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Complimentary Article

Annihilation, Exacerbation, Prematurity: Necrotizing Enterocolitis

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Necrotising enterocolitis is an intestinal inflammatory disorder predominantly affecting the preterm. The deterioration ranges from minimal mucosal trauma to pervasive necrosis of the bowel wall with perforation. The condition is an essential cause of neonatal mortality particularly the very low birth weight (VLBW) [1]. Considerable morbidity in the neonatal intensive care is delineated with necrotising enterocolitis despite early detection, diligent therapies and ameliorated consequences.

Prevalence

Necrotising enterocolitis is evidenced in up to 13% infants of ≤ 33weeks gestation or with a birth weight of < 2500gm [1,2,3]. Neonates at term or ≥ 35 weeks of gestation display enterocolitis like gastrointestinal symptoms accompanied by disorders such as congenital heart disease, perinatal asphyxia, polycythaemia, sepsis and respiratory disease.

Pathogenesis

The hyperactive environment of the premature intestine, central feeding and intestinal bacterial flora determine the progress of the disease. The preterm and full term intestinal tract are markedly dissimilar in the bacterial colonization, microcirculation, perfusion, maturation of the inherent gastrointestinal immune system etc, thereby describing the multi- factorial pathogenesis of necrotising enterocolitis. The Toll like receptor 4 (TLR4) is reinforced in the preterm, consequent to the upgraded TLR4 gene which modulates the normal gastrointestinal tract.

The TLR4 levels impact the preterm intestinal substratum along with the gram negative bacteria colonizing the gastrointestinal tract The preterm intestine with the intense TLR4 levels induces the enhanced enterocyte apoptosis, diminished mucosal healing with an intense pro-inflammatory cytokine release to activate the inflammation [4]. The gastrointestinal mucosal gram positive bacteria initiate the TLR4 on the immature bowel mesentery endothelium to diminish the blood flow and provoke intestinal ischemia and necrosis. This mechanism of inflammation is designated as "the cross switching hypothesis ". It presumes that the infection in the premature is secondary to bacterial colonization. The distinction between the preterm and full term host contributes as

• high baseline content of cellular endoplasmic reticulum which intensifies the apoptosis in the preterm intestinal epithelium.

• the mucus producing goblet cells in the premature intestine are diminished so the mechanical preservation is defective.

• the luminal contents are ineffectively removed based on the reduced gut motility.

• decreased digestion and nutrient absorption due to enterocyte evolution.

• improved micro-vesicular tone within the premature intestinal mesentery [5].

• the existence of immature tight junctions.

These factors contribute to the pro-inflammatory signals, bacterial modification and the appearance of necrotising enterocolitis [5]. T lymphocytes adapt the premature intestinal mucosa to bacterial colonization to establish the inflammation. Enterocolitis displays an excessive intestinal mucosal lymphocytic reaction as the epithelial TLR4 signal to modify the pro-inflammatory T helper cell 17 and restrict the protective T regulatory cells. Formulation of the relevant platelet activating factor occurs in the impaired mucosa with a barrier malfunction. An intensified production and circulation of platelet activating factor with an inadequate platelet activating factor acetyl hydrolase, the enzyme which recruits the protein, is delineated [6].

NEC stage	Findings		
	Clinical	Gastrointestinal	Radiographic
I	Apnoea, bradycardia	Gastric residuals	Mild intestinal dilatation
		Mild abdominal distension	
IIa	Apnoea, bradycardia	Grossly bloody stools	Marked intestinal dilatation
	Mild inflammation	Marked abdominal distension	Ileus
		Absent bowel sounds	
IIb	Thrombocytopenia	Abdominal tenderness	Pneumatosis intestinalis
	Mild acidosis		Portal venous gas
	Inflammation		
IIIa	Moderate acidosis	Abdominal discolouration	Pneumatosis intestinalis
	Coagulopathy		Portal venous gas
	Hypotension		
	Oliguria		
IIIb	Shock	Perforated bowel	Free abdominal air

Figure 1: *Diagnostic Features of NEC*

Enteral Provisions

Parenteral nutrition modifies the pro-inflammatory genes. Intestinal bacterial flora and intestinal splanchnic perfusion is interrelated with the parenteral nutrition. Parenteral prescriptions and human milk alter the host genetic expression and methylation. The existence of intestinal flora, circulating endo-toxins, bacterial blood culture/ sensitivity and 30% hydrogen content of the pneumatosis (gas exclusively produced by the intestinal bacteria) implicate a bacteria induced pathogenesis [7]. Heterogeneous intestinal bacteria are eradicated at the onset and the pathogenic bacteria predominate- facts noted in the premise of "dysbiosis".

