Recurrence of Clostridium difficile Disease: Association of Relapse with BI/NAP1/027

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Running title: Recurrent C. difficile infection

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Recurrent *Clostridium difficile* infection (CDI) occurs in up to 35% of patients. Recurrences can be due to either relapse with the same strain or re-infection with another strain. In this study, multi-locus variable number tandem repeat analysis (MLVA) was performed on *C. difficile* isolates from patients with recurrent CDI to distinguish relapse from re-infection. In addition, univariate and multivariate analyses were performed to identify risk factors associated with relapse. Among patients with a single recurrence, relapse due to the original infecting strain was more prevalent than re-infection and the interval between episodes was shorter than in patients who had re-infections. Among patients with > 1 recurrence, an equal distribution of either relapse or re-infection or a combination of the two episode types was observed. Initial infection with the BI/NAP1/027 epidemic clone was found to be a significant risk factor for relapse. This finding may have important implications for patient therapy. Classification of recurrent CDI episodes by MLVA can be utilized to make informed patient care decisions and to accurately define new CDI cases for infection control and reimbursement purposes.
INTRODUCTION

One of the most problematic aspects of *Clostridium difficile* infections (CDI) is the propensity of recurrence in 15-35% of patients who initially respond to antimicrobial therapy. In addition, recurrent CDI is difficult to treat and contributes to significant morbidity and mortality and increased healthcare expenditures (11, 12, 28).

The molecular epidemiology of CDI has changed since 2000 with the global spread of an epidemic clone, designated by restriction endonuclease analysis (REA), pulsed-field gel electrophoresis and PCR ribotyping respectively, as BI/NAP1/027. However, recent studies raise doubts regarding the role of BI/NAP1/027 in increased CDI incidence, severity, and recurrence rates (4, 22).

Recurrent CDI can be due to either relapse with the original infecting strain or re-infection with a new strain. Previous studies have demonstrated that continued non-CDI antibiotic treatment and a failed immune response to *C. difficile* toxins A and B are risk factors for recurrent CDI (16, 21, 26). Most recently, lower cure rates and higher rates of recurrence due to BI/NAP1/027 infection were reported in phase 3 clinical trials of fidaxomicin (27). Recent estimates suggest that 65-88% of recurrent CDI is attributable to relapse with the original infecting strain (2, 3, 13). However, some of the molecular typing methods used in these studies such as PCR ribotyping and random amplification of polymorphic DNAs (RAPD) lack sufficient discriminatory power and may have misclassified reinfections as relapses. In a study using restriction endonuclease analysis (REA), 83.3% of recurrences were due to relapse (9). In this study, multi-locus variable number tandem repeat analysis (MLVA), a highly discriminatory *C. difficile* genotyping method,
was used to define relapse in patients with recurrent CDI and to identify risk factors associated with relapse.

**MATERIALS AND METHODS**

**Setting.** The University of Pittsburgh Medical Center–Presbyterian (UPMC) is a 724-bed, tertiary-care teaching facility with a previously described CDI epidemic and enacted control measures (24, 25). Considering only first infections per person, the prevalence of BI/NAP1/027 at UPMC was 46.7%, 40.0%, and 50.7% in 2001, 2005, and 2009, respectively.

**Study patients.** This study was approved by the University of Pittsburgh Institutional Review Board. Cell culture cytotoxicity assay of stool (Diagnostic Hybrids, Athens OH) was performed for laboratory diagnosis of CDI throughout the entire study period. Patients with recurrent CDI were defined as having diarrhea (>2 bowel movements per day) and a *C. difficile* positive stool culture for both initial and subsequent episodes (interval of at least 14 days). *C. difficile* isolates were obtained from stool samples submitted for toxin testing by selective culture (23). A total of 149 patients with multiple positive stool cultures seen at UPMC between March 2001 and November 2009 were available for inclusion. For logistical purposes, a systematic sampling of these 149 patients was performed to limit the number of patients to 100.

