



Review Article

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Feeding Intolerance Patterns in Very Low Birth Weight Neonates: A Cohort Study

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Abstract

Very low birth weight (VLBW) neonates are frequently affected by feeding intolerance, a heterogeneously defined clinical syndrome encompassing excessive gastric residuals, abdominal distension, emesis, and stool changes that reflects an immature gut's struggle to process enteral nutrition. This article synthesizes the cohort, trial, and systematic-review literature on feeding intolerance in VLBW infants: how it is defined and scored, the physiological substrate of motility immaturity, microbial dysbiosis, and marginal splanchnic perfusion that underlies it, the feeding practices (human milk provision, feed-advancement rate, standardized protocols, probiotic supplementation) shown to modify its incidence, its relationship to and clinical distinction from necrotizing enterocolitis and spontaneous intestinal perforation, emerging biomarker and imaging tools for earlier recognition, and its documented associations with prolonged time to full enteral feeding, extended NICU stay, extrauterine growth restriction, and neurodevelopmental impairment. Read together, the evidence supports standardized, human-milk-centered feeding protocols and probiotic supplementation as the interventions with the clearest benefit, while definitional inconsistency across studies and the absence of validated biomarker thresholds for distinguishing benign intolerance from early necrotizing enterocolitis remain the field's most pressing open problems.

Keywords: feeding intolerance; very low birth weight; necrotizing enterocolitis; enteral feeding; preterm neonate

1. Introduction

Very low birth weight (VLBW, <1500 g) neonates are, almost by definition, born with a gastrointestinal tract that has not finished the job it was supposed to do in utero. Coordinated peristalsis, gastric emptying, and mucosal barrier function normally mature across the third trimester, and an infant delivered at 26 or 28 weeks arrives with an immature enteric nervous system, sluggish antroduodenal motility, and a gut immune system primed to react rather than tolerate [1]. Clinicians managing these infants confront, almost daily, the question of whether a given feeding — a larger gastric aspirate than expected, a distended abdomen, an episode of emesis — reflects a transient, benign adjustment to enteral nutrition or an early warning sign of something far more serious. That everyday clinical judgment call is what the term "feeding intolerance" is meant to capture, and it is a term that, on close inspection, does a surprising amount of unacknowledged work in neonatal intensive care.

The problem is that feeding intolerance (FI) has never had a single, agreed definition. A 2021 systematic review by Weeks, Marino, and Johnson found that studies of feeding intolerance in preterm infants use markedly different combinations of gastric residual volume thresholds, abdominal distension criteria, emesis frequency, and stool pattern changes to define the same clinical label, with correspondingly divergent reported prevalence figures across the literature [2]. This is not merely an academic quibble about terminology. A cohort study of feeding intolerance is only as good as the definition of the outcome it is measuring, and a field that cannot agree on what counts as feeding intolerance will struggle to compare trial results, aggregate risk factors across centers, or build a stable evidence base for how aggressively to intervene when it occurs. This article synthesizes what the literature on VLBW neonates has established about feeding intolerance: how it is recognized and defined, what drives it physiologically, which feeding practices raise or lower its incidence, how it relates to and must be distinguished from necrotizing enterocolitis (NEC), what tools exist to monitor and predict it, and what the downstream consequences are for growth and neurodevelopment. We close with the gaps that, in our reading, remain genuinely open.

It is worth being explicit about what this article is and is not. It is a synthesis of published cohort studies,

randomized trials, and systematic reviews — not a report of new primary data. Where we describe a specific number (an incidence, a risk ratio, a length-of-stay difference), that number comes directly from a cited source, verified against the original publication, and we have tried consistently to distinguish between findings with strong trial-level evidence and findings that remain associative, cohort-level observations pending confirmation.

2. Defining and Recognizing Feeding Intolerance

In everyday NICU practice, feeding intolerance is usually operationalized through some combination of four signs: gastric residual volumes considered excessive relative to the preceding feed, abdominal distension, emesis, and a change in stool pattern or blood in the stool that falls short of frank NEC. The trouble, as Weeks and colleagues documented, is that "excessive" gastric residual has been defined anywhere from a fixed volume threshold to a percentage of the prior feed volume to simple discoloration of the aspirate, and different units have applied these criteria with different thresholds and different degrees of clinical weight given to each sign [2]. A retrospective cohort of extremely low birthweight (ELBW) infants by Soffer and colleagues illustrates how consequential this heterogeneity can be in a single dataset: using their center's operational definition, feeding intolerance was identified in 78 of 133 ELBW infants (58%), a prevalence that would likely look rather different under a stricter or looser definition applied to the same cohort [3]. A working assumption in this literature, one we adopt here, is that feeding intolerance is best understood not as a single diagnosable condition but as a clinical syndrome — a bundle of signs whose common denominator is that the gut, for whatever underlying reason, is not yet ready to process the volume or rate of enteral intake it is being offered.

