CẬP NHẬT SINH LÝ BỆNH & DỰ PHÒNG VIÊM RUỘT HOẠI TỬ Ở TRẺ SINH NON

ThS BS CK2 Nguyễn Kiến Mậu
KHOA SƠ SINH- BV Nhi Đồng 1

NỘI DUNG

1. Đại cương
2. Sinh lý bệnh
3. Dự phòng
4. Kết luận

1. Đại cương

- VRHT là bệnh lý đường tiêu hóa cấp tính thường gặp ở giai đoạn sơ sinh.
- Tổn thương niêm mạc→ hoại tử ruột→ thủng ruột. Phần lớn tổn thương đoạn cuối hồi tràng và đại tràng (Nặng: toàn bộ đường tiêu hóa).
- Nguyên nhân chưa rõ, nhiều yếu tố có liên quan đến sinh bệnh học .
- Tỉ lệ mắc VRHT: 1-3/1000 trẻ sinh sống, 2 – 7% trẻ < 32 tuần, 5 – 22% trẻ có cân nặng < 1000gr.
- Tỉ lệ tử vong: 10 – 40%, NEC θ nội khoa là 17%, NEC có phẫu thuật 32%.

Region	Pooled Incidence (%)	95% CI
All	6.0	[4.0, 9.0]
North America, Western Europe and Australia	4.3	[2.5, 6.6]
Asia	3.9	[1.4, 7.3]
Income		
All	6.0	[4.0, 9.0]
High income countries (HIC)	7.0	[4.0, 10.0]
Low and middle-income countries (LMIC)	3.0	[1.0, 6.0]
Population at risk		
All	6.0	[4.0, 9.0]
VLBW infants	6.0	[3.0, 9.0]
Extremely premature	7.0	[2.0, 13.0]

Alsaied et al. Global incidence of Necrotizing Enterocolitis: a systematic review and metaanalysis BMC Pediatrics (2020) 20:344

1.Caplan, M. (2022). Chapter 73: Necrotizing Enterocolitis and Short Bowel Syndrome. In Avery's Diseases of the Newborn (11th ed., pp. 1022–1029). W.B. Saunders
2.Wolf MF, Rose AT, Goel R, Canvasser J, Stoll BJ, Patel RM. Trends and Racial and Geographic Differences in Infant Mortality in the United States Due to Necrotizing Enterocolitis, 1999 to 2020. JAMA Netw Open. 2023 Mar 1;6(3):e231511
3. Battersby C, Santhalingam T, Costeloe K, et al. Incidence of neonatal necrotising enterocolitis in high-income countries: a systematic review. Archives of Disease in Childhood - Fetal and Neonatal Edition 2018

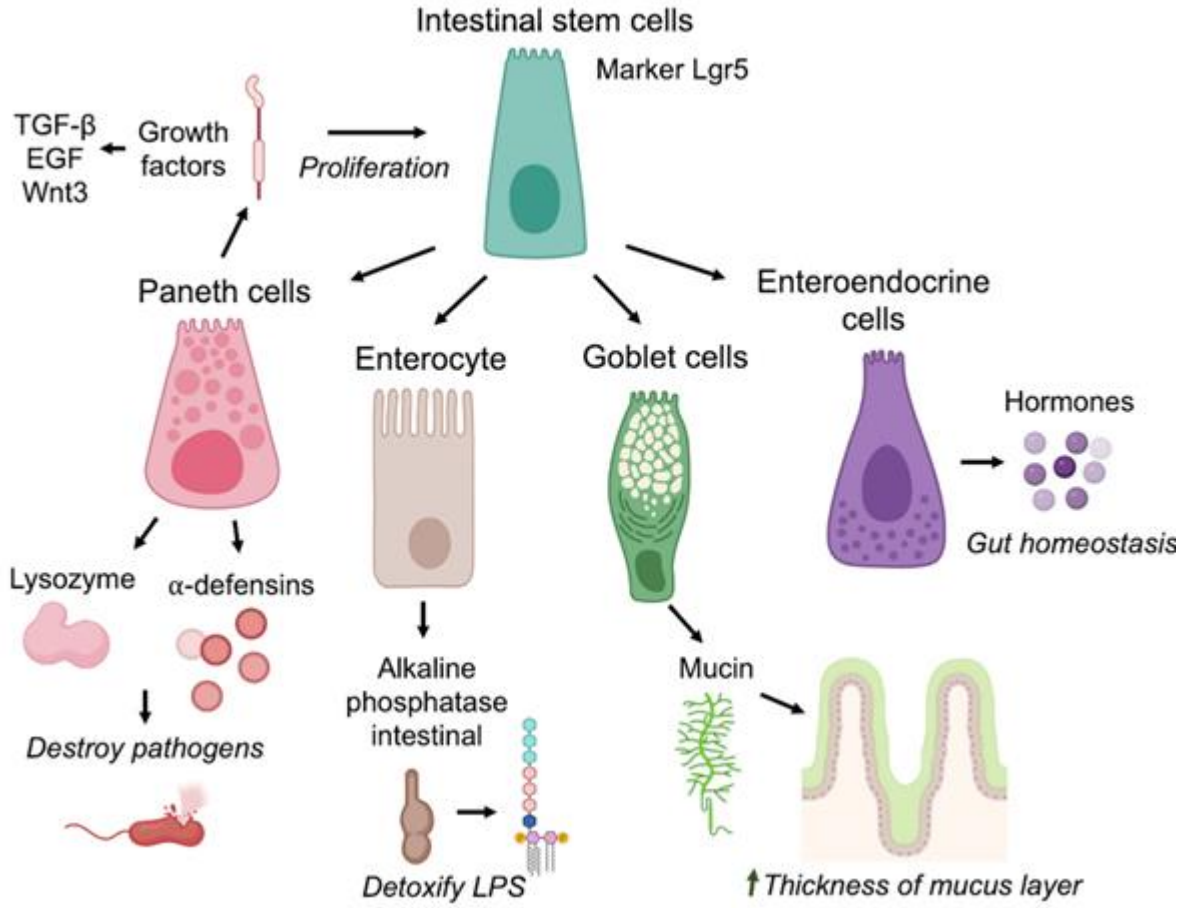
2. Sinh lý bệnh

Ruột của trẻ sinh non chưa hoàn thiện về cấu trúc và chức năng:

o Niêm mạc ruột mỏng hơn → dễ tổn thương khi có yếu tố kích thích

o Hàng rào bảo vệ kém do thiếu chất nhầy (mucin), IgA tiết và các peptide kháng khuẩn

o Giảm enzym tiêu hóa → làm tăng nguy cơ rối loạn hấp thu và tổn thương niêm mạc



Demers-Mathieu, Veronique. "The Immature Intestinal Epithelial Cells in Preterm Infants Play a Role in the Necrotizing Enterocolitis Pathogenesis: A Review." Health Sciences Review, vol. 4, Sept. 2022

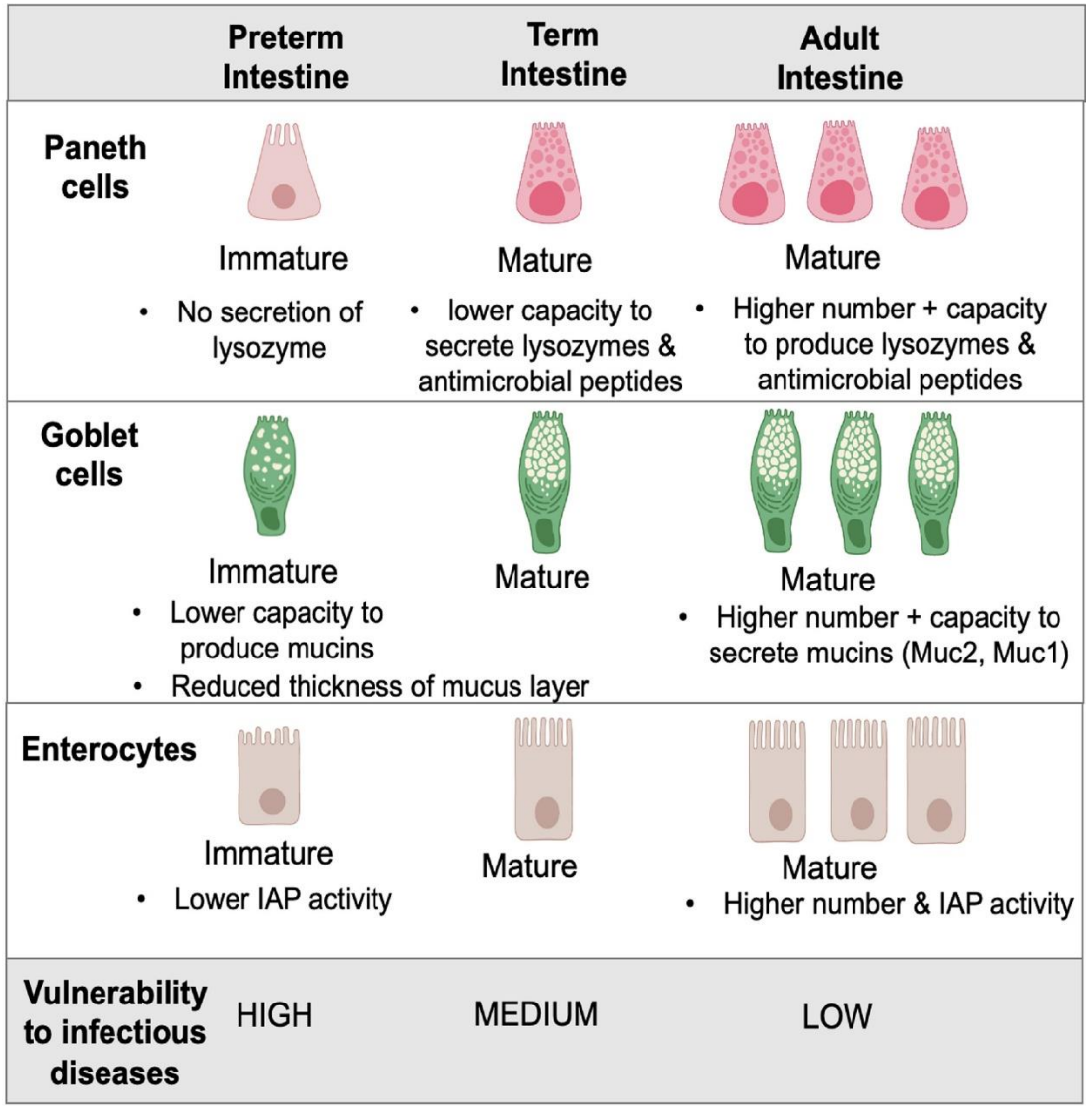
2. Sinh lý bệnh

- **Tế bào biểu mô ruột dễ bị tổn thương khi thiếu oxy**, làm tăng tính thấm thành ruột và tạo điều kiện cho vi khuẩn xâm nhập

Các chổ nối chặt (Tight Junctions): ZO-1, occludin, claudins duy trì tính toàn vẹn của hàng rào biểu mô.

Trong NEC:

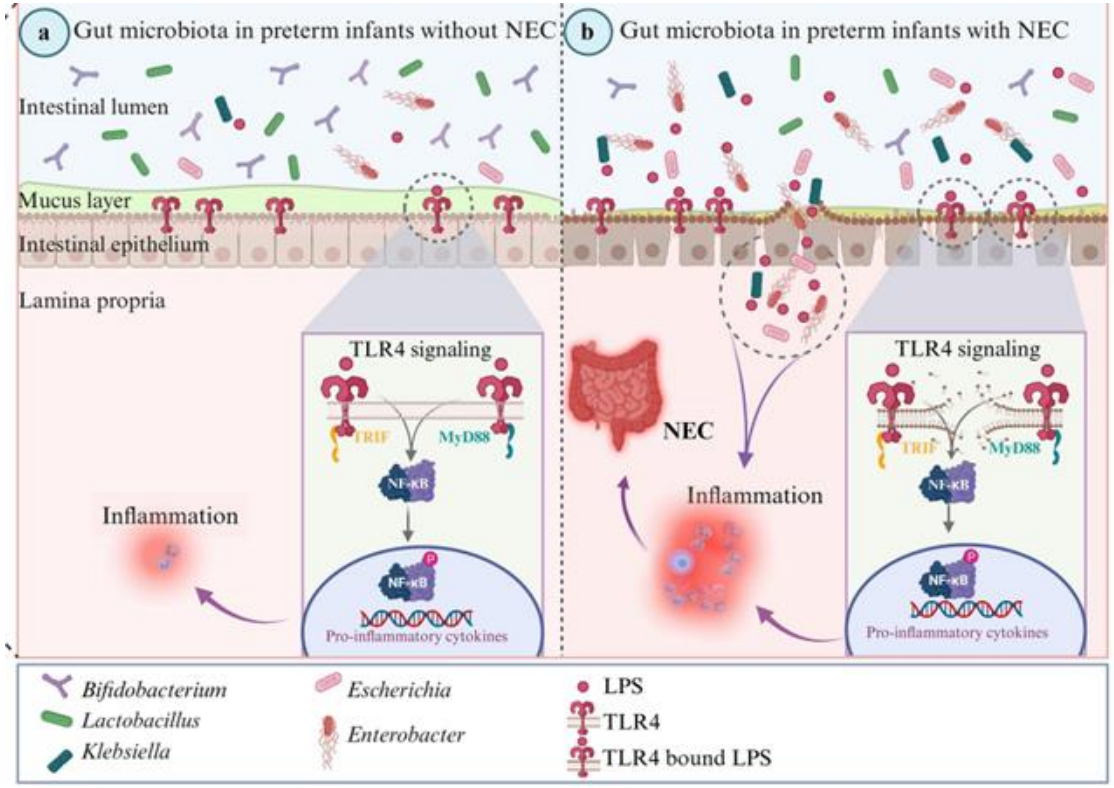
- Các chổ nối bị tổn thương làm tăng tính thấm của ruột → vi khuẩn xâm nhập và gây nhiễm trùng huyết toàn thân.
- Sự điều chỉnh giảm của claudin-3,4,7 làm suy yếu hàng rào bảo vệ.