**Chart review.** On retrospective chart review of the 100 patients, 18 did not meet the recurrent CDI definition. Therefore, 82 patients with recurrent CDI were available for analysis. Patient demographics, co-morbidities, clinical symptoms (diarrhea, emesis, abdominal pain, abdominal distension), laboratory parameters from -2 to +5 days from day of stool toxin testing (maximum white blood cell count, maximum band %, minimum albumin, lactate, maximum creatinine), length of hospital stay, length of ICU stay, concurrent infection, duration/class of non-CDI
antimicrobials prescribed (-5 to +10 days from day of testing), discharge to home versus another healthcare facility, and the survival to hospital discharge were collected. Radiology records were reviewed for evidence of pan-colitis, bowel wall thickening or edema, pneumatosis, ileus and ascites. Exposures to other hospitals or healthcare institutions, dialysis center, outpatient clinics, infants as well as outpatient and inpatient antibiotics, H₂ blocker/proton pump inhibitor (PPI) use, tube feeds, enemas, anti-motility agents and immunosuppressive drugs were determined for the 12 week period prior to CDI recurrence for each recurrent episode.

**Genotyping.** MLVA and tcdC genotyping were performed as previously described on 199 isolates (82 original and 117 recurrent) from 82 patients. (19). Isolates with the tcdC-1 genotype were defined as belonging to the BI/NAP1/027 epidemic clone (7). The sum of the tandem repeat differences (STRD) between MLVA genotypes from consecutive *C. difficile* isolates from each individual was used to define each recurrent episode as either relapse or re-infection. Consecutive episodes with STRD ≤ 2 were defined as relapse while consecutive episodes with STRD ≥ 3 were defined as reinfection. This cut-off was selected based on previous data from consecutive patient isolates demonstrating only 1-2 tandem repeat changes over as many as 90 days (18).

For comparison with MLVA, all recurrent CDI episodes for the 82 patients (n=117) were also classified according to the Centers for Disease Control and Prevention Ad Hoc *C. difficile* Surveillance Working Group recommendations (20). Under these guidelines episodes that occur 2-8 weeks after resolution of the last episode represent recurrent CDI and episodes that occur > 8 weeks after the onset of a previous episode represent new infections (20). The genetic diversity of BI/NAP1/027 was assessed by MLVA genotyping of 856 BI/NAP1/027 isolates collected from 2001 – 2009 at our institution.
Statistics. Univariate logistic regression analysis was performed to determine risk factors for relapse as compared to reinfections using SAS (v9.2, SAS Institute). Stepwise multivariable logistic regression analysis was performed to identify independent risk factors for relapse. All variables that were significant in the univariate analysis at p=0.2 were eligible for inclusion in the multivariable model. The stay criterion for the model was p<0.05. The OR was expressed as the odds for relapse.

Patients with >1 recurrence (≥3 episodes) were examined by intervals between first and second episode only. Interval was defined as the number of days between the stool specimen collect date from consecutive episodes. Given the potential for misclassification of isolates with STRD 3-9, analyses were performed that both included and excluded recurrent CDI episodes within this range.

RESULTS

Of the 82 patients that met the clinical definition of recurrent CDI, 51 had relapse and 31 had reinfection defined by MLVA. Patients with relapse or reinfection were similar when compared by age, gender, race, and Charlson index (Table 1). In univariate analysis of comorbidities, malignancy was more common in patients with relapse than in patients with reinfection and the opposite was true for neurologic disorders. Patients with relapse were more likely to have received an opiate than patients with reinfection (Table 1). In univariate analysis of characteristics associated with the index case, there was a strong association between prior BI/NAP1/027 infection and risk of relapse observed (OR, 3.8; 95% CI, 1.4, 10.1; P = 0.008).
In the multivariate analysis, prior infection with a BI/NAP1/027 strain and use of opiates were also associated with relapse (Table 2). In contrast, the use of non-CDI antibiotics during the initial episode, use of any antimicrobial in the 12 weeks prior to the second episode and inflammatory bowel disease (IBD) were associated with a second episode of CDI attributable to re-infection. Excluding the 7 patients with STRD 3-9 did not substantially change these results (data not shown).

