Clostridium Difficile Infection and Liver Disease

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Abstract
The rates of the predominantly hospital acquired infection, Clostridium difficile, have increased throughout the world. Several risk factors and susceptible patient populations have been identified. Patients with pre-existing liver disease represent an important cohort; recent evidence suggests Clostridium difficile infection (CDI) is associated with a worse outcome and increased health care costs. This review focuses on the epidemiology, risk factors, pathogenesis, treatment options and outcomes associated with CDI in patients with liver disease.

Keywords

Epidemiology of Clostridium difficile infection and LD
Clostridium difficile infection can either be classified as hospital or community acquired; the prevalence of LD has been described in both. In terms of nosocomial disease, retrospective single centre studies have revealed CDI is common amongst LT patients [8], and patients of a hepatology unit [13]. The former revealed 30/136 (22%) hospital acquired cases occurred in LT patients and the latter showed that compared to other hospital wards, higher rates of infection were evident on the hepatology ward (0.9% vs 0.29%). Most of the affected patients (22/23) in the latter case controlled study had cirrhotic LD (Child Pugh A (17%), B (50%) or C (28%)). Two large multicentre studies have also described the frequency of LD amongst hospitalised patients. The first, the Canadian Nosocomial Infection Surveillance Program (CNISP) reported 62/1430 (4%) CDI cases had underlying LD [16], and the second, a retrospective study from the United States (US) revealed 1,165/59,385 (2%) CDI cases discharged from hospital either had cirrhosis or cirrhosis related complications [6]. Both of these findings require further clarification; the definition of LD used by the CNISP was not mentioned and the reported rate in cirrhotics may have included asymptomatic carriers.

A number of studies have described the rates of CDI in certain LD [6-8, 10, 14, 18, 20, 21]. Investigations involving hospitalised patients have revealed that 2% of mild LD patients and 5.5% of cirrhotics are diagnosed with CDI [18, 21]. One case controlled study has demonstrated that 2/19 (11%) cirrhotic patients develop community acquired...
CDI [20]. Although diarrhoea on hospital admission has been reported in 7/54 (13%) cirrhotic patients with CDI [6], it is not clear whether all/any really fulfil the criteria for community acquired CDI. The recurrence rate of CDI varies from 15-35%; most are thought to be caused by another strain [22]. Recurrent episodes of CDI have rarely been described in patients with LD; rates post LT vary from 22-27% [8, 9].

Rates of CDI in patients with deceased donor LT vary from 3% to 8% [8, 14] and post ‘live’ donor LT transplant vary from 5% to 11% [9, 10]. Most cases (≥50%) occur within the first month of LT [8, 9, 14]; reports in patients > 1 year post LT are rare [8, 23]. The observed variance in rates may be attributed to the method of diagnosis, the timing/number of stool tests performed and study duration. Investigation periods have varied from less than four years [8] to more than eight [9]. A number of different techniques have been used to identify cases including enzyme immunoassays (EIA), stool cultures and polymerase chain reaction assays [7-9,11-13]. The specific method used may have influenced the diagnostic rate. Enzyme immunoassays have been most frequently used and whilst they are simple to perform and provide rapid results, several types are available each exhibiting a range of sensitivities and specificities compared to the reference method (the cytotoxin stool cell culture assay) [24]. During the first month post deceased donor LT, only 5/35 EIA positive specimens were culture positive [7].

The spectrum of disease associated with CDI also includes patients with asymptomatic carriage. Currently little is known about rates of asymptomatic carriage or hospital acquisition in LD patients; most of the data available refers to patients post LT [9, 25, 26]. Approximately 3% of the healthy adult population are colonised by *C. difficile*, increasing to over 20% in hospitalised patients [27]. Liver transplantation has been shown to be an independent risk factor for hospital acquisition (relative risk 4.2, 95% confidence interval [CI] 1.3-13.7) [25]. One small prospective study (n=15) revealed nine (60%) patients were colonised during the first 35 days post transplant [26]. Two thirds of cases were colonised by toxin producing strains; none were stool culture or toxin positive at the time of study induction. A more recent study involving less frequent stool testing, determined 16/27 (60%) LT patients with *C. difficile* were asymptomatic [9]. Only one patient was however carrying a toxin producing strain. As stool results on study entry were not reported, it is not possible to say whether the asymptomatic carriers were present from the time of admission or were cases of hospital colonisation or a combination of both. Asymptomatic carriage amongst cirrhotic patients may be as high as 20% [28].

