

Gut Health Bundle - Toward a NEC-Free Canada

Prevention of Necrotizing Enterocolitis in Canadian NICUs

Infants with necrotizing enterocolitis (NEC) have an estimated mortality rate of 15-30% and an average of 22 and 60 additional hospital days in those with medical and surgical NEC, respectively.¹ Although early recognition and aggressive management has improved clinical outcomes, NEC accounts for significant long-term morbidity in survivors, particularly in infants requiring surgery. Efforts to reduce the incidence or severity of NEC are directed at reducing exposure to risk factors and promoting interventions that will prevent the disease.

Aim:

To reduce the incidence of NEC in preterm infants $\leq 32^{6/7}$ weeks gestation from 4-5% to $\leq 2\%$ in the next 5 years.

Definition:

- NEC will be defined according to the Canadian Neonatal Network manual which is based on Bell's criteria of NEC stage 2 or higher as:
 - a) Definite pneumatosis or hepatic portal venous gas on x-ray or intestinal ultrasound, or
 - b) Surgical or autopsy diagnosis of NEC
- Diagnoses of 'suspected NEC' or x-rays showing pneumoperitoneum without pneumatosis are not classified as NEC.
- Agreement between at least two neonatologists with one involved in the patient care, or one neonatologist and one radiologist is highly encouraged.

Grading the Evidence:

Neonatal Gut Health Group utilized **GRADE (Grading of Recommendations, Assessment, Development and Evaluation) criteria for evidence-based medicine** to assess the quality of evidence for all modifiable factors for NEC.²

GRADE	Symbol	GRADE description for the evidence	Certainty of evidence*
A	⊕⊕⊕⊕	Strong; The evidence consists of results from studies of strong research design	High
B	⊕⊕⊕○	Moderate; The evidence consists of results from studies of strong research design, but there is some uncertainty because of inconsistencies among the results from the studies or because of minor doubts about clinical significance, generalizability and/or risk of bias.	Moderate
C	⊕⊕○○	Weak; Substantial uncertainty attached to the conclusion because of inconsistencies among the results from	Low

