Identifying patients at risk of severe *Clostridium difficile*-associated disease

Clostridium difficile *infection is responsible for a wide spectrum of clinical presentations, ranging from mild diarrhoea to fatal toxic colitis. This article reviews factors which may identify individuals who are at high risk of severe* C. difficile*-associated disease, and aims to help clinicians predict patients at risk of severe disease.*

Despite being known to cause infection leading to death in humans since 1962 (Smith and King, 1962), *Clostridium difficile* infection has received considerable medical and scientific attention in the last decade, along with significant media interest and public awareness. *C. difficile*, a Gram-positive, spore-forming, exotoxin-producing anaerobic bacillus, is a common cause of antibiotic-associated diarrhoea (*Figure 1*) (Lungulescu et al, 2011). *C. difficile*-associated disease is the most common type of infectious nosocomial diarrhoea in adults in the developed world and its incidence and severity is increasing in North America and Europe (Kuijper et al, 2006, 2007). *C. difficile* infection is implicated in 20–30% of all cases of antibiotic-associated diarrhoea, 50–75% of cases of antibiotic-associated colitis and more than 90% of cases of antibiotic-associated pseudomembranous colitis in hospitalized patients (Kelly et al, 1994).

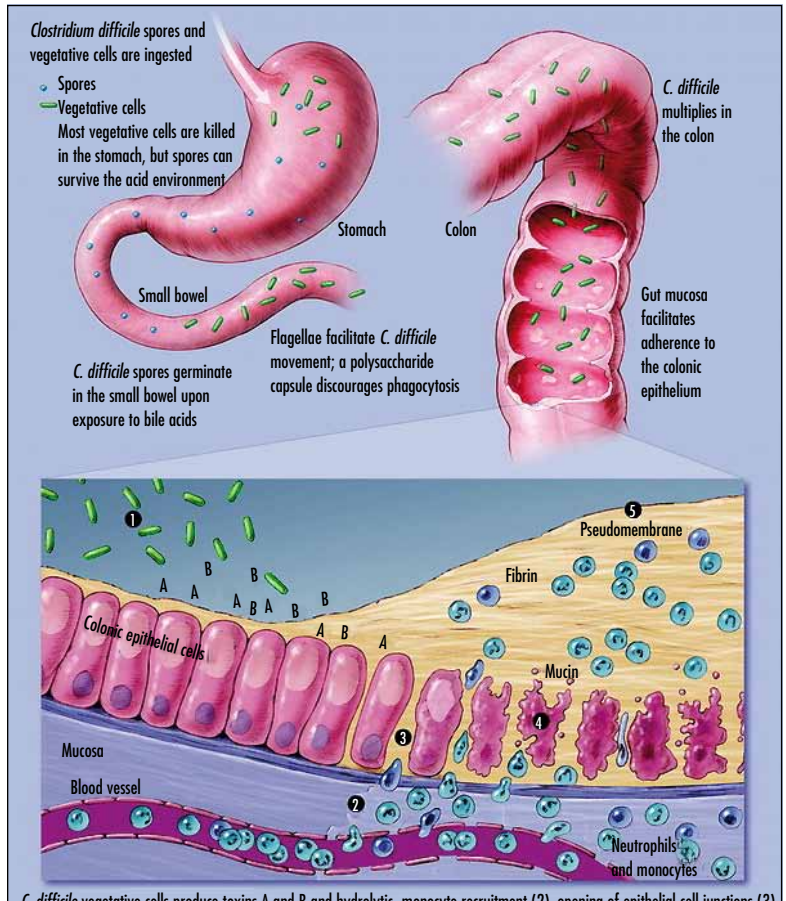
C. difficile infection is associated with a wide clinical spectrum ranging from mild diarrhoea to fulminant and fatal toxic colitis (Dudukgian et al, 2010). Fulminant colitis develops in 3–8% of patients with *C. difficile* infection (Adams and Mercer, 2007) with a mortality rate as high as 47% in those who undergo colectomy for fulminant pseudomembranous colitis (Ali et al, 2008). In the United States, the *C. difficile*-associated disease-related age-adjusted case-fatality rate rose from 1.2% in 2000 to 2.2% in 2004 (Zilberberg et al, 2008). Identifying individuals at risk of major complications has become increasingly important, and attempts have been made to determine the predictors of severe *C. difficile*-associated disease. This article reviews the variables which predict severe *C. difficile*-associated disease and thereby help identify patients at risk of serious complications, including death.

Patient characteristics

Age

Despite age being positively associated with the incidence of *C. difficile* infection, its relationship with disease severity remains controversial. A number of prospective and retrospective studies have identified age over 70 years as an independent risk factor for severe *C. difficile*-associated disease and adverse outcome including death (Andrews et al, 2003; Loo et al, 2005; Lamontagne et al, 2007; Henrich et al, 2009; Pepin et al, 2009). However, this association was not demonstrated in other studies (Ramaswamy et al, 1996; Nair et al, 1998; Kyne

Figure 1. Pathogenesis of* Clostridium difficile*-associated diarrhoea in adults. From Poutanen and Simor (2004).



C. difficile vegetative cells produce toxins A and B and hydrolytic enzymes (1). Local production of toxins A and B leads to production of tumour necrosis factor-α and proinflammatory interleukins, increased vascular permeability, neutrophil and monocyte recruitment (2), opening of epithelial cell junctions (3) and epithelial cell apoptosis (4). Local production of hydrolytic enzymes leads to connective tissue degradation, leading to colitis, pseudomembrane formation (5) and watery diarrhoea.

