Colostrum as Oral Immune Therapy to Promote Neonatal Health

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ABSTRACT

It is well known that the immune response is blunted and underdeveloped in the premature infant, but human milk supports the infant’s growth, function, and effectiveness. Thus, own mother’s colostrum (OMC) administered oropharyngeally has potential to deliver oral immune therapy (C-OIT) even before enteral feedings have begun. Colostrum interacts with lymphoid tissue in the oropharynx and gut. Colostrum as oral immune therapy is delivered by swabbing the cheeks in the first days of life. Little formal study has evaluated its effectiveness. However, small studies demonstrate that it is a practice that is safe, feasible, and well tolerated even by the smallest premature infants. Encouraging preliminary evidence supports the effect of C-OIT to reduce the time to full enteral feedings. Effects on other outcomes is unclear, in part because existing studies are underpowered to detect significant differences on outcomes like necrotizing enterocolitis, sepsis, and death. Another limitation in the evidence base is that adherence to the intervention and the number of doses of colostrum infants received in the studies is not consistently made clear. More well-designed studies are needed to demonstrate the impact on neonatal complications and how C-OIT supports the infant's immune development. Quality improvement and time series reports of differences pre- and postimplementation of OMC given orally should minimally include statistics for adherence to the intervention and/or the number of doses an infant received as a covariate. Even so, OMC is an immune therapy that poses little risk yet offers likely cost-effective benefit for vulnerable infants.

Key Words: breast milk, colostrum, extremely low birth weight, health promotion, human milk, infection prevention, neonate, neonatal intensive care, nutrition, oral immune therapy, very low birth weight

In the United States, 1 out of every 8 infants is born premature, and of those born very low birth weight (<1500 g), 30% will experience unintended complications effecting their neurologic, gastrointestinal, and/or respiratory health for life. Complications of prematurity including chronic lung disease, retinopathy of prematurity, sepsis, and necrotizing enterocolitis (NEC) all share a common beginning in an immature and exaggerated inflammatory response. However, premature infants have a treatment available to them that other critically ill adult patients do not—their own mother’s milk, beginning with colostrum. Own mother’s colostrum (OMC) provides an immune therapy to stimulate the development and response of the neonatal immune system. Human milk feeding, particularly if exclusive in the first 14 to 28 days of life, reduces neonatal complications by improving progression to enteral feeding and delivering powerful immune-boosting nutrition.

Very low-birth-weight (VLBW) infants unable to feed orally can still receive immunologic benefits of colostrum unless breast milk is contraindicated. Contraindication to breast milk feeding is rare and even controversial. In the United States, it is recommended that a mother with human immunodeficiency virus (HIV/AIDS) or human T-cell lymphotropic virus type 1 (HTLV-1) should not breastfeed or provide...
breast milk for her infant although the recommenda-
tion differs in less-developed countries with less access
to clean water and formula supplements. Other viral
illnesses in the mother such as chicken pox, hepatitis
B and C, herpes simplex, and cytomegalovirus should
be evaluated on an individual basis, depending on
when the mother acquires the virus and where the
lesions occur. An infant diagnosed with galactosemia
should not receive breast milk.6

A sometimes-devastating infection that preterm
and high-risk neonates are vulnerable to is NEC; however, implementation of prevention practices
could reduce NEC by at least half.7 A recently devel-
oped evidence-based bundle designed to increase
human milk feeding in California NICUs demonstrated
a statistically significant impact on NEC rates
when oral immune therapy using colostrum, prefer-
ential feeding of human milk, and use of standard-
ized feeding protocols were implemented together.8