That ambiguity has motivated attempts to formalize feeding intolerance into a scoring system rather than a binary judgment call. Ifran and colleagues developed and validated a feeding intolerance scoring system for very preterm and very low birth weight infants that combines standard clinical signs with point-of-care abdominal ultrasound findings — assessing bowel wall thickness, peristalsis, and free fluid — arguing that ultrasound adds objective information beyond what abdominal palpation and inspection alone can provide, particularly for distinguishing benign feeding

intolerance from early NEC [4]. Efforts like this reflect a broader trend in the field: moving away from single, subjectively-assessed signs (a nurse's impression of "too much" residual, in particular) toward composite, more reproducible assessment tools, precisely because the subjectivity of the older approach has made feeding intolerance such a difficult outcome to study consistently across centers.

Distinguishing feeding intolerance from its associated risk factors is also not straightforward, because many of the same clinical exposures that predict NEC also predict feeding intolerance, and the two outcomes are frequently studied together or conflated in individual papers. Soffer and colleagues' cohort found feeding intolerance was significantly more common among infants with bronchopulmonary dysplasia (88% of infants with BPD versus 43% of those without, $p < 0.001$) and was more frequent among infants supported with non-invasive positive pressure ventilation, at an incidence density of 8.1 episodes per 100 device-days, compared with 2.2 per 100 device-days on heated humidified high-flow cannula and 2.0 per 100 device-days on nasal CPAP [3]. Whether this association reflects a shared underlying vulnerability (sicker infants who need more respiratory support also have less mature guts) or a more direct mechanistic link (positive pressure ventilation modes may distend the stomach with swallowed air, or the work of breathing may itself compete with gut perfusion) is not fully resolved by a single retrospective cohort, and this is one of several places in the literature where association is easier to demonstrate than mechanism.

3. Pathophysiology: Gut Immaturity, Motility, and the Preterm Microbiome

The physiological substrate for feeding intolerance begins with motility. Antroduodenal motor activity — the coordinated contractions that move a bolus of milk from stomach to duodenum and onward — matures progressively across gestation, and infants born well before term simply have not yet developed the mature motor patterns that facilitate efficient gastric emptying and forward peristalsis; migrating motor complexes, the coordinated waves of activity that characterize mature gut motility between meals, are frequently disorganized or absent in the most immature infants [1]. This immaturity is compounded by the fact that enteral feeding itself is one of the principal stimuli that drives

gut maturation — meaning that infants whose feeds are withheld or minimized for a prolonged period risk entering something of a vicious cycle, in which limited feeding slows the very maturation that would allow feeding to be tolerated and advanced.

This observation underlies the rationale for trophic or minimal enteral feeding — small volumes of milk, generally well below nutritional requirement, given specifically to stimulate gut maturation rather than to provide calories. Terrin and colleagues studied this directly in a cohort of feed-intolerant VLBW newborns and found that minimal enteral feeding reduced the risk of subsequent sepsis relative to complete enteral fasting, a finding consistent with the broader argument that even small amounts of enteral substrate help preserve gut barrier function and reduce the translocation risk associated with a fully fasted, parenterally-nourished gut [5]. The mechanistic logic — that even nutritionally negligible feeding volumes protect gut integrity by stimulating trophic hormones, mucosal blood flow, and enzyme maturation — is a recurring theme across this literature and is part of why most contemporary neonatal units initiate at least trophic feeds within the first days of life for VLBW infants rather than withholding enteral nutrition entirely until the infant appears more stable.

Layered on top of motility immaturity is the preterm gut's distinctive, and distinctively unstable, microbial ecosystem. A term infant's gut is colonized in a relatively predictable succession shaped by mode of delivery, feeding type, and environmental exposure; a VLBW infant's gut, by contrast, is colonized under conditions of frequent antibiotic exposure, delayed or absent enteral feeding, and an NICU environment dominated by a narrow set of hospital-associated organisms, all of which push the developing microbiome toward reduced diversity and a higher relative abundance of Proteobacteria at the expense of the Firmicutes and Bacteroidetes that typically dominate a healthy infant gut [6]. Pammi and colleagues' systematic review and meta-analysis of studies profiling the preterm gut microbiome before the onset of NEC found a consistent pattern of dysbiosis preceding disease onset — lower microbial diversity and a relative expansion of Proteobacteria — across multiple independent cohorts, though the review is candid that no single organism or microbial signature has yet been validated as a reliable,

prospective predictor of which dysbiotic infant will go on to develop NEC rather than simply feeding intolerance that resolves [7]. This distinction matters enormously for the argument of this article: dysbiosis appears to be a shared upstream vulnerability for both feeding intolerance and NEC, but the field has not yet identified what separates an infant whose dysbiotic gut manifests as transient feeding intolerance from one whose gut progresses to frank necrotizing disease.

Gut perfusion adds a third physiological layer. Enteral feeding transiently increases splanchnic blood flow and oxygen demand as the gut does the metabolic work of digestion, and in a hemodynamically fragile preterm infant — one with a patent ductus arteriosus, recovering from an episode of hypotension, or receiving vasoactive medications — that postprandial demand may exceed what a compromised splanchnic circulation can supply. Thomas and colleagues validated that abdominal near-infrared spectroscopy (NIRS) can reliably and reproducibly measure regional splanchnic oxygen saturation changes in preterm infants, establishing the measurement technique itself as sound before it can be used to study feeding-related physiology prospectively [8]. Building on this measurement approach, Dani and colleagues found that splanchnic tissue oxygenation, measured non-invasively, was predictive of subsequent feeding tolerance in preterm infants, with infants who went on to tolerate feeds well showing a different postprandial splanchnic oxygenation trajectory than those who developed feeding intolerance [9]. Together, these lines of evidence sketch a physiological picture in which feeding intolerance is not one thing but the visible endpoint of several distinct, sometimes overlapping vulnerabilities — immature motility, an unstable and pro-inflammatory microbiome, and marginal splanchnic perfusion reserve — any of which can push a VLBW gut past the threshold of what it can currently process.

