Human milk fortifier: An occult cause of bowel obstruction in extremely premature neonates

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A B S T R A C T

Background: Human milk fortifier (HMF) is used in neonatal units throughout North America to facilitate growth of preterm infants. Little data is available on the gastrointestinal side effects and potential adverse events. The purpose of this paper was to present a series of infants presenting with bowel obstruction associated with HMF.

Methods: Cases of HMF obstruction were collected between January 2010 and December 2012. Charts were reviewed and relevant data was collected.

Results: During the study period, 7 premature infants presented with bowel obstruction secondary to intestinal concretions of HMF. All babies were premature with gestational ages from 25 to 27 weeks. Birth weight was less than 1000 grams in all patients. Patients presented with feeding intolerance, bilious aspirates, intestinal concretions of HMF. All babies were premature with gestational ages from 25 to 27 weeks. Birth weight was less than 1000 grams in all patients. Patients presented with feeding intolerance, bilious aspirates, abdominal distension, and obstipation. Four of the patients presented with acute deterioration and required urgent surgical intervention.

Conclusions: HMF is an important source of nutritional support in infants, which is felt to be safe. We present a series of infants where its use has resulted in significant complications. HMF should be used with caution in infants, especially those with a history of necrotizing enterocolitis. Further research should examine the calcium, protein, and fatty acid concentration tolerable in the gastrointestinal tract of infants.

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Human breast milk is recognized as an advantageous nutrition source for infants. Infants who are breastfed have improved immune and gastrointestinal function and decreased rates of necrotizing enterocolitis compared to infants that receive formula [1,2]. However human milk does not provide sufficient protein, sodium and micronutrients to meet the increased metabolic demands of preterm infants [3]. Several commercially prepared fortifiers have been developed to improve the nutritional content of human milk (human milk fortifier, HMF). In several studies, HMF has been shown to result in improved weight gain [4,5]. However there is insufficient data to conclude that there are no deleterious effects [6].

There have been a few case reports of lactobezoar related to formula ingestion in infants [7,8]. Recently there has been a single case report of calcium stone ileus in a premature infant because of human milk fortifier [9]. The purpose of this paper was to present a series of patients with bowel obstruction following the administration of human milk fortifier.

1. Methods

Patients undergoing treatment for bowel obstructions related to human milk fortifier ingestion between January 2010 and December 2012 were identified. All patient charts were reviewed and relevant data was collected. Data collected included demographic (gestational age, birth weight, gender), clinical (presentation, diagnostic variables, radiographic findings), nutritional and pathologic factors.

Infants admitted to the Neonatal Intensive Care Unit (NICU) at our institution are started on enteral nutrition as soon as clinically possible. Breast milk (both maternal expressed and donor milk) is the first choice of enteral support. HMF is introduced once feeds are established and there are concerns over adequate growth. Similac Human Milk Fortifier (Abbott Nutrition) was used during the study period. In our institution, HMF is only used in infants who are less than 34 weeks gestation or less than 2500 grams at birth. Once an infant is tolerating breast milk at a rate of 100 mL per kilogram per day, HMF will then be added if growth remains inadequate. Patients are initially started on half-strength HMF (created by adding one package of Similac HMF powder to 50 mL of expressed breast milk (EBM)), and once tolerance has been established patients advance to full strength HMF (two packets per 50 mL of EBM). Each packet provides 1 gram of protein, 14 calories, 117 mg of calcium with a total osmolality of 11.2 mOsm [10]. Full strength HMF fortification provides 24 kcal per...
found to have inspissated HMF concretions. Two of the 7 patients experienced an episode of NEC and were presumed to have a stricture. Elective contrast enemas each of which returned a large volume of HMF concretions. N-acetylcysteine via the NG tube and cessation of HMF. The other patient had three contrast enemas which showed evidence of small bowel obstruction with evidence of inspissated milk (Fig. 1). Two of these patients underwent emergent operative intervention. In all 4 patients a perforation was found with the obstructive symptoms and underwent emergent operative intervention. In the other patient, who was 39 weeks corrected gestational age, was negative.

The patients typically presented with obstructive type symptoms, including new onset feeding intolerance, abdominal distension, bilious nasogastric (NG) aspirations and decreased stooling. Four of the patients (cases 1, 3, 5, 7) presented with sudden deterioration in addition to the obstructive symptoms and underwent emergent operative intervention. In all 4 patients a perforation was found with evidence of inspissated milk (Fig. 1). Two of these patients deteriorated and ultimately passed away. Of the three patients presenting nonacutely, two underwent contrast enema which showed evidence of small bowel obstruction with filling defects because of milk/HMF concretions. One patient resolved their obstruction without surgery with N-acetylcysteine instilled via the NG tube and cessation of HMF. The other patient had three contrast enemas each of which returned a large volume of HMF concretions. Despite N-acetylcysteine via the NG and repeated enemas the obstruction never resolved and operative intervention was required. The final patient presented with obstructive symptoms and an abdominal radiograph (Fig. 2) that showed obstruction after an episode of NEC and was presumed to have a stricture. Elective operative intervention was planned and at the OR the patient was found to have inspissated HMF concretions. Two of the 7 patients passed away. The surviving patients went on to have their stoma closed and achieved enteral autonomy.

During the study period 1896 patients were admitted to our NICU, of which 451 received HMF. Of the 451 patients, 7 developed bowel obstructions involving HMF concretions, resulting in an incidence rate of 0.02%. During the same time period there were 30 confirmed cases of necrotizing enterocolitis. Of the patients with NEC, 17 received HMF, with 4 developing complications related to the HMF resulting in an incidence of 23% among this sub group of patients.