The importance of human milk in the manage-
ment of preterm and high-risk neonates is well docu-
mented and recommended by the American Academy
of Pediatrics, with colostrum being the perfect first
immune stimulator in infants.9 Human milk, in addi-
tion to being the perfect species-specific nutrition for
an infant, contains many types of protective agents.
Colostrum is the milk produced in the first few days
after birth when the tight junctions in the mammary
epithelium are open. Open tight junctions allow for
transport of many more immune components from
the mother’s circulation into the milk.10 Human milk
changes in response to antigens the mother is
exposed to or immunized against. These antigens
allow lymphocytes in the breast to secrete immuno-
globulin into the milk. Therefore, the more a mother
visits and holds her hospitalized infant skin to skin
(kangaroo care), the more likely her breast milk will
provide unique specific protection to her infant.6

**BIOLOGIC PLAUSIBILITY FOR COLOSTRUM AS ORAL IMMUNE
THERAPY**

The unique properties of human milk provide the
neonate with “immunologic, anti-infective, anti-
inflammatory, epigenetic, and mucosal membrane
protecting properties.”7,11,p175 Human colostrum has
higher concentrations of secretory IgA, growth fac-
tors, lactoferrin, anti-inflammatory cytokines, oligo-
saccharides, antioxidants, and other protective com-
ponents as compared with mature human milk.

In a theoretical paper describing the foundation
for how colostrum works as immune therapy, Rodriguez et al.10 described in detail how the composi-
tion of colostrum stimulates the immature neo-
natal immune system by a prebiotic mechanism.
Through lymphoid tissue in the oropharynx and the
gut, colostrum stimulates immune development.

When infants are fed via nasal gastric tube, the
immune benefits of human milk bypass the or-
pharyngeal mucosa-associated lymphoid tissue.
When given oropharyngeally, cytokines in the OMC
interact with lymphoid cells in the lymphoid tissue
in the mouth. Absorbing the immunologic factors
via the oral mucosa stimulates the immune system
systemically and promotes the mucosal differentia-
tion in the gut and thus, developing the protective
gut immune barrier. Stimulation of both the or-
pharyngeal mucosa-associated lymphoid tissue and
the gut-associated lymphoid tissue is important to
best overall immune development.

Lactoferrin is an important protein present in high
concentrations in colostrum; these levels are even
higher when a mother delivers prematurely.12
Lactoferrin, a glycoprotein and oligosaccharide (ie,
prebiotic) found in colostrum, supports the innate
immune response to maintain a wide range of physio-
logic norms.13 It has antimicrobial, anti-inflammatory,
and immunomodulatory functions. Interestingly, lac-
toferrin binds to iron, preventing pathogenic organ-
isms from obtaining iron from the infant necessary for
their survival.12,14,15 There have been several small
clinical trials showing that lactoferrin decreases the
incidence of lower respiratory tract infections, the
duration of dehydrating diarrhea, the severity of rota-
virus infection, and the colonization with giardia in
infants.14,16-19 Despite the significant evidence of the
benefit of human milk for this vulnerable population,
lactation rates for these infants in the NICU are lim-
ited.20 No parent is prepared to have their newborn
cared for in the NICU. It is extremely difficult to main-
tain the necessary pumping regimen needed to ensure
adequate milk production when parents cannot freely
touch or hold their newborn. In addition to being con-
cerned on a daily basis for the life of her infant, a
mother must rely on a mechanical breast pump, pumping
at least 8 times each day to establish and maintain
an adequate milk supply.

**PROCEDURE FOR COLOSTRUM AS ORAL IMMUNE THERAPY**

A proposed solution to early exposure of human
milk to neonates in the NICU is to use OMC as oral
immune therapy. A sample “colostrum as oral
immune therapy” (C-OIT) protocol is shown in
Table 1, derived from assembling the protocols of
the studies in this review. Oropharyngeal adminis-
tration of OMC is not given as an enteral feeding
and is in such small volumes that the infant does not
need to swallow. A small amount of milk (typically
0.2 mL divided between 2 cheeks) is placed on the
oral mucosa in the buccal cavity for absorption. A
sterile cotton swab or oral applicator is used for each
application of human milk. A caregiver, preferably
the parent, gently paints the inside of the mouth,
including the tongue, gums, and buccal area. Fresh colostrum is ideal and should be used whenever possible. Proper identifiers are a must to ensure that the patient receives only the milk of the biologic mother. Most tested protocols provide oral care with human milk every 3 to 4 hours.