**Risk factors for *Clostridium difficile* infection in patients with liver disease**

Few studies have described the risk factors associated with CDI in LD patients (Table I); those identified relate to cirrhotic and LT patients [6, 8, 9, 13]. Although formal comparisons between the rates and risk factors for CDI in patients receiving a deceased donor LT or live donor LT have yet to be done, different risk factors have been reported. Independent risk factors during the first three months of ‘live’ donor LT include male gender (odds ratio - OR 4.56, 95% CI 1.02-33.3) and an elevated pre-operative serum creatinine ≥1.5mg/dl (OR 15.99, 95% CI 3.85-68.3) [9]. Impaired host immunity in patients with deranged renal function may explain the latter finding. In contrast, a number of other risk factors have been identified in patients post deceased donor LT (Table I); stratification by CDI onset (early or intermediate) has revealed some important differences [8].

Early CDI (<28 days of LT) is associated with a higher model end stage liver disease (MELD) score, intra-abdominal haemorrhage, increased numbers of grafts and re-transplantation. In contrast, intermediate CDI (29-365 days post LT), is more likely in patients with vascular complications, bacterial infections and those requiring endoscopic retrograde cholangiopancreatography or percutaneous cholangiography [8]. Biliary complications, bile leaks and systemic infections are common to both. As the relationship in terms of antibiotic exposure was not assessed, there is the possibility that antibiotics used to treat complications were more important than the underlying cause. Biliary complications are also common after ‘live’ donor LT, however, the relationship to CDI has not been reported [29].

Antecedent antibiotic therapy is the most important risk factor for CDI, and antibiotic use in patients with cirrhosis and post LT is significant. Patients requiring LT routinely receive antibiotics as part of their management and whilst pre-operative antibiotic use [9], and selective decontamination have not been shown to increase the risk of CDI [30], the use of additional post-operative antibiotics maybe important [8]. This study demonstrated that 69% CDI patients post LT received additional antibiotics. One

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<th>Table I. Risk factors associated with <em>Clostridium difficile</em> infection in patients with liver disease</th>
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<td>Previous antibiotic use (Beta-lactams, Co-amoxiclav)</td>
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<td><strong>Post live donor liver transplant [9]:</strong></td>
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<td>Male sex</td>
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<td>Pre-operative serum creatinine ≥1.5mg/dl.</td>
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<td>Non-primary liver transplantation</td>
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Immunosuppressant medications are an important risk factor for CDI in patients with LT and whether certain drugs are more frequently associated with CDI has yet to be evaluated [41]. Corticosteroid use has been identified as a significant risk factor for relapses in transplant patients (risk ratio 4.19, 95% CI 1.41-13.06) [11]. Another common risk factor associated with CDI - age - has not been shown to be important in cirrhotic or post LT patients [6, 9, 13].

The relationship between proton pump inhibitor (PPI) use and CDI remains unclear; studies involving both community and hospital acquired cases have produced conflicting results [20, 32, 42, 43]. Reduced gastric acid is believed to play an important role in ensuring survival of any ingested active (vegetative) forms of *Clostridium difficile* [44]. In addition PPIs may also suppress the immune response to infection [45]. The only study to evaluate the relationship between PPI use and CDI in LD patients has involved cirrhotic patients. This investigation revealed that outpatient PPI use was an independent risk factor for CDI (OR 37.6, 95% CI 6.22-227.6) [6]. This finding suggests that a judicious prescribing policy may be required in this cohort [17]: one prospective study has shown that 39/51 (63%) of cirrhotics receive PPIs inappropriately [46].

Other possible risk factors in cirrhotics have also been described [6]. Although the tertiary referral component (58 infected vs 108 non-infected cirrhotics) of this study failed to show any association with age, gender or ethnicity, the nationwide component (n=1,165 infected vs 82,065 non-infected cirrhotics) demonstrated that infected cirrhotics were more likely (p<0.001) to be older (61 vs 58 years), female (46.0% vs 38.5%), Caucasian (57.4% vs 51.4%) and have a raised Charlson co-morbid score ≥ 3 (14.0% vs 11.9%). In addition, CDI was found to be more common (p<0.001) amongst cirrhotics with hepatorenal syndrome (4.8% vs 3.0%), pneumonia (14.2% vs 7.8%), spontaneous bacterial peritonitis (0.9% vs 0.5%) and a urinary tract infection (21.3% vs 12.1%) and less common in cirrhotics with encephalopathy (16.9% vs 19.0%) or a variceal bleed (4.1% vs 7.9%).