4. Feeding Practices and Their Influence on Tolerance

Because feeding intolerance is, definitionally, a response to how and what an infant is fed, the practices governing feeding initiation, advancement, and milk type are the most directly modifiable levers clinicians have. The type of milk is arguably the single most consistently supported factor in this literature. Sisk and colleagues' prospective cohort of 202 VLBW infants found that

infants receiving less than 50% of their intake as human milk during the first 14 days developed confirmed NEC at a rate of 10.6%, compared with 3.2% among infants receiving 50% or more human milk, and after adjusting for gestational age the higher human-milk group had roughly a sixfold reduction in the odds of NEC [10]. Where a mother's own milk is unavailable or insufficient, donor human milk is the next-best substitute: a Cochrane review by Quigley and colleagues concluded that feeding preterm or VLBW infants donor human milk rather than formula, when mother's own milk is not available, reduces the risk of necrotizing enterocolitis, a conclusion drawn across multiple randomized trials comparing the two feeding strategies [11]. The mechanistic account for why human milk protects the gut in this way spans several plausible, non-mutually-exclusive pathways — immunoglobulins, oligosaccharides that shape a more favorable microbiome, growth factors that support mucosal maturation, and a fat and protein composition more readily digested by an immature gut — reviewed in detail elsewhere and summarized in the broader NEC pathophysiology literature [6].

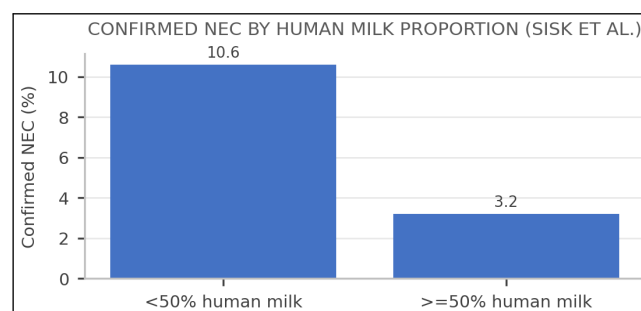


Figure 1: Confirmed necrotizing enterocolitis by proportion of human milk received during the first 14 days of life in a prospective cohort of 202 very low birth weight infants, illustrating the protective association between higher human-milk intake and NEC risk that motivates the strong emphasis on human milk feeding throughout the feeding-intolerance literature [10].

Fortification of human milk, necessary because unfortified breast milk alone does not meet a VLBW infant's protein, mineral, and calorie requirements, introduces its own set of tolerance questions, particularly around whether fortifier composition (bovine-derived versus human-milk-derived) influences NEC and feeding intolerance risk. A 2025 systematic review and meta-analysis by Reyes, Paul, and Ferry examined the state of evidence on human milk fortification and NEC in VLBW infants and found that an exclusive human milk diet — using a human-milk-derived rather than bovine-derived fortifier

— was associated with a lower risk of NEC compared with fortification strategies that introduce a bovine-derived product, though the authors were careful to note that the underlying trial evidence varies substantially in quality and that cost and availability remain real barriers to adopting exclusive human milk diets universally [12].

The rate at which feeds are advanced once initiated has been the subject of some of the largest and most methodologically rigorous trials in this literature. The Speed of Increasing Milk Feeds Trial (SIFT), led by Dorling and colleagues and involving 2,804 very preterm or VLBW infants randomized to faster or slower rates of milk volume increase, found no significant difference between the two feeding-advancement speeds in survival without moderate or severe neurodevelopmental disability at 24 months corrected age, the trial's primary outcome [13]. This large, definitive trial complements an earlier Cochrane review by Oddie and colleagues on slow versus faster advancement of enteral feed volumes specifically with respect to NEC prevention, which likewise did not find that slower feed advancement reliably reduces NEC risk relative to faster, more clinically typical advancement rates, tempering an intuitive but not fully evidence-supported assumption that "go slow" is inherently the safer default for every VLBW infant [14]. A separate, smaller randomized trial by Bozkurt and colleagues compared prolonged minimal enteral nutrition against earlier feeding advancement specifically in infants weighing 1250 g or less, adding further trial-level data to this same question of how aggressively feeds can safely be advanced in the smallest, most vulnerable infants [15]. Taken together, this body of trial evidence has meaningfully shifted practice away from uniformly cautious, slow feed advancement and toward protocols that advance feeds more briskly than was once standard, on the grounds that unnecessarily prolonged minimal feeding delays the achievement of full enteral nutrition and extends exposure to central line-associated risks without a clearly demonstrated NEC-prevention benefit.