**CLINICAL QUESTION AND SEARCH STRATEGY**

To answer the clinical question, “In critically ill neonates does oral immune therapy with colostrum compared with usual care without colostrum positively impact outcomes (eg, complication rates, time to full feedings, the number of feeding interruptions, and immune response),” a search of the literature was completed. The outcome in question was kept broad to reflect multiple potential benefits. Research articles were searched using several databases including CINAHL, Cochrane, PsycInfo, and PubMed. Terms used for the search included colostrum, neonate, neonatal intensive care, oral immune therapy, buccal care, and oropharyngeal administration of colostrum. Articles were retained if they had been published in the last 10 years, were reporting an original research study, and had full-text English language available. On the basis of these criteria, 5 research reports were retained. Very few studies were identified using this search strategy. To ensure a comprehensive search, dissertation abstracts indexed in ProQuest and conference proceedings for the International Society for Research on Human Milk and Lactation (ISRHML; 2011-2013) and Pediatric Academic Societies (PAS; 2009-2013) were also searched, yielding 2 additional research reports.

**RESULTS**

**Study Quality**

Overall, study quality was fair. Studies identified in the search included 2 feasibility trials, 2 small randomized controlled trials, 2 pre-/postcohort studies, and 1 study in which C-OIT was studied as part of a feeding protocol. The studies differed in the dosing frequency for oral immune therapy (eg, every 2 hours, every 3–4 hours, and every 4 hours), the duration of treatment, and the outcomes measured. Duration of therapy ranged from 48 hours to 7 days. Adherence to the intervention (ie, the number of daily doses of C-OIT) was incompletely measured, potentially explaining marginal effects. Small study samples were used, likely potentiating the inability to detect a group difference if they existed (ie, leading to a type II error likely with underpowered studies with small samples). Another limitation is that 2 of the studies were published in a journal with limited peer review, and 1 study was a dissertation, and a final study was a peer-reviewed conference abstract.

**Study Findings and Strength of Evidence**

Overall, C-OIT is safe and feasible with very low to no risk associated with the intervention. Infants who received C-OIT began enteral feedings sooner and were less likely to be growth restricted at 36 weeks’ postmenstrual age. In at least 1 study, when C-OIT was administered as part of a feeding protocol, the number of total parenteral nutrition days and total parenteral nutrition–related outcomes were impacted. Across the studies, small sample sizes yielded low statistical power and no differences were identified in infectious outcomes like NEC and VAP. Study results are summarized in Table 2.
### TABLE 2. Effect of Colostrum as Oral Immune Therapy on Neonatal Outcomes

