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ORIGINAL RESEARCH ARTICLE

The Role of Oral Administration of Immunoglobulin in Managing Diarrheal Illness in Immunocompromised Children

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Abstract

Introduction Immunocompromised children are susceptible to infectious diarrhea. Oral administration of human serum immunoglobulins to treat immunocompromised patients with viral gastroenteritis caused by viruses like rotavirus and norovirus has been reported.

Objective The aim of this study was to assess the efficacy of oral immunoglobulin (OIG) in treating hospitalized immunocompromised children with diarrheal illness.

Methods We conducted a retrospective cohort review of the Mayo Clinic electronic medical records from January 1, 2005, through April 30, 2019. We included children who were immunocompromised and received OIG as a treatment for a diarrheal illness that was classified as acute (< 4 weeks) or chronic (> 4 weeks) at the time of their treatment. Response to therapy was defined by 50% reduction in stool output.

Results Nineteen children were identified (11 males); average age at the time of treatment was 11 (0.25–18) years. In the acute diarrhea cohort, the mean duration of symptoms was 9.5 days (4–21). In the chronic diarrhea cohort, the mean duration of symptoms was 41 days (28–90). All 19 children were treated with OIG with doses in the range of 100–300 mg/kg/day for 1–5 days. Eighteen patients (95%) had improvement. Overall average time to response was 3.1 (1–9) days after receiving the OIG.

Conclusion Oral administration of human serum immunoglobulin in immunocompromised children presenting with acute and chronic diarrheal illness appeared helpful in reducing stool output by 50% in the majority of patients.

Key Points

Chronic diarrhea is a common problem in immunocompromised children.

Oral immunoglobulin can be useful in managing chronic diarrhea in immunocompromised children.

1 Introduction

Immunosuppressive and immunomodulatory medications are commonly used in induction and maintenance of remission in children with inflammatory bowel disease (IBD) [1]. These medications alter the immune system, including the response to infections [2]. In addition, the incidence of infectious diarrhea in immunocompromised solid organ transplant patients has increased due to the increase in number of solid organ transplants and an increase in their survival [3].

Immunocompromised children are especially prone to infectious diarrhea. Like in healthy children, viruses like rotavirus, norovirus, sapovirus and adenovirus are the most commonly recognized causes for infectious diarrhea in immunocompromised children [4–8]. Although most of the cases of infectious diarrhea are generally self-limited in immunocompetent patients, immunocompromised patients are at risk of having a severe prolonged disease course and developing complications like hypovolemia, dehydration, electrolyte imbalance, and malabsorption [9]. Chronic diarrheal illness and its related morbidity in immunocompromised patients can be cumbersome for the patients, their

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families, and medical providers [10]. The use of a highly sensitive and specific fecal polymerase chain reaction (PCR) test can help identify many viral causes of diarrhea in those children [11].

The administration of human serum immunoglobulins orally to treat diarrheal illness caused by rotavirus and norovirus in immunocompromised patients has been previously reported [12–15]. The utility of oral immunoglobulin has been reported in other countries besides the United States, such as the United Kingdom, Sweden, and Brazil [12, 16, 17]. The mechanism of action is thought to inhibit viral replication by binding to the virus, keeping it from adhering to the intestinal wall [18]. It has also been used to treat refractory bacterial gastroenteritis with *Campylobacter jejuni* and *Clostridium dificile* as a result of the toxin-neutralizing quality of immunoglobulin [16]. One study reported that oral immunoglobulin improved clinical management of IBD patients who are not fully managed by traditional therapies [19]. The recognition of the potential benefit of oral immunoglobulins in managing diarrheal illness in immunocompromised children could help accelerate recovery and shorten the length of hospitalization [15]. In this study we aim to evaluate the benefit of oral immunoglobulins (OIG) in managing diarrheal illness in immunocompromised children.

2 Methods

We performed a retrospective chart review of the Mayo Clinic electronic health records between January 2005 and April 2019. This study was approved by the Mayo Clinic Institutional Review Board. Diarrheal illness was considered acute if it lasted < 4 weeks at the time of OIG administration and chronic if it lasted ≥ 4 weeks. The patient's response, in terms of change in stool output and consistency, was evaluated. Two end points were identified and recorded: 50% reduction in stool volume within 10 days of initiation of therapy, and diarrheal illness resolution. Stool volume and frequency was obtained from the documentation of intake and output including stool by nursing staff in the medical charts, which didn't change during the study period.