Among the 52 patients with a single CDI recurrence, 36 (69.2%) were classified as relapse by MLVA and 16 (30.8%) patients had re-infections (Table 3). The median interval to relapse (48 days) was significantly shorter than the median interval to re-infection (108 days; \( P = 0.01 \)) in patients with a single recurrence. Among 30 patients with multiple recurrences, 11 patients had relapses, 8 patients had recurrences due solely to re-infections and 11 had recurrences attributed to both relapse and re-infection (Table 3). The median interval to relapse or re-infection in patients with multiple recurrences was not significantly different (30 and 40 days, respectively). The median interval to recurrence among the 11 patients with both relapse and re-infection was significantly longer than the interval to recurrence in patients with either relapse or re-infection alone (78 days; \( P = 0.03 \)). When all 117 episodes were stratified by the prior episode strain type (BI/NAP1/027 vs. non-BI/NAP1/027), the interval to recurrence tended to be shorter (43 vs. 62 days) for episodes due to BI/NAP1/027 strains than non-BI/NAP1/027 strains but this difference was not significant \( (P= 0.64) \). Similarly, among second episodes only (n=82), the interval to recurrence was shorter among BI/NAP1/027 (40 vs. 79 days) but not significantly \( (P = 0.11) \).

A comparison of all CDI recurrences defined by either MLVA or CDC recommendations (interval between episodes) was performed. There were 61 recurrent CDI episodes that occurred within 2-8 weeks (CDC – relapse) of the previous episode. Of these 17 (28%) were considered
reinfections by MLVA (STRD ≥ 3) (Figure). There were 56 recurrent CDI episodes that
occurred more than 8 weeks after the previous episode that would be considered reinfections by
CDC recommendations. Of these, 27 (48%) were classified as relapse by MLVA (STRD ≤ 2)
(Figure). Thus, the 8 week cut-off misclassifies 44/117 (38%) recurrent CDI episodes.

DISCUSSION

In this study, prior infection with the BI/NAP1/027 epidemic strain was a significant risk factor
for the development of recurrent CDI due to relapse. Two very recent studies have described
increased recurrence rates and a trend towards higher incidence of relapse among patients
infected with BI strains as defined by REA typing (9, 27). These data could have major
implications for treatment and development of new therapeutics that specifically target infection
with BI/NAP1/027 strains. Treatment of recurrent CDI is more difficult as no single therapy has
been proven to prevent recurrence in all patients (12). While reduced recurrence was observed in
patients treated with fidaxomicin compared to vancomycin, this effect was limited to patients
with non-BI/NAP1/027 infections (15.4% vs. 25.3%, p = 0.005) (17). Similar results were
observed in recent phase 3 clinical trials where recurrence rates were significantly reduced in
patients treated with fidaxomicin vs. vancomycin for non-BI/NAP1/027 infections but no
difference in rates of recurrence was observed in BI/NAP1/027 infections (27). Moreover, the
same study demonstrated that patients with BI/NAP1/027 infections have a reduced overall cure
rate (27). Together, these results demonstrate the need for further characterization of
BI/NAP1/027 to assess the biological basis for relapse among these strains.

The strong association of opiates with CDI relapse may be due to the antimotility effect of these
agents. The clinical utility of antimotility drugs for adjunctive therapy of CDI has recently been
questioned for several reasons including the finding that resolution of CDI symptoms correlates with a decrease in detectable *C. difficile* in patient stool (1, 10). Slowing the transit of bowel contents may impede effective elimination of the organism, lead to spore accumulation and contribute to future recurrent CDI episodes due to the original infecting strain.

This study demonstrated an association of IBD with CDI reinfection. This finding is consistent with a recent point-prevalence investigation of *C. difficile* environmental contamination in a hospital-based outpatient GI clinic (5). In that study, 3/6 GI examination rooms were found to be contaminated with toxigenic *C. difficile* (5). This finding not only highlights the need for improved infection control practices in outpatient clinics but also suggests that recurrent CDI in IBD patients could be due to reinfection from the clinic environment. Further molecular epidemiologic investigations of IBD reinfections are required to validate this hypothesis.

Understanding the relative rates of relapse and re-infection in recurrent CDI is important from a number of perspectives. This information can help elucidate the pathology of the organism and may reveal host immune deficiencies or genetic predispositions for relapse that have yet to be explored. In addition, rates of relapse and reinfection are important from a healthcare provider standpoint. Increased rates of reinfection indicate a need for enhanced infection control measures.