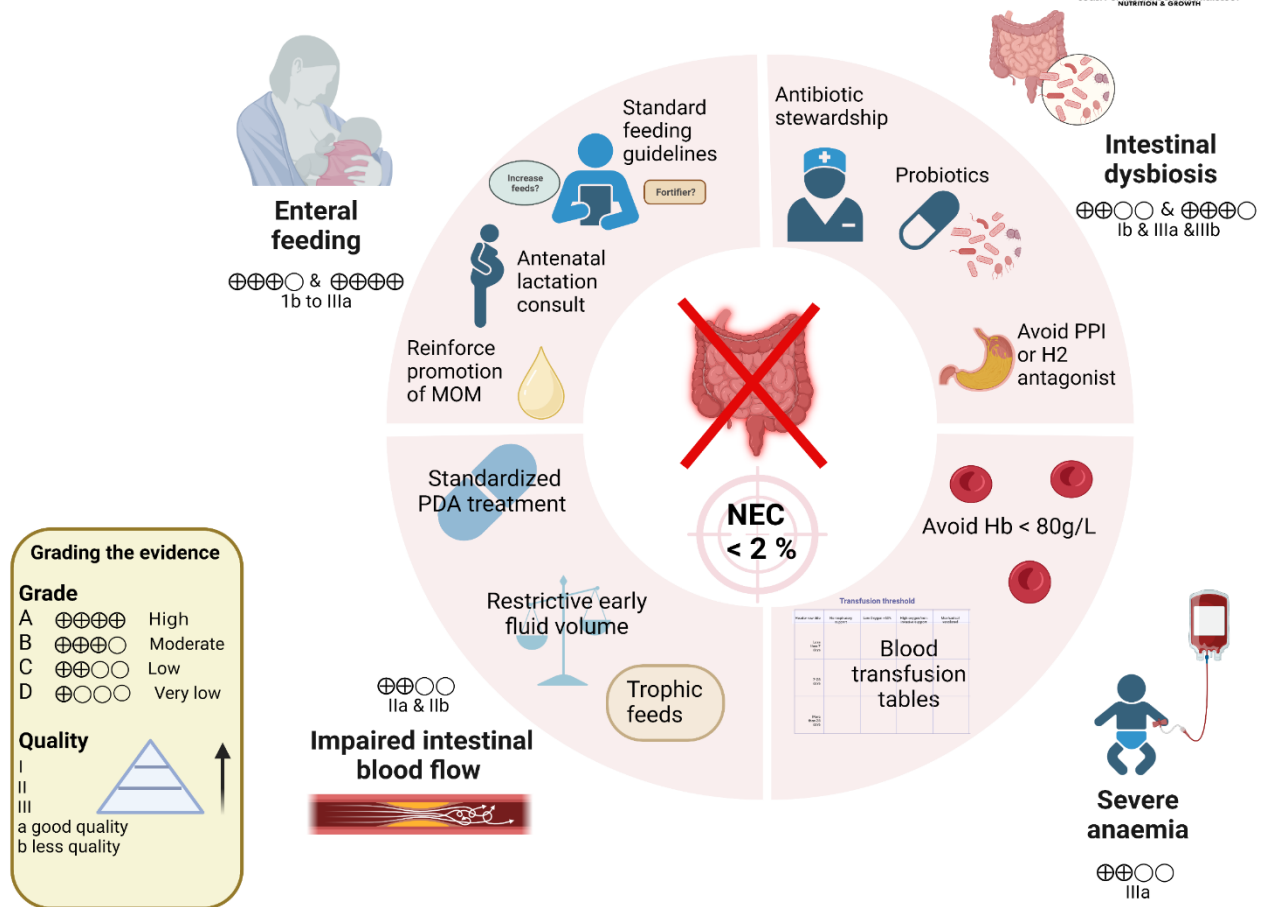
		different studies or because of serious doubts about clinical significance, generalizability and/or risk of bias.	
D	⊕○○○	A conclusion is either not possible or extremely limited: evidence is unavailable and/or of poor quality and/or is contradictory	Very low

***Quality of evidence classified as:**

- I: Systematic review with meta-analysis of homogenous randomized controlled trials (RCTs)
- II: Well-designed RCTs meta-analysis of non-homogenous RCTS
- III: Cohort or quasi experimental trials
- IV: Descriptive
- V: Expert opinion or consensus

Additional and lower-case letters are used as follows: a, good quality and b, lesser quality.

Towards a NEC free Canada



Prepared by Dr Sproat & Alshaikh on BioRender*

Summary of recommendations with level of evidence

Recommendations	Description	GRADE	Quality of evidence	Evidence source	Effect size
Strong recommendations: benefits outweigh the risk and any cost					
Antenatal steroids	For all preterm infants born \leq 34 6/7 weeks gestation	⊕⊕⊕⊕	I a	Cochrane 10 RCTs ³	RR 0.50 (0.32, 0.78)
Feeding human milk	Mother's own milk (MOM) or donor human milk (DHM) when MOM is not available	⊕⊕⊕⊕	I b	Meta-analysis of 6 RCTs ⁴	RR 0.62 (0.42, 0.93)
Oxygen exposure	Goal saturation of 91 to 95% compare to 85 to 90%	⊕⊕⊕⊕	I a	Cochrane 5 RCTs ⁵	RR 1.24 (1.05, 1.47)* with lower oxygen saturations
Probiotics	Lactobacillus/Bifidobacterium combination	- All RCTs: ⊕⊕○○ - High-quality RCTs: ⊕⊕⊕○	I b	Cochrane ⁶ - All RCTs: 54 - High-quality RCTs: 16	- All RCTs**: RR 0.54 (0.45, 0.65) - High-quality RCTs: RR 0.90 (0.68, 1.21)
Oral immune therapy	Studies focused on oropharyngeal colostrum	⊕⊕⊕○	II b	Meta-analysis of 8 RCTs ⁷	OR 0.51 (0.26, 0.99)
Implementation of established feeding regimens	Standardized feeding regimens	⊕⊕⊕○	III a	Meta-analysis of observational studies ^{8,9}	RR 0.22 (0.13, 0.36)
Weak recommendations: benefits likely outweigh the risk and cost is neutral					
Avoid severe anemia	Severe anemia is defined by hemoglobin of 80 g/L or less	⊕⊕○○	III a	Multicenter observational studies ^{10,11}	aHR 5.99 (2.00, 18.0)
Appropriate early postnatal fluid management	Careful restriction of water intake so that physiological needs are met without allowing dehydration	⊕⊕○○	II b	Cochrane 4 small RCTs ¹²	RR 0.43 (0.21, 0.87)

