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REVIEW ARTICLE

Necrotising Enterocolitis: Newer Insights

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ABSTRACT

Necrotising enterocolitis is the most common gastrointestinal emergency of the neonates with high mortality and morbidity. Despite 3 decades of extensive research and animal studies etio-pathogenesis, early diagnosis, preventive strategies and management options remain controversial. The present article reviews the literature for recent advances and newer insights for changing epidemiological trends, pathogenesis, role of inflammatory cytokines and various preventive and management strategies.

Key words: Necrotizing, enterocolitis, neonates

Introduction

Necrotising enterocolitis is the most common acquired gastrointestinal disease in the newborn infants, affecting 1-3 cases per 1000 live births, 2-5% of very low birth (VLBW) infants and 1-8% of all Neonatal Intensive care unit admissions [1]. The term 'Necrotisingenterocolitis' first appeared in the European literature in the early 1950s in articles by Schmid and Quaiser who described infants dying from necrotic lesions of the gastrointestinal tract [2]. Infants with NEC represent some of the sickest infants in the NICU and exhibit a high mortality rate ranging from 20-50%. Futhermore, once an infant is diagnosed with definite NEC, with the exception of supportive care, there is little one can do to alter the course of the disease. NEC is almost exclusively a disease of prematurity, with >90% of all cases occurring in premature infants and in infants less than 2000 gms [3], [4]. The disease is rare in countries where prematurity is uncommon such as Japan and Sweden [5].

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The lack of improvement in the mortality rate for NEC over the past 10 years has prompted the investigators to re-examine the epidemiologic and risk factors and search for strategies to prevent the disease. This article reviews the latest epidemiological trends and pathogenesis and preventive and management options reported in the literature by searching MEDLINE (1996-2006), EMBASE (1996-2006), CINAHAL, Cochrane reviews and hand search of major neonatal and perinatal journals.

Epidemiology

NEC has emerged as a disease of NICU survivors. The overall incidence is 1-3 cases per 1000 live births, with considerable variation observed among institutions and even within an institution. Hack et al and Uauy et al have reported an incidence of NEC varying from 4% to 19% among seven tertiary academic NICUs in USA [6],[7]. Similar variations have been reported from India and Australia [8], [9]. Analysis of data from 17 Canadian NICU's have however, not shown any significant variation in the risk-adjusted incidence of NEC with exception at one center [10]. The majority of NEC cases are endemic, however clustering and epidemics have also been reported. In most studies,

male and female infants are equally affected .NEC when occurs in term neonates is a different disease from preterm infants. [Tab/Fig 1] highlights the differences between NEC in term and preterm infants [10],[11], [12], and [13].

Recently Luig and Lui and the New South Wales (NSW) and Australian Capital Territory (ACT) NICUS group have reported an encouraging reduction in the incidence of NEC from 12% in 1986-87 and 1992-1993 to 6% in 1998-1999 for all infants born in NSW at 24-28 weeks gestation. However, the mortality rate remains unchanged at 27-37% as did requirement for surgical intervention at 41-57% [14]. Similar reduction in incidence from 5.3% to 3.2% for infants less than 32 weeks is also reported from the Australian and New Zealand Neonatal Network (ANZNN) [15]. This is however not supported from other large Neonatal databases . The Oxford – Vermont Network with 362 NICU's reported proven NEC cases varying from 6.2%-8.4% [16]. The National Institute of Child Health and Human Development Neonatal research network (NICHD) have reported rates increasing from 5% in 1991-1992 to 7 % in 1995-1996[17]. Various hypothesis suggested for the decline in the incidence of NEC in Australia (NSW) such as increased usage of antenatal steroids(88% in 1998-1999), liberal use of surfactant for hyaline membrane disease(74% in 1998-1999) and a decrease in births outside Level III hospitals for infants born < 32 weeks(8% in 1998-1999) were not supported by the data. However rates of proven NEC appear to relate to the overall quality of perinatal care and may be used as a clinical indicator or indirect measure of quality of perinatal care [18].