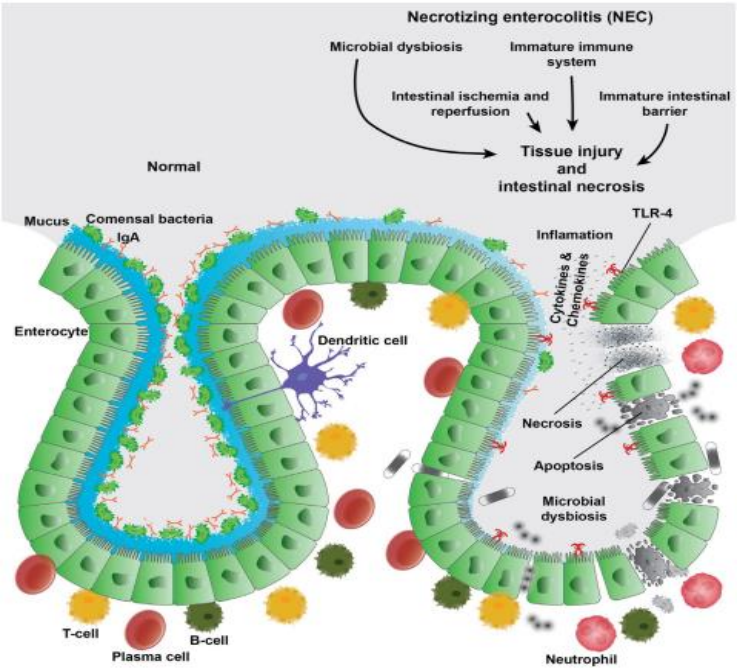
Demers-Mathieu, Veronique. "The Immature Intestinal Epithelial Cells in Preterm Infants Play a Role in the Necrotizing Enterocolitis Pathogenesis: A Review." Health Sciences Review, vol. 4, Sept. 2022

2. Sinh lý bệnh

Rối loạn hệ vi sinh vật đường ruột (Dysbiosis)



Trẻ đủ tháng	Trẻ non tháng	Trẻ bị NEC
• Increased biodiversity • ↑ *Streptococcus* spp, Enterobacteriaceae, *Staphylococcus* spp, bifidobacteria, and *Bacteroides* spp (7)(19)(20)	• Decreased biodiversity • ↓ Bifidobacteria and *Lactobacillus* • ↑ Multidrug-resistant organisms, gram-negative bacteria (*Klebsiella pneumoniae*) and *Clostridium difficile*, and fungal overgrowth (17)(19)	• Decreased biodiversity • ↓ Firmicutes and Actinobacteria • ↑ Proteobacteria, *Clostridium* spp, *Klebsiella*, and other Enterobacteriaceae (21)(22)(25)



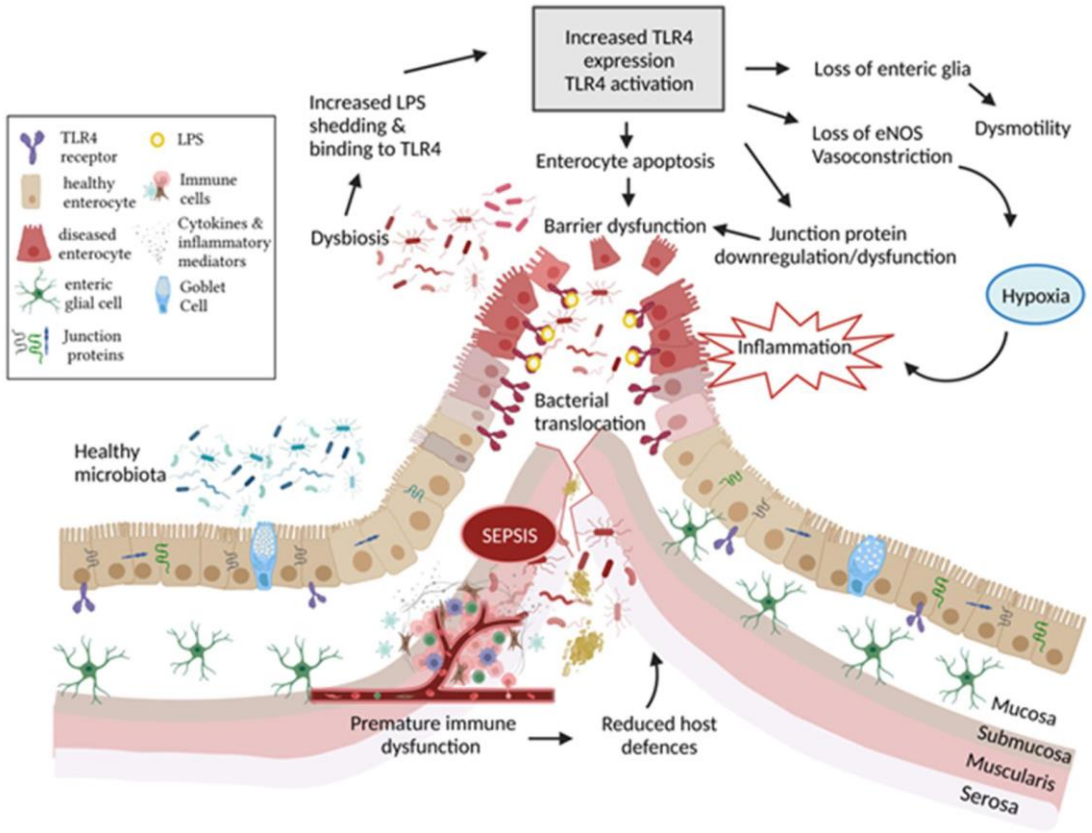
1.Stanikova A, et al. Role of the microbiome in pathophysiology of necrotizing enterocolitis in preterm neonates _BMJ Paediatrics Open 2023;7:e002172

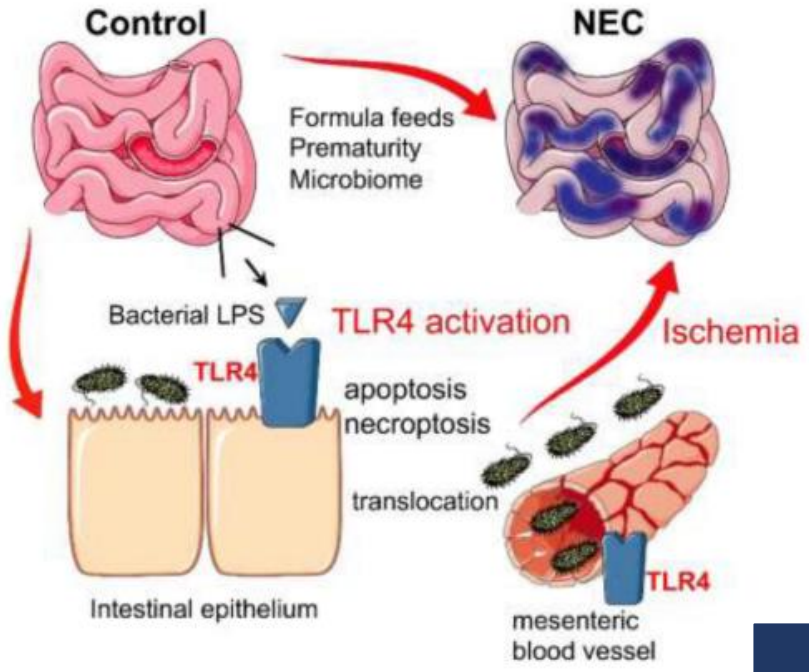
2.Laura N. Calvo, Rachel G. Greenberg, Keyaria D. Gray; Safety and Effectiveness of Probiotics in Preterm Infants with Necrotizing Enterocolitis. Neoreviews April 2024; 25 (4): e193–e206

.3. Deshuang Zhang et al (2025)-Digging deeper into necrotizing enterocolitis: bridging clinical, microbial, and molecular perspectives, Gut Microbes, 17:1, 2451071

Microbiota và sự hoạt hóa TLR-4

- **TLR-4** là receptor nhận diện nội độc tố vi khuẩn (LPS)
- VK gram âm phóng thích **lipopolysaccharide (LPS)→**
- **kích hoạt Toll-like receptor 4 (TLR-4)**, nó biểu hiện quá mức trong biểu mô ruột non của trẻ sinh non:
  - **Apoptosis tế bào ruột**
  - **Phá vỡ chổ nối chặt** → tăng tính thấm
  - **Phóng thích Cytokine** → p/ứ viêm
  - **Ức chế sự phục hồi tế bào biểu mô ruột**
  - Tắc nghẽn vi tuần hoàn ruột→nặng thêm tổn thương.





1.Duess, J. W. et al. (2023). Necrotizing enterocolitis, gut microbes, and sepsis. Gut Microbes, 15(1

2. Daniel J. Scheese et al- Semin Pediatr Surg. 2023 June ; 32(3): 151309

2. Sinh lý bệnh

Giảm tưới máu ruột

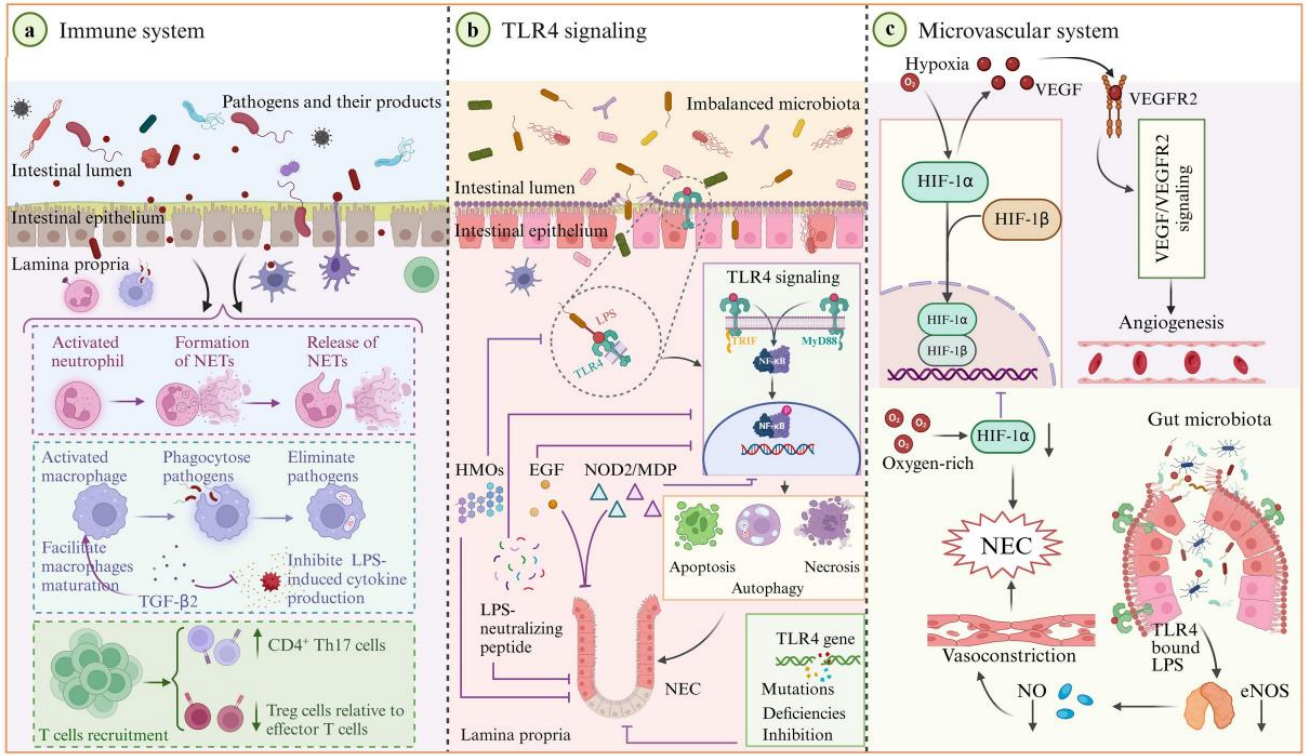
Trẻ sinh non có hệ thống tưới máu ruột chưa phát triển đầy đủ, dễ bị thiếu máu cục bộ khi có tình trạng:

- Hạ huyết áp, giảm oxy máu (suy hô hấp, nhiễm trùng huyết)
- Rối loạn tưới máu do PDA → Máu không đến đủ ruột
- Thiếu nitric oxide (NO) → gây co mạch mạc treo ruột

Hậu quả:

◇ Thiếu oxy ruột → tăng quá trình chết tế bào theo chương trình (apoptosis)

◇ Tổn thương niêm mạc → vi khuẩn và nội độc tố (LPS) xâm nhập, kích hoạt phản ứng viêm



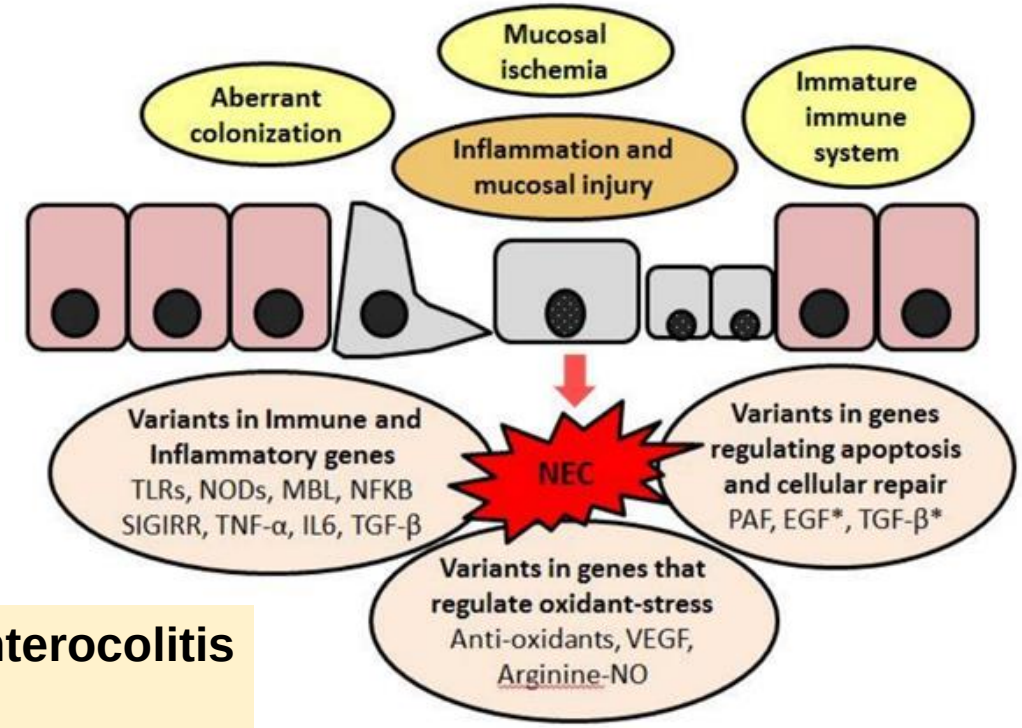
Duess, J. W., Sampah, M. E., Lopez, C. M., Tsuboi, K., Scheese, D. J., Sodhi, C. P., & Hackam, D. J. (2023). Necrotizing enterocolitis, gut microbes, and sepsis. Gut Microbes, 15(1

Deshuang Zhang et al (2025)-Digging deeper into necrotizing enterocolitis: bridging clinical, microbial, and molecular perspectives, Gut Microbes, 17:1, 2451071

2. Sinh lý bệnh

Các yếu tố di truyền có thể gây ra NEC khi có các yếu tố nguy cơ lâm sàng

- Đột biến đơn nucleotide ở các gen liên quan đến miễn dịch (như TLR4, NOD2) có liên quan đến nguy cơ mắc NEC cao hơn (Leaphart et al., 2007).