Standardization of feeding protocols themselves — independent of exactly how fast feeds are advanced — is one of the more consistently supported interventions in this literature specifically for reducing NEC. Jasani and Patole's updated systematic review, pooling 15

observational studies encompassing 18,160 infants, found that implementation of a standardized feeding regimen was associated with a substantially reduced risk of NEC, with a pooled risk ratio of 0.22 (95% CI 0.13–0.36) relative to non-standardized, clinician-discretion-driven feeding practices, and this effect was consistent whether the comparison studies were conducted in the earlier (1978–2003) or later (2004–2016) era of neonatal care [16]. This is among the largest effect sizes reported anywhere in the feeding-intolerance and NEC literature, and it is notable that the intervention being tested is not a specific milk type or a specific advancement rate but simply the act of protocolizing feeding decisions — removing unit-to-unit and clinician-to-clinician variability in how gastric residuals, distension, and advancement decisions are handled — which suggests that a substantial share of NEC risk in less standardized units may be attributable not to any single "wrong" feeding choice but to inconsistency itself.

Probiotic supplementation represents a different category of intervention, aimed less at feeding logistics and more directly at shaping the dysbiotic gut microbiome described earlier. A Cochrane review by Sharif and colleagues, synthesizing randomized trials of probiotic supplementation in very preterm or VLBW infants, concluded that probiotics reduce the risk of severe NEC and of all-cause mortality relative to placebo or no treatment, while flagging ongoing uncertainty about which specific probiotic strains, doses, and formulations are optimal, and about supplement quality control and regulatory oversight in a product category that, unlike a pharmaceutical, is not uniformly standardized across manufacturers [17]. The combination of a plausible mechanism (directly countering the Proteobacteria-dominant dysbiosis implicated in NEC pathogenesis), consistent trial-level benefit, and remaining practical uncertainty about implementation is a pattern that recurs across several of the interventions reviewed in this article: the population-level direction of effect is reasonably clear, while the specifics of optimal protocol remain a live area of ongoing trial work.

5. Necrotizing Enterocolitis: The Critical Complication to Distinguish

The reason feeding intolerance commands so much clinical attention, beyond its own direct morbidity, is

that it sits on a spectrum whose far end is necrotizing enterocolitis — a disease that remains one of the most feared complications of prematurity and one that, in its most severe (modified Bell stage III) presentation, carries substantial mortality and, among survivors, a high burden of short bowel syndrome and neurodevelopmental impairment [6]. The clinical challenge is that early NEC and benign feeding intolerance can look remarkably similar at the bedside — both may present with increased gastric residuals, abdominal distension, and feeding-related discomfort — and the tools clinicians have traditionally relied on to distinguish the two have real limitations.

Gastric residual volume monitoring is the paradigmatic example of this tension. For decades, an "excessive" gastric residual before a scheduled feed was treated as an early warning sign, prompting feed-holding, and in some units as one of the diagnostic criteria feeding into a working NEC concern. Bertino and colleagues' risk factor analysis of NEC in VLBW infants specifically examined the role of gastric residuals in this context, contributing to a body of evidence questioning how reliably residual volume alone predicts NEC as opposed to simply reflecting normal variability in an immature gut's gastric emptying [18]. More recent randomized evidence has directly tested whether routinely checking and acting on gastric residuals actually improves outcomes. Williams and colleagues' randomized controlled trial compared routine versus no assessment of gastric residual volumes in preterm infants fed via intermittent tubes and found that abandoning routine gastric residual checks did not increase adverse events, adding trial-level support to the argument that gastric residual volume, used in isolation as a screening tool, may do more to slow feeding advancement unnecessarily than to meaningfully improve NEC detection [19]. The GRASS trial, a multi-centre, assessor-blinded randomized trial led by Branagan and colleagues, likewise examined how gastric residual assessment practice influences the time preterm neonates take to reach full enteral feeding, directly testing the practical downstream consequence of this monitoring strategy in a randomized design rather than an observational one [20]. The direction of this newer evidence has, on balance, pushed several contemporary units toward de-emphasizing routine gastric residual checks in hemodynamically stable infants without other concerning signs, reserving closer monitoring for infants

who already show additional clinical evidence of intolerance.

A related but conceptually distinct entity that must be kept separate from feeding-intolerance-progressing-to-NEC is spontaneous intestinal perforation (SIP): a focal bowel perforation, typically affecting the terminal ileum, that occurs in extremely preterm and VLBW infants independent of the inflammatory, multifocal bowel necrosis that characterizes NEC, often earlier in postnatal life and often in infants who have received minimal or no enteral feeds at all, which is itself an important clue that SIP and NEC are pathophysiologically distinct processes despite both presenting as neonatal surgical bowel emergencies. A large Neonatal Research Network cohort study by Speer and colleagues examined outcomes following both surgical NEC and SIP and found that both conditions were associated with severe postnatal growth failure among survivors, underscoring that regardless of which of these two distinct pathways a bowel emergency follows, the downstream nutritional and growth consequences for the infant are substantial and warrant dedicated post-illness nutritional support [21]. Clinically, this distinction matters because SIP's association with minimal feeding (rather than feeding advancement itself) argues against interpreting every case of neonatal bowel perforation as evidence that feeding was advanced too aggressively, and argues instead for careful case-by-case classification before drawing lessons about feeding practice from any single adverse outcome.