Table/Fig 1

Characteristics	Term	Preterm
Incidence	0.05-0.71/ 1000 births *	1-3/1000 births
Mean Age of onset(days)	1.0 - 4.1	7- 28 (inverse relation with gestational age)
Mode of delivery	Caesarean section **	
Associated anomalies	Congenital heart disease (35%) & Endocrine (17%) †	No association
Risk factors	More common	
Site of disease	Colon **	Small intestine (jejunum, ileum, ileocaecal valve)
Clinical features	Fewer systemic manifestations, perforation and transmural bowel necrosis less frequent	
Outcome	Favorable (mortality 5-7%)	High mortality (10-20%)

Differences in Necrotisingenterocolitis in term/preterm neonates

* Ref No [11], [13] ; ** Ref No[13] ; † Ref No. [11]

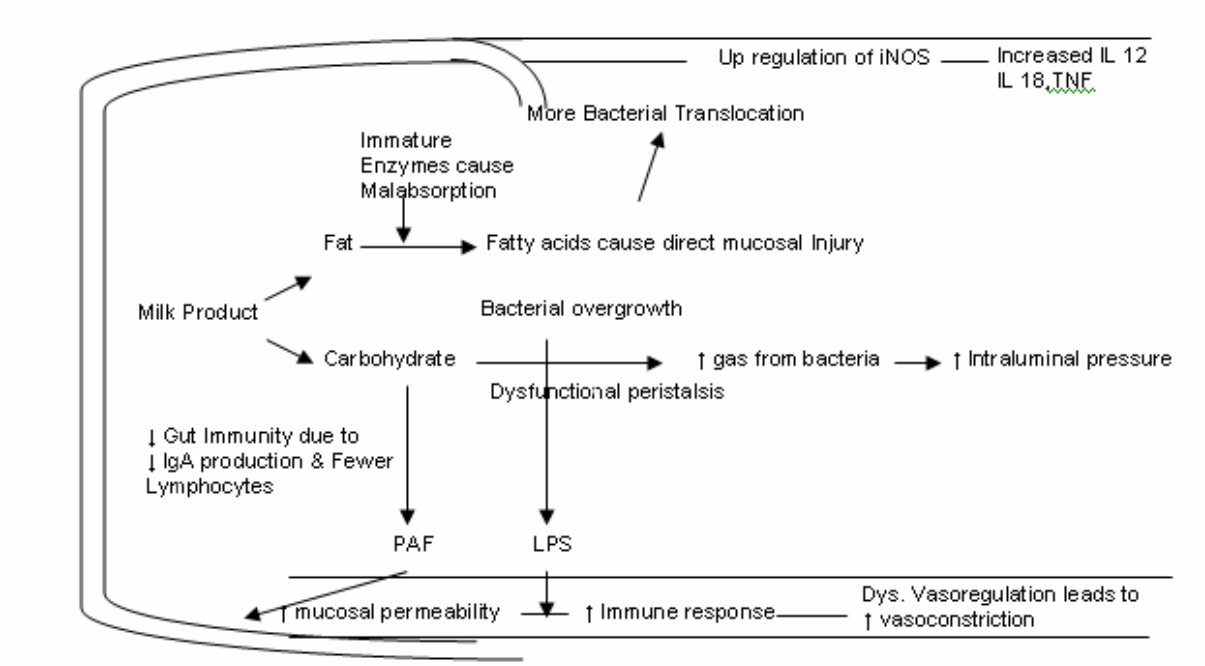
Table/Fig 2: Risk Factors for the development of NEC