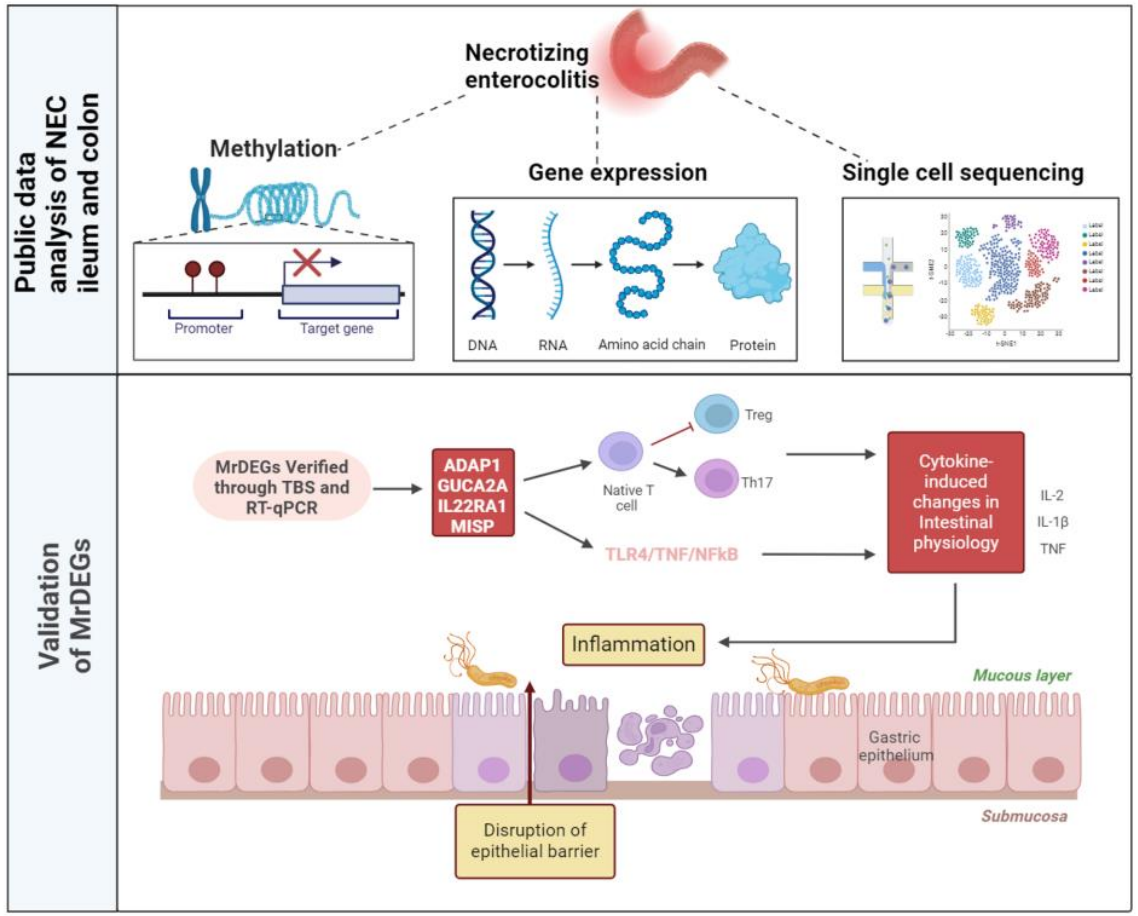
NOD2 Loss-of-Function Mutations and Risks of Necrotizing Enterocolitis or Focal Intestinal Perforation in Very Low-birth-weight Infants

Results: In the whole cohort of VLBW infants, carriers of ≥2 NOD2 variant alleles had an increased risk for NEC requiring surgery (odds ratio [OR], 3.57; 95% confidence interval [CI], 1.27–10.04; $P = 0.03$) and NEC or FIP requiring surgery (OR, 3.81; 95% CI, 1.70–8.51; $P = 0.004$) as compared with wild-type genotypes. In a multivariable logistic regression analysis including gestational age, birth weight, gender, multiple birth, and inborn delivery, the association between ≥2 NOD2 variant alleles and NEC surgery (OR, 4.14; 95% CI, 1.41–12.12; $P = 0.009$), FIP surgery (OR, 3.50; 95% CI, 1.02–12.04; $P = 0.047$), and NEC or FIP surgery (OR, 4.10; 95% CI, 1.74–9.73; $P = 0.001$) proved to be independent. We also performed a regression analysis in the subgroup of infants with available information on *Lactobacillus acidophilus/Bifidobacterium infantis* probiotic supplementation (n = 3638). Although probiotics had a protective effect on NEC and NEC or FIP requiring surgery, the NOD2 variants had no significant impact in this subgroup.

Conclusions: VLBW infants carrying ≥2 NOD2 genetic risk factors of inflammatory bowel disease in adults have an increased risk for severe gastrointestinal complications, such as NEC requiring surgery. Therefore, infants might benefit from NOD2 genotyping followed by supplementation with probiotics. Replication studies are needed along with genome-wide arrays to allow risk-adapted prevention and therapeutic strategies.

Christoph Härtel et al- Inflamm Bowel Dis . 2016 Feb;22(2):249-56

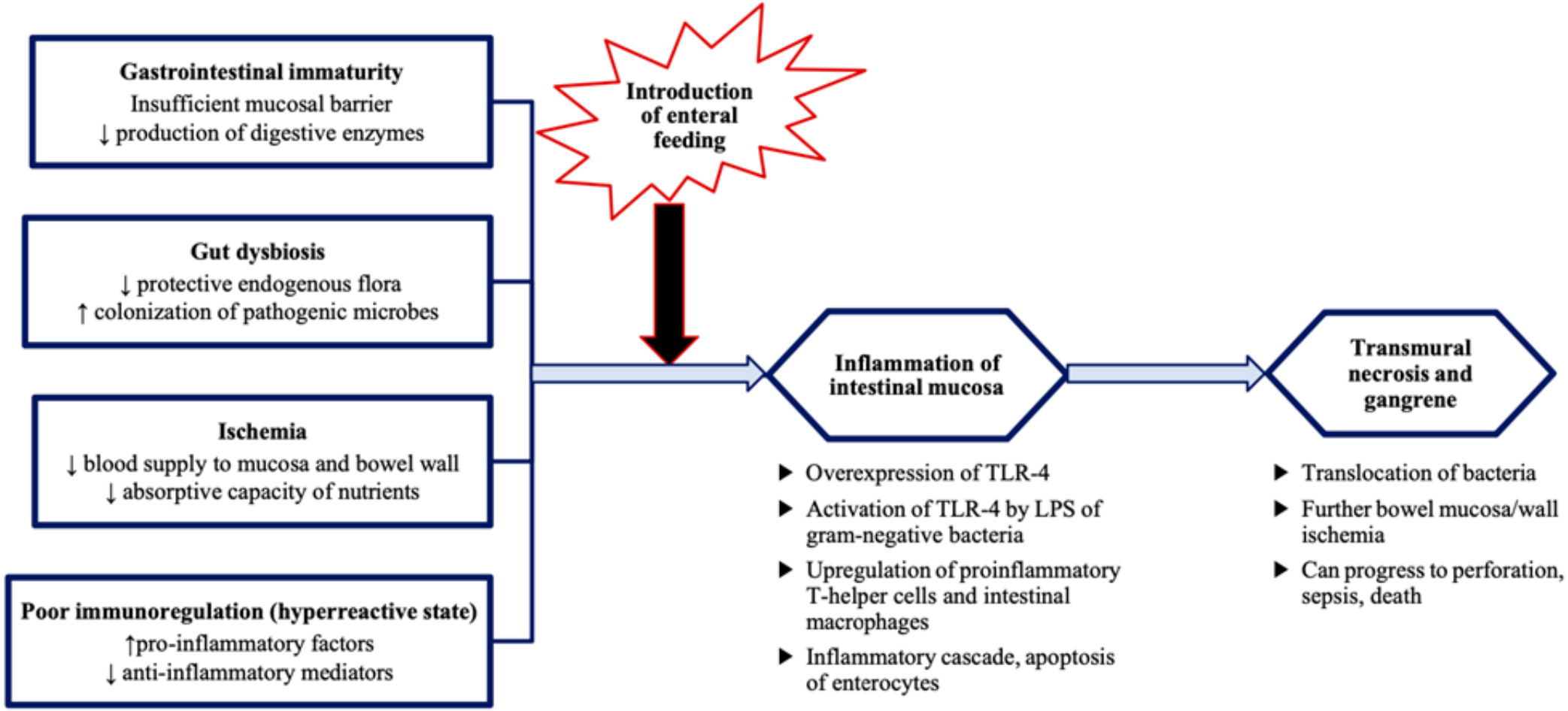
2. Sinh lý bệnh



Tóm tắt —Nghiên cứu xác định các dấu ấn sinh học mới được điều hòa bởi methyl hóa trong mô ruột của bệnh nhân NEC thông qua phân tích đa hệ gen (multiomics). Phân tích bộ dữ liệu methyl hóa DNA và bộ phiên mã RNA từ các mẫu mô hồi tràng và đại tràng của bệnh nhân NEC. **Các gen biệt hóa liên quan đến methyl hóa (MrDEGs)** bao gồm ADAP1, GUCA2A, BCL2L14, FUT3, MISP, USH1C, ITGA3, UNC93A và IL22RA1 chủ yếu nằm trong phần biểu mô ruột của mô ruột. Các MrDEGs này đã được xác minh bằng phương pháp giải trình tự bisulfite gen đích và RT-qPCR. Xác định **các gen ADAP1, GUCA2A, IL22RA1 và MISP, chủ yếu được biểu hiện trong các tế bào nhung mao biểu mô ruột thông qua dữ liệu đơn bào.** Thông qua phân tích làm giàu bộ gen theo từng gen đơn lẻ cho thấy **các gen này chủ yếu tham gia vào quá trình bệnh lý liên quan đến biệt hóa tế bào T và ức chế viêm ruột ở bệnh NEC**.

Bowen Tian et al-Inflammation. 2025 Feb;48(1):236-253.

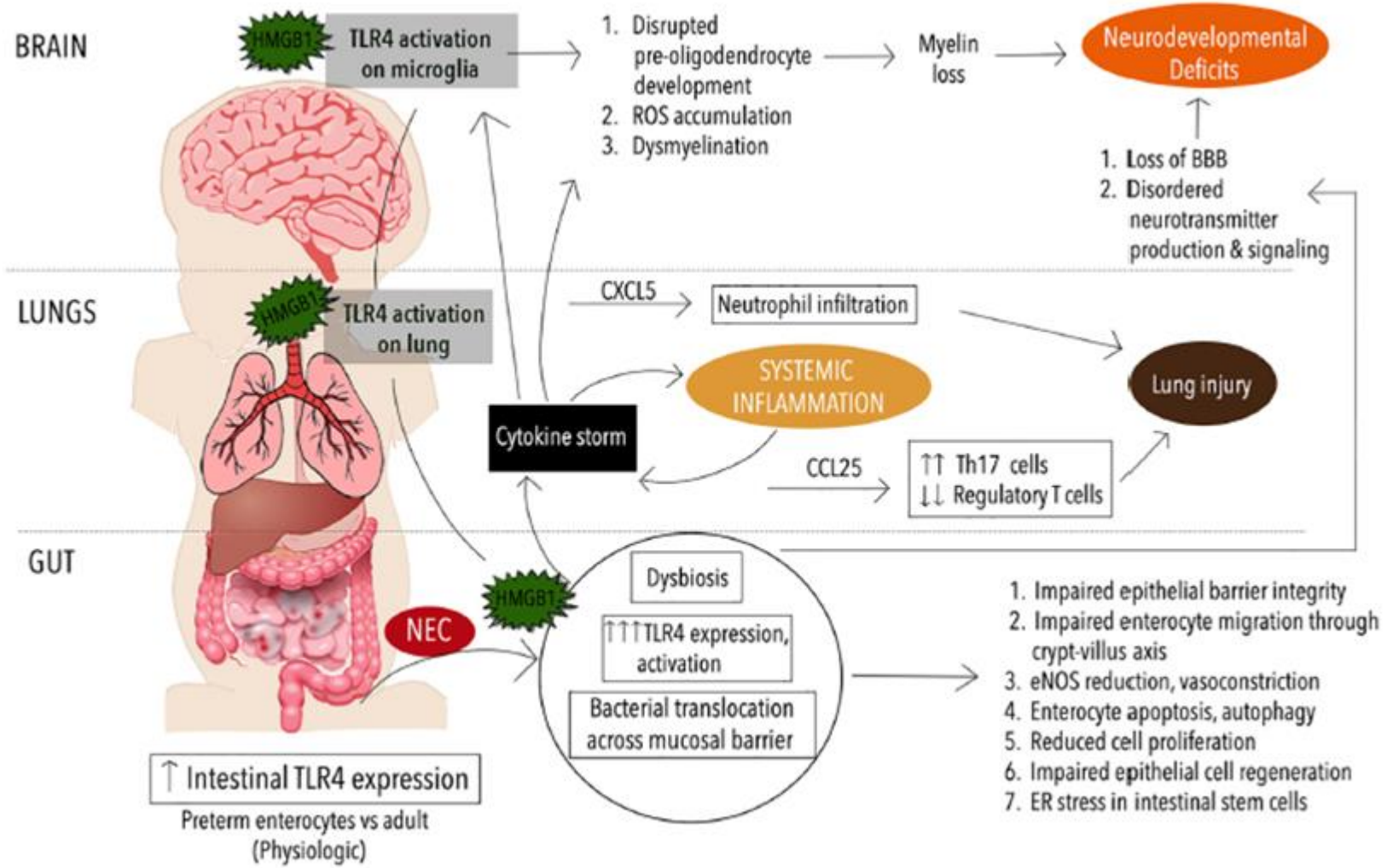
2. Sinh lý bệnh



Laura N. Calvo, Rachel G. Greenberg, Keyaria D. Gray; Safety and Effectiveness of Probiotics in Preterm Infants with Necrotizing Enterocolitis. Neoreviews April 2024; 25 (4): e193–e206