6. Monitoring, Biomarkers, and Emerging Tools

Because clinical signs alone are an imperfect guide to which infant with apparent feeding intolerance is on a trajectory toward NEC, a body of work has pursued biomarkers and imaging tools intended to add objective, quantitative information to the bedside assessment. Fecal calprotectin — a neutrophil-derived protein that rises with intestinal inflammation and is already an established biomarker in pediatric and adult inflammatory bowel disease — has attracted particular interest in the neonatal NEC literature. Yoon and colleagues measured fecal calprotectin concentrations in neonates with confirmed NEC and found levels substantially elevated relative to unaffected controls, consistent with the underlying biological rationale that calprotectin should track the degree of active intestinal

inflammation regardless of its underlying cause [22]. The practical appeal of a stool-based biomarker is considerable — it requires no blood draw, can in principle be measured serially without added risk to a fragile infant, and does not depend on the same subjective bedside judgment that has made clinical feeding-intolerance criteria so heterogeneous across studies. Its current limitation, echoing a theme raised earlier regarding microbiome signatures, is that elevated calprotectin has not yet been established as reliably distinguishing NEC from other, less severe causes of intestinal inflammation and feeding intolerance, which constrains its use today to a supportive rather than a standalone diagnostic role.

Imaging-based tools occupy a complementary niche. Ifran and colleagues' feeding intolerance scoring system incorporated point-of-care abdominal ultrasound findings — bowel wall thickening, altered peristalsis patterns, free peritoneal fluid — specifically because these ultrasound signs can appear before radiographic findings on plain abdominal X-ray become apparent, potentially giving clinicians an earlier window into whether a given episode of feeding intolerance is likely to be benign or is evolving toward something requiring surgical or intensive medical intervention [4]. Near-infrared spectroscopy offers a physiological rather than structural window onto the same underlying question: because splanchnic hypoperfusion is thought to be a contributing mechanism in both feeding intolerance and NEC, monitoring regional oxygen saturation trends around feeding times, using the validated NIRS methodology described by Thomas and colleagues, gives clinicians a non-invasive, continuous readout of gut perfusion that changes on a faster timescale than clinical signs typically become apparent, and Dani and colleagues' work linking splanchnic oxygenation patterns to subsequent feeding tolerance is an early proof of concept for using this signal predictively rather than only retrospectively [8,9].

What is notable across this monitoring and biomarker literature, read as a whole, is the consistent gap between promising association and validated clinical utility. Elevated calprotectin, abnormal ultrasound findings, and abnormal splanchnic oxygenation trajectories are each associated with worse feeding outcomes in the studies that have examined them, but none has yet been incorporated into widely adopted clinical decision

algorithms with prospectively validated thresholds analogous to, say, a troponin cutoff in cardiology. This is not a criticism specific to any one biomarker so much as an honest description of where a genuinely difficult diagnostic problem — distinguishing benign feeding intolerance from early NEC in an infant whose clinical signs overlap substantially between the two — currently stands.

7. Feeding Intolerance and Longer-Term Outcomes

Feeding intolerance is not merely a transient inconvenience that resolves once an infant's gut matures; the cohort literature increasingly documents that it carries measurable costs even when it never progresses to NEC. Soffer and colleagues' cohort found that ELBW infants who developed feeding intolerance took substantially longer to reach full enteral feeding (median 18 days versus 14 days in infants without feeding intolerance, $p < 0.001$) and had considerably longer NICU stays (median 89.5 days versus 47 days, $p < 0.001$), alongside a trend toward lower weight z-scores at discharge (-2.55 versus -1.87) that did not reach statistical significance in their cohort but pointed in a direction consistent with cumulative nutritional deficit [3]. Longer time to full enteral feeding matters beyond the days themselves, because every additional day of predominantly parenteral nutrition extends exposure to central-line-associated bloodstream infection risk, parenteral-nutrition-associated cholestasis, and the general morbidity burden of prolonged NICU dependence — meaning feeding intolerance's costs compound through pathways well beyond the gut itself.

Table 1: Representative quantitative findings from the cohort and systematic-review literature on feeding intolerance and its clinical consequences in very low birth weight and extremely low birth weight neonates. [16,3].

Finding	Source	Study Design / Population	Reported Result
Standardized feeding regimen and NEC risk	Jasani & Patole [16]	Systematic review, 15 studies, 18,160 infants	NEC risk ratio 0.22 (95% CI 0.13-0.36) vs non-standardized feeding
Time to full enteral feeding, with vs without feeding intolerance	Soffer et al. [3]	Prospective cohort, 133 ELBW infants	Median 18 days (FI) vs 14 days (no FI), $p < 0.001$
NICU length of stay, with vs without feeding intolerance	Soffer et al. [3]	Prospective cohort, 133 ELBW infants	Median 89.5 days (FI) vs 47 days (no FI), $p < 0.001$
Feeding intolerance and bronchopulmonary dysplasia	Soffer et al. [3]	Prospective cohort, 133 ELBW infants	FI in 88% of infants with BPD vs 43% without, $p < 0.001$

Finding	Source	Study Design / Population	Reported Result
Feeding intolerance incidence by respiratory support mode	Soffer et al. [3]	Prospective cohort, 133 ELBW infants	8.1/100 device-days (NIPPV) vs 2.2 (HHHFNC) vs 2.0 (nCPAP)

The growth consequences documented in individual cohorts connect to a broader concern about extrauterine growth restriction (EUGR), the phenomenon in which a preterm infant's growth trajectory falls further below expected percentiles after birth than would be predicted from intrauterine growth alone. Zhao and colleagues' retrospective cohort study specifically examined feeding intolerance as a risk factor for EUGR and neurodevelopmental impairment among small-for-gestational-age preterm infants, finding that feeding intolerance functioned as an independent predictor of both worse postnatal growth and worse neurodevelopmental outcomes in this particularly vulnerable subgroup, who arrive already growth-restricted and can least afford further nutritional compromise during the NICU stay [23]. This finding is a useful corrective to any framing of feeding intolerance purely as a short-term NICU management problem: if it independently predicts neurodevelopmental outcome, then the stakes of getting feeding-advancement decisions right extend well past the hospital discharge date that most acute-care outcome measures stop at.