1. Prematurity(<28 weeks
2. Enteral feeding(90% are fed enterally)
3. Growth restricted neonate(SGA) †
4. Maternal hypertensive disease of Pregnancy(OR 5.21 , 95% CI 1.64- 16.58)*
5 Placental abruption
6. Absent or reversed end diastolic flow velocity†
7. Use of umbilical catheters**
8. Low Apgar scores**
9. Higher SNAP-II and NTISS scores**
10. PDA (T/t with Indomethacin OR 1.53, untreated OR 1.85)‡
11. Packed cell transfusions††

* Bashiri et al. Ref No.[20] † McDonnell, Semin Neonatol 1997; 2:291-296 ** Ref No. [10], [19], [22]

Table/Fig 3 Factors making premature infant's gut susceptible to NEC

1.	**Mechanical factors(Barrier integrity)**
	Decreased peristalsis
	Mucus layer deficiency
	Composition of lipids(premature gut is more permeable)
2.	**Bacterial factors**
	Delayed or altered bacterial colonization
	Paucity of anaerobic bacteria
3.	**Miscellaneous**
	Decreased gastric acid production
	Decreased lactase levels
	Decreased bile acids(insufficient to form bile micelles)



Table/Fig 4: Unifying concept of Pathogenesis of NEC* (With Permission from Elsevier) [27]

Risk Factors

Prematurity (especially < 28 weeks) is the only consistent risk factor for NEC. Various other risk factors quoted in literature are summarized in [Tab/Fig 2],[10], [19], [20], [21], [22].

