Review: Treatment of Necrotizing Enterocolitis

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Available evidence supports use of prophylactic probiotics to prevent NEC?

When is the optimal timing to use probiotics, if they are given? At birth? First 24 hours of life? First week? When full feeds are tolerated?
Prophylactic Probiotics

- Cochrane Review in 2011
- Safety and efficacy of prophylactic probiotics (before NEC)

- Primary outcomes:
  - Incidence of severe (Bell Stage ≥ 2) NEC
  - Nosocomial sepsis
Prophylactic Probiotics

- Sixteen trials – 3000 infants
- Infants <37 weeks gestation, <2500 g
- Any live microbial supplement for > 7 days compared to placebo or nothing
- Variable timing of administration
  - First 24 hours, first feed, feeds tolerated
- Variable formulations
  - *Lactobacillus, Bifidobacterium, Saccharomyces boulardii*
Prophylactic Probiotics

- Probiotics reduced the incidence of severe NEC
  - RR 0.35 (95% CI -0.24 to 0.52)
- Infants <1500 g also had benefit
  - RR 0.34 (95% CI 0.23 to 0.50)
- Reduction in total hospital days
- Reduction in time to full feeds
Prophylactic Probiotics

- No difference in time on TPN
- No difference in long term developmental outcomes
- No systemic infections from probiotics
- Not able to extract data for infants <1000 g
Prophylactic Probiotics

- Available evidence supports use of prophylactic probiotics to prevent NEC.

- No definite optimal time to give them – but usually early.
Human Breast Milk vs. Formula

- In preterm infants, how does formula feeding affect:
  - Incidence of NEC?
  - Weight/length gain?
  - Feeding tolerance?
Human Breast Milk vs. Formula

- Two Cochrane Reviews addresses this question
- First compared donor breast milk to formula
- Included preterm infants (<37 weeks) or low birth weight (<2500g)
Human Breast Milk vs. Formula

- Randomized controlled trials

- Primary outcomes of growth and development

- Secondary outcomes of neonatal death, NEC, time to full feeds, feeding intolerance, and invasive infections
Eight studies fulfilled criteria
  ◦ Most in late 70’s and early 80’s

About 1000 infants included
  ◦ Average gestation < 32 weeks
  ◦ Average weight <1800 grams

Formula feeding associated with:
  ◦ Higher rate of weight gain
  ◦ Faster increase in length
  ◦ Faster increase in head circumference
Human Breast Milk vs. Formula

- Formula feeding associated with an increased incidence of NEC
  - RR 2.5, 95% CI 1.2 to 5.1

- Subgroup analyses determined a modest increase in NEC incidence with formula
  - Term formula vs. donor breast milk
  - Preterm formula vs. donor breast milk
  - Formula as sole diet vs. breast milk sole diet
  - Formula as a supplement to breast milk
  - Formula vs. nutrient fortified breast milk
Human Breast Milk vs. Formula

- Second Cochrane Review

- Formula vs. Maternal Breast Milk
  - Preterm infants <37 weeks
  - Low Birth Weight <2500 grams
Human Breast Milk vs. Formula

- Primary outcome of weight gain and growth and development

- Secondary outcomes of morbidity and mortality
  - NEC
  - Time to full feeds
  - Feeding intolerance
  - Occurrence of invasive infections
Human Breast Milk vs. Formula

- Six studies identified for evaluation

- All excluded
  - Not randomized studies
  - Received both maternal and donor breast milk

- No conclusions
Human Breast Milk vs. Formula

- In preterm infants, formula feeding is associated with:
  - Increased NEC
  - Faster weight and length gain
  - Increased feeding intolerance
Timing and rate of feeds

- Delaying enteral feeds for 5 to 7 days after birth in preterm infants helps prevent NEC?

- Does slow advance of feeds (<24ml/kg/day) have a decreased incidence of NEC?
Timing of feeds

- Cochrane Review
- Randomized studies
- Very low birth weight (<1500 grams)
- Very preterm (<32 weeks)
- “Delay” of more than 4 days after birth vs. earlier feeds
Timing of feeds

- Primary outcome variables
  - Any stage of NEC
  - Neonatal mortality

- Secondary outcome variables
  - Growth and development
Timing of feeds

- Five trials with 600 infants total
- No benefit to delaying initial feeds
  - RR of NEC 0.89, 95% CI 0.58 to 1.37
- Delay of initial feeds resulted in a delay in time to full enteral feeds
Rate of feeds

- Very low birthweight (<1500 grams)
- “Slow” advance of <24 ml/kg/day
- “Fast” advance of 30-35 ml/kg/day
Rate of feeds

- Four randomized studies identified
- Included almost 500 patients
- No association with development of NEC
  - RR 0.91, 95% CI 0.47 to 1.75
- Slow advancement led to longer time to regain birth weight and reach full enteral feeds
Timing and rate of feeds

- Delaying enteral feeds for 5 to 7 days after birth in preterm infants does not prevent NEC.