2. Sinh lý bệnh

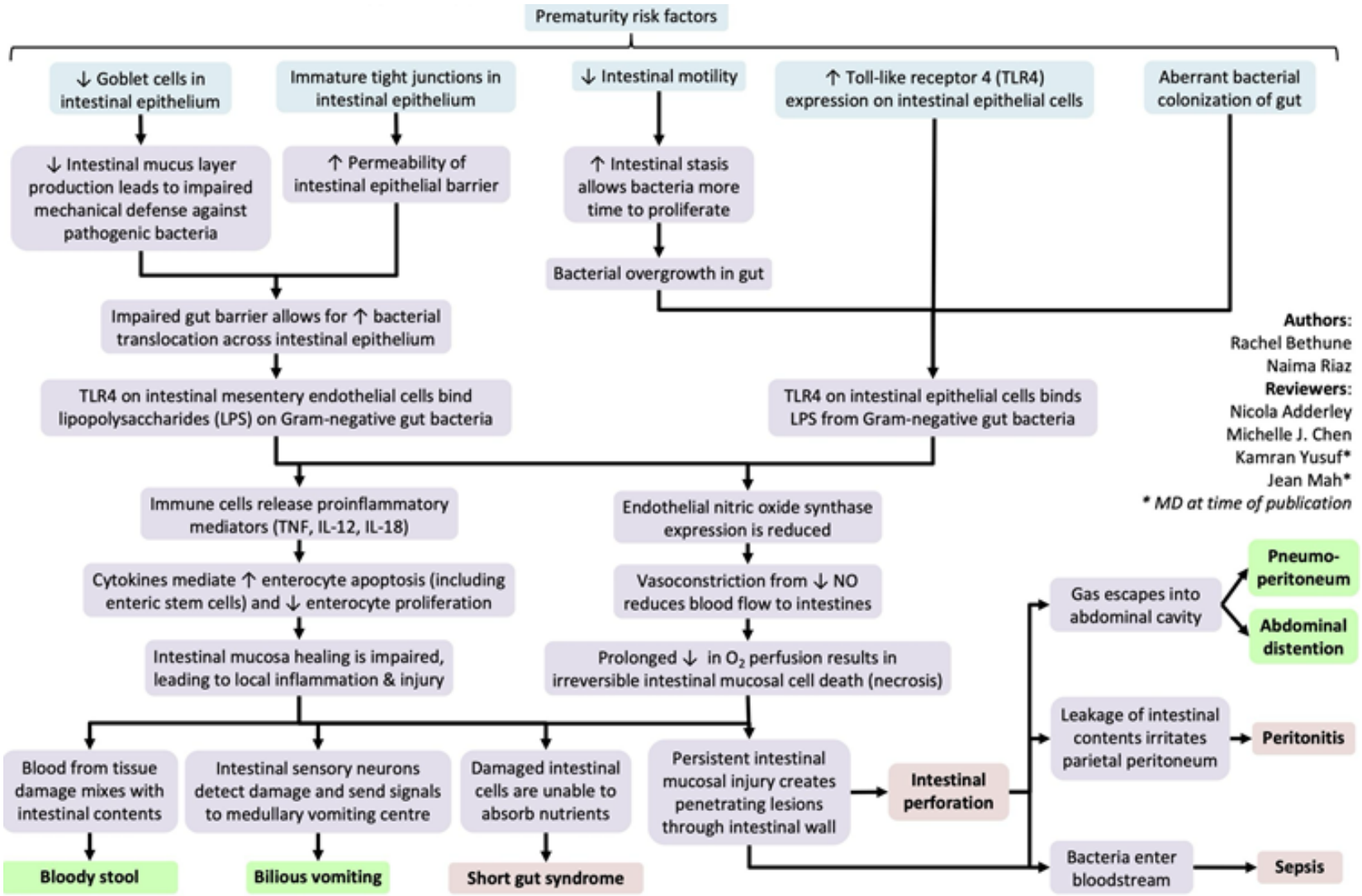
BIỂU HIỆN MIỄN DỊCH TOÀN THÂN /NEC



Sampah and Hackam- Frontiers in Immunology | www.frontiersin.org 2 April 2021 | Volume 12 | Article 650709

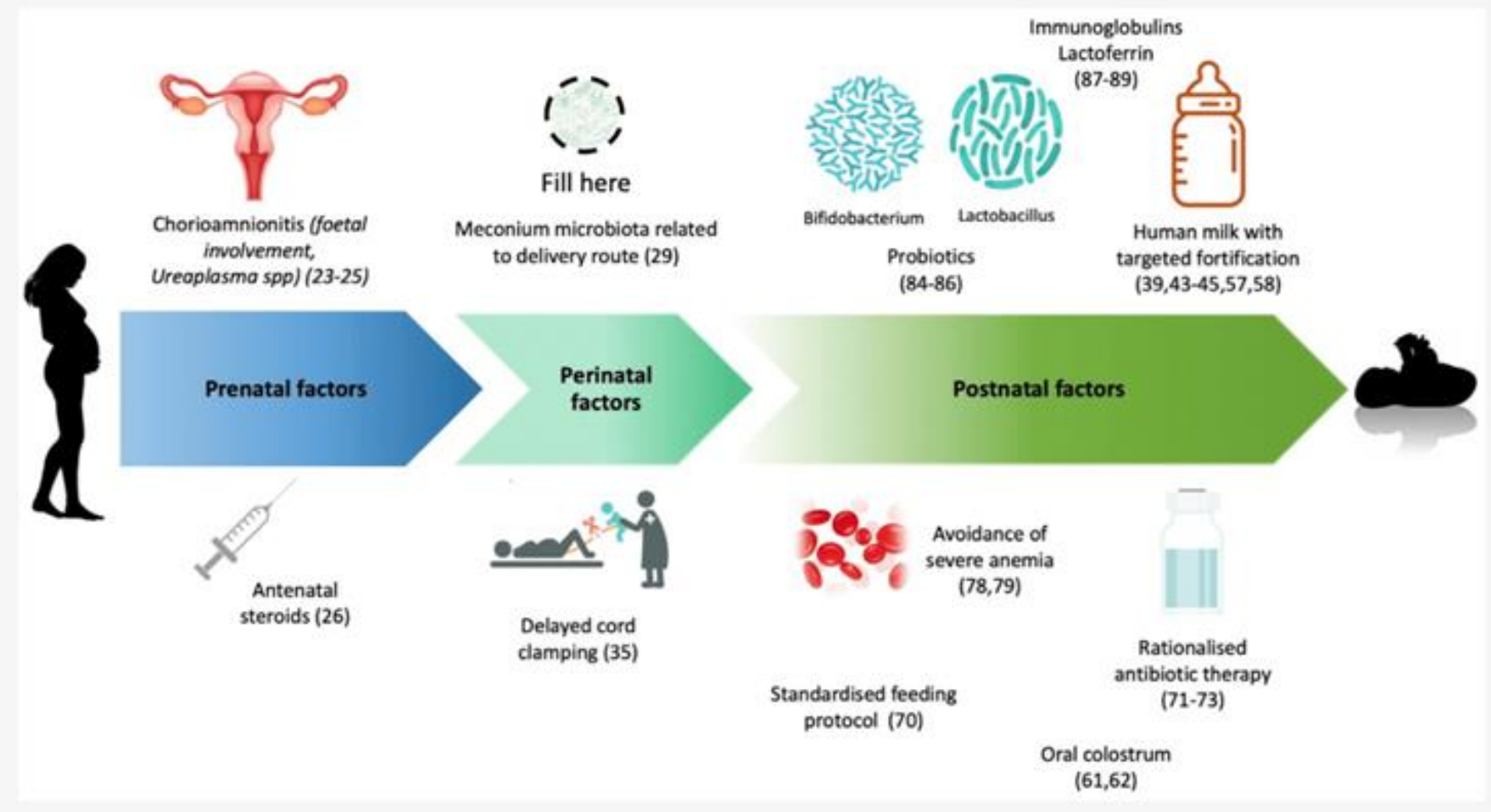
2. Sinh lý bệnh

SLB và biểu hiện lâm sàng NEC



Neonatal Necrotising Enterocolitis in Premature Neonates. (2024, March 21). The Calgary Guide to Understanding Disease. https://calgaryguide.ucalgary.ca/neonatal-necrotising-enterocolitis-in-premature-neonates/

3. Dự phòng



Moschino L, Duci M, Fascetti Leon F, Bonadies L, Priante E, Baraldi E, Verlato G. Optimizing Nutritional Strategies to Prevent Necrotizing Enterocolitis and Growth Failure after Bowel Resection. Nutrients. 2021; 13(2):340

3. Dự phòng trước sinh

Giảm nguy cơ sinh non:

- Sử dụng corticosteroid trước sinh giúp:
  + Tăng trưởng thành phổi và ruột.
  + Giảm tỷ lệ NEC ở trẻ sinh non
- Quản lý bệnh lý thai kỳ
  + Điều trị tăng huyết áp thai kỳ, tiểu đường thai kỳ, nhiễm trùng ối để giảm nguy cơ sinh non.
- Hạn chế kháng sinh không cần thiết
- Bổ sung dinh dưỡng cho mẹ

Moschino L, Duci M, Fascetti Leon F, Bonadies L, Priante E, Baraldi E, Verlato G. Optimizing Nutritional Strategies to Prevent Necrotizing Enterocolitis and Growth Failure after Bowel Resection. Nutrients. 2021; 13(2):340

3. Dự phòng sau sinh

Sữa mẹ

RECOMMENDATION 1

Mother's own milk (MOM) is strongly recommended for feeding the low birth weight infant. *Specific nutrient supplementation needs to be made in preterm very low birth weight infants.*

Strong recommendation, not graded

Mother's own milk has been associated with reduced risk of infection RR 0.44 –0.56 (0.24, 0.82)

Mother's own milk feeding is associated with increased cognitive development scores adjusted mean difference about 5, including in SGA term infants.

Mother's own milk feeding is reported with slower growth in length and weight compared to formula fed neonates but this difference has not been found significant at 18 months follow up.

Health Outcomes

Mother's own milk contains macronutrients and micronutrients as well as active biological components, including immunoglobulins, cytokines, growth factors, hormones, antimicrobial agents, immune cells, stem cells, and prebiotic oligosaccharides.[8] A substantial portion of the breast milk microbiome comprises probiotic bacteria.[9] Mother's own milk has been associated with multiple health benefits for VLBW infants, including lower incidences of necrotizing enterocolitis (NEC), late-onset sepsis, chronic lung disease, retinopathy of prematurity, and neurodevelopmental impairment (Tables 2 and 3).

1. *NNF India Evidence-based Clinical Practice Guidelines January 2020*
2. *Pediatrics (2021) 148 (5): e2021054272.*

3. Dự phòng sau sinh

Formula versus donor breast milk for feeding preterm or low birth weight infants

Cochrane Library 2019

Maria Quigley[1], Nicholas D Embleton[2], William McGuire[3]

Meta-analysis showed that donor human milk reduces the risk of NEC (risk ratio (RR) 0.53, 95% confidence interval (CI) 0.37 to 0.76; I^2 = 4%; risk difference (RD) −0.03, 95% CI −0.05 to −0.01; 11 trials, 2261 infants; high certainty evidence). Donor human milk probably has little or no effect on late-onset invasive infection (RR 1.12, 0.95 to 1.31; I^2 = 27%; RD 0.03, 95% CI −0.01 to −0.07; 7 trials, 1611 infants; moderate certainty evidence) or all-cause mortality (RR 1.00, 95% CI 0.76 to 1.31; I^2 = 0%; RD −0.00, 95% CI −0.02 to 0.02; 9 trials, 2116 infants; moderate certainty evidence).

Authors' conclusions

The evidence shows that donor human milk reduces the risk of NEC by about half in very preterm or VLBW infants. There is probably little or no effect on late-onset invasive infection or all-cause mortality before hospital discharge.

Sữa mẹ hiến tặng &
Sữa công thức

RECOMMENDATION

(a). If mother's own milk is not available, pasteurized donor human milk from human milk bank, should be used for feeding low birth weight infants.

Applicable to settings with facilities for providing donor milk; associated with lower weight gain, linear growth and head growth and hence need monitoring and possibly fortification.

(b). If donor human milk is not available, formula milk is to be considered.

Formula milk is costly and may also be associated with higher risk of necrotizing enterocolitis and sepsis. Utmost care should be taken for maintenance of asepsis and proper dilution.

Strong Conditional recommendation, based on Moderate quality evidence

1. *NNF India Evidence-based Clinical Practice Guidelines January 2020*
2. *Lingyu Fang et al. Food & Nutrition Research 2021, 65: 5346*

3. Dự phòng

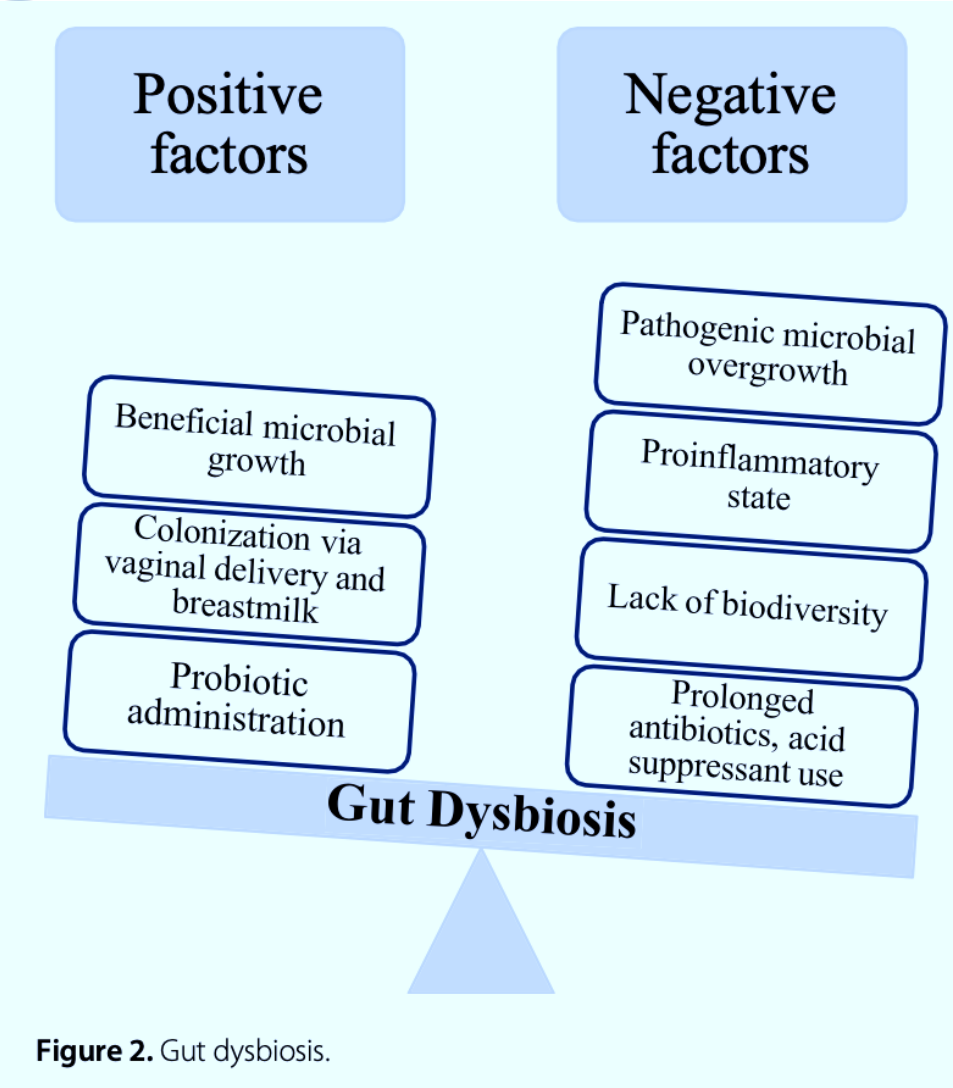
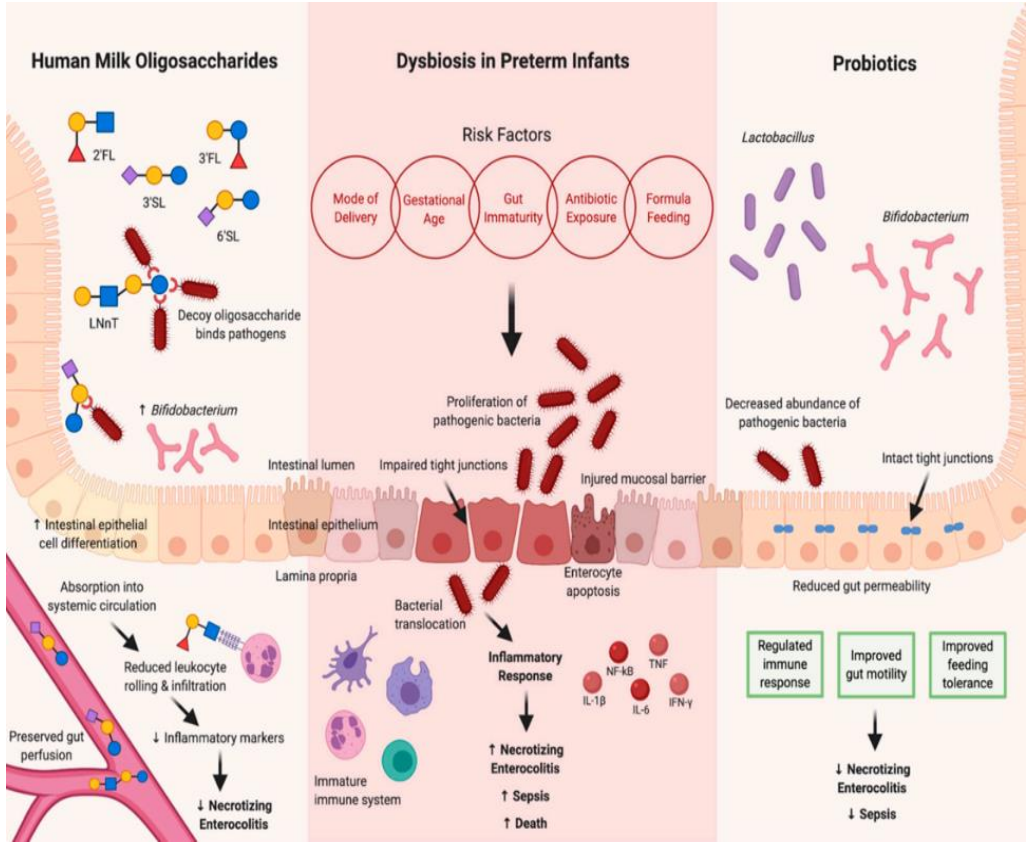