Comparisons between patients with LD and CDI to those with CDI alone have rarely been done [6]. This large population based study demonstrated that infected cirrhotics (n=1,165) were more likely (p<0.001) to be younger (61 vs 69 years), male (54.0% vs 40.8%) and Hispanic (11.6% vs 5.1%) than non-cirrhotic CDI patients (n=58,220) and less likely to have a raised Charlson comorbid score ≥ 3 (14.0% vs 18.8%), pneumonia (14.2% vs 17.2%) or a urinary tract infection (21.3% vs 26.1%). Both cohorts excluded LT patients.

**Pathogenesis**

*Clostridium difficile* is predominantly transmitted as spores via the faecal-oral route. Following ingestion, primary bile salts and their derivatives facilitate germination to the vegetative (active) state within the small bowel. The bacteria then migrates to the colon where under favourable conditions (antibiotic mediated disruption of colonic flora), proliferation occurs and strains capable of producing toxins (A,B) cause...
intestinal inflammation and disease [47, 48]. Disturbances and thus reduced levels of colonic bacteria possessing the enzyme 7-alpha hydroxylase activity, such as Lactobacillus and Bifidobacteria species, are believed to play an important role in facilitating C. difficile growth [47].

Altered gut flora has been reported in LD patients [49-52], and may provide a favourable environment for C. difficile colonisation and proliferation. All of these studies have been conducted in Asia. Compared to normal controls, cirrhotic patients (mostly with viral hepatitis) have been shown to have significantly reduced levels of Bifidobacterium and increased levels of Clostridium, respectively [49]. In addition to antibiotic use, possible reasons for the changes in gut flora include delayed intestinal motility and increased intestinal pH [49]. Reduced levels of Bifidobacterium have also been reported in patients with chronic severe hepatitis and chronic hepatitis [51], and both Lactobacilli and Bifidobacteria amongst alcoholic patients [52]. Experimental animal models of acute liver failure have also demonstrated reduced levels of Lactobacillus in the ileum and colon [52].

Selective bowel decontamination is predominantly aimed at aerobic gram-negative bacteria. Maintenance of the gram positive flora (including Bifidobacteria and Lactobacilli) may provide a plausible explanation for the lack of any association between selective bowel decontamination and CDI in LT patients [30].

Not all patients colonised by toxin producing strains develop disease; protective host factors include an intact immune system and a lack of significant co-morbidity [53,54]. Disturbed immune function has been observed in patients with LD [13, 55] and may account for the apparent increased risk in patients with autoimmune hepatitis [13]. Hypogammaglobulinaemia may be an important risk factor in LT patients; just over a quarter of LT patients have reduced immunoglobulin levels (IgG levels <560 mg/dl) [55]. Risk factors for reduced IgG levels include a diagnosis of non A/B hepatitis, rare LD such as autoimmune hepatitis and reduced platelet transfusion requirements. Although this study did not assess outcome in terms of CDI, hypogammaglobulinaemia is associated with CDI in other patient populations e.g. those post cardiac transplantation [55, 56].

**Clinical features**

The clinical manifestations associated with CDI are diverse, ranging from asymptomatic carriage through to severe colitis and life threatening sepsis [22]. Symptom onset is variable and may range from one day to several weeks following antimicrobial exposure [57]. Typical features of CDI include watery diarrhoea and abdominal discomfort. Systemic features develop in patients with more severe disease and in some cases an ileus/megacolon may develop [22]. Recent national and international guidelines now incorporate a number of clinical, laboratory and radiological parameters to define severity [58-60].