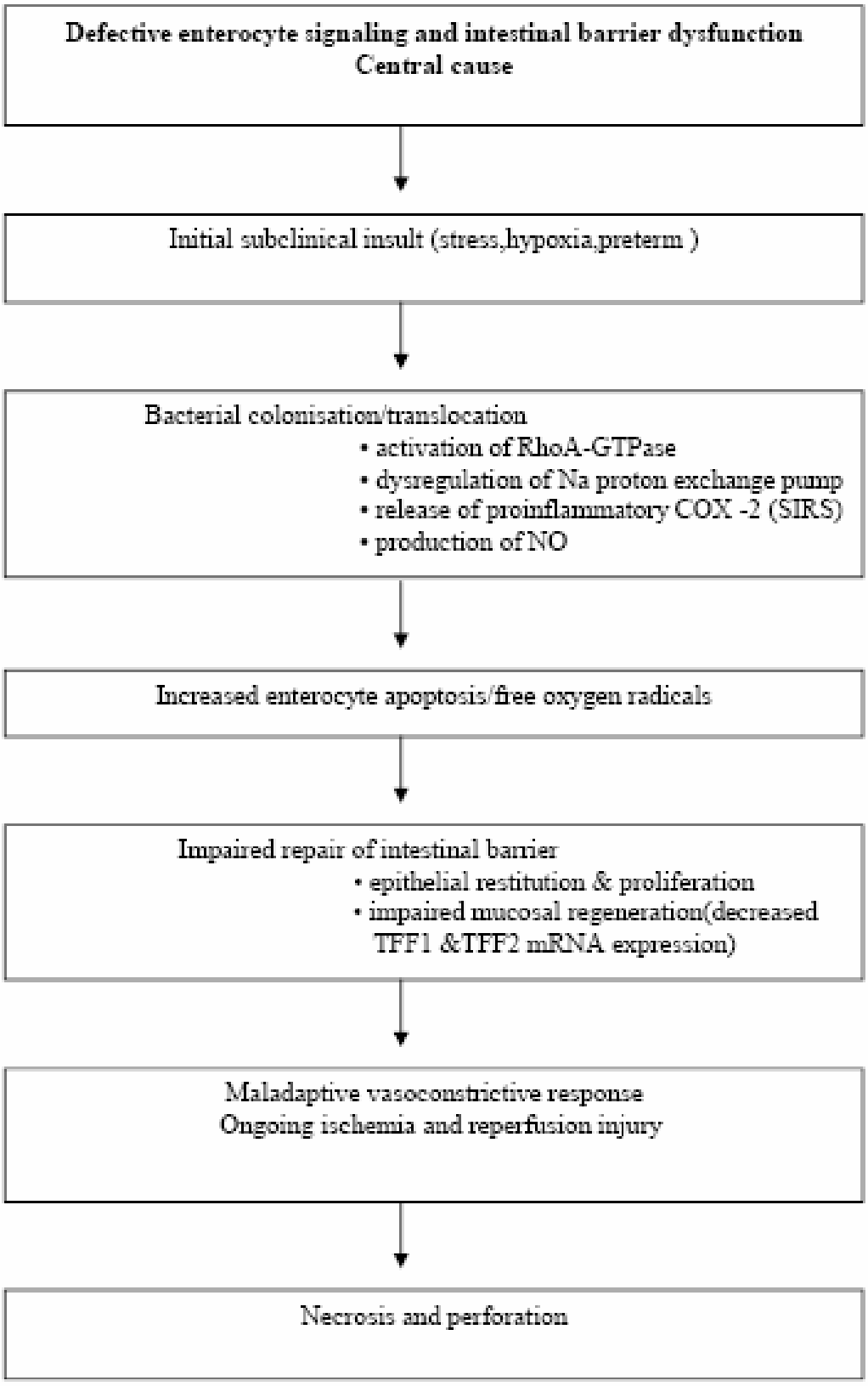
Pathogenesis

The pathogenesis of NEC has not been fully elucidated. The classic histologic finding is coagulation necrosis which is present in over 90% of specimens [23]. Various theories (Santulli, Lawrence, and Kosloske) have been proposed based on clinical, pathologic and epidemiological observations [24],[25],[26].But none of these can explain all the cases of NEC. Recent research has focused on elucidation of the molecular mechanisms contributing to the pathogenesis of NEC. Many new inflammatory mediators (cytokines and hepatic mediators), role of Nitric oxide, infective factors combined with a premature gut which is susceptible [Table/Fig 3] to insult provides newer insights and forms a link for unifying concept for pathogenesis [Table/Fig 4], [Table/Fig 5] ,[27].

(1)Disordered enterocyte signaling

Various studies have clearly indicated a central role for defective enterocyte signaling in the pathogenesis of NEC and recently Hackam et al have proposed a model how this can lead to intestinal barrier dysfunction [28]. Rather than serving as a mere absorptive surface for nutrients, the enterocytes form a tight epithelial barrier that restricts the passage of microbial pathogens and regulates mucosal antigen sampling. The enterocytes are capable of functioning as immune effector cells because they can sense the presence of pathogenic organisms and when stimulated can mount an immune response resulting in the release of proinflammatory cytokines and other mediators. Perturbations in the enterocyte signaling can lead to disruption of the epithelial barrier, bacterial translocation and activation of the inflammatory cascade resulting in full blown NEC [28].

Table/Fig 5: Recent proposed model for pathogenesis of NEC (Ref. no. 28)



(2) Pathophysiologic mediators

(a)Ischemic Reperfusion injury

Ischemia causes accumulation of free oxygen radicals generated by the conversion of xanthine dehydrogenase to xanthine oxidase [29].During reperfusion process there is a further burst of superoxide which causes tissue damage. Thromboembolism is not supported as a cause by histological evidence and diving reflex does not seem to be a plausible explanation considering the timing of occurrence of NEC.

Table/Fig 6: Potentially better Feeding practices (implementation reducing incidence of NEC)*

Feeding practice	*Benefit*	*Level of evidence†*
1.Consistent and comprehensive monitoring of growth and nutritional intake	Improved and more cost-effective nutrition outcomes for VLBW infants	Levels 2-5
2. Early initiation of enteral feeding	Enhance gastrointestinal development, ↓ days required to reach full feeds, ↓ days needed for parenetral nutrition	Levels 2-5
3.Consistent systematic advancement of enteral feeding 10-20ml/kg once trophic feedings established	Enhances growth and outcome	Levels 2-5
4.Uniform consensus and written definations and guidelines for withholding feedings should be adopted		Levels 2,3 and 5
5.Breast milk preferred nutritional substrate for preterm neonates		Levels 1-4
6.Initiation of TPN should be instituted soon as infant is medically stabilized preferably withih 24 hrs of life		Levels 2,3,5
7.Nutrition outcome measures integral aspects of the medical management of preterms		Levels 3-5
8. Use of appropriate enteral products to maintain growth and meet nutrient needs of preterms		Levels 2-5