<table>
<thead>
<tr>
<th>Citation, Funding and Study Location</th>
<th>Research Design Sample</th>
<th>Intervention</th>
<th>Outcomes Measured</th>
<th>Results</th>
<th>Study Limitations</th>
<th>Strengths</th>
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<tbody>
<tr>
<td><strong>Feasibility studies</strong></td>
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<tr>
<td>Rodriguez et al, 2010&lt;sup&gt;22&lt;/sup&gt;</td>
<td>Quasiexperimental design using a pretest and posttest in a single center</td>
<td>0.2 mL OMC oropharyngeally every 2 h for 48 consecutive hours, beginning at 48 h of life.</td>
<td>Feasibility and variation in secretory immunoglobulin A and lactoferrin in urine and tracheal aspirates.</td>
<td>Feasible and safe.</td>
<td>First study of its kind; nonrandomized; clinical outcomes not measured; no adverse events reported.</td>
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<tr>
<td>NINR funded Midwest, the United States</td>
<td>N = 5 ELBW</td>
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<td>Montgomery et al, 2010&lt;sup&gt;21&lt;/sup&gt;</td>
<td>Prospective, descriptive single-center feasibility pilot from June 1, 2007, to May 31, 2008</td>
<td>0.2-mL OMC as soon as available after birth every 3 h for 7 consecutive days</td>
<td>Feasibility statistic number of oropharyngeal colostrum administrations given divided by the number planned</td>
<td>Number of mothers willing to supply OMC increased from 82% in first 6 mo to 92% in 2nd 6 mo. First OMC given at 40 ± 28 h of birth. 75%-80% of planned administrations were actually given. Feasibility statistic = 77 ± 36%.</td>
<td>Length of C-OIT longer than other studies. Clinical outcomes not assessed, no adverse events reported.</td>
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<tr>
<td>Mountain West, the United States</td>
<td>VLBWs N = 56 eligible</td>
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<td><strong>Colostrum as oral immune therapy studies</strong></td>
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<tr>
<td>Rodriguez et al, 2011&lt;sup&gt;23&lt;/sup&gt;</td>
<td>Prospective, single-blinded RCT Sample: ELBW s N = 15 C-OIT group = 9 Placebo group = 6</td>
<td>Protocol included OMC or sterile water 0.2 mL to buccal mucosal tissue (0.1 mL to each cheek) every 2 h for 48 h</td>
<td>Change in secretory IgA, Lactoferrin (Lf), and IL-10 (tracheal aspirates and serum) Day of life to reach full enteral feeding (150 mL/kg per day)</td>
<td>Treatment group reached full enteral feeding volumes 10 d before placebo group (M = 14.3 ± 5.7 vs 24.2 ± 8.7 d; P = .032). Trend toward change in urine sIgA (moderate effect, urine), and urine Lf (large effect).</td>
<td>Rigorous design with blinding. Underpowered, likely resulting in a type II error.</td>
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<tr>
<td>NIH/NINR funded Midwest, the United States</td>
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</table>
TABLE 2. Effect of Colostrum as Oral Immune Therapy on Neonatal Outcomes (Continued)