MLVA is an objective, highly-discriminatory molecular genotyping tool that can be used to define relapse versus reinfection in recurrent CDI cases. We report lower rates of relapse in our study compared to recent reports that used either PCR-ribotyping, multi-locus sequence typing (MLST) and REA to classify recurrent CDI (8, 9, 14). These methods may overestimate relapse and underestimate re-infection rates because they are less discriminatory than MLVA (15). The
MLVA data presented in this study suggests that definitions of recurrent CDI based on the interval between episodes alone are not an accurate measurement of the relative frequencies of relapse and reinfection. MLVA, on the other hand provides a more reliable estimate of the contribution of relapse and re-infection to recurrent CDI.

This study used a strict MLVA cut-off of STRD ≤ 2 to define relapse. This cut-off was selected based upon a previous study which demonstrated that MLVA genotypes obtained from consecutive isolates from individual patients varied by 1-2 tandem repeats at one or two loci over as many as 90 days (6). There were 16 isolates in the current study with STRD 3-9 when compared to the previous episode’s isolate. Seven of these isolates were single locus variants with STRD 3-5, and shared the same \textit{tcdC} genotype as the previous isolate. Further investigation of the mutation rates at MLVA loci are required to determine whether these recurrent isolates could be classified as relapse. Thus, the definition of relapse in this study is conservative.

While some patient samples in this retrospective study were collected during a BI/NAP1/027 epidemic at our institution, it is unlikely that the association of BI/NAP1/027 with relapse results from misclassification bias resulting from hospital transmission of circulating clones identical by MLVA. Substantial genetic diversity of BI/NAP1/027 strains at our institution was observed by MLVA and a conservative STRD cut-off of ≤ 2 was used to define relapse. Among 856 BI/NAP1/027 isolates at our institution, 439 different MLVA genotypes were identified. Only 10 MLVA genotypes include ≥10 isolates and no genotype includes more than 20 isolates. This study is limited by the fact that only patients with recurrent CDI from a single institution were included. Prospective studies of CDI patients are required to validate the role of BI/NAP1/027 in recurrent CDI due to relapse.
In summary, this study used MLVA to define recurrent CDI as either relapse with the original infecting strain or reinfection with a new strain. Based upon this analysis, we demonstrate that an initial infection with BI/NAP1/027 is a significant risk factor for relapse in patients with recurrent disease. Thus, strain-specific characteristics may play a role in recurrent CDI. This finding may have important implications for the rational design of future therapeutics targeting BI/NAP1/027 infections.

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Figure Legend

Figure. Recurrent CDI episodes (n=117) plotted as a function of STRD and interval (days).

Episode 2, (n = 82), episode 3 (n = 30), episode 4 (n = 5); Vertical and horizontal dashed lines indicate interval and MLVA cut-offs respectively for defining relapse and re-infection. STRD, summed tandem repeat difference.
Table 1. Comparison of Characteristics of Patients (n=82) with a Second Episode of CDI.