There is also a rehabilitative angle to this outcomes picture that deserves mention. A retrospective analysis by Zhao and colleagues examined risk factors and clinical features of feeding intolerance in preterm infants alongside the effect of a multimodal oral-sucking- oromotor training intervention, reporting that structured oromotor stimulation was associated with improved feeding-related outcomes in their cohort, which is consistent with a broader premise in neonatal nutrition: that feeding tolerance is not solely a passive function of gut maturation timing but can, to some degree, be actively supported through targeted intervention rather than simply waited out [24]. This complements the developmental-physiology account of feeding intolerance described earlier in this article — if immature motility and coordination are part of the underlying problem, then interventions that specifically target oromotor and gut-motor coordination represent a logically complementary approach to the nutrition-focused interventions (milk type, advancement rate, standardized protocols) that

dominate the rest of this literature.

8. Open Challenges

Several gaps recur across the literature synthesized here and are worth stating plainly. First, definitional heterogeneity remains the field's most basic unresolved problem: as long as different cohorts and trials use materially different operational definitions of feeding intolerance, comparing incidence, risk factors, and intervention effects across studies will remain an exercise in comparing not-quite-the-same outcome measured not-quite-the-same way [2]. A consensus definition, validated prospectively across multiple centers, would materially improve the comparability of future cohort studies and trials, and its absence is arguably the single change that would do the most to advance this field's evidence base.

Second, the biomarker and imaging literature, while promising, has not yet crossed the threshold from association to validated clinical decision-making. Fecal calprotectin, abdominal ultrasound scoring, and splanchnic NIRS monitoring have each shown associations with feeding outcomes in individual studies, but prospective, multi-center validation of specific thresholds — the kind of work that would let a clinician say "calprotectin above X predicts NEC progression with sensitivity Y" — remains largely undone [22,4,9]. Third, the mechanistic gap between dysbiosis and disease progression is still wide open: the microbiome literature has convincingly shown that dysbiosis precedes NEC, but has not yet explained what distinguishes the dysbiotic infant whose gut resolves toward benign feeding intolerance from the dysbiotic infant whose gut progresses to necrotizing disease, and closing that gap would have direct implications for which infants warrant closer surveillance or earlier intervention [7].

Fourth, much of the feeding-practice literature, including some of its largest and most consequential trials, was conducted at centers with substantial neonatal infrastructure, and it remains genuinely unclear how well findings like the SIFT trial's null result on feeding-advancement speed, or the standardized-feeding-regimen literature's strong effect size, generalize to lower-resource settings where donor human milk banking, continuous physiological monitoring, and rapid surgical NEC intervention may not be uniformly available [13,16]. Fifth, and more

practically: probiotic supplementation has clear population-level trial support, but the field still lacks consensus on which specific strains, doses, and combinations to use, and on how to ensure consistent product quality across the range of commercially available probiotic formulations, a gap that sits between good randomized-trial evidence and confident, standardized clinical implementation [17]. None of these gaps undermine the substantial progress this literature has made in moving feeding management away from reflexive caution and toward evidence-informed, protocolized care; they are, read together, a reasonably clear agenda for where the next decade of cohort studies and trials in this area should focus.

9. Conclusion

The literature reviewed here supports a coherent, if still incomplete, account of feeding intolerance in VLBW neonates. It is best understood as a heterogeneously defined clinical syndrome arising from the intersection of gut motor immaturity, an unstable and often pro-inflammatory preterm microbiome, and marginal splanchnic perfusion reserve, sitting on a spectrum whose far end — necrotizing enterocolitis — is the complication that makes accurate, early recognition of feeding intolerance clinically urgent rather than merely a matter of nutritional bookkeeping [1,7,6]. The feeding practices with the strongest evidentiary support — prioritizing human milk over formula, standardizing feeding protocols rather than leaving advancement decisions to individual clinician discretion, and supplementing with probiotics — converge on a broader lesson: much of the achievable reduction in NEC risk appears to come less from any single "correct" feeding recipe and more from consistency, evidence-based protocolization, and supporting the gut's own maturation rather than working around it [10,16,17]. At the same time, some long-held cautious defaults, particularly very slow feed advancement and routine gastric residual monitoring as gatekeeping tools, have not held up well against more recent, better-powered randomized evidence, and contemporary practice has shifted accordingly [13,14,19].