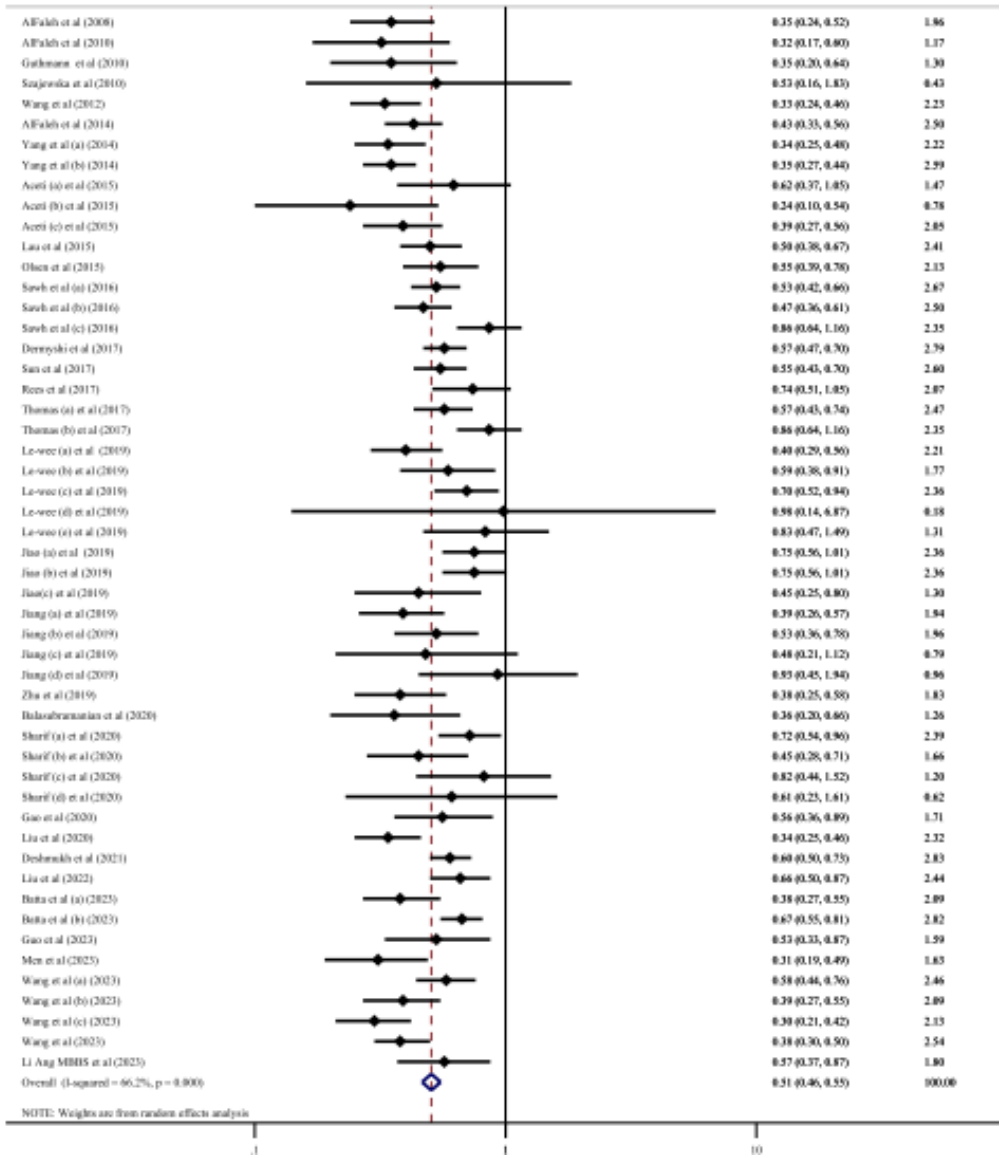
Figure 2. Gut dysbiosis.



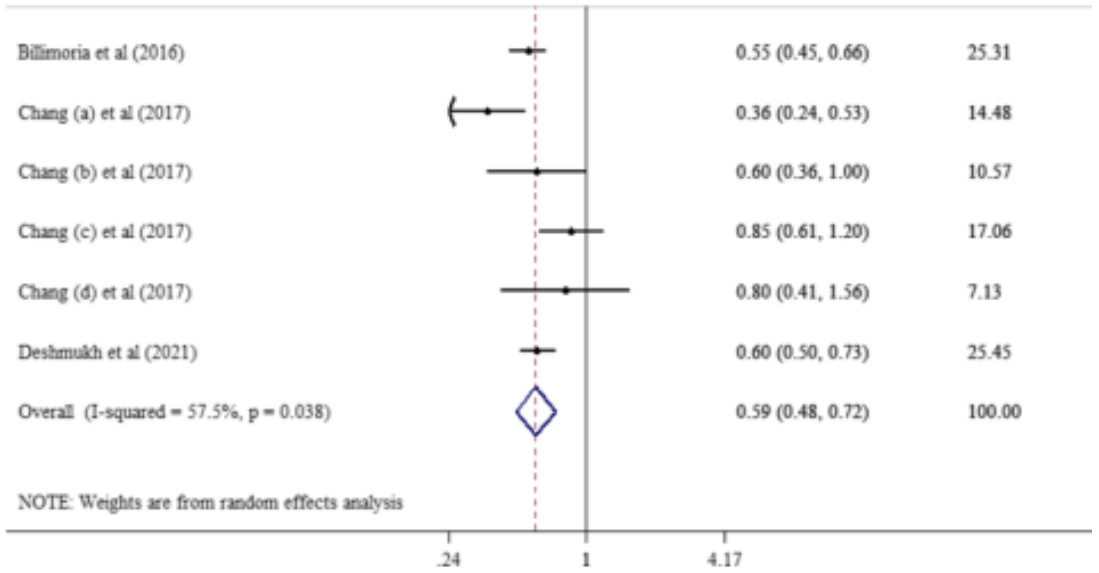
Tác động của loạn khuẩn lên hàng rào ruột ở trẻ sinh non & **tác dụng bảo vệ của oligosaccharides sữa mẹ và Probiotic** đường ruột

Laura N. Calvo, Rachel G. Greenberg, Keyaria D. Gray; Safety and Effectiveness of Probiotics in Preterm Infants with Necrotizing Enterocolitis. Neoreviews April 2024; 25 (4): e193–e206
LLila S. Nolan_Nutrients 2020, 12, 3052

3. Dự phòng sau sinh

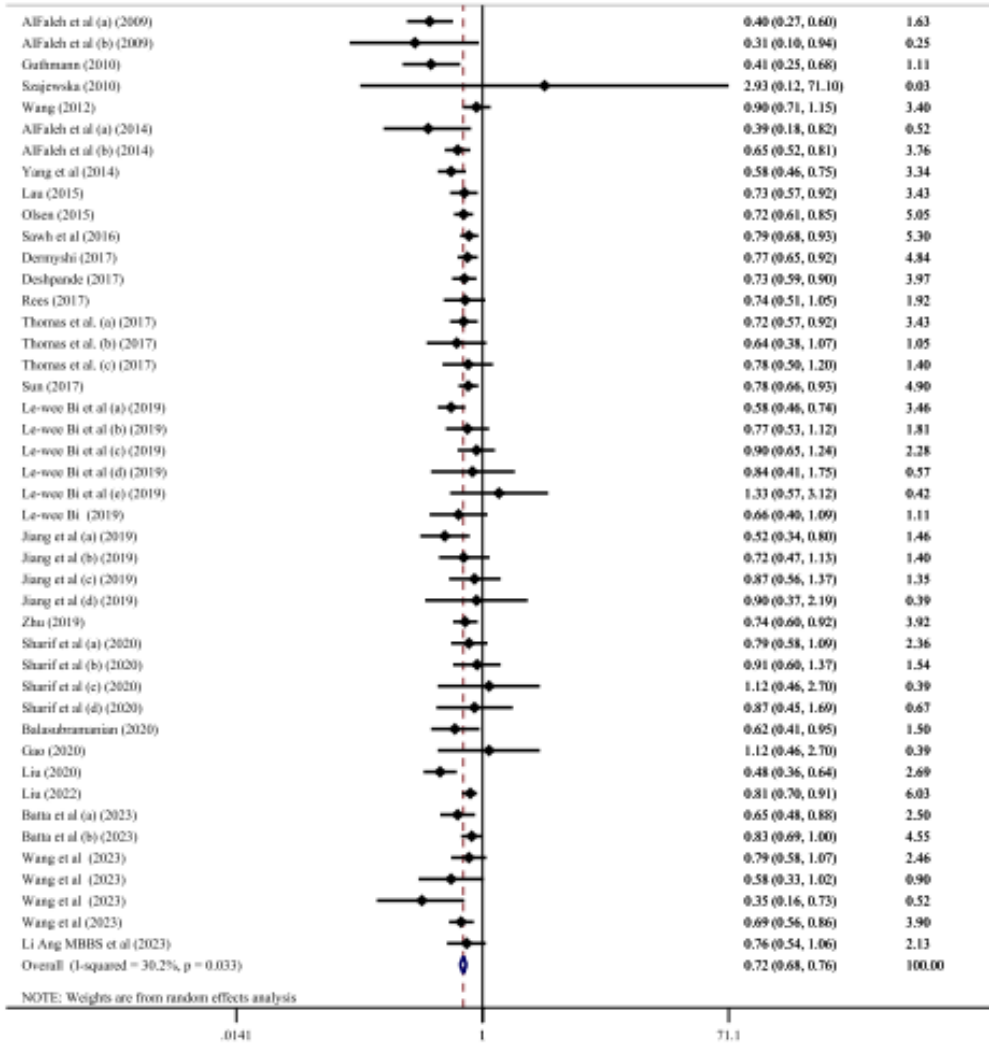


Probiotics trong dự phòng NEC

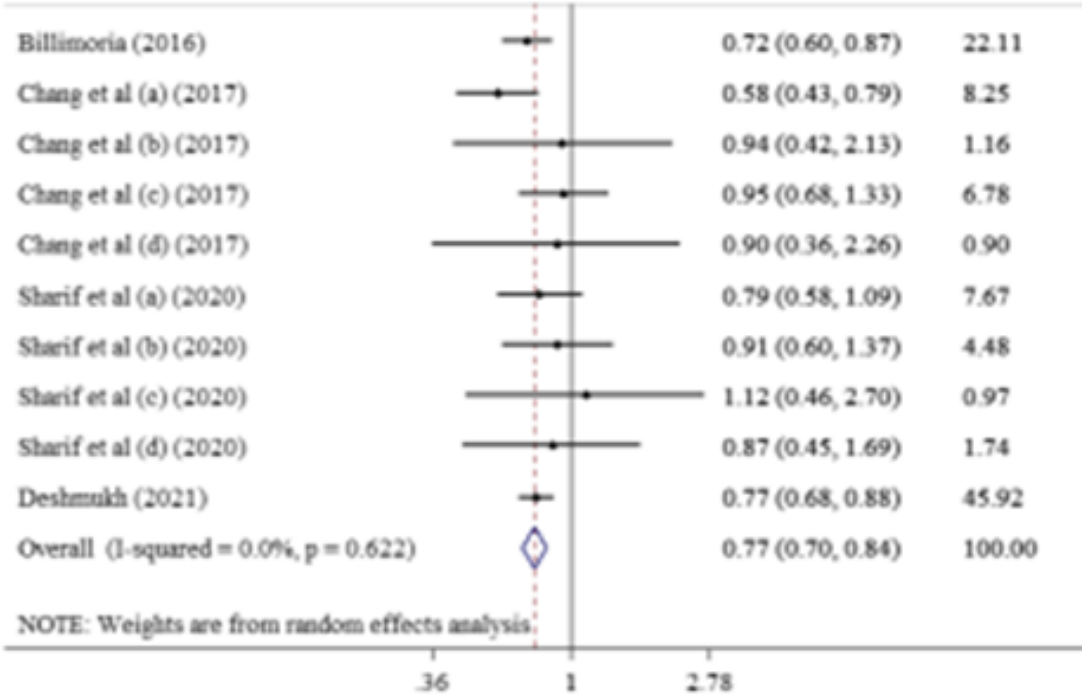


Han et al. The efectiveness of treatment with probiotics in preventing necrotizing enterocolitis and related mortality: results from an umbrella meta-analysis on metaanalyses of randomized controlled trialsBMC Gastroenterology (2025) 25:245

3. Dự phòng sau sinh



Dự phòng Probiotics trên tử vong do NEC



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3. Dự phòng sau sinh

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Informed decisions.
Better health.

