The Financial Burden of an Undiagnosed Congenital Diarrhea Disorder

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Congenital diarrheal disorders (CDD) are a group of rare conditions with diverse pathophysiologies that are often associated with significant morbidity or mortality. Most are caused by monogenic disorders that lead to intestinal epithelial deficits, including transporter trafficking defects (1). The correct diagnosis of the underlying condition has often been protracted or elusive, adding to the significant economic burden of treatment. Although costly, new genetic, molecular, and histochemical techniques may offer additional avenues for the early diagnosis and correct treatment of underlying disorders. Reduction in the time before diagnosis could consequently lead to a significantly reduced economic burden (1). We managed a patient who developed severe chronic diarrhea in the first few days of life whose narrative illustrates the importance of incorporating these techniques into the diagnostic approach to congenital diarrheas.

The patient was referred to the pediatric gastroenterology clinic at 7 weeks of age for vomiting and severe malnutrition. He was directly admitted to the gastroenterology service for management of failure to thrive. During this first admission, he was noted to have diarrhea. The hospitalization lasted 11 weeks because of electrolyte instability (hypokalemia, hypocalcemia), refeeding syndrome, meningitis, a central line-associated blood stream infection, and feeding intolerance. Esophagogastroduodenoscopy was nondiagnostic and showed villous blunting with patchy gastric epithelial metaplasia in the duodenum. Electron microscopy was normal. Stool studies sent for malabsorption were normal except for an elevated fecal fat. Immunology was consulted and the work-up was negative for an immunologic disorder. He underwent surgery to have a central line and gastrostomy tube placed. He was discharged home on an amino acid-based formula and total parenteral nutrition (TPN). However, his symptoms of diarrhea and the side effects of persistent diarrhea continued.

Overall, this patient was admitted to the hospital 31 times before the correct diagnosis was reached with some stays requiring ICU-level care. He underwent 14 central line procedures. He required enoxaparin injections for a deep vein thrombosis. He underwent a total of 7 endoscopies. He also suffered from hypogammaglobulinemia and required intravenous immunoglobulin infusions. He was transferred at one point to another major institution for a second opinion.

His course was complicated as he was initially diagnosed with autoimmune enteropathy (AE) at 15 months of age when his anti-enterocyte IgA antibody (AEA) returned positive, and his routine histologic examination showed nonspecific villous atrophy. Between 15 and 40 months of age, his AE was treated with multiple different medications including steroids, tacrolimus, abatacept, and infliximab but he never completely improved during this time period.

At 42 months of age, we reviewed his histopathology again using immunohistochemical staining for brush border proteins and apical transporters to assess for their presence in enterocytes and their correct polarization. We observed significant loss of apical transporters and enzymes in enterocytes at the tips of the villi, including loss of SGLT1, CD10, DPPIV, and NHE3. This suggested that the diagnosis of autoimmune enteropathy was incorrect. Subsequently, a homozygous mutation in DGAT1 (chromosome 8, 145541756 A→G) was found on whole-exome sequencing (WES), which causes a truncation of the protein. All symptoms resolved once the correct diagnosis of DGAT1 deficiency was made and he was placed on the low-fat formula Tolerex (2–4).

To better understand the costs of misdiagnosis to the health care system, we analyzed the cost of patient care in this congenital diarrhea patient. In this case, it took almost 3.5 years to make the correct diagnosis. The patient spent 586 days in our hospital. Total hospital charges at our institution before the diagnosis amounted to $4,666,010. With WES, the diagnosis was made in only a few months, and total charges for the first 1.5 years after diagnosis and diet change amounted to $138,000 (Table 1). The bulk of these charges were from slowly weaning TPN because of parental fear of stopping TPN too fast and surgery for central line removal. He has had only 1 48-hour admission for diarrhea since the mutation in DGAT1 was discovered.

An earlier correct diagnosis would have prevented months in the hospital and spared the patient from exposure to multiple medications with significant side effects. The charge of WES for both the patient and the mother at the time was $4000, which although expensive, is still insignificant when compared with total charges.

As CDD are diverse conditions, the work-up is not straightforward. The initial diagnosis of AE in this patient was made based on a positive AEA. However, AEA are not specific to AE, and the patient never had a significantly robust response to AE treatments (5). In addition to stool tests and endoscopy to visualize the epithelium, patients must undergo genetic sequencing and immunohistochemical staining to identify cell types present and cell structure. For novel mutations, functional studies are needed to describe the changes in the epithelium caused by the mutation (1). WES is not needed in every patient as the initial genetic test since there are now congenital diarrhea genetic panels that evaluate a large number of genes, but as this case indicates, early genetic testing is crucial to timely diagnosis.

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TABLE 1. Differences in hospital charges and total total parenteral nutrition days before and after the diagnosis of DGAT1 deficiency

Charges by category	Before diagnosis	After diagnosis
Clinical charges	$92,551	$5909
Imaging charges	$106,883	$4988
Lab charges	$595,500	$20,193
Pharmacy charges	$1,131,206	$34,115
Supply charges	$24,763	$0
Other charges	$2,715,107	$73,214
Total hospital charges	$4,666,010	$138,419
Total TPN days	315 days	27 days

TPN = total parenteral nutrition.

