Outcomes of Norovirus Treatment in Pediatric Kidney Transplantation

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Abstract
Norovirus is a common cause of diarrhea in kidney transplant recipients, affecting up to 17% over a 2-year period. There is currently no approved treatment, but decreased immunosuppression, nitazoxanide, enteral immune globulin, and sirolimus have been reported as possible therapies. We were part of a multicenter study through the Pediatric Nephrology Research Consortium (PNRC) aimed at reporting the frequency of use and outcomes of these treatment strategies in pediatric kidney transplant recipients. Here we report a case series of eligible patients from Rady Children's Hospital.

Introduction
Norovirus is the most common cause of viral gastroenteritis in the United States.1,2 The duration of symptoms and period of asymptomatic viral shedding can be prolonged in immunocompromised patients and has been associated with acute kidney injury (AKI), toxic tacrolimus trough levels, and a more rapid decline in eGFR among kidney transplant recipients.3,4 Multiple case series have also reported episodes of rejection among patients with norovirus being managed with reduced immunosuppression.4,5

There is currently no approved treatment for norovirus, but several possible therapies have been reported. Reduction of immunosuppression, common practice6 but raises the concern for rejection. Nitazoxanide has been shown to decrease duration of norovirus diarrhea in children in two small randomized controlled trials7,8 and a phase II clinical trial is ongoing (NCT03395405). Sirolimus may have some antiviral properties and replacing an antimetabolite immunosuppressant with an mTOR inhibitor has been effective in two case reports.1 Entically administered immune globulin has been associated with resolution of chronic diarrhea, and case series of its use to manage norovirus infection in solid organ transplant recipients have shown mixed results.2

As part of a multicenter study through the Pediatric Research Consortium (PNRC), we aim to report the current treatment practices for norovirus diarrhea among pediatric kidney transplant recipients and compare their effectiveness, as shown by days of diarrhea after initiation of therapy. Here we report a case series of 7 patients from Rady Children’s Hospital who were eligible for this multicenter study.

Materials and Methods
We took part in a multisite retrospective cohort study through the PNRC. The main research site is the University of Minnesota. We identified qualifying patients through a search of the electronic medical record at Rady Children’s Hospital for patients with a positive norovirus test or an ICD-10 diagnosis of norovirus gastroenteritis (A08.11) from 1/1/2008 through 12/31/2018.

The study population includes kidney transplant recipients with a functioning allograft, age 17 years of age or less, who were diagnosed with norovirus by stool PCR. Patients with a history of multiorgan transplant, post-transplant lymphoproliferative disease requiring chemotherapy, or other oncologic process prior to norovirus diagnosis were excluded from the study. Patients diagnosed with a bacterial or parasitic stool infection, including Giardia, Cryptosporidium, and Clostridium difficile at the same time as their norovirus infection, and patients who did not have a routine bacterial stool culture at the onset of symptoms, were also excluded from the study.

7 patients from Rady Children’s Hospital were eligible to include in this multicenter study. Here we report the data from these patients as a case series. Given the small sample size, we are precluded from utilizing statistical analysis.

Results
For diarrhea lasting less than or equal to 25 days, supportive care was the mainstay of treatment. For diarrhea lasting greater than 25 days, supportive care, probiotics and oral IgG were employed. Oral IgG was initiated with diarrhea lasting greater than or equal to 86 days. Although the total duration of diarrhea was longer than oral IgG compared to supportive care alone, the duration of diarrhea from treatment initiation was similar. For supportive care only, the range of duration of diarrhea from treatment start was 2 to 40 days. For oral IgG, the range of duration of diarrhea from treatment start was 22 to 25 days. The duration of diarrhea from treatment start for probiotics was slightly longer at 26 days.

Conclusion
Norovirus is the most common cause of gastroenteritis in the US and can result in significant consequences in pediatric kidney transplant recipients including AKI, acute rejection, tacrolimus toxicity, and more rapid decline in GFR. We are part of a multicenter study through the PNRC aimed at reporting the current treatment practices for norovirus diarrhea among pediatric kidney transplant recipients and compare their effectiveness, as shown by days of diarrhea after initiation of therapy. In our case series including 7 patients at Rady Children’s Hospital, we found that supportive care was utilized for diarrhea lasting less than 25 days. Oral IgG was initiated when diarrhea lasted greater than 86 days, but had similar effectiveness from treatment initiation compared to supportive care alone. This may indicate that oral IgG may be utilized earlier in the diarrheal course in order to shorten the total duration of diarrhea. In turn, shorter total duration of diarrhea may lead to improved long-term outcomes in kidney transplant function. It will be important to include our data into the larger multicenter PNCR data set to improve the power and quality of the study.

References

Table 1. Norovirus treatment, total duration of diarrhea (in days), time to treatment (in days), and duration of diarrhea from treatment start (in days) among the 7 subjects.

<table>
<thead>
<tr>
<th>Subject</th>
<th>Norovirus Treatment</th>
<th>Total Duration of Diarrhea (d)</th>
<th>Time to Treatment (d)</th>
<th>Duration of Diarrhea from Treatment Initiation (d)</th>
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<tr>
<td>1</td>
<td>Supportive care</td>
<td>5</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>2</td>
<td>Supportive care</td>
<td>14</td>
<td>1</td>
<td>13</td>
</tr>
<tr>
<td>4</td>
<td>Supportive care</td>
<td>25</td>
<td>1</td>
<td>24</td>
</tr>
<tr>
<td>5</td>
<td>Probiotics, Supportive care</td>
<td>31</td>
<td>4</td>
<td>26</td>
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<tr>
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<td>Supportive care</td>
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<td>0</td>
<td>40</td>
</tr>
<tr>
<td>7</td>
<td>Oral IgG, Supportive care</td>
<td>86</td>
<td>63</td>
<td>22</td>
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<tr>
<td>8</td>
<td>Oral IgG, Supportive care</td>
<td>150</td>
<td>126</td>
<td>25</td>
</tr>
</tbody>
</table>

Chart 1. Total duration of diarrhea (in days) and the 7 subjects.

Chart 2. Duration of diarrhea from treatment start (in days) among the 7 subjects.

Duration of Diarrhea from Treatment Initiation

Days

Subjects
Supportive care only
Probiotics
Oral IgG

Chart 3. Duration of diarrhea from treatment start (in days) among the 7 subjects.