2023

Cochrane Database of Systematic Reviews

[Intervention Review]

Probiotics to prevent necrotising enterocolitis in very preterm or very low birth weight infants

Summary of findings 1. Probiotics compared to control in very preterm or very low birth weight infants

Probiotics compared to placebo or no probiotics in very preterm or very low birth weight infants

Patient or population: very preterm or very low birth weight infants
Setting: neonatal care centres worldwide
Intervention: probiotics
Comparison: placebo or no probiotics

Outcomes	Anticipated absolute effects* (95% CI)		Risk ratio (95% CI)	№ of participants (trials)	Certainty of the evidence (GRADE)
	Risk with control	Risk with probiotics			
Necrotising enterocolitis (before hospital discharge)	60 per 1000	33 per 1000 (28 to 39)	**0.54** (0.46 to 0.65)	10,918 (57)	⊕⊕⊙⊙ **Low**[a,b]
All-cause mortality (before hospital discharge)	63 per 1000	48 per 1000 (42 to 57)	**0.77** (0.66 to 0.90)	10,484 (54)	⊕⊕⊕⊙ **Moderate**[a]
Late-onset invasive infection (before hospital discharge)	173 per 1000	154 per 1000 (142 to 168)	**0.89** (0.82 to 0.97)	9876 (49)	⊕⊕⊕⊙ **Moderate**[a]
Neurodevelopmental impairment (18 months to 3 years)	194 per 1000	200 per 1000 (163 to 245)	**1.03** (0.84 to 1.26)	1518 (5)	⊕⊕⊙⊙ **Low**[a,c]

***The risk in the intervention group** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval.

Summary of findings 2. Probiotics compared to control in extremely preterm or extremely low birth weight infants

Probiotics compared to placebo or no probiotics in extremely preterm or extremely low birth weight infants

Patient or population: extremely preterm or extremely low birth weight infants
Setting: neonatal care centres globally
Intervention: probiotics
Comparison: placebo or no probiotics

Outcomes	Anticipated absolute effects* (95% CI)		Risk ratio (95% CI)	№ of participants (trials)	Certainty of the evidence (GRADE)
	Risk with control (extremely preterm or ELBW)	Risk with Probiotics			
Necrotising enterocolitis (before hospital discharge)	94 per 1000	87 per 1000 (65 to 114)	**0.92** (0.69 to 1.22)	1836 (10)	⊕⊕⊙⊙ **Low**[a]
All-cause mortality (before hospital discharge)	132 per 1000	121 per 1000 (95 to 156)	**0.92** (0.72 to 1.18)	1723 (7)	⊕⊕⊙⊙ **Low**[a]
Late-onset invasive infection (before hospital discharge)	274 per 1000	255 per 1000 (214 to 299)	**0.93** (0.78 to 1.09)	1533 (7)	⊕⊕⊙⊙ **Low**[a]
Neurodevelopmental impairment (18 months to 3 years)	No trials provided subgroup data for analysis.				

***The risk in the intervention group** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval.

3. Dự phòng sau sinh

For reducing the risk of NEC in preterm infants, provided all safety issues are met, HCPs may recommend:

- *L rhamnosus* GG ATCC53103 (at a dose ranging from 1×10^9 CFU to 6×10^9 CFU) (certainty of evidence: low; grade of recommendation: weak) or
- Combination of *B infantis* BB-02, *B lactis* BB-12, and *Str thermophilus* TH-4 at 3.0 to 3.5×10^8 CFU (of each strain) (certainty of evidence: low; grade of recommendation: weak).

or born at less than 27 weeks' gestation. The American Academy of Pediatrics has stated that current evidence does not support the routine use of probiotics in preterm infants.

Probiotics could be considered in the NICU for prevention of NEC as part of a comprehensive approach for prevention in an at-risk population that should include standardized feeding guidelines, exclusive human milk–based diet, and the judicious use of antibiotics and acid suppressant medication. However, which probiotic product to choose is still unknown, and larger, multicentered RCTs that focus on specific strains will provide this insight.

Probiotics for the Management of Pediatric Gastrointestinal Disorders: Position Paper of the ESPGHAN Special Interest Group on Gut Microbiota and Modifications

Due to insufficient evidence, no recommendation can be made *for* or *against*

- *L reuteri* DSM 17938 (certainty of evidence: very low) or
- Combination of *B bifidum* NCDO 1453 *and L acidophilus* NCDO 1748 (certainty of evidence: very low to moderate)

Due to the lack of efficacy, HCPs may *not* recommend:

- *B breve* BBG-001 (certainty of evidence: low to moderate; grade of recommendation: weak)
- *S boulardii* (certainty of evidence: very low to moderate; grade of recommendation: weak).

WARNING REGARDING USE OF PROBIOTICS IN PRETERM INFANTS

Subject: **Risk of Invasive Disease in Preterm Infants Given Probiotics Formulated to Contain Live Bacteria or Yeast**

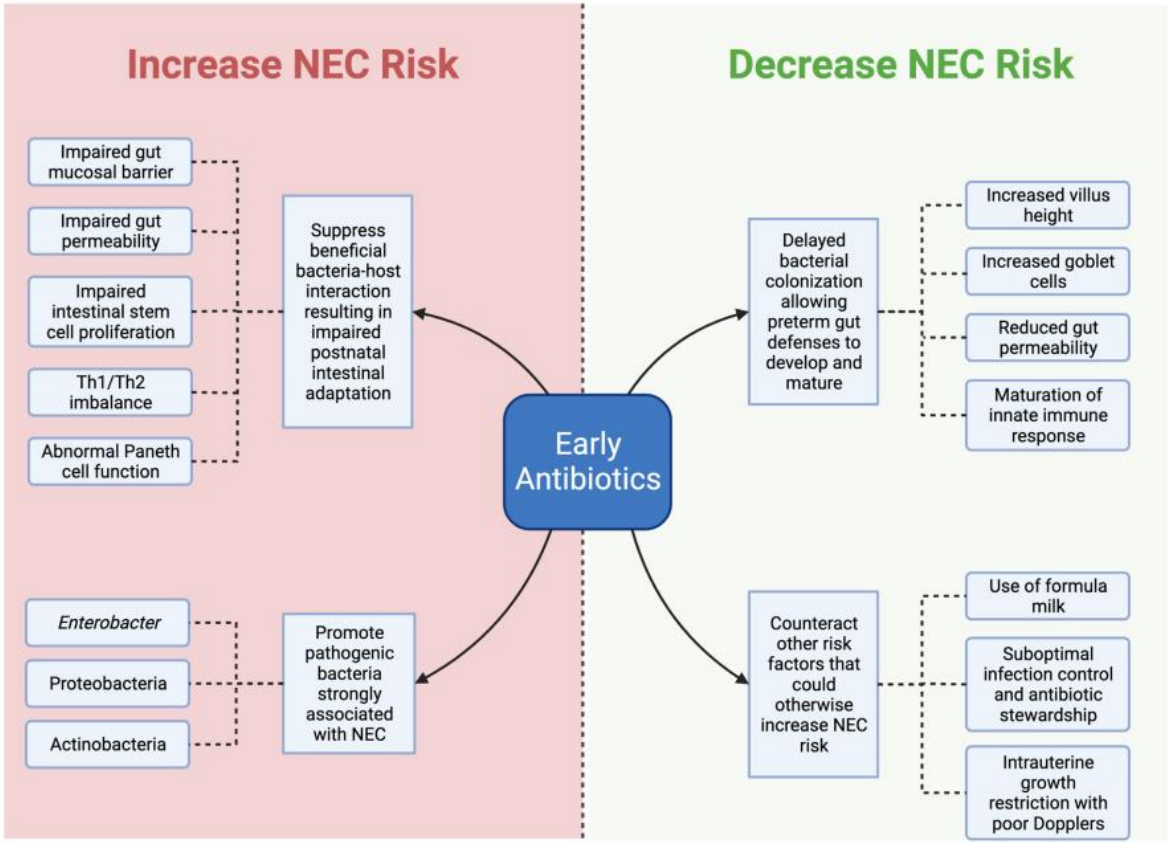
September 29, 2023

1. JPGN • Volume 76, Number 2, February 2023 2. *FDA, September* 2023

3. Dự phòng sau sinh

Tránh nhiễm trùng và viêm nhiễm

- Giảm thiểu kháng sinh không cần thiết trong NICU
- Kiểm soát tốt nhiễm trùng bệnh viện, tránh lây nhiễm vi khuẩn kháng thuốc
- Ức chế Toll-Like Receptor 4 (TLR4): TLR4 là con đường quan trọng trong NEC. Một số nghiên cứu thử nghiệm ức chế TLR4 bằng kháng thể đặc hiệu



Cuna A, Morowitz MJ and Sampath V (2023) Early antibiotics and risk for necrotizing enterocolitis in premature infants: A narrative review. Front. Pediatr. 11:1112812.

3. Dự phòng sau sinh

Tránh dùng kháng sinh kéo dài

Several observational studies suggest prolonged early, empiric antibiotic use is associated with an increased NEC risk [56–63]. In a retrospective cohort study of 4,039 ELBW infants, Cotton et al. examined associations between length of first antibiotic course and NEC [56]. The authors concluded that prolonged empiric antibiotics (≥5 days) were associated with an increased risk of NEC or death compared to treatment < 5 days (OR 1.30, 95% CI 1.10–1.54). Similarly, a multi-center retrospective case–control study compared 224 NEC cases with 447 matched controls and found early, empiric antibiotic treatment for ≥ 5 days was associated with increased odds of NEC (aOR 2.02, 95% CI 1.55–3.13) [60]. Another large multi-center retrospective cohort study of over 14,000 VLBW infants demonstrated that early antibiotics for > 3 days increased the risk of negative outcomes, composite outcome of mortality, or any major morbidity, including NEC) (aOR 1.24, 95% CI 1.09–1.41 and aOR 1.38, 95% CI 1.25–1.51, respectively) [64].

Colarelli AM, Barbian ME, Denning PW. Prevention Strategies and Management of Necrotizing Enterocolitis. *Curr Treat Options Pediatr*. 2024;10(3):126-146

Pediatr Res. 2025 Feb 15. doi: 10.1038/s41390-025-03928-y. Online ahead of print.

Effect of early antibiotic exposure on necrotizing enterocolitis and growth in extremely preterm infants

Katie M Strobel [1], Thomas R Wood [2], Gregory C Valentine [2], Olivia C Brandon [2],

Results: A total of 891 infants survived the first week and were included in the NEC analyses, while 828 infants survived to discharge and were included in the growth analyses. For every 1-day increase in infant antibiotic exposure during the first week after birth, there was a significantly increased adjusted hazard of NEC (aHR/day 1.14 [1.01-1.28], p = 0.034). Antibiotics for 3-4 days and 5-7 days total in the first week were associated with increased odds of weight GF (aOR 1.90 [1.21-2.99], aOR 2.32 [1.44-3.74]), length GF (aOR 1.76 [1.22-2.59], aOR 1.88 [1.26-2.80]), and HC GF (aOR 1.75 [1.08-2.84], aOR 1.87 [1.14-3.08]).

Conclusion: **Increased antibiotic exposure in the first week after birth was associated with NEC and GF risk.**

3. Dự phòng sau sinh

Published in final edited form as:
Early Hum Dev. 2016 August ; 99: 27–30. doi:10.1016/j.earlhumdev.2016.05.010.

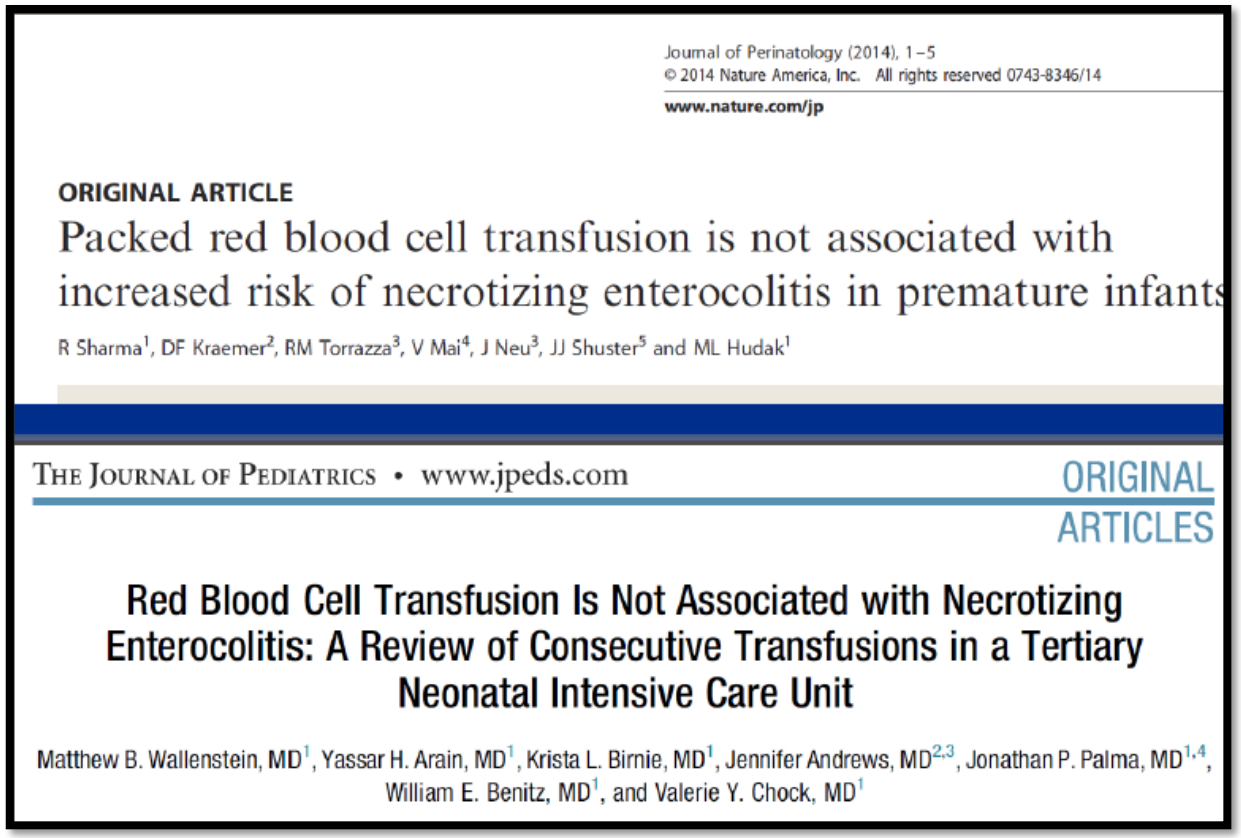
Tránh dùng Thuốc ức chế H2

Safety of Histamine-2 Receptor Blockers in Hospitalized VLBW Infants

Outcome	H_2-blocker N=20,288 (%)	No H_2-blocker N=107,419 (%)	P-value
Death or NEC *	3,176 (16)	14,279 (13)	<0.001
Death or sepsis	5,033 (25)	18,787 (17)	<0.001
Death, NEC, or sepsis	6,429 (32)	21,714 (20)	<0.001

3. Dự phòng sau sinh

Truyền máu & NEC



Journal of Perinatology (2014), 1–5
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www.nature.com/jp

ORIGINAL ARTICLE

Packed red blood cell transfusion is not associated with increased risk of necrotizing enterocolitis in premature infants

R Sharma[1], DF Kraemer[2], RM Torrazza[3], V Mai[4], J Neu[3], JJ Shuster[5] and ML Hudak[1]

THE JOURNAL OF PEDIATRICS • www.jpeds.com ORIGINAL ARTICLES

Red Blood Cell Transfusion Is Not Associated with Necrotizing Enterocolitis: A Review of Consecutive Transfusions in a Tertiary Neonatal Intensive Care Unit

Matthew B. Wallenstein, MD[1], Yassar H. Arain, MD[1], Krista L. Birnie, MD[1], Jennifer Andrews, MD[2,3], Jonathan P. Palma, MD[1,4], William E. Benitz, MD[1], and Valerie Y. Chock, MD[1]

Timing of Red Blood Cell Transfusions and Occurrence of Necrotizing Enterocolitis A Secondary Analysis of a Randomized Clinical

RESULTS: 1690 were included in the present analysis (mean [SD] gestational age, 26.0 [1.5] weeks; 899 infants [53.2%] were female). After categorizing 4947 hazard periods and 5813 control periods, we identified 133 NEC cases. Fifty-nine of these cases (44.4%) occurred during hazard periods. Baseline and clinical characteristics of infants with NEC during hazard periods did not differ from those of infants with NEC during control periods. The risk of NEC was 11.9 per 1000 posttransfusion hazard periods and 12.7 per 1000 control periods (adjusted risk ratio, 0.95; 95% CI, 0.68-1.32; P = .74). This risk did not differ significantly between randomization groups, but the incidence rate of NEC per 1000 days peaked between postnatal days 20 and 29 in the lower hemoglobin transfusion threshold group.