Interpretation

Interpretation is based on the precise clinical, radiographic and laboratory data. The classic presentation is a robust preterm with a regular intake, abdominal distension, bloody diarrhoea and indications of sepsis.

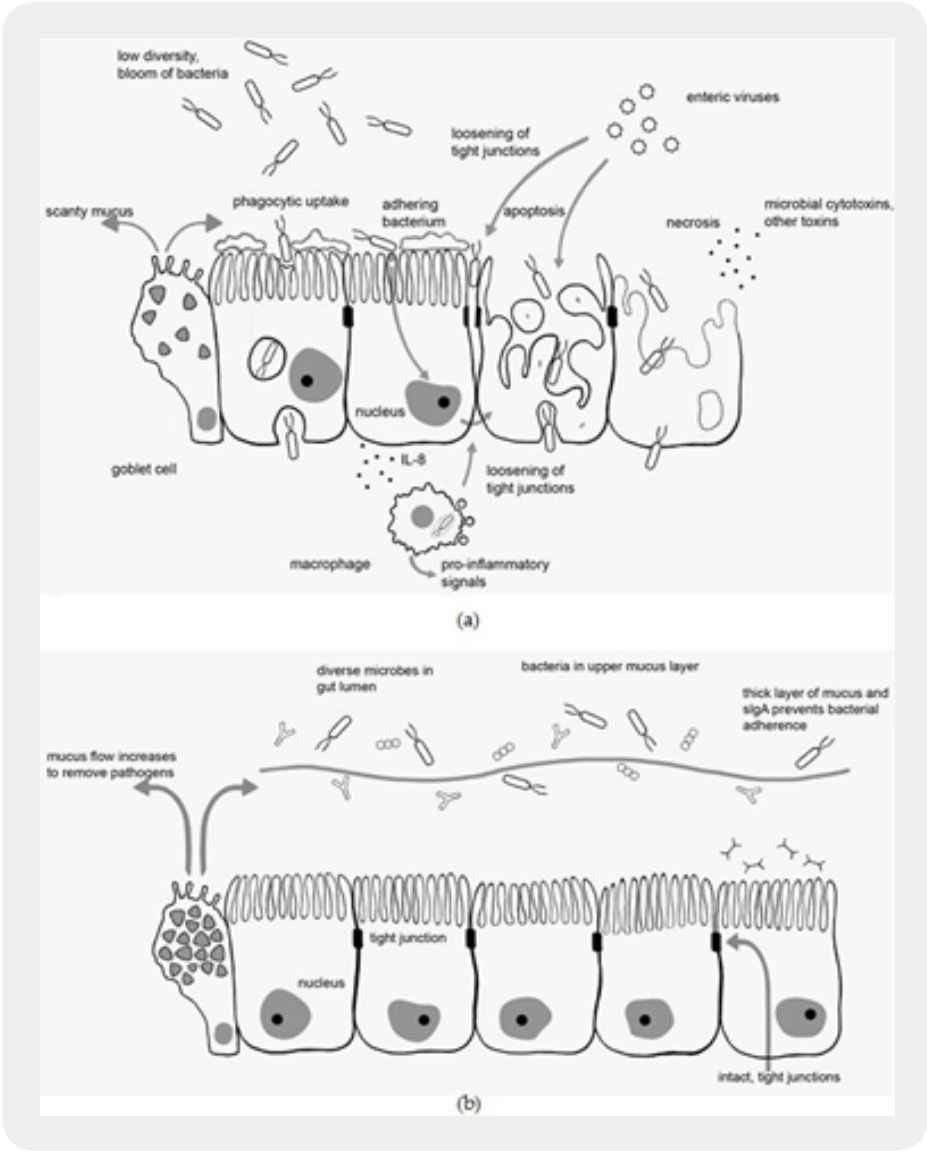

Figure 2: *Mechanism of Invasion*

Stage	I	2A	2B	3A	3B
Description	Suspected	Mild	Moderate	Severe	Severe
Systemic Clues	Inconstant temperature, Apnoea, Bradycardia	Similar to Stage 1	Mild acidosis, thrombocytopenia	Respiratory and metabolic acidosis, need for mechanical ventilation, hypotension, oliguria, disseminated intravascular coagulation	Further deterioration and shock
Intestinal Clues	Increase gastric residuals, mild abdominal distension, occult blood in the stool	Marked abdominal distension± tenderness, absent bowel sounds grossly blood stool	Abdominal wall edema and tenderness ± palpable mass	Deteriorating wall edema with erythema and induration	Evidence of perforation
Radiographic Clues	Normal or mild ileus	Ileus, dilated bowel loops, focal pneumatosis	Extensive pneumatosis, early ascites± portal venous gas(PVG)	Prominent ascites, fixed bowel loop, no free air.	Pneumoperitoneum

