Neonatal Necrotizing Enterocolitis: A Generic Injury Response of the Developing Intestine to Diverse Forms of Injury?

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Objectives

- Review the clinical presentation and progression of NEC
- Using histopathology as a guide, discuss current understanding of the pathophysiology of NEC
- Briefly review the quality of evidence to support current clinical management of NEC

Necrotizing Enterocolitis

Histopathological Features of NEC

NEC: Clinical Features

Stage I (Suspect Disease)
- Non-specific signs
- Feeding intolerance, abdominal distention
- Radiographic: normal/dilated loops

NEC: Clinical Features

Stage II (Definite Disease)
- Mild systemic signs
- Intestinal: absent bowel sounds, tenderness
- Radiographic: ileus, pneumatosis intestinalis
**NEC: Clinical Features**

**Stage III (Advanced Disease)**
- Multiple Organ Dysfunction Syndrome
- Intestinal: marked distention, generalized peritonitis
- Radiographic: ascites or free air

**NEC: Pathophysiology**

- **Coagulative Necrosis** is a prominent histopathological feature in NEC

**Clinical Associations of NEC**

- **Bacterial Overgrowth/Translocation During NEC**

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(Images and references are from Walsh and Kliegman, 1986, and Maheshwari, 2011)
NEC: A Common Tissue Injury Response of the Developing Intestine?

Mechanically-obstructed Intestine may show Features of NEC

Viruses can Induce NEC-like features

HSV

Rotavirus

Intestinal Stasis and Enterocolitis in Hirschsprung’s disease could induce NEC-like features

Bacterial Translocation and NEC

Several Stimuli can Evoke a Common, Generic Tissue Injury Response
‘Commensal’ Bacteria cause Mucosal Inflammation in Premature Infants during NEC

In the Mature Intestine, Macrophages are Tolerant to Bacterial Products such as LPS

Resident Macrophages Regulate Mucosal Inflammatory Responses to Bacteria

NEC is Marked by a Macrophage-rich Infiltrate

Macrophages in Preterm Intestine Express Inflammatory Cytokines

Does Immaturity of Gut Macrophages Predispose the Developing Intestine to NEC
Macrophages in Preterm Intestine Express Inflammatory Cytokines

During Development, Intestinal Macrophages are Downregulated for their Inflammatory Properties

Inflammatory Downregulation of Intestinal Macrophages is Mediated via TGF-β

Inflammatory Downregulation of Intestinal Macrophages is Mediated via TGF-β_2_

How Can We Prevent/Ameliorate NEC

Suppress inflammatory activation of macrophages

Prevent accumulation of macrophages

Mice Conditionally Deficient in TGF-β Activity
Wild type mice treated with PAF + LPS DNIIR mice after 3-day Zn supplementation, treated with PAF + LPS DNIIR mice after 7-day Zn supplementation, treated with PAF + LPS

Mucosal Injury Score

p<0.05

INTESTINAL INJURY INDUCED BY INTRAPERITONEAL PAF AND LPS

N.S.

p<0.05

p<0.01

1.5
1
0.5
0

TGF-β2 Expression is Decreased During NEC

NEC in Preterm Baboons

TGF-β2 Induces its Own Expression
TGF-β Signaling Pathway

Macrophage Infiltration in NEC

Macrophage Infiltration in NEC

CXCR2 Ligands Recruit Macrophage Precursors during NEC
Macrophage Infiltration in NEC

Intestinal Macrophages Lose Podosomal Structures During NEC

Histopathological Features of NEC

Decompression: Intramural pressures in Distended Intestinal Loops may exceed Systolic BP in Premature Infants

Antibiotic Regimens

Parenteral antibiotics used for the treatment of NEC; anaerobic coverage frequently included in stage III NEC

Limited data on regimens and duration of antibiotic treatment for NEC. One study included 90 infants with definite NEC; 46 were treated with ampicillin and gentamicin, while 44 received cefotaxime and vancomycin. Infants > 2200 g birthweight had similar outcomes with either regimen

Smaller infants given cefotaxime and vancomycin had a lower risk of culture-positive peritonitis (P < 0.01), were less likely to die (P = 0.048) or develop thrombocytopenia (P = 0.064). Data suggest that carefully chosen antibiotics can improve outcome
Surgical Therapy

Surgical management may include peritoneal drainage vs. exploratory laparotomy

In NECSTEPS trial, no difference in 90 day survival, dependence on PN, or length of stay in 117 VLBW infants randomly assigned to PD or LAP. However, 40% (21/55) of patients initially treated with PD required subsequent laparotomy. PD was effective as definitive treatment in only 11% (4/35) with 75% (26/35) requiring a delayed laparotomy.

Meta-analysis of 3 prospective observational studies and 2 RCTs suggested a significant excess mortality of 55% associated with PD

(Moes, 2008) 21 properly-designed RCT
(Goe, 2009)

Prevention

Oral antibiotics: 5 RCTs (456 infants); reduced risk of NEC (RR 0.47 (0.26, 0.78); NNT 10 (6, 25))

Standardized feeding regimens: 6 studies; risk ratio 0.13 (95% CI 0.03 to 0.50)

Supplementation of L-arginine or glutamine, showed promise in small cohorts but not in larger studies

Enteral probiotics reduced severe NEC (stage II or III) (RR 0.35, 95% CI 0.24 to 0.52)

Prebiotics promoted lactobacilli and bifidobacteria in stool without affecting weight gain

Conclusions

Luminal bacterial and their products play an important role in the activation of inflammatory signaling during NEC.

TGF-β, particularly TGF-β2, mediates the normal maturationally regulated downregulation of intestinal macrophages.

Intestinal expression of TGF-β2 is maturationally regulated and is deficient in the developing intestine.

Tissue expression of TGF-β2 (and TGF-β1) is markedly suppressed during NEC. In the NICHD cohort, ELBW infants who developed NEC had low plasma levels of TGF-β2.

Mice deficient in TGF-β signaling have an exaggerated inflammatory mucosal injury in experimental models of NEC. This injury can be prevented by enterally-supplemented TGF-β2.

During NEC, the loss of TGF-β receptors may further sensitize intestinal macrophages to bacterial products and augment inflammatory injury.

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