CONCLUSIONS: The findings of this post hoc analysis suggest that, among ELBW infants with the hemoglobin ranges occurring in the TOP trial, **exposure to RBC transfusions was not temporally associated with a higher risk of NEC during 72-hour posttransfusion hazard periods**

Ariel A. Salas et al - Trial_JAMA Network Open. 2024;7(5):e249643.

Nghiên cứu mới trong dự phòng NEC

1. Liệu pháp exosome từ sữa mẹ

• Exosome trong sữa mẹ có tác dụng bảo vệ ruột.

• Đang nghiên cứu để sử dụng như một liệu pháp bổ sung

2. Tế bào gốc

• Tế bào gốc từ sữa mẹ hoặc tế bào gốc trung mô có thể giúp phục hồi niêm mạc ruột

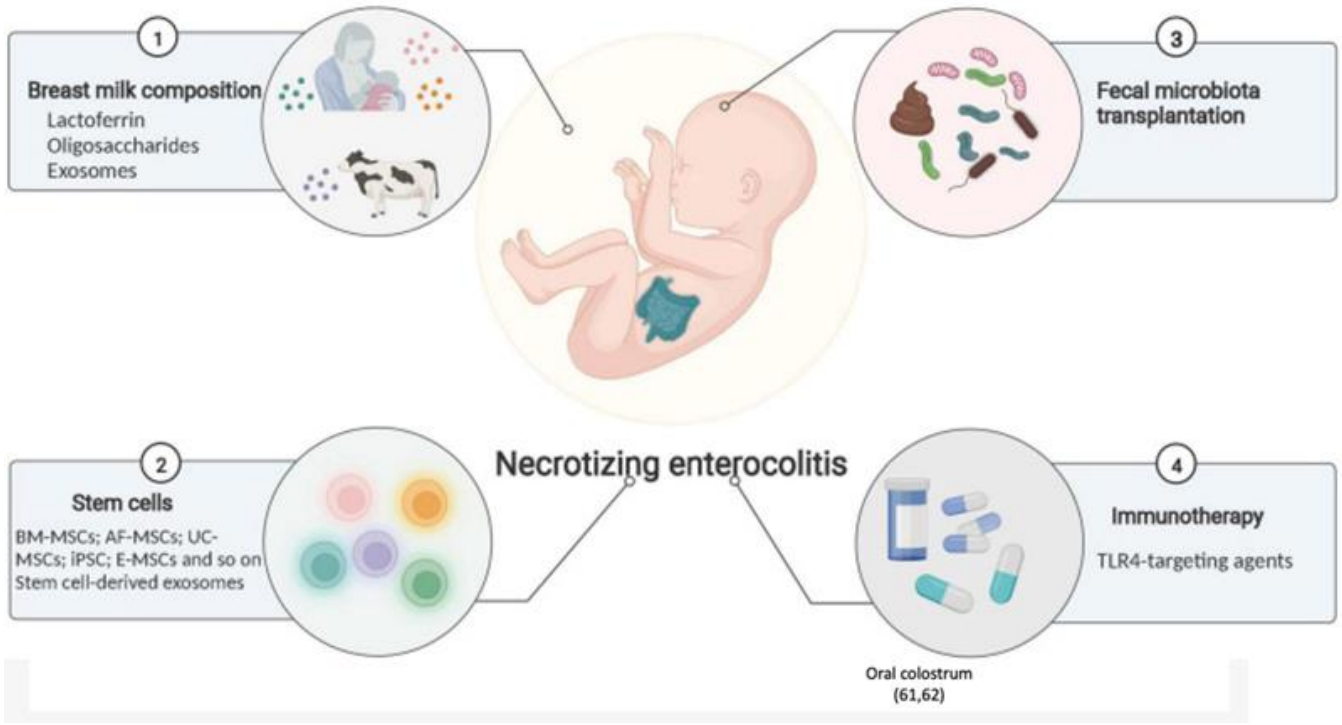
• Đang thử nghiệm lâm sàng

3. Cấy ghép vi khuẩn đường ruột trong phân

4. Liệu pháp chống viêm

• Interleukin 10 (IL-10): Giảm viêm, bảo vệ ruột

• Ức chế COX-2: Giảm viêm ruột, đang được nghiên cứu trên động vật



Wu H, Guo K, Zhuo Z, Zeng R, Luo Y, Yang Q, Li J, Jiang R, Huang Z, Sha W, Chen H. Current therapy option for necrotizing enterocolitis: Practicalities and challenge. Front Pediatr. 2022

1 số thành phần sữa mẹ

Component		Mechanisms of Action	Experimental Evidence	Limitations
Lactoferrin	**Major protein in colostrum (5–6.7g/L)**	Anti-inflammatory (↓ IL-6, TNF-α); Enhances epithelial growth and Reduces apoptosis;	Effective in some preclinical models	Meta-analysis of 9 RCTs in neonates: **no significant reduction** in NEC, mortality, or sepsis
HMOs (Human Milk Oligosaccharides)	Types: • **DSLNT** (disialyllacto-N-tetraose) • **Sialylated HMOs**	Act as prebiotics and protect the gut via: • Inhibiting **TLR4/NLRP3 pathway**. • Enhancing **crypt cell turnover**	DSLNT & sialylated HMOs effective in rodents; inconsistent piglet data	Inconsistent results in large animals; not yet standardized

Milk-derived Exosomes	Nano-vesicles containing proteins, mRNA, miRNA	• Promote intestinal development, reduce oxidative stress via **Wnt/β-catenin pathway**.
		• Increase:
		  • Goblet cell function
		  • Stem cell proliferation
		  • Epithelial barrier regeneration
			Animal studies (human, rat, bovine, porcine milk) show protective effects	Not yet tested in clinical trials; remains experimental

Wu H, Guo K, Zhuo Z, Zeng R, Luo Y, Yang Q, Li J, Jiang R, Huang Z, Sha W, Chen H. Current therapy option for necrotizing enterocolitis: Practicalities and challenge. Front Pediatr. 2022

Tế bào gốc

- Tế bào gốc từ sữa mẹ hoặc tế bào gốc trung mô
- Đang thử nghiệm lâm sàng

- **Chống viêm**: Giảm IL-6, TNF-α; tăng IL-10.
- **Thúc đẩy quá trình chữa lành niêm mạc** thông qua Wnt/β-catenin và các con đường tái tạo khác.
- **Khôi phục cân bằng nội môi** đường ruột và cải thiện chức năng hàng rào ruột.

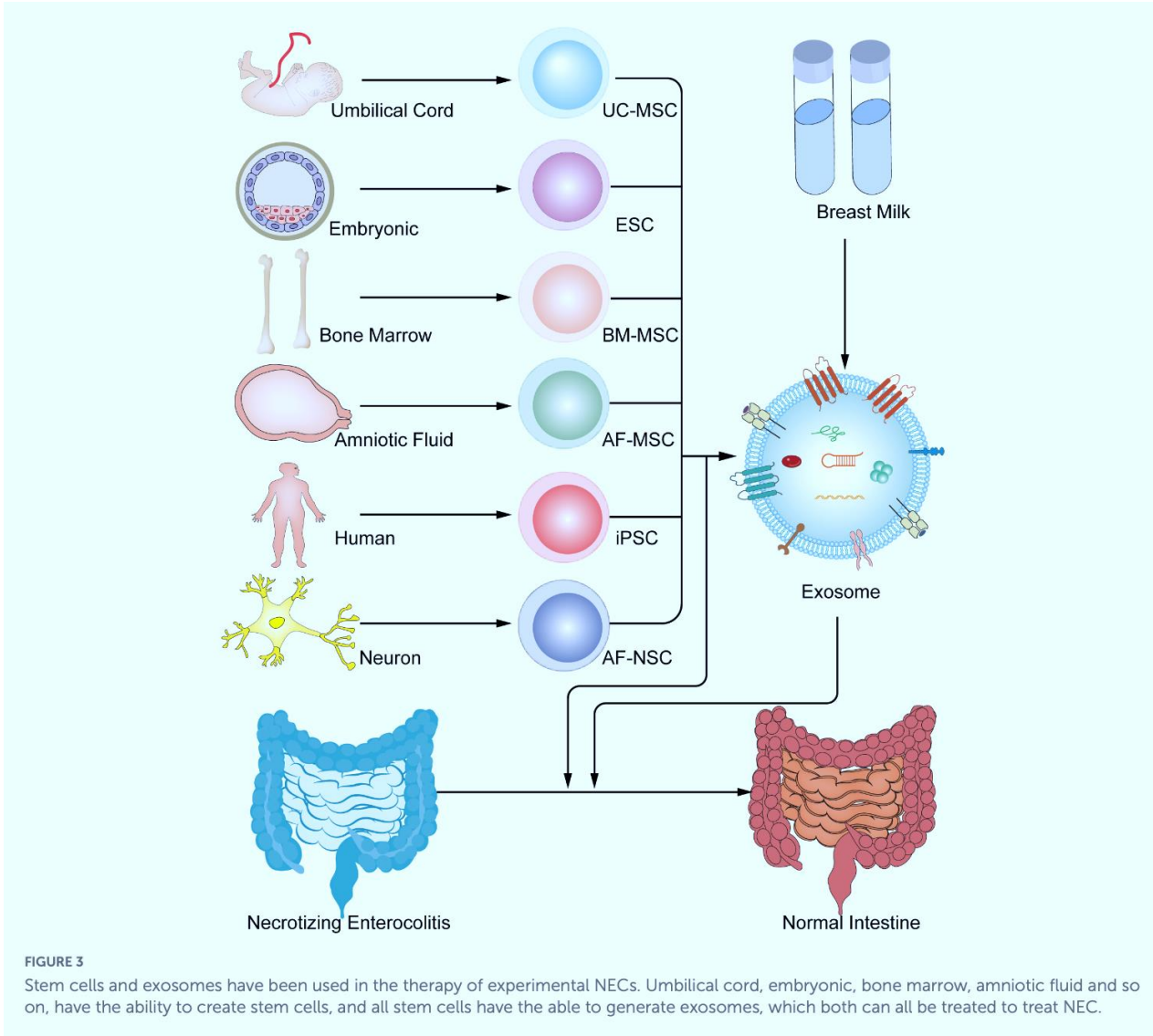


FIGURE 3
Stem cells and exosomes have been used in the therapy of experimental NECs. Umbilical cord, embryonic, bone marrow, amniotic fluid and so on, have the ability to create stem cells, and all stem cells have the able to generate exosomes, which both can all be treated to treat NEC.

Wu H, Guo K, Zhuo Z, Zeng R, Luo Y, Yang Q, Li J, Jiang R, Huang Z, Sha W, Chen H. Current therapy option for necrotizing enterocolitis: Practicalities and challenge. Front Pediatr. 2022

Tế bào gốc

TABLE 2 Applications of stem cells and stem cells-derived products in NEC.