To identify study subjects, the terms immunocompromised, immunosuppressed, oral immunoglobulin, and diarrhea were used. Inclusion criteria included children < 18 years of age who were immunosuppressed, on immunosuppressive medication, or taking chemotherapy, and developed diarrheal illness represented by increased stool frequency, volume, or increased ileostomy output in patients with ileostomy. All patients were hospitalized at the time of diarrheal illness. The charts of identified children were reviewed for demographics and data collection, including clinical presentation, laboratory results, medication list, intake and output documentation, and past medical and surgical history.

All children had a fecal pathogen PCR panel done, which checks for 21 pathogens (electronic supplementary material). All patients received human-derived serum immunoglobulin that was given via the enteral route. Age, time to response, and length of hospitalization were reported as mean (standard deviation).

3 Results

We identified 19 children who were immunocompromised and were treated with OIG. Eleven were males with an average age of 11 (0.25–18) years at the time of treatment. Of those, six children had solid organ transplant, three had malignancy, and ten had colitis. Specific diagnoses and medications are outlined in more detail in Table 1. Eight were receiving oral glucocorticosteroids, four were on anti-tumor necrosis factor medications (2 adalimumab and 2 infliximab), one on 6-mercaptopurine (6-MP), five children on mycophenolate and/or tacrolimus, one on etoposide and ifosfamide, and one on fludarabine and cytarabine. Three children with colitis were on combined therapy (hydrocortisone/6-MP, adalimumab/methotrexate, and adalimumab/tacrolimus). Nine children were on more than one immunosuppressive medication at the time of their diarrheal illness. All patients required hospitalization.

Based on the length of their symptoms, ten children had acute diarrhea (< 4 weeks) and nine had chronic diarrhea (> 4 weeks). In the acute diarrhea cohort, the median (range) duration of symptoms was 7 days (4–21). Three children had norovirus, three had rotavirus, one had adenovirus, one had astrovirus, and one had both sapovirus and rotavirus. One child had diarrhea with a negative stool pathogen panel. In the chronic diarrhea cohort, the median (range) duration of symptoms was 30 days (28–90). Two of those children had norovirus, four had rotavirus, one had sapovirus, and two had diarrhea with negative pathogen panel. In the two patients with negative pathogen panel, both had a fecal leukocyte assessment, which were negative to few. None of these patients had other markers of colonic mucosal inflammation, such as lactoferrin or calprotectin. All patients received human derived serum immunoglobulin, which was given either orally or via nasogastric tube. Fifteen children received Privigen®, three received Carimune®, and one received Gamimune®. Treatment regimen dose and length varied between providers (summarized in Table 1). Included children were treated with 100–300 mg/kg/day for 2–5 days.

Eighteen of nineteen children (95%) responded to the treatment with OIG with 50% reduction in their documented stool output within 10 days of initiation of therapy. The median time (range) to response was 3 (1–9) days. Children

Table 1 Patients treated with oral immunoglobulin broken down by age, sex, underlying pathology, stool pathogen panel result, brand, dose and duration of therapy, and number of days to response