Clinical features associated with CDI in LD have been mostly described in LT patients, diarrhoea, fever and abdominal pain are common presenting symptoms in this cohort [9, 12, 61]. Diarrhoea may last for up to 43 days (range 5-43 days) [9]. Diarrhoea is extremely common in the first few weeks post LT and it is important to rule out other infectious (e.g. Cytomegalovirus) or non-infectious (e.g. drugs) causes [62]. Severe cases of CDI have also been reported in this cohort [8, 9, 14, 63, 64]. Although hospitalised transplant patients are more likely to develop symptomatic CDI [25], one retrospective study has failed to show any significant difference in severity (death, intensive care unit admission or colectomy within 30 days of diagnosis) between transplant (n=80) and non-transplant patients (n=86) [11]. Fever (67%) and diarrhoea (13%) are also common amongst cirrhotic patients with CDI [6].

Extra-intestinal CDI has been reported in patients with LD [65], including splenic and liver abscesses [5,15]. Liver disease patients with ascites are susceptible to developing bacterial peritonitis and there have been a few instances in which C. difficile has been cultured from peritoneal fluid [5, 65, 66].

**Diagnosis**

Several methods of diagnosis are available including microbiology (stool culture/toxin testing), histology and endoscopy. The reference method of diagnosis is the stool cytotoxin culture assay (detects Toxin B). Use of this technique has now largely been superseded by the more rapid technique of EIA. Concerns over the sensitivity and specificity of EIA have resulted in a growing consensus to confirm all positive EIA cases with the reference method [24]. Use of a ‘two’ or ‘three’ step approach to diagnosis is believed to be more cost effective than using the reference method alone [22]. Most studies involving LD patients have used EIA to diagnose CDI [7-9, 11, 12], additional testing of positive EIA cases has rarely been done [7, 9]. Stool toxin analysis by polymerase chain reaction has also been done [13].

Stool sampling from patients with an ileus may not be possible; in such cases endoscopy and radiological findings may provide important clues. Histological and endoscopy findings in patients with CDI vary from non specific colitis to pseudomembranous colitis (severest form of disease) [57]. Pseudomembranous colitis has been described in LT patients and unique histological findings have also been reported [14]. Two patients had mucosal evidence of neutrophilic capillaritis/venulitis. Clinicians should also be alert to the possibility of CDI in cirrhotic patients with computerised tomography evidence of right colon pneumatosis or diffuse colonic pneumatosis/pancolonic thickening [67].

**Treatment**

Management of CDI can be either medical and/or surgical. Current medical treatment involves oral metronidazole for mild to moderate CDI cases and oral vancomycin +/- intravenous metronidazole for severe/ life threatening cases [58, 60, 68]. Important additional measures
include barrier nursing, antibiotic rationing, avoidance of antimotility agents and hand washing. Disease severity of CDI is a continuum and progression may occur hence regular/daily assessment is recommended [58, 60, 68]. Several other treatment options are available/being evaluated [31, 69], including the antibiotics rifaximin, tigecycline, fidaxomicin and nitazoxanide. In addition, immunotherapy and faecal transplantation may also prove to be effective in the future. Recurrent CDI can occur in up to 35% of cases and treatment maybe difficult, often requiring longer courses of vancomycin or metronidazole. Other possible treatment options include cholestyramine, tolevamer, immunoglobulin infusions and the infusion of colonic bacteria [22, 31, 69]. Treatment of asymptomatic carriers is ineffective and not recommended [70]. Although development of a vaccine for high risk patients may prove beneficial, its application may be limited in immunosuppressed patients.

Patients that fail to respond to medical therapy may require a colectomy; symptom resolution is expected within a mean time of 3-6 days [22]. Colectomy rates vary from 0.17% [71] to 3.5% [72] and are associated with a high mortality (11.1-66%) [73, 74]. The recommended surgical treatments are a subctal colectomy and ileostomy [75], or a total colectomy and ileostomy [76]. Indications for colectomy include the development of peritonitis and toxic megacolon, leukocytosis (>20x10^9/L) and a raised lactate (2.2-4.9 mmol/L) may also serve as important markers [77].

In terms of LD, the majority of reports and studies have used vancomycin to treat CDI [1, 3, 4, 6, 9, 15, 23, 78]. Metronidazole has also been successfully used [8]. Cholestyramine has rarely been required [1]. Cholestyramine binds to bile acid and is widely used to treat pruritus in patients with cholestatic LD; its mechanism of action against C. difficile involves binding toxins. Colectomies have rarely been required [6, 8, 64, 79]; mortality rates following a colectomy are much higher in cirrhotic than non-cirrhotic patients [80]. Recurrences have also been infrequently reported [1, 9, 15, 75]; episodes have been successfully treated with either repeat courses of vancomycin or metronidazole. One recent case series has also demonstrated that rifaximin may prove an effective treatment option for recurrent CDI in patients post LT [37].