Avoid histamine-2 receptor antagonists and proton pump inhibitors	Histamine-2 receptor antagonists and proton pump inhibitors can alter intestinal microbiota	⊕⊕○○	III b	Meta-analysis of 3 observational studies ¹³	OR 2.81 (1.19, 6.64)
Avoid prolonged (>3 days) empiric antibiotic therapy	Avoid extending empiric antibiotic therapy beyond 3 days when blood culture is negative	⊕⊕○○	III a	Large cohort studies ¹⁴	aOR 1.30 (1.10–1.54) for NEC or death
Ibuprofen instead of indomethacin for treatment of PDA	Oral or IV ibuprofen is associated with a lower incidence of NEC (any stage) compared with oral or IV indomethacin	⊕⊕○○	II a	Cochrane 18 small RCTs ¹⁵	RR 0.68 (0.49, 0.94)
Avoid extended use of feeding tube beyond 7 days	Duration of any single NG/OG tube	⊕⊕○○	IV b	A cohort of QI project	-
Weak recommendation/no recommendation: Potential benefits but more research is needed to confirm that and justify the cost					
Avoid fortification with cow's milk protein-derived fortifiers	<ul style="list-style-type: none"> Fortification with human milk-derived HMF instead of cow's milk-derived fortifiers High volume human milk feeding without any fortification 	⊕⊕○○	II b	<ul style="list-style-type: none"> Cochrane review of 1 eligible RCT One pilot study 	RR 0.95 (0.20, 4.54) <ul style="list-style-type: none"> Feeding formula is associated with increased risk of NEC Fortification of bovine-derived HMF has not shown to increase risk of NEC
Skin-to-skin care with parents	<ul style="list-style-type: none"> Recommended for reasons other than NEC Decrease mortality and improve other outcomes 	⊕⊕○○	II b	Meta-analysis of 3 RCTs ¹⁶	RR 0.96 (0.45 to 2.04)
Arginine supplementation	More research is needed before wide implementation	⊕⊕○○	II b	Cochrane 3 small RCTs ¹⁷	- NEC II: RR 0.51 (0.25, 1.06) - NEC III: RR 0.13 (0.02 to 1.03)

Holding feed during and around time of blood transfusion	<ul style="list-style-type: none"> • Hold feeding around the time of blood transfusion • Hold fortification with cow's milk protein around blood transfusion 	⊕○○○	III b	Cochrane with only 1 small RCT ¹⁸ (no cases of TANEC) Observational studies	No evidence yet to support this practice ¹⁹ WHEAT trial is ongoing to address this strategy
Slowly advancing milk feeds	Advancing enteral feed volume at a rate <24 mL/kg per day	⊕⊕⊕○	I b	Cochrane of 14 RCTs ²⁰	RR 1.06 (0.83, 1.37) (no benefit)
Closure of patent ductus arteriosus	<ul style="list-style-type: none"> • Medical or surgical treatment vs conservative management 	⊕⊕○○	II b	Systematic review ²¹⁻²⁴	RR 1.09 (0.73, 1.61) ²¹ No strong evidence to support either practice

*Consider in NICUs with high all-cause mortality. ** Evidence to support its use in ELBW infants is still lacking. There is a need to audit any infection with any probiotic strain when using probiotics. aHR, adjusted Hazard ratio; WHEAT trial, WithHolding Enteral feeds around packed red cell Transfusion to prevent NEC; HMF, human milk fortifier; TANEC, transfusion-associated necrotizing enterocolitis.