### 3. Discussion

Lactobezoar refers to a coagulum of milk curds in the stomach or the small bowel, causing intestinal obstruction. Many of the reported cases have occurred in low birth weight and preterm infants who received high-caloric density formulas rich in casein and calcium [7,8,11]. Rarely does this occur in infants who receive breast milk. In the past three years, we have treated 7 infants with obstruction secondary to lactobezoar from concretions of breast milk with added human milk fortifier.

While human milk remains the preferred form of nutrition for infants, those who are extremely premature and/or small for gestational age require more calories and macronutrients than can be provided by breast milk [3]. Consequently, human milk fortifier has been developed to provide added calories, protein and micronutrients including calcium. HMF has been widely adopted in NICUs across North America. The studies supporting HMF have shown that it promotes improved growth in premature infants and does not result in increased rates of NEC or sepsis [1,2]. A recent Cochrane review concluded that while HMF did result in short term improvements in weight gain, there was no evidence to support long term benefits from its use and insufficient evidence to be reassured that there were no deleterious effects [6].

We describe 7 patients who present with bowel obstruction secondary to HMF bezoar. All but one of the patients required operative intervention to relieve the obstruction and two of the patients died as a result.

### Table 1

<table>
<thead>
<tr>
<th>Case</th>
<th>Gender</th>
<th>GA (weeks)</th>
<th>BW (gm)</th>
<th>Comorbidities</th>
<th>NEC</th>
<th>Start of SBO (DOL)</th>
<th>Type of nutrition</th>
<th>Days of HMF</th>
<th>Management</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Male</td>
<td>25</td>
<td>675</td>
<td>BPD, PDA</td>
<td>No</td>
<td>36</td>
<td>EBM</td>
<td>9</td>
<td>Laparotomy</td>
<td>Alive</td>
</tr>
<tr>
<td>2</td>
<td>Male</td>
<td>25 + 5</td>
<td>910</td>
<td>BPD, anemia</td>
<td>Yes</td>
<td>53</td>
<td>EBM</td>
<td>7</td>
<td>Laparotomy</td>
<td>Alive</td>
</tr>
<tr>
<td>3</td>
<td>Male</td>
<td>25 + 5</td>
<td>978</td>
<td>PDA</td>
<td>Yes</td>
<td>45</td>
<td>EBM</td>
<td>11</td>
<td>Laparotomy</td>
<td>Died</td>
</tr>
<tr>
<td>4</td>
<td>Male</td>
<td>25</td>
<td>505</td>
<td>Ischemic limb, BPD</td>
<td>No</td>
<td>26</td>
<td>EBM</td>
<td>10</td>
<td>Mucomyst</td>
<td>Alive</td>
</tr>
<tr>
<td>5</td>
<td>Male</td>
<td>25 + 1</td>
<td>570</td>
<td>IVH, PDA</td>
<td>Yes</td>
<td>28</td>
<td>EBM</td>
<td>7</td>
<td>Laparotomy</td>
<td>Died</td>
</tr>
<tr>
<td>6</td>
<td>Female</td>
<td>26 + 4</td>
<td>855</td>
<td>BPD, PDA</td>
<td>No</td>
<td>29</td>
<td>EBM</td>
<td>11</td>
<td>Laparotomy</td>
<td>Alive</td>
</tr>
<tr>
<td>7</td>
<td>Male</td>
<td>25 + 1</td>
<td>711</td>
<td>PDA, IVH, BPD</td>
<td>Yes</td>
<td>21</td>
<td>EBM</td>
<td>n/a</td>
<td>Laparotomy</td>
<td>Alive</td>
</tr>
</tbody>
</table>

Fig. 1. Photo of intraoperative findings of HMF obstruction.
Given the complicated and multifactorial etiology of bowel obstruction in premature infants it is impossible to determine if HMF was the causative agent in our population. It is possible that among the patients with NEC the presence of a stricture confounded their presentation. However all patients in the study demonstrated tolerance of enteral nutrition prior to introduction of HMF and the presentation of bowel obstruction, suggesting that the addition of HMF was a potential factor contributing to bowel obstruction. Chemical analysis was not able to be completed on the concretions found in the patients in this study. It is unknown if there is a concentration of nutritional components (especially calcium and protein), osmolality or pH that results in the formation of concretions of HMF in the neonatal gastrointestinal tract. This is an area for further research. Finally the infants in our study only received a single type of powdered HMF. To date we have not encountered patients with bowel obstructions when liquid HMF is utilized, suggesting that it may be a safer alternative in high risk patients.

Human milk fortifier is an important source of nutritional support to promote growth in premature infants. While it is largely felt to be safe we present a series of infants where its use has resulted in infrequent but significant harm. Human milk fortifier should be used with caution in premature and small infants. Further research is required to determine the ideal calcium, protein and fatty acid concentration tolerable in the gastrointestinal tract of premature infants, and the ideal modality and preparation of supplemental fortifiers. HMF should be avoided in infants with a history of necrotizing enterocolitis, until an associated stricture has been excluded.

The cause of bezoars in premature infants is unknown, but is likely related to factors of gastrointestinal immaturity and function as well as feeding regimens. It has been suggested that precipitation of fatty acids and calcium may be responsible [11]. To date, there have been two other single patient case reports of HMF obstruction [9,11]. In the case reported by Murase et al., the impacted material was analyzed and found to be fatty acid calcium stones. Human milk fortifier may alter the solubility of calcium contributing to the formation of concretions [12]. In all reported cases the infants were premature and had low birth weight (all less than 1000 grams) suggesting that this patient population may be more prone to inspissation. Consequences of HMF bezoar in this population can be especially harmful. In our series two patients died and the patient reported by Murase et al. also died as a consequence of the obstruction.

While the presentation of the patients in our study is significant, our study does represent the limitations of a retrospective case series.

Fig. 2. Abdominal x-ray of patient with HMF obstruction.