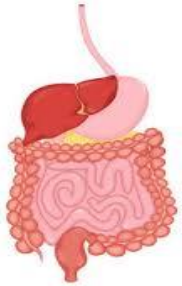

بِسْمِ اللهِ الرَّحْمَنِ الرَّحِيمِ

PROBIOTICS in NEC

Z.HASHEMI MD
NEONATOLOGIST
SUMS

NEC

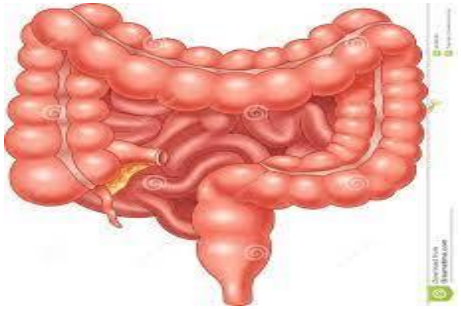
- A **severe** and potentially **lethal** intestinal disease.
- **More than 90 percent** of cases occur in BW <1500 g born at <32 weeks gestation.
- The incidence of NEC decreases with increasing gestational age and BW.



NEC

- Usually develops between the 2nd week and 2nd month of life.

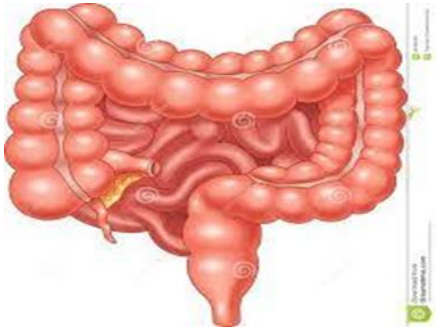
- **Rarely** occurs in utero or prior to the first feeding



NEC

- **Main Risk factors :**
- Prematurity
- Intestinal dysbiosis
- SGA
- PROM
- Assisted ventilation
- Sepsis
- Circulatory instability
- Anemia

- **Modifiable risk factors:**
- Formula feeding (may trigger an allergic response)
- Exposure to acid suppression medication
- Use of antibiotics



NEC

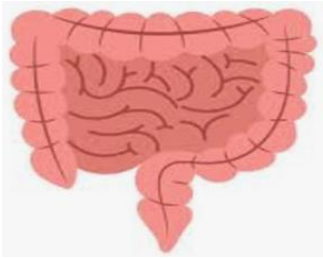
- Modifiable risk factors **alters the intestinal microbiome**, which supports the hypothesis that:

Dysbiosis is an important determinant factor leading to NEC

pathogenesis of NEC

multi-factorial mechanism

prematutity	• Immature intestinal tract • Immature immune system
Dysbiosis	• Disruption of the normal intestinal bacterial • Increased growth of potentially pathogenic bacteria
Inflammation	• Exaggerated inflammatory host response mediated by toll-like receptor-4 (TLR-4) and release of cytokines and chemokines



evidence-based strategies to decrease NEC:

(1) A standardized feeding protocol

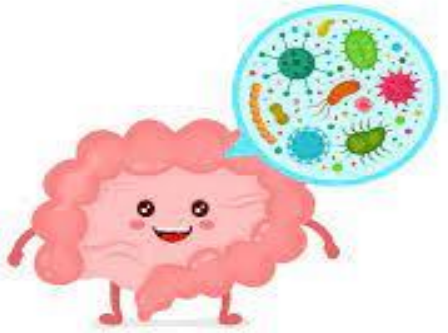
(2) Early initiation of enteral feeding using human milk

(3) Optimizing the osmolality of preterm milk

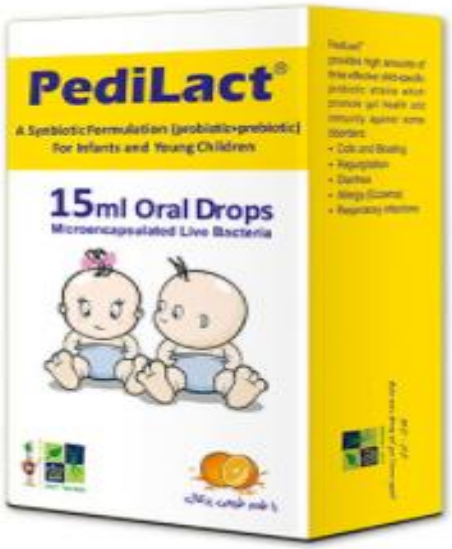
(4) Promotion of healthy microbiome

promotion of healthy microbiome

1. Early oral care with **colostrum**
2. **Restriction** of high-risk medications, and prolonged use of empirical **antibiotics** **and** **acid suppression** medication
3. Using **probiotics**