Biomarkers

Biomarkers and non-invasive acute phase reactants such as the CRP (C Reactive protein) and pro-inflammatory cytokines (Tumour necrosis factor TNF α, Interleukin 1 IL1 and Interleukin 6 IL6) are equivocal. Organ specific biomarkers like the enterocyte impairment, intestinal barrier deterioration, intestinal fatty acid binding protein, liver fatty acid binding protein, faecal calprotectin are requisite for early recognition of the disease. The intestinal fatty acid binding protein (I-FABP) is a cytoplasmic protein with an enterocyte lipid metabolite found in the circulation and secreted into urine following enterocyte injury. It is comparable to the magnitude of intestinal necrosis and is a quantitative parameter. The I-FABP prevents the detection of the inflammation as the plasma ½ life is fleeting and the normal range in preterm infants is variable. Abundant necrosis with continuing injury has a decreased I-FABP because of a shortened half-life. Urinary peptides and protein imply a poor prognosis [8]. Plain radiography is the elementary imaging technique for diagnosis and ratification of necrotising enterocolitis. Abdominal ultrasound delineates pneumatosis intestinalis and portal venous gas (PVG) earlier than a plain x-ray. Ultrasound demonstrates specific aspects of perfusion, the gut wall diameter and motility and assists in predicting the disease progression and surgical outcomes. The free intra-abdominal gas/ fluid and intestinal perforation is determined by the abdominal ultrasound. The modality of colour doppler evaluates the celiac trunk and the blood velocity of the superior mesenteric artery.

It delineates the poor perfusion and viability of the intestinal wall in potential patients [9]. Near infra-red spectroscopy (NIRS) demonstrates the progressive or inconclusive cases of intestinal inflammation. The skin probes of NIRS concentrate on the tissue to oxygenate the intestinal substratum instead of the entire length. Thus it assesses the splanchnic tissue oxygenation in the preterm infants with progressive intestinal inflammation and those lacking inflammation.

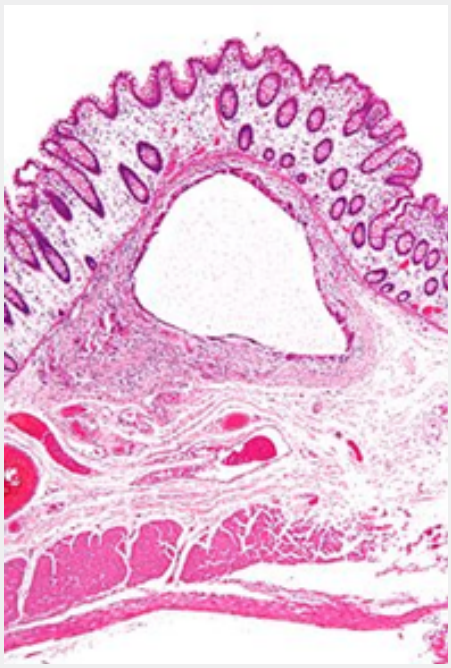

Figure 3: *Microscopic changes in Necrotising enterocolitis*

Preventive Policies

Breast milk diminishes the extent of enterocolitis. Human milk comprises of beneficial bioactive elements. It restricts the TLR4 signal by prohibiting the glycogen synthase kinase 3β. The coordinated TLR4 signal can thus activate of intestinal stem cell production and mucosal repair. The events are partly controlled by the stimulation of epidermal growth factors signal receptors. Human milk components which safeguard against the emergence of inflammation are i) Lactoferrin ii) Oligosaccharides and pre-biotics iii) Secretory IgA iv) L-Arginine v) Nitrate/ Nitrite vi) Platelet activating factor acetyl hydrolase vii) Anti-oxidant factors viii) Growth factors (Epidermal GF, Heparin binding EGF like GF, Transforming GF-β2 ix) Erythropoietin.

Donor breast milk acts as a replacement or additive to formula feeding is an efficient strategy for the preventing the condition.

Probiotics

Probiotics are live organisms that improve the bacterial milieu and the constitution of the host. The medium prevents the development of inflammation, decreases the disease severity, extent and mortality in the preterm [10]. Nevertheless, the specific agent, time of administration and duration of the therapy are have not been specified. The pro-biotic bacteria lactobacillus ramonsus induces the enterocyte multiplication and differentiation of the Paneth cells. The Cp G with the bacterial DNA triggers the Toll like receptor 9 and inhibits TLR4. Thus a substitute to the live pro-biotic is available.

Therapeutics

Bell stage I or II inflammation is treated with pertinent supportive therapy i) termination of parenteral nutrition ii) encourage ventilation iii) maintain fluid/ electrolyte and acid-base balance iv) adjust persisting coagulopathy and/or thrombocytopenia v) bowel rest vi) optimal antibiotics for an appropriate duration [8].