<table>
<thead>
<tr>
<th>Citation, Funding and Study Location</th>
<th>Research Design Sample</th>
<th>Intervention</th>
<th>Outcomes Measured</th>
<th>Results</th>
<th>Study Limitations Strengths</th>
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<tbody>
<tr>
<td>Thibeau et al, 2013²⁶</td>
<td>Retrospective pre-/ poststudy of mechanically ventilated infants (&lt;1500 g) 2006-2009</td>
<td>Oral suction followed by painting oral mucosa with sterile tips of 2 cotton swabs saturated with Mothers’ own milk (not just OMC) as oral care as part of VAP bundle. Minimum every 4 h until feeding orally.</td>
<td>Safety and feasibility. Rate of positive tracheal aspirates, positive blood cultures, number of ventilator days, length of stay</td>
<td>Median doses = 48 (range, 0-243). No adverse events. Days of mother’s own milk increased from median of 15 d (range 0-93 d) in the precohort to median of 33 d (range, 0-123d ) post. No significant differences in ventilator days or length of stay ($P = .46$, $P = .36$). Rates of positive tracheal aspirates and blood cultures trended down but not statistically significant ($P = .15$).</td>
<td>Underpowered to detect a risk difference in low incidence condition like VAP.</td>
</tr>
<tr>
<td>Seigel et al, 2013²⁵</td>
<td>Retrospective, single-center cohort study of inborn ELBWs from January 2007 to September 2011</td>
<td>OMC 0.2 mL every 4 h for 5 d beginning in first 48 h of life</td>
<td>Day of life feedings began</td>
<td>Began feedings sooner ($P &lt; .001$). Days reached 100 mL/kg per day ($P = .09$). Heavier at 36 wk (adjusted for weight at birth, $P &lt; .01$). 85% received some C-OIT No differences in surgical NEC or SIP</td>
<td>Adherence to the intervention not measured. Unclear how many C-OIT doses each infant received. Underpowered to detect NEC or SIP differences.</td>
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<tr>
<td>Institutional NIH funding</td>
<td>Southeast, the United States</td>
<td>N = 369 Pre: n = 280 Post: n = 89</td>
<td>Day reached 100 mL/kg per day Day regained BW Weight at 36 wk NEC or SIP</td>
<td>(continues)</td>
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</tr>
<tr>
<td>Citation, Funding and Study Location</td>
<td>Research Design Sample</td>
<td>Intervention</td>
<td>Outcomes Measured</td>
<td>Results</td>
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<td>Caprio et al, 2013&lt;sup&gt;27&lt;/sup&gt;</td>
<td>Descriptive pre-/posttest after a feeding protocol was initiated including C-OIT in a single center Infants &lt; 1250 g N = 58 (baseline = 39; postintervention = 19)</td>
<td>C-OIT with feeding protocol (standard start, advance, early trophic feeds, feeding intolerance algorithm, withdraw TPN at 120 mL/kg per day enteral volume)</td>
<td>Number of TPN days TPN-related cholestasis Central line days Lab draws blood transfusions Growth at discharge</td>
<td>Fewer TPN days (P ≤ .002; baseline 27.4 ± 17 vs intervention 18.2 ± 12.4 d). Fewer central line days (baseline 28.2 ± 173 vs intervention 18.9 ± 13, P ≤ .02). Lower maximum direct bilirubin levels (P &lt; .01). Lower maximum alkaline phosphatase (P &lt; .0005). 32% reduction in infants discharged small for gestational age (P &lt; .007). No significant difference noted in lab draws, late onset sepsis, and NEC.</td>
<td>Feeding protocol with OMC as OIT decreased days of TPN and central lines. Improved growth in the postintervention group. Did not separate out the contribution of OIT. Underpowered to detect differences in low-incidence outcomes like sepsis and NEC.</td>
</tr>
<tr>
<td>McFadden, 2012&lt;sup&gt;24&lt;/sup&gt;</td>
<td>RCT with 3 groups GA 26-34 wk BW 590-2530 g N = 29 Infants who were mechanically ventilated or supported with nasal continuous airway pressure Oral care with colostrum (n = 11), sterile water (n = 10), or saline (n = 8)</td>
<td>Oral care with colostrum (n = 11), sterile water (n = 10), or saline (n = 8)</td>
<td>Differences in colonization of mouth for colostrum, sterile water, or saline.</td>
<td>Cultures were all positive for bacterial growth by week 2 or 3. Coagulase negative staph most common. Groups were not significantly different by BW or GA but did not report illness severity differences by group.</td>
<td>Study attrition (n = 2) and challenges with obtaining oral cultures limited reliability of findings. Did not measure feeding or infection outcomes.</td>
</tr>
</tbody>
</table>

Abbreviations: BW, birth weight; C-OIT, colostrum as oral immune therapy; ELBW, extremely low birth weight; GA, gestational age; IgA, immunoglobulin A; IL-10, interleukin 10; Lf, Lactoferrin; NEC, necrotizing enterocolitis; NIH, National Institutes of Health; NINR, National Institute of Nursing Research; OIT, oral immune therapy; OMC, own mothers’ colostrum; RCT, randomized controlled trial; sIgA, secretory IgA; SIP, spontaneous intestinal perforation; TPN, total parenteral nutrition; VAP, ventilator-acquired pneumonia; VLBW, very low birth weight.
IMPLICATIONS FOR PRACTICE

At this time, the theoretical explanation for how C-OIT acts to stimulate the immune response is supported by preclinical and early clinical studies. It appears to be safe and feasible. Although strong evidence about its impact on clinical outcomes is lacking, it poses little risk to infants. When parents administer OMC, they appear to enjoy the process and time to connect with their infant. It is undeniably important for mothers to begin expressing their milk very early in the NICU stay to sustain their long-term supply, making any encouragement they can derive from the process invaluable.