- Probiotics are **live bacteria** that confer **health benefits** on the host when administered in **adequate amounts**



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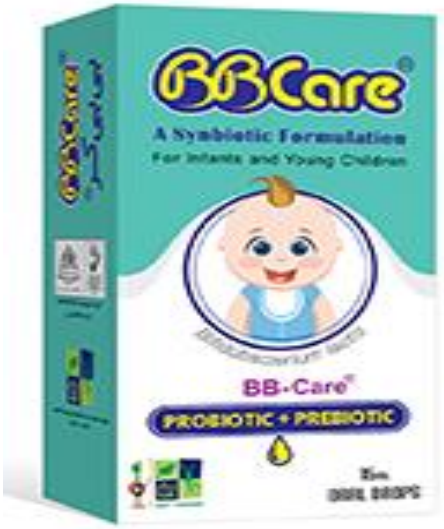

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mechanisms of probiotics function

Probiotics have different sites of action

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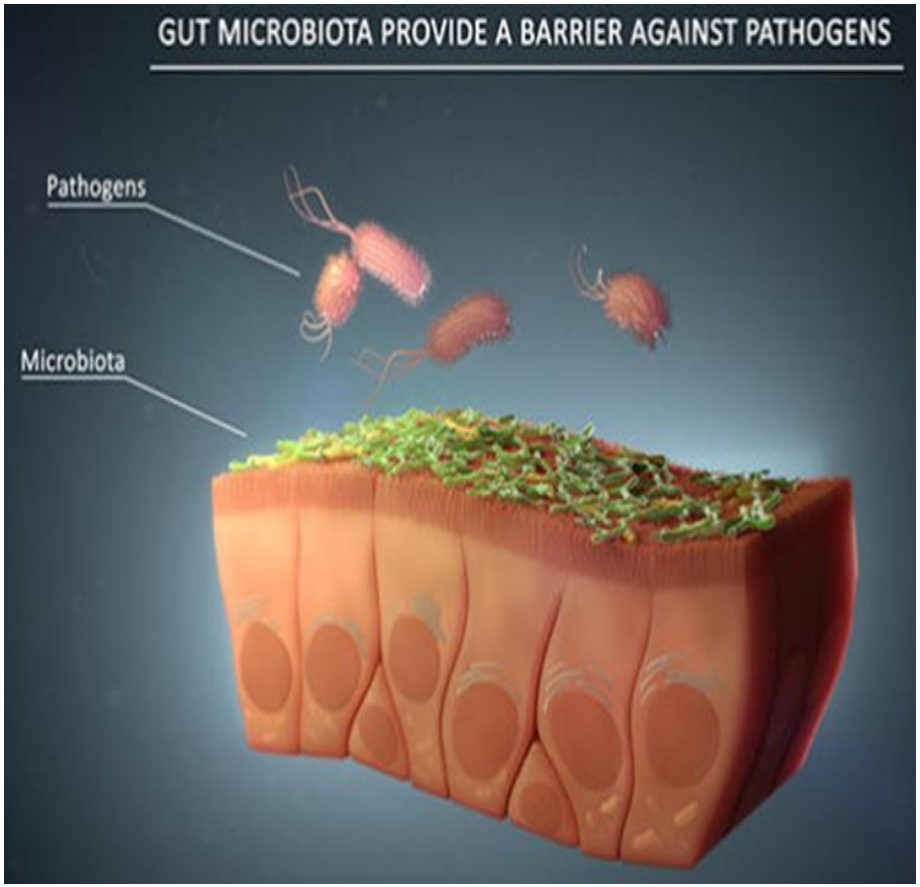
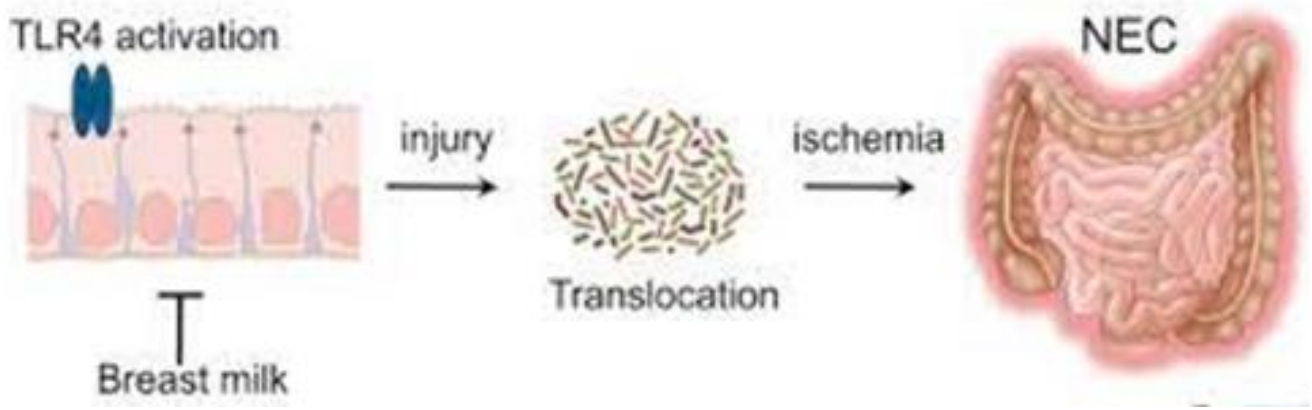
protect the premature intestine