*Ref No. 54 † Muir Gray Classification system (1997)

(b)Inflammatory mediators

Studies show that intestinal cells of premature infants elaborate higher concentrations of pro-inflammatory cytokines compared to mature cells [30]. IL-18 and IL-12 are up regulated in distal ileum in rat model [31]. IL-10 levels have been shown to be reduced in ileum but increased in serum with babies of NEC [32].Hepatic

inflammatory mediator TNF-α suggest a role of gut-bile axis [33].Epidermal growth factor has maturational effects on intestinal mucosa and its deficiency predisposes infants to NEC [34]. Similarly Platelet activating factor –degrading enzyme (PAF-AH) is decreased in neonates with NEC suggesting role of PAF [35]. The role of Nitric oxide is controversial with low levels been protective by modulating PAF activity and limiting neutrophil adhesion whereas high levels causing generation of peroxy-nitrite radicals causing intestinal barrier dysfunction [36],[37].

(3) Infective factors

The well documented epidemics of NEC and isolation of strains of E.coli and Clostridia as well as improvement in attack rate following the implementation of strict infection control policies and decrease in incidence with prophylactic antibiotics validate the role of infection in the pathogenesis of NEC [38]. Recently in a study on 12 neonates with weekly stool examination by gel electrophoresis 3 neonates who developed NEC have abnormal bands for Clostridium perfringens as compared to control infants [39].However in another study on 422 duodenal aspirates collected from 122 VLBW infants no association was found between duodenal colonization with particular strains of Enterobacteriacae and NEC [40].

Preventive strategies

Various preventive strategies based on patho-physiolgical considerations have been tried with an attempt to prevent this disease with high morbidity and mortality. These strategies fall into three categories: those with proven or probable efficacy, those with unproven efficacy or limited data and experimental strategies.

(1)Breast Milk

The presence of many protective factors in breast milk supports one of the manifold advantages of human milk [41]. Lucas and Cole in a prospective study on 926 preterm infants noted that confirmed NEC was 6 to 10 times more likely in exclusively formula-fed babies than in those who received exclusive human milk and three times more common in those who received formula plus human milk [42]. Meta-analysis of 4 small clinical trials concluded that infants who received Donor human milk were 3 times less likely to develop NEC and 4 times less likely to have confirmed NEC (RR 0.34,95 % CI 0.12- 0.99) [43].

(2) Antenatal steroids

Antenatal glucocorticoids have been shown to induce intestinal microvillus maturation in rats [44]. Crowley reviewed the literature to assess the effects on fetal and neonatal morbidity and mortality and showed that treatment with antenatal corticosteroids is associated with a reduction in the incidence of RDS, IVH and a trend towards reduction in the incidence of NEC(p= 0.051)[45]. Paradoxically Kamitsuka et al in a retrospective study and Guthrie et al in a study of national database noted an increased risk of NEC with antenatal exposure to glucocorticoids [22], [46]. Possible explanations for the increase in NEC include the increased survival of more immature infants, increased use of antenatal steroids and perhaps a tendency to institute and advance feeds more rapidly than is prudent given the improved pulmonary status of these neonates.

(3) Fluid Restriction

Excess fluid intake has been implicated in the pathogenesis of NEC [47]. Cochrane review which included 3 studies concluded that restricted water intake significantly reduces the risks of morbidities like NEC (RR 0.30, 95% CI 0.13-0.17) [48].