The use of probiotics containing specific strains of Lactobacilli and Bifidobacteria have been shown to reduce the rates of bacterial infection in patients post LT and have also been shown to improve liver function in patients with alcoholic liver disease and non-alcoholic fatty liver disease [52, 81, 82]. In addition, combination therapy with rifaximin and probiotics may also reduce the risk of hepatic encephalopathy [35]. Use of specific probiotic strains may not be effective in all patients with LD; the effect in patients with viral hepatitis has been less dramatic [83]. Modulation of the intestinal flora may also help to prevent/reduce rates of CDI. Probiotics may act by augmenting the antibody response against Toxin A, suppressing C. difficile colonisation, adhesion and invasion and by directly inhibiting the actions of Toxin A and B [69]. Lactulose may also have a preventative role against CDI in LD patients, possibly by reducing colonic exposure to toxins [28].

**Outcome**

Amongst CDI cases, patients with comorbid LD are at an increased risk of a severe outcome including admission to an intensive care unit, surgery (colectomy) and/or death (OR 2.62, 95% CI 1.12-6.15) [16]. One retrospective study investigating CDI cases on ICU (n=278) revealed that 18/278 (6.5%) of patients had underlying cirrhosis; 5/18 (28%) of these cases died [84]. Amongst CDI cases requiring a colectomy, the presence of LD is infrequently reported: 11% may have cirrhosis [79], and 5% may have had a LT [64]. Only one study has investigated the morbidity, mortality and associated healthcare costs in CDI patients with LD. This large retrospective study, involving cirrhotic patients [6], demonstrated that infected cirrhotics (n=1,165) were more likely (p<0.001) to die (13.8% vs 9.6%), have prolonged hospital stays (mean stay 14.4 vs 12.7 days) and higher healthcare costs ($79,351 vs $ 57,708) than patients with CDI alone (n=58,220).

In terms of cirrhotic patient population alone, those with CDI (n=1,165) are more likely to die (OR 1.79, 95% CI 1.51-2.12), require longer lengths of hospital stay (7.1 days, 95% CI 6.2-8.1 days) and incur higher healthcare costs ($40,596, 95% CI $ 31,870-$49,321), than those not infected (n= 82,065) (p<0.001). The mortality rate was influenced by ethnic (African American>Caucasians>Hispanics), insurance group (uninsured>private>Medicare) and geographical differences (midwest America<north east America) [OR 0.75, 95 % CI 0.64 –0.88, p<0.01] [6]. Mortality was not influenced by hospital status (teaching vs non-teaching) or setting (urban vs rural). After adjusting for all these factors, CDI remained an independent risk factor for in-hospital death amongst cirrhotics (OR 1.55, 95% CI 1.29–1.85). This study also demonstrated the mortality risk associated with CDI was similar to those from other cirrhotic related complications such as hepatic encephalopathy (OR 1.94, 95% CI 1.83-2.06), variceal bleeding (OR 1.63, 95% CI 1.49-1.78), spontaneous bacterial peritonitis (OR 1.98, 95% CI 1.45-2.70) and ascites (OR 1.30, 95% CI 1.22-1.38), highlighting the importance of CDI in this patient population. In terms of LT patients, cases with CDI rarely die or require colectomy [8, 9, 14].

**Conclusions**

It is important to recognise that whilst the proportion of CDI cases that have underlying LD is relatively small, affected patients are at risk of increased morbidity and mortality. The significance of CDI amongst cirrhotic patients and those post LT is increasingly being reported. However, little is known about the rates and significance in patients with acute and chronic non-cirrhotic LD. A small number of studies have identified risk factors associated with CDI in certain LD (post LT and cirrhotic) patient populations.
These require further validation and assessment in other LD groups. Metronidazole and vancomycin are the main treatment options available. Use of probiotics, in certain liver conditions, and lactulose may help reduce rates of infection. Recurrent cases have rarely been reported and the apparent increase in socio-economic costs merit further evaluation.

Conflicts of interest
None declared.

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C. difficile and liver disease

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