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Relapse (%)</th>
<th>Re-infection (%)</th>
<th>OR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Median, range)</td>
<td>64 (29-87)</td>
<td>64 (18-93)</td>
<td>1.0 (0.97, 1.02)</td>
<td>0.57</td>
</tr>
<tr>
<td>Male gender</td>
<td>24 (47.1)</td>
<td>14 (45.2)</td>
<td>1.1 (0.4, 2.6)</td>
<td>0.87</td>
</tr>
<tr>
<td>Black race</td>
<td>13 (25.5)</td>
<td>9 (29.0)</td>
<td>0.8 (0.3, 2.3)</td>
<td>0.73</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Comorbidity</th>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Modified Charlson Index (Median, range)</td>
<td>5 (0-11)</td>
<td>4 (0-16)</td>
<td>1.0 (0.9, 1.1)</td>
<td>0.92</td>
</tr>
<tr>
<td>Chronic renal insufficiency</td>
<td>17 (33.3)</td>
<td>9 (29.0)</td>
<td>1.2 (0.5, 3.2)</td>
<td>0.69</td>
</tr>
<tr>
<td>Diabetes</td>
<td>20 (39.2)</td>
<td>12 (38.7)</td>
<td>1.0 (0.4, 2.6)</td>
<td>0.96</td>
</tr>
<tr>
<td>Diverticulosis</td>
<td>9 (17.6)</td>
<td>5 (16.1)</td>
<td>1.1 (0.3, 3.7)</td>
<td>0.86</td>
</tr>
<tr>
<td>Infection</td>
<td>32 (62.7)</td>
<td>17 (54.8)</td>
<td>1.4 (0.6, 3.4)</td>
<td>0.48</td>
</tr>
<tr>
<td>Ischemic vascular disease</td>
<td>21 (41.2)</td>
<td>17 (54.8)</td>
<td>0.6 (0.2, 1.4)</td>
<td>0.23</td>
</tr>
<tr>
<td>Inflammatory bowel disease</td>
<td>2 (3.9)</td>
<td>4 (12.9)</td>
<td>0.3 (&lt;0.1, 1.6)</td>
<td>0.15</td>
</tr>
<tr>
<td>Immunocompromised host</td>
<td>23 (45.1)</td>
<td>16 (51.6)</td>
<td>0.8 (0.3, 1.9)</td>
<td>0.57</td>
</tr>
<tr>
<td>Lung disease</td>
<td>13 (25.5)</td>
<td>14 (45.2)</td>
<td>0.4 (0.2, 1.1)</td>
<td>0.07</td>
</tr>
<tr>
<td>Malignancy</td>
<td>20 (39.2)</td>
<td>5 (16.1)</td>
<td>3.4 (1.1, 10.2)</td>
<td>0.03</td>
</tr>
<tr>
<td>Neurologic disorder</td>
<td>3 (5.9)</td>
<td>7 (22.6)</td>
<td>0.2 (&lt;0.1, 0.9)</td>
<td>0.04</td>
</tr>
<tr>
<td>Obesity</td>
<td>6 (11.8)</td>
<td>1 (3.2)</td>
<td>4.0 (0.5, 34.9)</td>
<td>0.21</td>
</tr>
<tr>
<td>Abdominal Surgery</td>
<td>24 (47.1)</td>
<td>14 (45.2)</td>
<td>1.1 (0.4, 2.6)</td>
<td>0.87</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Medication Use (during 1st episode)</th>
<th>Relapse (%)</th>
<th>Re-infection (%)</th>
<th>OR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metronidazole as CDI treatment</td>
<td>34 (69.4)</td>
<td>22 (71.0)</td>
<td>0.9 (0.3, 2.5)</td>
<td>0.88</td>
</tr>
<tr>
<td>Non-CDI antibiotic</td>
<td>34 (66.7)</td>
<td>26 (83.9)</td>
<td>0.4 (0.1, 1.2)</td>
<td>0.09</td>
</tr>
<tr>
<td>Antimotility (excluding opiates)</td>
<td>8 (16.3)</td>
<td>2 (6.5)</td>
<td>2.8 (0.6, 14.3)</td>
<td>0.21</td>
</tr>
<tr>
<td>Antacid</td>
<td>17 (34.7)</td>
<td>6 (19.4)</td>
<td>2.2 (0.8, 6.4)</td>
<td>0.14</td>
</tr>
<tr>
<td>PPI</td>
<td>28 (57.1)</td>
<td>16 (51.6)</td>
<td>1.2 (0.5, 3.1)</td>
<td>0.63</td>
</tr>
<tr>
<td>Opiates</td>
<td>30 (61.2)</td>
<td>10 (32.3)</td>
<td>3.3 (1.3, 8.6)</td>
<td>0.01</td>
</tr>
<tr>
<td>Probiotics</td>
<td>17 (34.7)</td>
<td>16 (51.6)</td>
<td>0.5 (0.2, 1.2)</td>
<td>0.14</td>
</tr>
<tr>
<td>Tube Feeding (12 wks prior to 2nd episode)</td>
<td>19 (37.3)</td>
<td>15 (48.4)</td>
<td>0.6 (0.3, 1.6)</td>
<td>0.32</td>
</tr>
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</table>
### Exposures (following 1st episode)