mechanisms of probiotics function

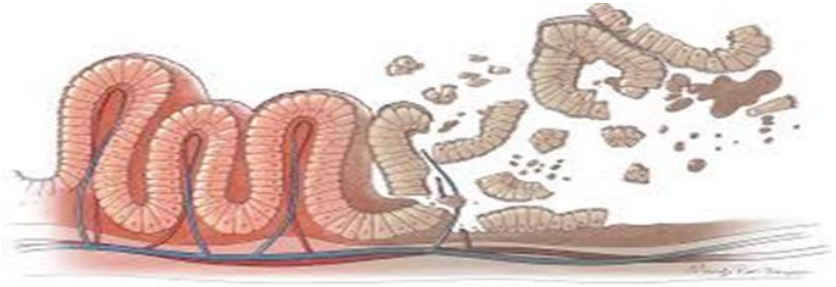
1. The most important mechanisms is the **modulation** of toll-like receptors (TLRs)



Essential function of TLRs4:

- **Recognition of components of pathogenic microbes** and trigger of specific inflammatory response

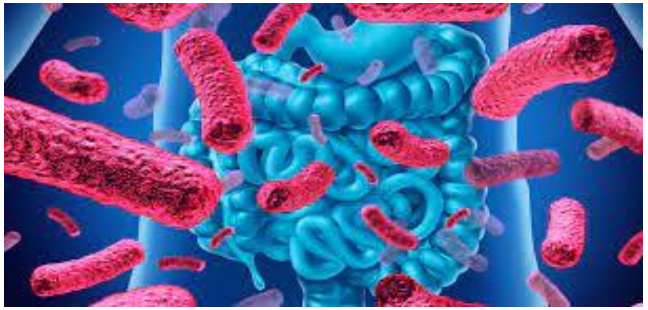
- Change in injury and repair balance in the intestinal epithelium and **epithelial daeth and NEC**



mechanisms of probiotics function

probiotics

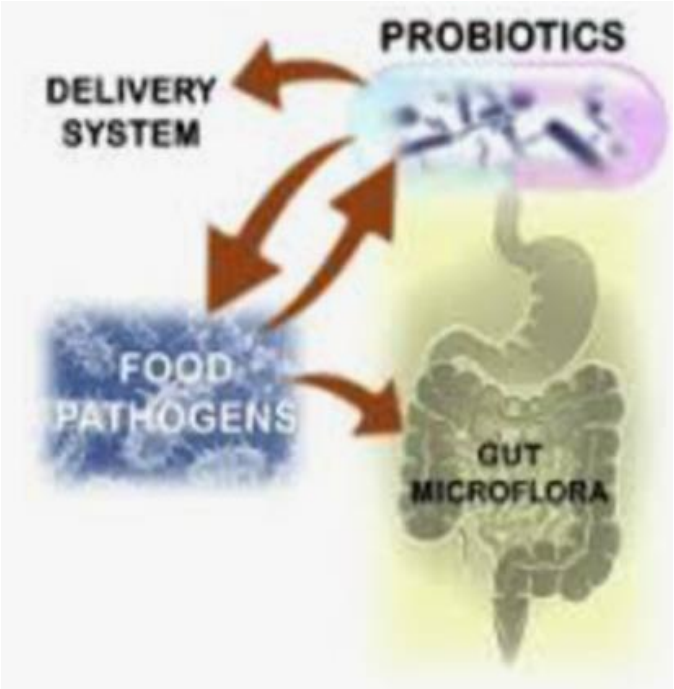
- Stimulate the production of TLR 9
- Prevent TLR 4 signaling



mechanisms of probiotics function

- immature intestine is constantly **exposed to** newly colonizing **pathogenic bacteria**