What remains genuinely unresolved is less about whether feeding intolerance matters — the growth and neurodevelopmental data make clear that it does, independent of progression to NEC [3,23] — and more

about how to recognize it earlier and more reliably, and how to distinguish, at the bedside and in real time, the infant whose gut needs a day of caution from the infant whose gut is already on a trajectory toward necrotizing disease. Biomarkers, ultrasound scoring, and splanchnic oxygenation monitoring each offer a piece of that puzzle, but none yet closes it. Continued, carefully designed cohort studies — precisely the kind of study this synthesis has drawn on throughout — remain the mechanism by which this field will keep narrowing that gap.

10. References

1. Patole, S. (2013) Developmental Physiology of the Gastrointestinal Tract and Feed Intolerance in Preterm Neonates. In: *Nutrition for the Preterm Neonate: A Clinical Perspective*. Springer, Dordrecht: 3-25. DOI: [10.1007/978-94-007-6812-3_1](https://doi.org/10.1007/978-94-007-6812-3_1)
2. Weeks, C.L., Marino, L.V., Johnson, M.J. (2021) A systematic review of the definitions and prevalence of feeding intolerance in preterm infants. *Clinical Nutrition*, 40(11): 5576-5586. DOI: [10.1016/j.clnu.2021.09.010](https://doi.org/10.1016/j.clnu.2021.09.010)
3. Soffer, S., Mandel, D., Herzlich, J., Mendelsohn, R., Lubetzky, R., Moran-Lev, H. (2025) Associated factors and clinical outcomes of feeding intolerance in preterm extremely low birthweight infants. *Scientific Reports*, 15: 28189. DOI: [10.1038/s41598-025-14386-1](https://doi.org/10.1038/s41598-025-14386-1)
4. Ifrani, E.K.B., Hegar, B., Rohsiswatmo, R., Indriatmi, W., Yuniarti, T., Advani, N., Santoso, D.I.S., Masui, M., Hikmahrachim, H.G., Huysentruij, K., Vandenplas, Y. (2024) Feeding intolerance scoring system in very preterm and very low birth weight infants using clinical and ultrasound findings. *Frontiers in Pediatrics*, 12: 1370361. DOI: [10.3389/fped.2024.1370361](https://doi.org/10.3389/fped.2024.1370361)
5. Terrin, G., Passariello, A., Canani, R.B., Manguso, F., Paludetto, R., Cascioli, C. (2009) Minimal enteral feeding reduces the risk of sepsis in feed-intolerant very low birth weight newborns. *Acta Paediatrica*, 98(1): 31-35. DOI: [10.1111/j.1651-2227.2008.00987.x](https://doi.org/10.1111/j.1651-2227.2008.00987.x)
6. Nyenga, A.M., Mukuku, O., Ziazia, J.S., Wembonyama, S.O. (2026) Necrotizing Enterocolitis in Preterm Infants: An Inflammatory Condition at the Crossroads of Intestinal Immaturity, Dysbiosis, and Nutrition. *International Journal of Pediatrics*, 2026: 9191604. DOI: [10.1155/ijpe/9191604](https://doi.org/10.1155/ijpe/9191604)
7. Pammi, M., Cope, J., Tarr, P.I., Warner, B.B., Morrow, A.L., Mai, V., et al. (2017) Intestinal dysbiosis in preterm infants preceding necrotizing enterocolitis: a systematic review and meta-analysis. *Microbiome*, 5: 31. DOI: [10.1186/s40168-017-0248-8](https://doi.org/10.1186/s40168-017-0248-8)