Roles and responsibilities for major domains in NEC prevention

Antenatal steroids	Delivery	Promotion of mother's own milk ¹			
Breastfeeding discussion ¹		Breastfeeding discussion ¹	Standardized feeding plan ²	Probiotics	Oxygen exposure
<ul style="list-style-type: none"> • Midwives and labour and delivery nurses • Lactation consultants • Obstetrician team • Neonatal team 		<ul style="list-style-type: none"> • Lactation consultants • NICU medical team • Neonatal nurses • Dietitians 	<ul style="list-style-type: none"> • Direct support: Neonatal nurses & Lactation consultants, Dietitians • Discussion: all physicians including Neonatologists, neonatal fellows, NNPs, residents, and clinical assistants 	<ul style="list-style-type: none"> • NICU medical team • Pharmacist • Neonatal nurses • Dietitians 	<ul style="list-style-type: none"> • Neonatal nurses • NICU medical team • RRTs

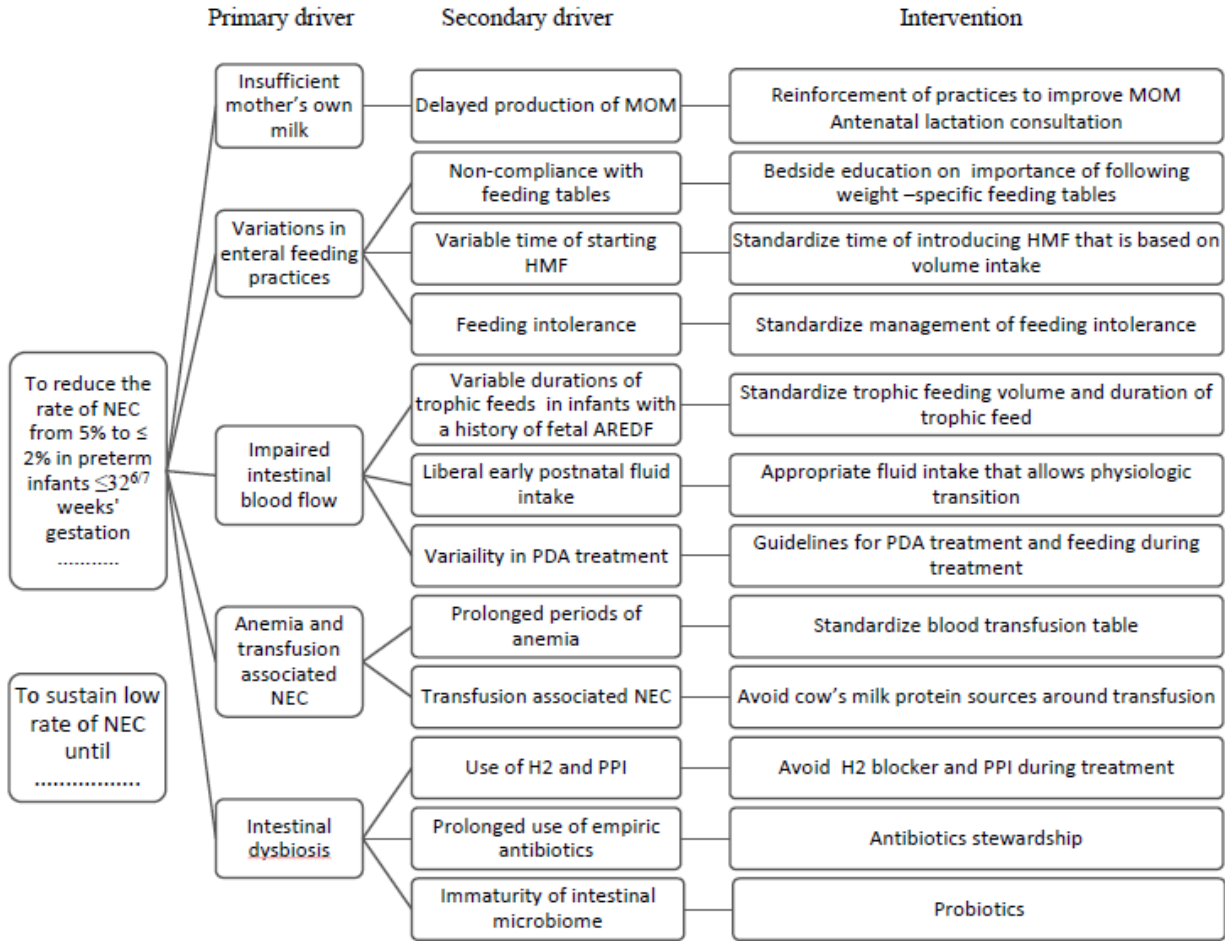


NNPs, neonatal nurse practitioners; RRTs, registered respiratory therapists.

Implementation focus and NICU-specific approach based on the rate of NEC

Main domain	Implementation Strategies	Tracking
Antenatal steroids	Should be targeted in NICUs if rates of antenatal steroids is less than (90%)	% Antenatal steroid
Promote human milk (MOM, or DHM if MOM is not available or insufficient in volume)	<ul style="list-style-type: none"> • Include breast milk discussion/education and obtain consent for use of DHM (if available at institution) in antenatal consults when preterm delivery is anticipated. • Supply colostrum collection kits to birthing units and educate staff and mothers about importance of beginning pumping within 6 hours of delivery and continuing frequently using both electric and hand pumping. • Follow established institutional policies for donor milk use. • Discuss early pumping (within the first 2 hours of delivery) during the antenatal consultation and upon admission to NICU: <ul style="list-style-type: none"> ○ Provide “early