Surgical Intervention

Surgical intervention is required in half the cases with inflammation and eliminates the necrotic intestine. An abdominal drain and peritoneal irrigation is adequate in some. Laprotomy with peritoneal drainage produces similar results. Primary peritoneal drainage is restricted to patients with elevated intra-abdominal pressure or for very small infants (< 750gm).

Current Modalities

Pentoxifylline with antibiotics is recommended for treating neonatal sepsis and prospective necrotising enterocolitis 0.62. Intra-peritoneal pentoxifylline decreases the extent and severity of the infection.

• Stem Cells: Amniotic fluid stem cells (AFS), mesenchymal stem cells and enteric neural stem cells have a capability to alter the course of the disease [11].

• Amniotic Fluid: *in vitro* proliferation and transfer of the gut epithelial cells is accomplished by the human amniotic fluid. It decreases the extent and severity of inflammation.

• Growth factors: Heparin binding EGF like growth factor is an accepted biologic agent for the regression of the infection. Specified mucosal healing, intestinal stem cell activity and vascular proliferation is elucidated.

• TLR4 inhibitor is the nontoxic oligosaccharide that inhibits TLR4 and diminishes intestinal inflammation.

• Human milk oligosaccharides prohibit and treat the inflammation.

• Lactoferrin: Prophylactic oral lactoferrin with or without pro-biotic is recommended in possible cases (gestational age < 32 weeks, birth weight < 1500gm).

Consequences

The mortality of necrotising entero-colitis is 20%-30%. Infants with a surgical intervention delineate a 50% mortality regardless of the proficient surgical and medical. The intestinal or systemic damage presents survivors with co-morbidities [8].

Complications

• Recurrence of the infection occurs in 10% cases, requiring an extended parenteral support [8].

• Subsequent to a surgical therapy, 25 % infants display intestinal strictures [8].

• Gut failure: Considerable number of infants (the low birth weight, antibiotic use, ventilation requirement, extensive bowel resection etc) terminate in intestinal failure [8].

• Parenteral nutrition results in complications.

• Neuro-developmental disarray occurs in almost half the neonates, the mechanism of which is inappreciable.

• Affected neonates demonstrate white matter changes visible on Magnetic Resonance Imaging at term with a possible motor impairment [12,13].

Bibliography

1. Stoll, B. J., *et al.* (2015). Trends in care practices, morbidity and mortality of extremely preterm neonates 1993-2012. *JAMA., 314*(10), 1039-1051.

2. Holman, R. C., *et al.* (2006). Necrotising enterocolitis hospitalization among neonates in the United States. *Paediatrics and Perinatal Epidemiology, 20*(6), 498-506.

3. Yee, W. H., *et al.* (2012). Incidence and timing of presentation of Necrotising Enterocolitis in preterm infants. *Paediatrics, 129*(2), 298-304.

4. Lu P., *et al.* (2014). Toll like receptor regulator of intestinal development and inflammation in the pathogenesis of necrotising enterocolitis. *Pathophysiology, 21*(1), 81-93.

5. Watkins, D. J., *et al.* (2013). The role of intestinal microcirculation in Necrotising enterocolitis. *Seminars in Paediatr Surg., 22*(2), 83-87.

6. Soliman, A., *et al.* (2010). Platelet activating factor indices TLR4 expression in the intestinal epithelial cell: implication for pathogenesis of necrotising enterocolitis. *PLoS ONE, 5*(10), e15044.

7. Scheifele, D. W. (1990). Role of bacterial toxins in neonatal necrotising enterocolitis. *Journal of Paediatrics, 117*(1 pt 2), S44-S46.

8. Sylvester, K. G., *et al.,* (2014). Urine protein biomarkers for the diagnosis and prognosis of necrotising enterocolitis in infants. *Journal of Paediatrics, 164*(3), 607-612.

9. Zani, A., *et al.* (2015). Necrotising Enterocolitis: Controversies and Challenges. *F1000 Research,* 4PII F1000 Faculty Rev1373.

10. Neu, J. (2014). Probiotics and Necrotising Enterocolitis. *Clinics in Perinatology, 41*(4), 967-978.

11. Eaton, S. *et al.* (2013). Stem cells as a potential therapy for necrotising enterocolitis. *Expert Opinion on Biological Therapy, 13*(12), 1683-1689.

12. Epelman, M., *et al.* (2007). Necrotising enterocolitis: state of the art imaging findings with pathologic correlation. *Radiographics, 27*(2), 285-305.

13. Rees, C. M. *et al.* (2008). Perinatal Drainage or laprotomy for neonatal bowel perforation? A Randomized Control Trial. *Annals of Surgery, 248*(1), 44-51.

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15. Image 2 Courtesy: Intech open.

16. Image 3 Courtesy:Pathology Outlines.