IMPLICATIONS FOR RESEARCH

Undeniably, there is theoretical and preclinical support for this practice but more real-world clinical studies with vulnerable infants are needed. Like Rodriguez and colleagues’ study, immune outcomes can be measured, particularly urine secretory IgA and urine lactoferrin. Examining cytokine levels for infants receiving C-OIT compared with those who do not could strengthen our understanding of how C-OIT impacts the immune response. Challenges in conducting these studies will be to account for confounders as covariates in the statistical models and to ethically consider how randomization is best carried out.

Without a doubt, well-designed randomized controlled trials will provide the most definitive evidence for C-OIT’s effects. However, given the preclinical evidence and the very high cost risks of not providing immune stimulation (eg, sepsis and NEC), it can be argued that randomly assigning infants to a control when mothers wish to provide colostrum is not ethical. Given the early stage of the evidence base, a table of evidence snapshot can help guide the research.

### TABLE 3. Evidence Snapshot

<table>
<thead>
<tr>
<th>Evidence demonstrates</th>
<th>Evidence is unclear</th>
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<tbody>
<tr>
<td>Both the dose and proportion of enteral feeding is important to reduce neonatal morbidity.</td>
<td>What is the impact of C-OIT on morbidity outcomes such as necrotizing enterocolitis, sepsis, retinopathy of prematurity or chronic lung disease?</td>
</tr>
<tr>
<td>Colostrum is the first human milk mothers produce. It contains vital immune stimulating components that premature infants lack.</td>
<td>What is the optimal dose and duration of C-OIT?</td>
</tr>
<tr>
<td>When C-OIT is used, time to full enteral feedings is reduced. When C-OIT is combined with a standardized feeding protocol, impacts are greater.</td>
<td>What is the impact of C-OIT for critically ill infants &gt; 1500 g (eg, congenital heart disease, birth defects)?</td>
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<td>How does neonatal inflammatory response change (eg, measured using cytokine levels) after C-OIT?</td>
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<tr>
<td>Is C-OIT more protective than other oral care products (eg, Biotene) for ventilator-associated infection prevention?</td>
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</table>

<table>
<thead>
<tr>
<th>What we need to study</th>
<th>What we can do today</th>
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<tbody>
<tr>
<td>Inflammatory marker response to C-OIT.</td>
<td>Encourage mothers to provide human milk within the first 4 h of delivery.</td>
</tr>
<tr>
<td>C-OIT in infants &gt; 1500 g who are critically ill. Effects of C-OIT using <em>comparison groups</em> either using an experimental design or time series designs with historical controls. Another option is to use case-control designs with matching based on gestational age, birth weight, race, severity of illness.</td>
<td>Share the science of human milk with parents, describing it as an immune therapy (not solely nutrition).</td>
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<tr>
<td>Help the parents to keep track of the volume and frequency of human milk expression and praise their success.</td>
<td>Help the parents to keep track of the volume and frequency of human milk expression and praise their success.</td>
</tr>
<tr>
<td>Continually support parents and advocate for “never-fail” and “always use” of human milk for all infants.</td>
<td>Give human milk in the order it was pumped.</td>
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<tr>
<td>Use creative approaches to support human milk use in the NICU.</td>
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</table>

Abbreviations: C-OIT, colostrum as oral immune therapy; NICU, neonatal intensive care unit.
Colostrum as Oral Immune Therapy to Promote Neonatal Health

CONCLUSION

Increasing the exposure of human milk to neonates in the NICU setting must become standard of practice, yet the evidence-supported effects of early colostrum is still a topic for study (see Table 3 for a summary of key points). Early exposure to even small amounts of mother’s milk significantly reduces the use of parenteral fluids, decreases the risk of infection, and lessens the duration of hospitalization without adverse effect. Evidence suggests that when healthcare providers convey the importance of human milk for infants, it empowers parents to support a pumping regimen to maintain a milk supply for their infant. In an environment where a parent often has very little direct control over the care of their infant, providing human milk allows a significant contribution by the mother. More studies are needed to demonstrate a correlation between the use of human milk for oral care and the potential immune effects against infections, especially NEC.

References