages and further evaluate long-term clinical outcomes.

How to improve feeding tolerance

Feeding intolerance in premature infants is a multifactorial issue often linked to motor immaturity and poor coordination of sucking, swallowing, and breathing. Comuk Balci et al. administered oral-motor therapy to early preterm infants, consisting of 15–20-minute sessions three days a week for one month. The intervention included massage of oral and swallowing muscles, tactile stimulation around and inside the mouth to promote sucking, and non-nutritive sucking exercises. Results demonstrated improved feeding skills and earlier transition to breastfeeding. Similarly, Ostadi et al. studied 45 infants (mean gestational age 28.5 weeks, birth weight 1,193 g) divided into groups receiving non-nutritive sucking alone, both sucking and swallowing exercises, or standard care. Infants in the intervention groups required less tube feeding at discharge[36]. In another study, Kim et al. implemented a 2-week enteral nutrition massage program in infants born before 34 weeks, resulting in earlier attainment of full enteral feeding, increased mesenteric artery blood flow, and enhanced growth [37].

Extensive research highlights the positive impact of skin-to-skin care (SSC) on neonatal outcomes. SSC involves placing the newborn directly on the parent's chest, ensuring direct skin contact. This simple, effective practice supports neonatal adaptation and development by promoting weight and height gain, stabilising body temperature and reducing infection risk and mortality. Moreover, SSC enhances parent–infant bonding and stabilises heart rate, respiratory rate, and thermoregulation. Significantly, it improves feeding tolerance by promoting physiological stability, enhancing gastrointestinal function, and facilitating breastfeeding initiation and maintenance [38,39].

Kato et al. demonstrated SSC's benefits in infants ventilated with NAVA, showing reductions in Edi peak and tonic diaphragmatic activity (Edi minimum), indicating improved respiratory comfort and potential enhancement of feeding tolerance [39]. Souka et al. (2022) analysed 138 respiratory episodes—109 during invasive NAVA and 29 during non-invasive NAVA. During invasive NAVA, peak Edi, minimum Edi, neural respiratory rate, backup ventilation time, PIP, and mean airway pressure were significantly lower during SSC compared to incubator care. Similar reductions were observed during non-invasive NAVA. Since peak Edi reflects respiratory effort, its decrease signifies reduced work of breathing, while a lower minimum Edi indicates greater diaphragmatic stability. These results align with evidence that SSC mitigates pain and stress by increasing oxytocin and reducing cortisol levels.

Shetty et al. further evaluated SSC during NIV-NAVA therapy in preterm infants with bronchopulmonary dysplasia (BPD), finding improved respiratory parameters, reduced diaphragmatic workload, and enhanced breathing efficiency by the end of SSC sessions. These findings suggest that SSC contributes to greater physiological stability, even in infants with evolving or established BPD [40].

Collectively, the studies by Kato, Souka, and Shetty underscore SSC's multifaceted benefits in preterm infants requiring ventilatory support. Enhanced respiratory efficiency and comfort may, in turn, support improved feeding tolerance—an essential aspect of neonatal recovery. Together with interventions such as oral-motor therapy, SSC represents a key evidence-based approach promoting feeding tolerance, physiological stability, and developmental outcomes in this vulnerable population.

Summary and conclusion

FI in preterm infants is a common and clinically significant challenge in the NICU, with implications for growth, nutritional status, and overall clinical outcomes. The available evidence indicates that the influence of different NIV modes on FI remains poorly understood. CPAP, HFNC, non-synchronised NIPPV, and NIV-NAVA are all commonly used, yet each exerts distinct physiological effects on gastrointestinal function, swallowing coordination, and gastric insufflation risk.

The current literature suggests that CPAP and NIPPV may be associated with abdominal distension and potential delays in achieving full enteral feeding, particularly at higher pressures or when synchronisation is absent. HHFNC appears broadly comparable to CPAP for FI, with some evidence of improved patient comfort. NIV-NAVA offers potential advantages through improved patient–ventilator synchrony, which may reduce gastric insufflation and decrease work of breathing; however, its specific impact on FI remains insufficiently studied.

Across studies, the lack of a standardised, clinically practical definition of FI hampers both research comparability and evidence-based decision-making. Furthermore, the current body of knowledge is dominated by small, observational studies, limiting the strength and generalizability of existing recommendations.

The principal conclusions from this review are: (1) FI is a multifactorial condition influenced by ventilatory mode, synchronisation, and applied pressures; (2) Patient–ventilator synchrony is likely to play an essential role in minimising FI, with synchronised modes such as NIV-NAVA representing a promising avenue for further investigation; (3) standardised FI definitions are urgently needed to enhance research quality and guide consistent clinical practice.

Skin-to-skin care represents a simple, low-cost, and highly effective intervention with significant clinical benefits for very immature preterm infants, while also emphasising the essential role of parents as integral partners in neonatal care. This aspect remains insufficiently acknowledged and systematically integrated into routine clinical practice.

There is a strong need for well-designed randomised controlled trials—particularly those focused on synchronised modes of NIV—to determine their role in improving feeding tolerance.

Declarations

Authors' Contributions
Patryk Kwapień conceived the idea for the review, conducted the literature search, and wrote all sections of the manuscript.
Mark Johnson, Tomasz Szczapa, Jennifer Beck, and Christer Sinderby contributed to verifying the scientific accuracy of the content, critically revised the manuscript for important intellectual content, and assisted in identifying and analysing relevant studies.
All authors read and approved the final version of the manuscript and agree to be accountable for all aspects of the work, ensuring its accuracy and integrity.

Conflict of interest statement
The authors declare no conflict of interest.

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