As genetic sequencing becomes more widely used and less costly, it is probable that new monogenetic causes of CDD will be identified. These mutations will require further study to understand the changes they cause on a cellular level like in the case of DGAT1 deficiency (4,6). The Pediatric Congenital Diarrhea and Enteropathy Consortium (PediCoDE) was established because of the difficulty in making the correct diagnosis in these patients. In addition, the consortium provides a resource for physicians and centers unable to perform this extensive work-up. By finding the mutations earlier, the hope is to provide better supportive care and identify possible treatment pathways for these patients.

REFERENCES

1. Thiagarajah JR, Kamin DS, Acra S, et al., PediCODE Consortium. Advances in evaluation of chronic diarrhea in infants. *Gastroenterology* 2018;154:2045e6-2059e6.
2. Haas JT, Harland SW, Lim E, et al. DGAT1 mutation is linked to a congenital diarrhea disorder. *J Clin Invest* 2012;233:4680–4.
3. Gluchowski NL, Chitraju C, Picoraro JA, et al. Identification and characterization of a novel DGAT1 missense mutation associated with congenital diarrhea. *J Lipid Res* 2017;58:1230–7.
4. van Rijn JM, Ardy RC, Kuloğlu Z, et al. Intestinal failure and aberrant lipid metabolism in patients with DGAT1deficiency. *Gastroenterology* 2018;155:130.e15–43.e15.
5. Lerner A, Kushak RI, Jeremias P, et al. Anti enterocyte autoantibodies in pediatric celiac disease. *J Clin Cell Immunol* 2016;7:445.
6. Schlegel C, Lapierre LA, Weis VG, et al. Reversible defects in apical transporter trafficking associated with deficiency in diacylglycerol acyltransferase. *Traffic* 2018;19:879–92.

Evidence-based Usage of Probiotics for Pediatric Acute Gastroenteritis

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See ''Use of Probiotics for the Management of Acute Gastroenteritis in Children: An Update'' by Szajewska et al on page 261.

In this issue of the *Journal of Pediatric Gastroenterology and Nutrition* (*JPGN*), an updated review of the role of probiotics in management of acute pediatric gastroenteritis is published (1). Since their last review in 2014, there have been 3 large randomized controlled trials (RCTs) that were null for this endpoint, so it is important to know if these newer studies change underlying recommendations for probiotic use. This review is of high quality and follows the GRADE system for evaluating evidence. Szajewska et al (1) required at least 2 randomized controlled trials (RCTs) for a given probiotic strain to be eligible for a recommendation. Considering the low risk of probiotic use, this criterion is strict (equivalent to drug-level evidence), but reasonable for this therapeutic use.

The authors make some useful recommendations for certain probiotic strains to decrease the duration of acute pediatric diarrhea. A weak recommendation is made for *Saccharomyces boulardii* (low to very low certainty of evidence); *Lactobacillus rhamnosus* GG (very low certainty of evidence); *Lactobacillus reuteri* DSM 17938 (low to very low certainty of evidence); and *L rhamnosus* 19070-2 plus *L reuteri* DSM 12246 (very low certainty of evidence). A strong recommendation is made against the usage of *Lactobacillus helveticus* R0052 plus *L rhamnosus* R0011 (moderate certainty of evidence); and a weak recommendation is made against the use of *Bacillus clausii* strains O/C, SIN, N/R, and T (very low certainty of evidence). These strain-specific recommendations are an important reminder that efficacy cannot be extrapolated from 1 strain to another.

The authors appropriately note quality problems with available studies. For example, although they identified 29 RCTs that randomized 4217 participants for *S boulardii*, only 38% of these trials adequately generated their randomization sequence, only 17% of trials adequately concealed allocation, and only 1 trial adequately blinded participants, study personnel, and outcome assessors. These are factors that must be controlled in the conduct of high-quality probiotic research.

As thorough a review as this was there are a few additional points that that provide context for understanding the conclusions made by this review. First, although the *S boulardii* studies suffer from certain quality flaws, the sheer number of trials provides a measure of confidence in the statistically significant and clinically relevant findings of a decrease in days with diarrhea (1.06) and duration of hospitalization (0.85 days). The 1-day reduction in duration of disease is similar to what a primary care doctor would expect when treating with antibiotics for streptococcal pharyngitis or antivirals for influenza (2,3). Such comparisons may have been beyond the scope of the review but are important to assure that clinicians recognize this is an actionable finding, worth implementing in care.

Second, considering available data at least on the short-term safety of probiotic administration, the authors over-emphasize the risk of probiotic use. The authors state, ''harms-related outcomes in trials evaluating probiotics are often lacking or inadequate,'' leading them to impugn probiotic safety based on case reports. However, case reports are, a weak level of evidence, and instead it is more convincing to consider adverse events reported in many well conducted RCTs that have followed a large number of subjects, including vulnerable subjects, such as neonates, for months (4,5). If medicine relied on case reports for safety assessments, no interventions would be considered safe. A physician could not even recommend aerobic exercise, based on the many case reports of

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