<table>
<thead>
<tr>
<th>Exposure</th>
<th>First Episode</th>
<th>Second Episode</th>
<th>Odds Ratio (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthcare facility since discharge for previous episode</td>
<td>44 (86.3)</td>
<td>27 (90.0)</td>
<td>0.7 (0.2, 2.9)</td>
<td>0.62</td>
</tr>
<tr>
<td>Home*</td>
<td>13 (25.5)</td>
<td>5 (16.7)</td>
<td>1.7 (0.5, 5.4)</td>
<td>0.36</td>
</tr>
<tr>
<td>Antibiotics (outpatient /outside hospital)</td>
<td>25 (50.0)</td>
<td>22 (73.3)</td>
<td>0.4 (0.1, 1.0)</td>
<td>0.04</td>
</tr>
<tr>
<td>Antimicrobials (12 wks prior to 2nd episode)</td>
<td>40 (81.6)</td>
<td>29 (93.5)</td>
<td>0.3 (&lt;0.1, 1.5)</td>
<td>0.15</td>
</tr>
</tbody>
</table>

### Characteristics of index case

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>First Episode</th>
<th>Second Episode</th>
<th>Odds Ratio (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infection with BI/NAP1/027 strain</td>
<td>29 (56.9)</td>
<td>8 (25.8)</td>
<td>3.8 (1.4, 10.1)</td>
<td>0.008</td>
</tr>
<tr>
<td>High CD prognosis score (&gt;3)</td>
<td>9 (17.6)</td>
<td>6 (19.4)</td>
<td>0.9 (0.3, 2.8)</td>
<td>0.85</td>
</tr>
<tr>
<td>Radiologic abnormality</td>
<td>25 (49.0)</td>
<td>10 (32.3)</td>
<td>2.0 (0.8, 5.1)</td>
<td>0.14</td>
</tr>
<tr>
<td>Days between positive cultures</td>
<td>40 (17-402)</td>
<td>90 (18-1260)</td>
<td>1.0 (0.99, 1.00)</td>
<td>0.01</td>
</tr>
<tr>
<td>Length of hospitalization (Median, range)</td>
<td>15 (0-257)</td>
<td>10 (0-122)</td>
<td>1.0 (0.99, 1.02)</td>
<td>0.45</td>
</tr>
</tbody>
</table>

*Excludes patients exposed to rehab and skilled nursing facilities or other hospitals prior to discharge.
Table 2. Multivariate Analysis of Factors Associated with Relapse or Re-infection Among 82 patients with a Second Episode of CDI

<table>
<thead>
<tr>
<th></th>
<th>OR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Factors associated with relapse</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infection with BI/NAP1/027 strain</td>
<td>6.9 (1.7, 28.2)</td>
<td>0.007</td>
</tr>
<tr>
<td>Opiate use during previous episode</td>
<td>13.1 (3.2, 54.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Factors associated with re-infection</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-CDI antibiotic (previous episode)</td>
<td>0.1 (0.02, 0.5)</td>
<td>0.007</td>
</tr>
<tr>
<td>Inflammatory bowel disease</td>
<td>0.04 (0.0, 0.5)</td>
<td>0.011</td>
</tr>
<tr>
<td>Antimicrobials (12 wks prior)</td>
<td>0.1 (0.01, 0.8)</td>
<td>0.033</td>
</tr>
</tbody>
</table>


<table>
<thead>
<tr>
<th>Episode Type</th>
<th>No. of patients</th>
<th>Interval (days)</th>
<th>Range (days)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single Recurrence (n=52)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Relapse (n=36)</td>
<td>36 (69.2%)</td>
<td>48</td>
<td>19 - 402</td>
<td>0.01</td>
</tr>
<tr>
<td>Re-infection (n=16)</td>
<td>16 (30.8%)</td>
<td>108</td>
<td>23-1260</td>
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</tr>
<tr>
<td>Multiple Recurrence (n=30)</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Relapse (n=23)</td>
<td>11 (36.7%)</td>
<td>30</td>
<td>15 - 319</td>
<td>0.03</td>
</tr>
<tr>
<td>Re-infection (n=17)</td>
<td>8 (26.6%)</td>
<td>40</td>
<td>17 - 325</td>
<td></td>
</tr>
<tr>
<td>Relapse &amp; Re-infection (n=25)</td>
<td>11 (36.7%)</td>
<td>78</td>
<td>17 - 778</td>
<td></td>
</tr>
</tbody>
</table>