- Rate of increase of feeds does not matter.
Peritoneal Drain vs. Laparotomy

- Is there a mortality difference between use of peritoneal drainage and laparotomy to treat perforated NEC?

- Is there any difference in neurodevelopmental outcomes in patients treated with peritoneal drainage compared to laparotomy for perforated NEC?
Peritoneal Drain vs. Laparotomy

- Two prospective randomized trials
- Moss study (2006, NEJM)
- Infants with perforated NEC
- Weight <1500 grams
- Clinical suspicion of bowel perforation as determined by the treating physicians
- Peritoneal drainage intended as definitive management
Peritoneal Drain vs. Laparotomy

- Sample size calculation of 130 patients
  - Expected mortality reduction from 50 to 25%
  - Power of 0.82

- Randomization stratified by birth weight
  - <1000 grams
  - 1000 – 1499 grams
Peritoneal Drain vs. Laparotomy

- 117 infants randomized
- Study concluded when funding ended

- No survival difference at 90 days
  - 34.5% mortality for peritoneal drain
  - 35.5% mortality for laparotomy

- No difference in TPN dependence
- No difference in length of stay
Peritoneal Drain vs. Laparotomy

- Intention to treat analysis

- 21 patients “crossed over” to laparotomy
  - 5 “early,” 16 “late”
Peritoneal Drain vs. Laparotomy

- Infants with perforated NEC
- Weight < 1000 grams
- Documented pneumoperitoneum
- Laparotomy “rescue” allowed as soon as 12 hours after peritoneal drain
Peritoneal Drain vs. Laparotomy

- Sample size calculation of 208 patients
- 20% expected survival difference
- 0.90 power
Peritoneal Drain vs. Laparotomy

- 69 patients enrolled and randomized
- Enrollment terminated due to slow accrual

- No mortality difference at 1 and 6 months
  - 34.3% PD vs. 24.2% laparotomy at 1 month
  - 48.6% PD vs. 36.4% laparotomy at 6 months
Peritoneal Drain vs. Laparotomy

- No difference in length of stay
- No difference in ventilator dependence
- No difference in need for TPN

- “Crossover” rate of 74% in the peritoneal drain group
  - Failure of clinical stabilization
  - Average of 2.5 days after drainage
Peritoneal Drain vs. Laparotomy

• Ongoing study to evaluate neurodevelopmental outcomes at 18 to 22 months of age following treatment for perforated NEC

• Background from NICHD Neonatal Research Network data

• 16 participating NICUs
Peritoneal Drain vs. Laparotomy

- Prospective cohort study
- Infants <1000 grams
- Thought by treating physicians to warrant surgical intervention
- No direction of type of operative treatment
Peritoneal Drain vs. Laparotomy

- 156 infants enrolled
  - 49% initial laparotomy, 51% initial drainage

- No survival difference between treatments

- Suggestion of laparotomy patients having improved neurodevelopmental outcomes
  - 38% of laparotomy survivors “impaired”
  - 63% of peritoneal drain survivors “impaired”

- Combined outcomes of death or neurodevelopmental impairment favor laparotomy for improved outcomes
  - OR 0.56, 95% CI 0.19 to 1.69

- Possible that infants receiving peritoneal drainage were higher risk
Peritoneal Drain vs. Laparotomy

- There is NO mortality difference between use of peritoneal drainage and laparotomy to treat perforated NEC.
  - Studies did not reach enrollment goals.

- Evaluation of neurodevelopmental outcomes is underway, but laparotomy patients may have a better outcome based on retrospective data.
Primary Anastomosis versus Enterostomy in Necrotizing Enterocolitis
Does primary anastomosis vs. enterostomy at laparotomy as treatment for NEC affect mortality or long-term morbidity?
Anastomosis vs. Enteroostomy

- Traditional approach at laparotomy for NEC has been resection and creation of enterostomy
- Risks of anastomotic complications have been considered high in setting of infection, ischemia and hemodynamic instability
- Since the ‘70’s and 80’s some surgeons have advocated primary anastomosis citing complications of enterostomy and second laparotomy
Studies

- Ten articles identified
- No randomized clinical trials
- Retrospective case series (n=8) or cohort studies (n=2)
- No study ensured baseline similarities of groups
- 5 of 10 studies did not perform any statistical analysis
- Studies overall were inconclusive due to selection bias and lack of power
Studies

- Small sample sizes
  - About 20 in each group
- Selection bias
  - Unstable, complex patients ostomy
- Conclusions not based on data
- Randomized trials ongoing to answer question
Conclusion

There is lack of comparative evidence to support primary anastomosis over enterostomy after intestinal resection during laparotomy for acute NEC in infants.