Stem cells and stem cells-derived products	Administration	Species	Outcome	Year	References
BM-MSC	Intraperitoneal injection	Rat	Showed weight gains, improve clinical sickness scores, reduced histopathological damage	2011	(35)
BM-MSC	Intraperitoneal injection	Mouse	HB-EGF promoted BM-MSC proliferation, and migration and decreased BM-MSC apoptosis. HB-EGF and BM-MSC act synergistically to reduce injury and improve survival in NEC	2012	(37)
BM-MSC	Intraperitoneal injection Intravenous injection	Rat	Reduced the incidence and severity of NEC, and preserved intestinal barrier function in NEC.	2019	(42)
AF-MSC	Intraperitoneal injection Intravenous injection	Rat	Reduced the incidence, and severity, and preserved intestinal barrier function in NEC.	2019	(42)
AF-MSC	Intraperitoneal injection	Rat	Improved gut barrier function in NEC. AF-MSC, BM-MSC, AF-NSC, and E-NSC all reduce the incidence of NEC, which is not largely different.	2017	(41)
AF-MSC	Intraperitoneal injection	Mice	Rescued intestinal injury and restored epithelial regeneration., increased ISC and epithelial proliferation by Wnt signaling.	2020	(43)
UC-MSC	Intraperitoneal injection	Rat	Improved clinical sickness scores.	2019	(45)
UC-MSC	Intravenous injection	Infant	Enhanced intestinal blood supply in subsequent jejunostomies	2019	(48)
AF-NSC	Intraperitoneal injection Intravenous injection	Rat	Reduced the incidence, and severity, and preserved intestinal barrier function in NEC.	2019	(42)
AF-NSC	intraperitoneal injection	Rat	Reduced the incidence and severity of NEC.	2017	(41)
E-NSC	Intraperitoneal injection	Rat	Reduce the incidence and severity of NEC.	2017	(41)
BM-MSC-Ex	Intraperitoneal injection	Rat	Decreases the incidence and severity of NEC.	2018; 2016	(36, 46)
AF-MSC-EX	Intraperitoneal injection	Mice	Rescued intestinal injury, restored epithelial regeneration, increased ISC and epithelial proliferation by Wnt signaling and decreases the incidence and severity of NEC	2018; 2020	(36, 43)
AF-NSC-EX	Intraperitoneal injection	Rat	Decreases the incidence and severity of NEC.	2018	(36)
E-NSC-EX	Intraperitoneal injection	Rat	Decreases the incidence and severity of NEC.	2018	(36)

Hạn chế

- Hầu hết bằng chứng là từ các nghiên cứu tiền lâm sàng trên động vật gặm nhấm.
- Chưa có thử nghiệm trên người quy mô lớn nào.
- Những lo ngại về:
  - Nguồn tế bào
  - Khả năng tương thích miễn dịch
  - Tính an toàn lâu dài (ví dụ: nguy cơ khối u)

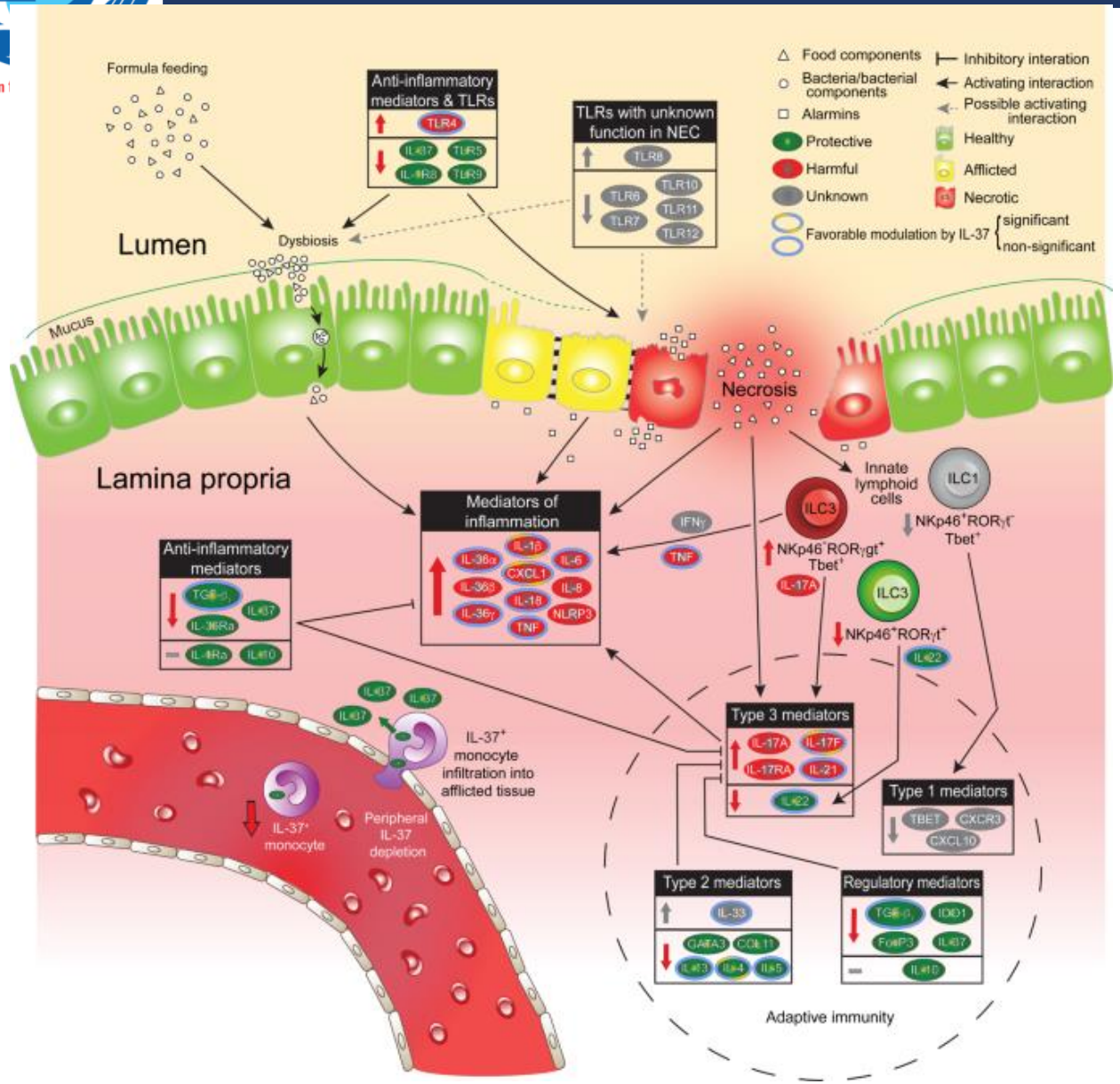
Wu H, Guo K, Zhuo Z, Zeng R, Luo Y, Yang Q, Li J, Jiang R, Huang Z, Sha W, Chen H. Current therapy option for necrotizing enterocolitis: Practicalities and challenge. Front Pediatr. 2022

Cấy ghép vi khuẩn đường ruột trong phân

- Phân của người khỏe mạnh được chuyển đến những bệnh nhân bị loạn khuẩn đường ruột để cân bằng hệ vi khuẩn đường ruột
- Phục hồi sự đa dạng của vi khuẩn chí
- Tăng sự cư trú của vi khuẩn thường trú
- Ức chế các con đường gây tiền viêm và Enterobacteriaceae
- Hạn chế
  - + Chỉ có bằng chứng trên động vật thí nghiệm
  - + Khả năng nhiễm trùng
  - + Hậu quả lâu dài trên miễn dịch và phát triển vẫn chưa được biết

Wu H, Guo K, Zhuo Z, Zeng R, Luo Y, Yang Q, Li J, Jiang R, Huang Z, Sha W, Chen H. Current therapy option for necrotizing enterocolitis: Practicalities and challenge. Front Pediatr. 2022

Miễn dịch trị liệu



Can thiệp vào **phản ứng viêm quá mức** trong viêm ruột hoại tử (NEC), đặc biệt liên quan đến:

- Tín hiệu TLR4
- Hoạt hóa NF-κB
- Cơn bão cytokine (tăng TNF-α, IL-6; giảm IL-10,…)

Miễn dịch trị liệu

Cell Reports Medicine
CellPress OPEN ACCESS

Preview

Cytokine therapy in necrotizing enterocolitis: A promising treatment for preterm infants

Bingjie Wang[1,2] and Meghan A. Koch[2,3,*]
[1]Molecular and Cellular Biology Program and Medical Scientist Training Program, University of Washington, Seattle, WA 98195, USA
[2]Basic Sciences Division, Fred Hutchinson Cancer Research Center, Seattle, WA 98109, USA
[3]Department of Immunology, University of Washington, Seattle, WA 98109, USA
*Correspondence: mkoch@fredhutch.org
https://doi.org/10.1016/j.xcrm.2021.100324

Necrotizing enterocolitis (NEC) is an intestinal disorder that disproportionately affects premature infants and lacks in effective therapeutics. Mihi and colleagues[1] demonstrated that the cytokine interleukin-22 promotes intestinal epithelial regeneration and reduces disease severity in an experimental model of NEC.

Trong mô hình chuột, việc sử dụng interleukin-22 tái tổ hợp (rIL-22) dẫn đến::

- ↓ độ nặng NEC và tổn thương niêm mạc
- ↓ cytokines tiền viêm(IL-1β, CXCL2)
- ↑ tăng sinh TB biểu mô ruột
- ↑ toàn vẹn của chổ nối chặt(anti-occludin staining)

Ở trẻ sơ sinh:

- Biểu hiện IL-22 rất thấp, ngay cả khi NEC, có thể do sực chưa trưởng thành **ILC3** and **CD4+ T cells**
- **bổ sung IL-22 từ ngoài cho thấy tiềm năng như một liệu pháp hỗ trợ điều trị.**

ELSEVIER
International Immunopharmacology
Volume 101, Part B, December 2021, 108358

Inhibition of Interleukin-6 signaling: A novel therapeutic approach to necrotizing enterocolitis

Objectives: This study investigated the effects of tocilizumab on the prevention and treatment of experimental necrotizing enterocolitis (NEC) in newborn rats.

Methods: Forty-two newborn Sprague-Dawley rats were randomly separated into three groups: NEC + placebo, NEC + tocilizumab, and the control group. NEC + placebo and NEC + tocilizumab groups were given 1 mg/kg lipopolysaccharide intraperitoneally once only on the first day, were fed with a special rodent formula every 3 h, inhaled 100% CO2 for 10 min, were exposed to cold stress at + 4 °C for 5 min, and 97% O2 for 5 min twice a day for 3 days. NEC + tocilizumab group was treated with 8 mg/kg/day tocilizumab (Actemra®) intraperitoneally, while NEC + placebo group was given intraperitoneal 0.9% saline at a dose of 2 mL/kg/day from the first day to the end of the study. All newborn rats were sacrificed on day 4. Specimens were taken for histopathologic, immunohistochemical and biochemical evaluation from the ileum and proximal colon.

Results: NEC + tocilizumab group had higher weight gain and survival rate compared to NEC + placebo group and clinical sickness score was reduced in NEC + tocilizumab group ($p < 0.05$). Lower tissue damage and apoptosis were found in the NEC + tocilizumab group compared to the NEC + placebo group ($p < 0.01$). Tissue Interleukin-6, Interleukin-1β, TNF-α, myeloperoxidase and caspase-3 levels were significantly decreased in the NEC + tocilizumab group ($p < 0.01$).

Conclusions: Tocilizumab could be a potential option in the prevention and treatment of NEC.

Miễn dịch trị liệu

ARTICLE

https://doi.org/10.1038/s41467-020-19400-w OPEN

Characterization of the pathoimmunology of necrotizing enterocolitis reveals novel therapeutic opportunities

Steven X. Cho et al.#

In mouse model

- **Transgenic expression** of IL-37 in mice → major protection from NEC (↓ mortality, ↓ tissue damage, ↑ microbiome diversity)
- **Recombinant IL-37** → moderate benefit (↓ jejunal injury)
  - ↓ Inflammatory cytokines (e.g., IL-6, IL-1β, IL-36, TNF)
  - ↓ Histological injury (jejunal damage)

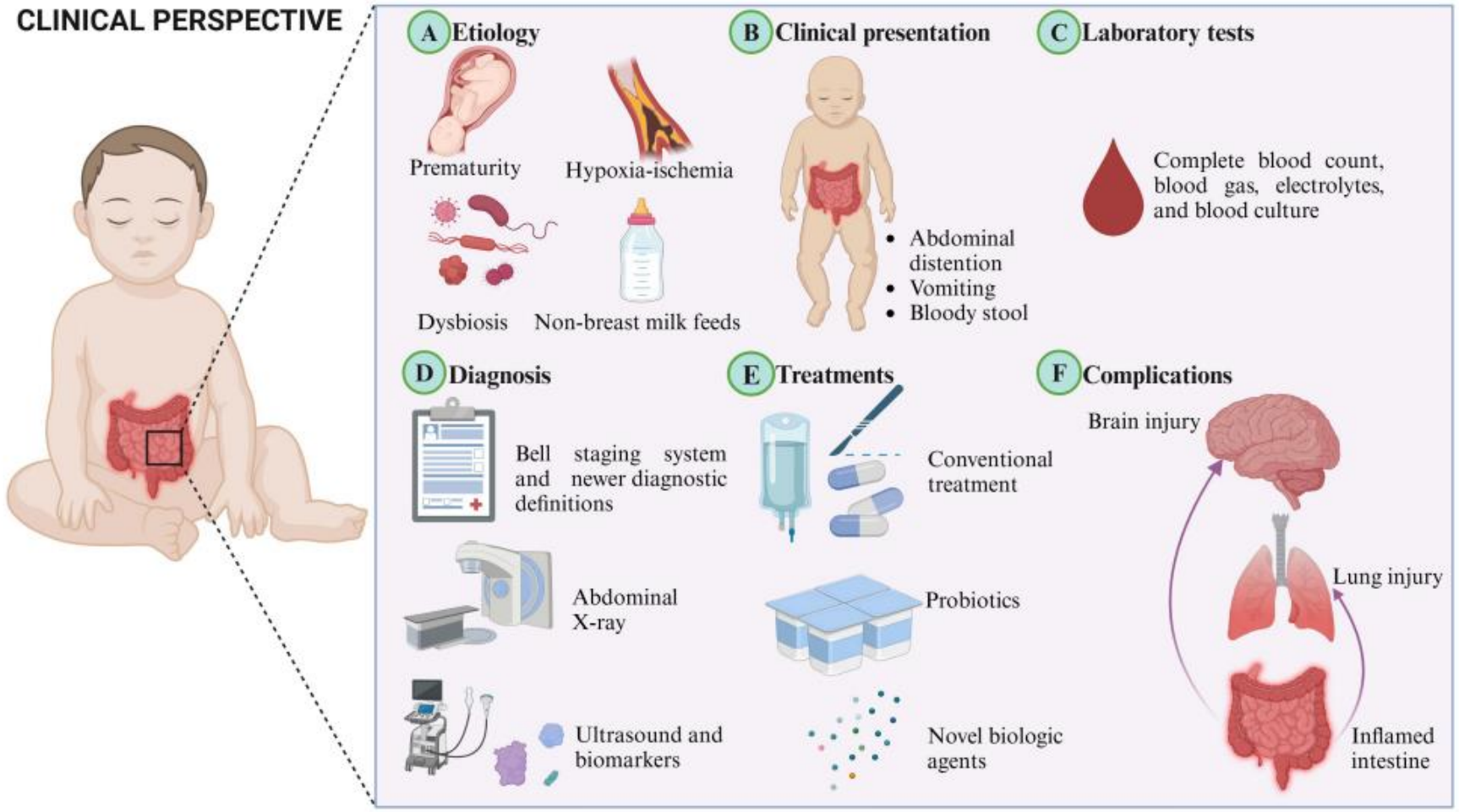
NEC patient tissue showed:

- **Marked reduction** of **IL-37** and **IL-1R8** expression.
- Suggests a **deficiency in this regulatory pathway** contributes to disease progression.

→ IL-37 has **potential as both therapy and biomarker** for NEC.

IL-37 có thể vừa là liệu pháp điều trị vừa là dấu ấn sinh học cho bệnh NEC.

4. Take-Home Messages



-Phòng ngừa là yếu tố then chốt.

+Sữa mẹ giúp giảm đáng kể nguy cơ mắc NEC.

+ Probiotic có thể sử dụng, nhưng cần cân nhắc kỹ lưỡng do các lo ngại về độ an toàn.

+ Tránh theo dõi tồn dư dạ dày nếu không cần thiết và tăng sữa chậm ở những trẻ có nguy cơ cao.

-NEC phải phẫu thuật có tỷ lệ tử vong cao hơn và dễ gặp biến chứng lâu dài.

-Dự hậu cần được theo dõi.

Deshuang Zhang et al (2025)-Digging deeper into necrotizing enterocolitis: bridging clinical, microbial, and molecular perspectives, Gut Microbes, 17:1, 2451071

BỆNH VIỆN NHI ĐỒNG 1
1956
Thầy thuốc tận tâm - Chăm màm đất nước

Thank you