Age	Sex	Diagnosis	Immunosuppressive medication	Virus	Brand	Dose (mg/kg/day)	Duration (days)	Days to response
17	F	Liver transplant	Prednisone	Norovirus	Privigen	300	3	9
11	F	Acute lymphocytic leukemia	Tacrolimus	None	Privigen	300	3	3
6	M	Indeterminate colitis	Hydrocortisone	Astrovirus	Privigen	300	3	3
17	F	Liver transplant + Crohn's disease	Adalimumab, tacrolimus	Rotavirus	Privigen	300	3	4
19	F	Collagenous colitis	Hydrocortisone	Adenovirus	Privigen	300	3	1
13	M	Kidney transplant	Tacrolimus, mycophenolate	Rotavirus, sapovirus	Privigen	300	3	2
1	F	Liver transplant	Tacrolimus, mycophenolate, prednisone	Norovirus	Carimune	150	3	4
17	M	Crohn's disease	Infliximab	Rotavirus	Carimune	150	3	5
7	M	Ewing sarcoma	Etoposide, ifosfamide	Norovirus	Privigen	100	2	2
12	M	Ulcerative colitis	Adalimumab	Rotavirus	Privigen	300	3	2
17	F	Ulcerative colitis	Hydrocortisone, 6-mercaptopurine	Norovirus	Privigen	100	3	2
0.25	F	Indeterminate colitis	Hydrocortisone	Rotavirus	Carimune	300	2	2
18	M	Crohn's disease	Adalimumab, methotrexate	Rotavirus	Gamimune	300	3	2
12	M	Ulcerative colitis	Infliximab	Rotavirus	Privigen	300	3	3
2	F	Acute myelogenous leukemia	Fludarabine, cytarabine	Rotavirus	Privigen	300	3	5
12	M	Kidney transplant	Tacrolimus, mycophenolate	None	Privigen	100	5	3
6	M	Kidney transplant	Tacrolimus, mycophenolate	Sapovirus	Privigen	100	3	3
18	M	Crohn's disease	Hydrocortisone	None	Privigen	150	3	NR
3	M	Eosinophilic colitis	Hydrocortisone	Norovirus	Privigen	300	3	2

NR no response

with acute diarrhea responded in a median of 3 days, and children with chronic diarrhea responded in 2.5 days. Three of the nineteen children with initial improvement had recurrence of diarrhea within 1 week (16%). Complete resolution of diarrhea was clearly documented in 8/19 (42%) patients. For those with documented resolution, there was no statistical significance in diarrhea resolution based on underlying disease or length of diarrhea (acute vs chronic). Median time to complete resolution in these eight children was 7.5 days (range of 5–14). Median length of hospitalization for all included children was 11 (2–82) days, 6.5 days in children with acute diarrhea and 25 days in children with chronic diarrhea. The children with the longest hospitalization (82 and 62 days), remained as inpatients for ongoing care unrelated to their diarrhea. There were no reported side effects or reactions to OIG. The only child who didn't benefit from OIG had a negative fecal PCR panel. Of the three children in this study without an identified viral etiology, one had no response to OIG, one had recurrence, and one improved.

There was no statistically significant correlation between OIG dose and days to 50% improvement in stool output. Neither rotavirus nor norovirus (the two most common viruses in our cohort) were associated with increase rate of recurrence or statistically different response. Age of patients was not associated with response or recurrence.

4 Discussion

Our results suggest that OIG may be helpful in decreasing stool output and shortening the duration of diarrheal illness in immunocompromised hospitalized children. OIG may decrease their length of hospital stay, complications, morbidity, and improve their quality of life. Our findings are similar to other studies showing that OIG is a safe medication to shorten the duration of diarrhea in rotavirus and norovirus [12–14]. We showed that OIG can be as effective in children with astrovirus-, adenovirus-, and sapovirus-induced diarrhea. OIG did not seem to be as effective in patients with a negative stool pathogen panel. One of the three patients without an identified viral etiology did not respond to the OIG, and another had a recurrence of diarrhea within 1 week of OIG administration. Prolonged hospitalization in immunocompromised children increases their risk of hospital-acquired infections, hence any possible intervention that can shorten their hospitalization should be

considered. Further research is needed to determine if the length of hospitalization is significantly shortened by using oral immunoglobulin.

Infectious diarrhea is generally self-limited in children, but it is not clear if the children in our cohort would have cleared their infection without OIG administration. Change in stool output was variable in this cohort. Improvement of 50% or more seems to signify the improvement in stool output was more likely from the intervention of OIG administration rather than by chance. Prospective comparison data is needed to compare the duration of diarrhea between treated and untreated children. Our study limitations include the retrospective nature and the small sample size. While all children were immunocompromised, the population was heterogeneous with different underlying pathology, OIG doses and duration of therapy. However, this is the largest data set in immunocompromised children to our knowledge. Future prospective research is needed to control for these limitations.

5 Conclusion

Administration of OIG in immunocompromised children with diarrheal illness reduced the stool output in the majority of these patients. OIG could be considered in hospitalized immunocompromised children with acute or chronic diarrheal illness.

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