Currently only Level IV evidence exists, Grade D recommendation.
Antibiotics and Recurrence in Necrotizing Enterocolitis
Does length or type of antibiotic treatment affect recurrence rate of NEC?
Antibiotics and Recurrence

- Recurrence of NEC: 4-6%

- Alteration of neonatal intestinal flora by various parenteral and enteric antibiotic combinations

- Clinical consequences unclear
  - Surgical Infection Society and the Infectious Diseases of Society of America
    - Ampicillin, gentamicin, and metronidazole; ampicillin, cefotaxime, and metronidazole; or meropenem for medical management of NEC
    - Vancomycin instead of ampicillin for suspected MRSA or ampicillin-resistant enterococcus
  
  - WHO recommendation: ampicillin or penicillin, gentamicin, and metronidazole

- NEC recurrence rate **not** used as outcome for these recommendations
Review Findings

Three articles

◦ addressed factors contributing to recurrence
◦ compared the clinical outcomes of parenteral antibiotic regimens used in the treatment of NEC
Compared peritonitis, perforation, mortality, thrombocytopenia, stricture, and recurrence rates between two antibiotic regimens used to treat NEC


5 recurrences among 46 patients (10.9%) in the ampicillin/gentamicin group, 0 of 44 patients in the cefotaxime/vancomycin group

- Most recurrences in patients under 2200 grams (4 of 5 recurrences)
- Difference not statistically significant

Additional Studies

- Stringer
  - Retrospective case review, 200 patients, 1981-1991
  - 16 recurrences
  - 12/16 had undergone surgery before recurrence
  - No association: feeding patterns, method of management of the original episode (medical or surgical); did not address antibiotics

Additional Studies

• Faix

  ◦ Randomized controlled trial

  ◦ 42 patients, ampicillin/gentamicin vs. ampicillin/gentamicin/clindamycin

  ◦ Clindamycin group with higher stricture
    • 6/15 vs. 1/18, p = 0.022

  ◦ Demonstrated that antibiotic choice can affect outcomes

  ◦ Did not address recurrent NEC

Conclusion

There is a lack of evidence upon which to base recommendations for antibiotic protocols that may decrease NEC recurrence.
Summary

1) Does the use of prophylactic probiotics reduce the rate of NEC in newborn infants?

**Grade A/B recommendation:** Routine supplementation of enteral intake with probiotics in premature infants reduces the incidence of NEC.
Summary

2) Does exclusive use of human breast milk rather than formula affect the rate of NEC in newborn infants?

Grade A/B recommendation: Formula-fed preterm and low birth weight infants have an increased risk of NEC compared to breast milk.
Summary

3) Does the introduction and rate of feeding affect development of NEC in preterm infants?

**Grade C recommendation:** Delaying in feeds in preterm infants does not avoid NEC.

**Grade B recommendation:** Slow progression of feeds does not avoid NEC.
Summary

4) Does peritoneal drainage versus laparotomy as treatment for perforated NEC affect mortality or long term sequelae such as neurodevelopmental outcomes and stricture rates?

Grade B recommendation: Two RCT’s showed no significant difference in survival between drainage versus laparotomy. One of these studies recommended peritoneal drainage for temporizing measure only.

Level IV evidence: Stricture rates, wound dehiscence, and intraabdominal infections were not different between drainage and laparotomy. Neurodevelopmental outcomes are better in the laparotomy group, but there may be inherent selection bias.
Summary

5) Does primary anastomosis at laparotomy vs enterostomy as treatment for NEC affect mortality or long term sequela such as neurodevelopmental outcomes and stricture rates?

Level IV evidence, Grade D recommendation: Data regarding outcomes between these two therapies are currently inconclusive.
Summary

6) Does length or type of antibiotic treatment affect recurrence rate of NEC?

Level IV evidence, Grade D recommendation: Data regarding antibiotic types and duration of treatment for recurrent NEC are currently inconclusive.
Questions to Panel