8. Thomas, R.A., Ballard, M-R., Aladangady, N., Banerjee, J. (2022) Abdominal Near Infrared Spectroscopy can be reliably used to measure splanchnic oxygenation changes in preterm infants. *Journal of Perinatology*, 43(6): 716-721. DOI: [10.1038/s41372-022-01576-2](https://doi.org/10.1038/s41372-022-01576-2)
9. Dani, C., Pratesi, S., Barp, J., et al. (2015) Splanchnic Tissue Oxygenation for Predicting Feeding Tolerance in Preterm Infants. *Journal of Parenteral and Enteral Nutrition*, 39(3): 306-312. DOI: [10.1177/0148607114538671](https://doi.org/10.1177/0148607114538671)
10. Sisk, P.M., Lovelady, C.A., Dillard, R.G., Gruber, K.J., O'Shea, T.M. (2007) Early human milk feeding is associated with a lower risk of necrotizing enterocolitis in very low birth weight infants. *Journal of Perinatology*, 27(7): 428-433. DOI: [10.1038/sj.jp.7211758](https://doi.org/10.1038/sj.jp.7211758)
11. Quigley, M., Embleton, N.D., Meader, N., McGuire, W. (2024) Donor human milk for preventing necrotising enterocolitis in very preterm or very low-birthweight infants. *Cochrane Database of Systematic Reviews*, 2024(9): CD002971. DOI: [10.1002/14651858.CD002971.pub6](https://doi.org/10.1002/14651858.CD002971.pub6)
12. Reyes, S.M., Paul, T.L., Ferry, J. (2025) Human Milk Fortification and Necrotizing Enterocolitis in Very Low Birthweight Infants: State of Evidence and Systematic Review with Meta-Analysis. *Nutrients*, 17(21): 3384. DOI: [10.3390/nu17213384](https://doi.org/10.3390/nu17213384)
13. Dorling, J., Abbott, J., Berrington, J., Bosiak, B., Bowler, U., Boyle, E., et al. (2019) Controlled Trial of Two Incremental Milk-Feeding Rates in Preterm Infants. *New England Journal of Medicine*, 381(15): 1434-1443. DOI: [10.1056/NEJMoa1816654](https://doi.org/10.1056/NEJMoa1816654)
14. Oddie, S.J., Young, L., McGuire, W. (2021) Slow advancement of enteral feed volumes to prevent necrotising enterocolitis in very low birth weight infants. *Cochrane Database of Systematic Reviews*. DOI: [10.1002/14651858.CD001241.pub8](https://doi.org/10.1002/14651858.CD001241.pub8)
15. Bozkurt, O., Dizdar, E.A., Bidev, D., Sari, F.N., Uras, N., Oguz, S.S. (2020) Prolonged minimal enteral nutrition versus early feeding advancements in preterm infants with birth weight ≤ 1250 g: a prospective randomized trial. *The Journal of Maternal-Fetal & Neonatal Medicine*, 35(2): 341-347. DOI: [10.1080/14767058.2020.1716723](https://doi.org/10.1080/14767058.2020.1716723)
16. Jasani, B., Patole, S. (2017) Standardized feeding regimen for reducing necrotizing enterocolitis in preterm infants: an updated systematic review. *Journal of Perinatology*, 37(7): 827-833. DOI: [10.1038/jp.2017.37](https://doi.org/10.1038/jp.2017.37)
17. Sharif, S., Meader, N., Oddie, S.J., Rojas-Reyes, M.X., McGuire, W. (2020) Probiotics to prevent necrotising enterocolitis in very preterm or very low birth weight infants. *Cochrane Database of Systematic Reviews*, 2020(10): CD005496. DOI: [10.1002/14651858.CD005496.pub5](https://doi.org/10.1002/14651858.CD005496.pub5)
18. Bertino, E., Giuliani, F., Prandi, G., Coscia, A., Martano, C., Fabris, C. (2009) Necrotizing enterocolitis: risk factor analysis and role of gastric residuals in very low birth weight infants. *Journal of Pediatric Gastroenterology and Nutrition*, 48(4): 437-442. DOI: [10.1097/MPG.0b013e31817b6dbe](https://doi.org/10.1097/MPG.0b013e31817b6dbe)
19. Williams, S., Bostain, R., Couch, N., Kamdar, T., Oh, W., Thompson, L., Pepe, J., Yi, F., Dereddy, N. (2023) Routine versus no assessment of gastric residual volumes in preterm infants receiving enteral feeding via intermittent feeding tubes: a randomized controlled trial. *The Journal of Maternal-Fetal & Neonatal Medicine*, 36(1): 2211200. DOI: [10.1080/14767058.2023.2211200](https://doi.org/10.1080/14767058.2023.2211200)
20. Branagan, A., Murphy, C., O'Sullivan, A., Bodnarova, I., Feyereislova, S., Berka, I., Miletin, J., Stranak, Z. (2024) Influence of gastric residual assessment in preterm neonates on time to achieve enteral feeding (the GRASS trial)-Multi-centre, assessor-blinded randomised clinical trial. *European Journal of Pediatrics*, 183(5): 2325-2332. DOI: [10.1007/s00431-024-05483-w](https://doi.org/10.1007/s00431-024-05483-w)
21. Speer, A.L., Lally, K.P., Pedroza, C., Zhang, Y., Poindexter, B.B., Chwals, W.J., Hintz, S.R., Besner, G.E., Stevenson, D.K., Ohls, R.K., Truog, W.E., Stoll, B.J., et al. (2024) Surgical Necrotizing Enterocolitis and Spontaneous Intestinal Perforation Lead to Severe Growth Failure in Infants. *Annals of Surgery*, 280(3): 432-443. DOI: [10.1097/SLA.0000000000006378](https://doi.org/10.1097/SLA.0000000000006378)
22. Yoon, J.M., Park, J.Y., Ko, K.O., Lim, J.W., Cheon, E.J., Kim, H.J. (2014) Fecal calprotectin concentration in neonatal necrotizing enterocolitis. *Korean Journal of Pediatrics*, 57(8): 351-356. DOI: [10.3345/kjp.2014.57.8.351](https://doi.org/10.3345/kjp.2014.57.8.351)
23. Zhao, H., Guo, C., Xie, G., Tong, Y., Wu, Y. (2026) Feeding intolerance as an independent risk factor for extrauterine growth restriction and neurodevelopmental impairment in small-for-gestational-age preterm infants: a retrospective cohort study. *European Journal of Medical Research*, 31: 589. DOI: [10.1186/s40001-026-04197-z](https://doi.org/10.1186/s40001-026-04197-z)
24. Zhao, H., Qi, H., Xu, R., Xie, G. (2026) Risk factors and clinical features of feeding intolerance in preterm infants and the effect of multimodal oral-sucking-omomotor training: a single-center retrospective analysis. *The Journal of Maternal-Fetal & Neonatal Medicine*, 39(1). DOI: [10.1080/14767058.2026.2617714](https://doi.org/10.1080/14767058.2026.2617714)

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Conflict of Interest

The authors declare that they have no competing interests relevant to the content of this article.

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Ethical Approval

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