- Probiotics **compete** and may **limit** the overgrowth of such pathogens



mechanisms of probiotics function

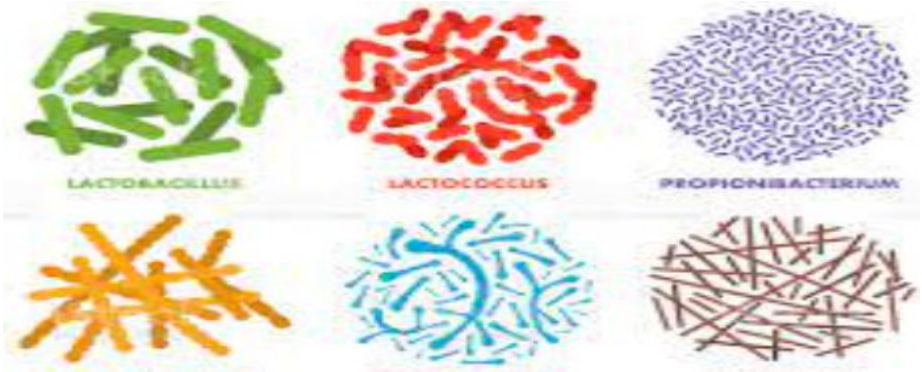
- support **barrier maturation** and **function** of the intestinal wall

- lower the pH via the production of lactate, impairing the overgrowth of pathogenic Enterobacteriaceae

- probiotic bacteria are present in mother's milk, and maternal milk has a protective effect against NEC.

Breast milk is not always available, especially in mothers of preterm infants

Many studies have been conducted in the past decades to study the role of probiotics in the prevention of this disease.



The most controversial topic in **NEC prevention** is **use of probiotics**

- **The largest** randomized doubleblinded, placebo-controlled trial

"published in 2013"

- Used a **combination of three bacteria** in the intervention group:
  - **Bifidobacterium infantis**
  - **Streptococcus thermophilus**
  - **Bifidobacterium lactis**

- ✓ **primary outcomes**: late-onset sepsis and all-cause mortality
- ✓ **secondary outcome**: NEC incidence

- No differences in primary outcomes between the groups
- The incidence of NEC was reduced from 4.4% in the control group to 2% in the intervention group(**P = 0.03**)

- In 2014 the manufacturer recalled the product used in the intervention group .

- A report by CDC ⟹ contamination of the product by a fungus Rhizopus oryzae, which caused a lethal infection in a premature infant

In 2016 Results of a large study were published :

- ✓ Evaluated the effect of the probiotic bacterium **Bifidibacterium breve** on NEC and sepsis

No statistically significant reduction of NEC in the intervention group

About **half of the infants in the control group** were colonized with the bacterium (potential cross-contamination of infants)

Ongoing concerns about the routine use of probiotics

1. May not be as effective in extremely low birth weight infants (BW <1000 g)
2. Bacteremia from the bacterial probiotic strain or contamination of the probiotic product.
3. Clinical trials failed to answer the important question of the **optimal probiotic strains** and **doses** and **duration of therapy**

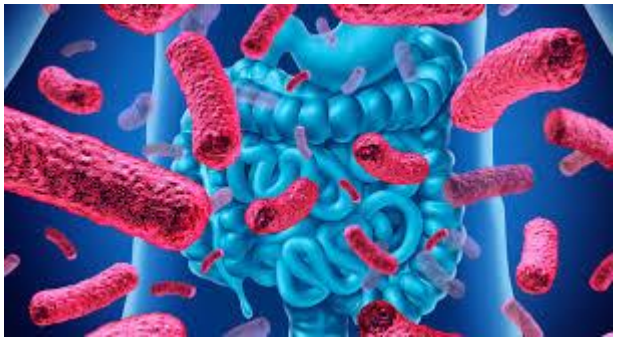
Probiotic in NEC

A 2020 network meta-analysis :

combination use of probiotic therapy was more effective than a single probiotic strain

As of 2021, the US-FDA:

has not approved **any probiotic product** as a therapeutic agent for the prevention of NEC



Eligibility criteria

"that need to be addressed prior to administration"

1. Gestational age and Birth weight
2. Product to be used(**optimal strain)**
3. Clinical protocol :
   - when to start
   - what dosing regimen to use
   - when to stop
4. Efforts to prevent contamination
5. Monitoring for adverse events

- we should not recommend them for **routine use** in NICUs at this time

Thanks for your attention