(4) Prophylactic Enteral Antibiotics

Cochrane review included five trials of intermediate quality which were heterogeneous in use of enteral antibiotics and age of starting of treatment. The administration of prophylactic enteral antibiotics resulted in a statistically significant reduction in NEC [RR 0.47 (0.28, 0.78] and NEC-related deaths [RR 0.32 (0.10, 0.96)]. A statistically significant increase in the incidence of colonization with resistant bacteria was also shown [RR 1.73 (1.00, 2.97)].Thus routine use of prophylactic antibiotics cannot be recommended [49].

(5) Feeding strategies

(a) Cautious advancement of feeds

Cochrane group reviewed 3 good randomized controlled trials comparing slow versus rapid advancement of feeds in preterm neonates receiving parenteral nutrition. There was no significant effect on Necrotisingenterocolitis (relative risk [RR] = 0.97; 95% confidence interval [95% CI] = 0.50, 1.87).All the three trials were heterogeneous in term of inclusion criteria

(weight) and different definitions used for slow and rapid rates of feeding advancement [50].

(b)Trophic feeding (Minimal enteral nutrition)

Cochrane review included 8 studies which were of poor quality in terms of study design, inability to blind the caregivers, heterogeneity regarding outcome measures and concluded that there was no significant effect on Necrotisingenterocolitis (RR = 1.10, 95%CI ,0.63-1.90)[51].

(c) Standardized feeding Regimens (SFR)

Epidemiological data suggests variations in clinical practices including feeding strategies as an iatrogenic component related to NEC [52]. There are major disagreements among neonatologists for enteral feeding practices which have been shown in a recent survey of Australian neonatologists [53].The Vermont Oxford network "Got Milk" focus group developed eight potentially better practices implementation of which in three NICU's in USA showed reduction in the incidence of NEC Table 4 [54]. A recent Meta-analysis has reported that introduction of a SFR reduced incidence of NEC by 87% (Pooled RR 0.13, 95% CI 0.03-0.50) in LBW infants, 43% in VLBW infants (Pooled RR 0.57, 95% CI, 0.31-1.06, p= 0.08, heterogeneity p=0.02) and overall decrease in the incidence by 29%. However these findings need to be interpreted with caution due to heterogeneity across trials and randomized controlled trials are needed to study the efficacy of SFR [55].

(6) Oral Immunoglobulins

Premature newborns possess decreased levels of immunoglobulin, particularly secretory IgA [56]. Thus, many investigators have evaluated prophylactic immunoglobulin administration on the incidence of NEC. Cochrane review included five studies heterogeneous in terms of entry criteria of neonates, use of placebo (none vs. albumin), type of immunoglobulin use (combination of IgG/IgA, only IgG, IgG with a trace of IgM and IgA and none using IgA alone), dose of immunoglobulin and timing of administration (within 24 hrs to waiting till initiation of enteral feeds) [57]. The oral administration of IgG or an IgG/IgA combination did not result in a significant reduction in the incidence of definite NEC [RR 0.84 (95%CI 0.57, 1.25)].

(7) Arginine supplementation

A relative deficiency of arginine leading to inadequate NO production might predispose the premature infant to inadequate tissue NO levels, vasoconstriction, ischemic-reperfusion injury and ultimately the development of NEC. Amin et al in a prospective trial on 152 neonates showed that the incidence of NEC was significantly lower in group A (receiving supplemental arginine with feeds till 28 days) compared with group B (5/75 vs. 21/77, p< 0.001).However literature is limited to recommend any practice[58].

(8) Probiotics

Probiotics are live microbial organisms which enhance mucosal IgA responses, increase production of anti-inflammatory cytokines and normalize gut ecology [59]. A recent trial on 377 VLBW (<1500 gms) infants randomized to receive Infloran (Lactobacillus acidophilus and Bifidobacterium infantis) with breast milk twice daily until discharge or placebo have shown a significant reduction in incidence from 5.3% to 1.1 % (RR, 0.21, p=0.04)[56].However invasive disease have been reported with sacchromyces in adults and thus it's use need caution[60].