pumping” handout ○ Lactation consultant referral ○ Encourage mothers who expect to have a preterm infant and are admitted for maternal reasons to attend a breastfeeding class offered by the post-partum lactation consultants ○ Discussion with parents after delivery: <ul style="list-style-type: none"> ▪ Importance of hand expression with “hands on pumping” ▪ Pumping routine, every 3 hours during the day and at least once during the night ▪ Value of colostrum (i.e., “every drop counts”) ▪ Protective effects of breast milk for preterm infants “golden drops” 	MOM volume^{25,26}: - Day 7: ≥400 mL/d - Day 14: ≥500 mL/d Any breast milk feeding at discharge
Probiotics	<ul style="list-style-type: none"> • Combination of lactobacillus and bifidobacterium • Should be given with first feeds regardless of the milk volume 	- Age at first dose - % Infants received probiotics
Goal 90-95% O2Sat	<ul style="list-style-type: none"> • Should be considered in NICUs with high all-cause mortality and NEC rate 	Daily review of 24 h histograms
	The standardized practices related to feeding introduction and increments in your NICU is the most important factor	Compliance with feeding

Implementation of established feeding guidelines	<ul style="list-style-type: none">• Introduce enteral feeding within first 6 hours• Advance feeding rate as per your institutional guidelines• Follow established milk storage and preparation guidelines• Develop or follow established guidelines for dealing with feeding intolerance• Add fortification (i.e. HMF, other nutrients) as per institutional guidelines	introduction and increments
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MOM, mother's own milk; HMF, human milk fortifier; NEC, necrotizing enterocolitis; PDA, patent ductus arteriosus, AREDF, absent or reverse end diastolic flow; H2 antagonist, histamine 2 antagonist; PPI, proton pump inhibitor.

Driver diagram for preventing NEC in NICU

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