(9) Prophylaxis for PDA

Diastolic steal from a patent ductus arteriosus (PDA) leading to splanchnic under perfusion has been implicated as a risk factor for the development of NEC [61].Cassady et al in a small randomized trial has shown that early prophylactic ligation of PDA reduces the risk of NEC [62]. However recent Cochrane review found no statistically significant difference between surgical closure and indomethacin treatment in mortality during hospital stay, chronic lung disease or Necrotisingenterocolitis [63]. Cochrane review has also shown that prophylactic indomethacin is not associated with an increased risk for development of NEC.

(10) Polyunsaturated Fatty acids supplements

Long chain fatty acids have been proposed to modulate inflammation and immunity [64]. Recently Carlson has shown reduced incidence of NEC in group supplemented with egg phospholipids (2.9 vs. 17.6%, p< 0.05) [65].

(11) Acidification of gastric contents

Carrion and Egan have documented that acidifying the feedings of preterm neonates to a pH low enough to inhibit gastric bacterial proliferation significantly lowers the risk of NEC(1/34 vs. 8/34, p=0.02)[66].

Early Diagnosis

The other important issue which arises after prevention of NEC is to suspect NEC at the earliest stage. Feeding intolerance is thought as a precursor for the development of NEC. Recently Cobb et al found that the maximum volume of residuals was significantly higher in cases (definite NEC) as compared to controls for the 6 days preceding the diagnosis of NEC (4.5ml vs. 2.0 ml; p< 0.001). However, they also noted that the clinical utility of this is limited due to overlap of variables [67].Various experimental strategies(blood, urine and stool tests, radioactive assays and MRI) have been tried which have poor clinical utility due to accessibility issues, high costs, expert assistance, etc [68].

Management

Medical management of NEC is mostly supportive and consists of bowel rest, correction of metabolic acidosis, deranged coagulation profile, maintenance of normoglycemia and normotensive status and adequate antibiotic coverage. A crucial part of medical management is close observation and serial abdominal radiographs and taking timely decision for surgery.

Surgical management

Up to 50% of neonates with NEC develop advanced disease that requires operative treatment [69]. Butter et al have reported an increase in operative rate from 46% in 1990-1994 to 69% in 1995-1999 primarily due to increase in percentage of Stage III patients and post –NEC strictures [70]. Considered the most common surgical emergency during the neonatal period, the operative approach to NEC still provokes doubts, whether with respect of the best time to intervene or the best technique to use because of the different stages of the disease and the great variability in weight and gestational age of the patients affected.

The absolute indications for surgery include presence of pneumo-peritoneum, indicating perforation of the intestine, clinical deterioration despite maximal medical treatment, abdominal mass with intestinal obstruction and development of Intestinal stricture. Relative indications include fixed dilated intestinal loop(in one configuration for more than 24 hrs), presence of portal gas , thrombocytopenia (sensitivity 69%, specificity 60% and positive predictive value 89%) and rapid fall in platelet count (sensitivity 32%, specificity 89% and positive predictive value 92%)[71].

There is evidence in the literature to show that surgery for NEC in unstable babies should be encouraged in NICU itself rather than Operation theatre. Frawley et al compared surgery for NEC in NICU vs. OT during two time periods (1989-1993, 1994-1997). Mortality was similar in the two groups (p=0.14) but hypothermia, deterioration of oxygenation parameters and platelet counts in the OT group was noted to be more [72].

Choice of surgical procedure remains controversial among surgeons due to absence of prospective data. This is shown by a recent survey of pediatric surgeons of UK (95% used peritoneal drainage, 36% in < 1000 Gms and 58% considered it a definite treatment) [73]. There are two multi-centric prospective trials underway evaluating primary peritoneal drainage and laparotomy for babies with NEC (NET trial in < 1000 Gms in UK and NECSTEPS trial in < 1500 Gms neonates in USA).

Post NEC issues

(1)Early feeding

There is no standard recommendation for when enteral feedings should be reinitiated after NEC.

Early initiation of enteral feeding may help in recovery of intestinal mucosa whereas delaying for more than one week predisposes it to recurrent intestinal injury and feeding intolerance [74]. Bohnhorst et al compared two feeding regimens in neonates post NEC. Group I received feeds when serial abdominal Ultrasounds did not showed evidence of portal venous gas for three consecutive days(Average 4 days, range,3-14) vs. Group II which received feeds starting at the discretion of neonatologists (average 10 days, range, 8-22 days). Early feeding group was associated with shorter time to reach full feeds (p<0.01), reduced duration of central venous access (p<0.01) and a shorter duration of hospital

stay ($p<0.05$) [75]. Early feeding is also supported by the fact that gastrointestinal hormonal profiles of preterm infants with an ileostomy are normal to increased [76].

(2) Short bowel syndrome (SBS)

Short bowel syndrome is the most challenging issue in management in post NEC survivors. The clinical course is unpredictable and may result in prolonged requirement of parenteral nutrition which may lead to complications such as infectious processes, cholestasis, inadequate bone mineralization and death. Andorsky et al has reviewed case records of 30 children of SBS (half due to NEC) and showed that presence of an intestinal segment greater than 83 cm (±67cm) ($r = -0.475$) , enteral feeding with maternal milk ($r = -0.821$) or amino acid formula
($r = -0.793$) were associated with shorter period of parenteral nutrition use[77]. Similarly Quirós-Tejeira has reviewed case records of 78 children with SBS requiring TPN for more than 30 days and showed that best survival rate was associated with a remaining small intestine segment of more than 38 cm, an intact ileo-cecal valve, intestinal reconstruction after stomas and primary anastomosis[78].

Prognostic Indicators

Poor outcome has been associated with stage of the disease (stage III, been shown as independent predictor of post op mortality), extent of intestinal involvement (67% for pan-intestinal, 12% for focal and 30% for multi-focal), birth-weight and gestational age [79]. Recently Severe thrombocytopenia has been shown as predictor of mortality (OR 6.39; $p=0.002$) and NEC related GI complications (OR 5.47; $p=0.006$) [80]. Ironically platelet transfusions have not been shown to reduce any mortality but instead increase morbidity [81]. .Portal venous gas is not a predictor of either operative intervention or mortality [82]. .In a recent multiple logistic regression study on 70 neonates (<1000 gms) post operative mortality was predicted best by the number of associated co-morbidities rather than the choice of operative modality [83]. Hall et al have recently shown that hyperglycemia (>11.9 mmol/l) is also associated with late mortality and longer NICU stay [84].

Outcome

The outcome shows a pessimistic picture with 20-50% mortality, 20-30% developing fibrosis and stricture, 10% developing short gut syndrome and 5-10% developing recurrent disease [71]. Besides this adverse long term developmental outcomes are shown in NEC survivors [85],[86].Surgical NEC (Not medical NEC) have been shown as an independent risk factor for adverse Mental development index <70, Psychomotor developmental index <70 and neuro-developmental impairment [87].

Conclusion

With the advances in perinatal care there are changing epidemiological terns for NEC with increasing number of ELBW neonates surviving. Research for understanding of pathogenesis is focused on molecular mechanisms and unifying concept of pathogenesis is emerging. Various preventive strategies for NEC remain inconclusive with utilization of potentially better feeding practices suggested as a global approach for prevention. It remains a disease of high morbidity and mortality with adverse long term outcomes. Future research needs to direct towards clinically useful preventive and diagnostic strategies based on recent emerging concepts of pathogenic mechanisms (role of cytokines, nitric oxide, cyclo-oxygenases, etc).

Conflict of Interest: None

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