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et al, 1999; Dharmarajan et al, 2000; Moshkowitz et al, 2007; Bishara et al, 2008; Gujja and Friedenberg, 2009; Dudukgian et al, 2010; Arora et al, 2011; Lungulescu et al, 2011). It is argued that older patients may not be able to mount an effective immune response to the *C. difficile* infection (Andrews et al, 2003), thus leading to severe disease and poor outcome in the elderly. However, others claim that factors associated with advancing age such as comorbidities, refractory sepsis and hypoalbuminaemia are the contributing factors linked to more serious outcome (Dharmarajan et al, 2000).

Gender, ethnicity and body weight

Most studies found no relationship between gender and disease severity (Ramaswamy et al, 1996; Kyne et al, 1999; Dharmarajan et al, 2000; Andrews et al, 2003; Lamontagne et al, 2007; Moshkowitz et al, 2007; Bishara et al, 2008; Gujja and Friedenberg, 2009; Lungulescu et al, 2011). However, in a prospective study Arora et al (2011) found male gender to be associated with severe disease.

Despite most studies having been carried out in institutions that care for patients of various ethnic origin, only two studies investigated the association between ethnicity and *C. difficile*-associated disease severity (Gujja and Friedenberg, 2009; Arora et al, 2011), but found no relationship. Similarly, body weight has also not been found to have an association with severity (Gujja and Friedenberg, 2009; Arora et al, 2011).

Cognitive impairment and physical dependency

Kyne et al (1999) found cognitive impairment, measured by the abbreviated mental test score at the onset of symptoms, to be associated with severe disease, as was debility using the Barthel index. Similarly, Anand et al (1994) found higher mortality in debilitated, older nursing home patients. However, Dharmarajan et al (2000) showed no association between dementia and adverse outcome in *C. difficile*-associated disease, supporting the argument that cognitive impairment is simply more common in aged patients.

Comorbidity

Comorbidity is another risk factor for severe disease (Andrews et al, 2003; Hardt et al, 2008). Although Kyne et al (1999) found patients with severe *C. difficile*-associated disease to have a median of four comorbidities while those with milder disease had a median of three, this did not reach statistical significance. Similarly, Lamontagne et al (2007) showed no relationship between the Charlson comorbidity score and 30-day mortality in patients with *C. difficile*-associated disease.

A number of other studies have investigated the association between disease severity and individual pre-existing illnesses involving major organ systems, such as chronic renal insufficiency, chronic pulmonary disease, malignancy, cardiovascular disease and diabetes, but found contradicting results (Rubin et al, 1995; Dharmarajan et al, 2000; Henrich et al, 2009; Dudukgian et al, 2010; Arora et al, 2011; Lungulescu et al, 2011). For example, Dudukgian et al (2010) reported pre-existing renal and pulmonary insufficiency as risk factors for increased mortality in *C. difficile*-associated disease, but not malignancy, whereas Lungulescu et al (2011) showed an association between *C. difficile*-associated disease severity and history of malignancy (excluding limited skin cancers), but not chronic renal failure.

Interestingly, despite being widely accepted that patients with diabetes have an increased propensity to develop infections, none of the studies demonstrated an association between diabetes and disease severity. As with advanced age, the inability to mount an effective immune response is suspected to be the underlying cause of increased disease severity with major comorbid illnesses (Andrews et al, 2003).

Medications

Antibiotics

Much work has been performed to investigate the relationship between antibiotic use and the incidence of *C. difficile*-associated disease. These studies demonstrate the use of broad-spectrum antibiotics as a predisposing factor for the development of *C. difficile*-associated disease. Alteration of the normal equilibrium of colonic flora by the use of broad-spectrum antibiotics creates an environment that allows *C. difficile* to flourish. This has been accepted as a likely cause of the increasing incidence of *C. difficile*-associated disease. However, less is known about the effects of antibiotics on disease severity.

Concurrent use of more than three or four antibiotics before onset of *C. difficile* infection and prolonged use of antibiotics (>4 weeks) have been identified as risk factors for death related to *C. difficile*-associated disease (Ramaswamy et al, 1996; Dharmarajan et al, 2000). Among the antibiotics investigated, only clindamycin and penicillin showed an association with severe *C. difficile* colitis (Rubin et al, 1995; Dharmarajan et al, 2000). However, a number of studies found no association between severity and class or total number of antimicrobials used before the onset of symptoms (Andrews et al, 2003; Moshkowitz et al, 2007; Henrich et al, 2009; Lungulescu et al, 2011). Concurrent use of multiple antibiotics or a prolonged course of antibiotics is common practice in the presence of recurrent or refractory infection. It is argued that this longstanding, debilitating infection is likely to lead to poorer outcome, while the use of antibiotics is merely an innocent bystander (Dharmarajan et al, 2000).

Acid suppression therapy

A number of retrospective and prospective studies have shown a close link between acid suppression treatment, especially proton-pump inhibitors, and the incidence

of *C. difficile*-associated disease (Cunningham et al, 2003; Dial et al, 2004; Akhtar and Shaheen, 2007; Aseeri et al, 2008; Dalton et al, 2009). Increased survival of vegetative forms of *C. difficile* in conditions of reduced acidity, influence of proton-pump inhibitors on growth and differentiation of the colonic mucosa, and interference of proton-pump inhibitors with human immune function have been put forward as possible mechanisms of this association (Klingensmith et al, 1999; Agastya et al, 2000; Yoshida et al, 2000; Zedtwitz-Liebenstein et al, 2002; Jump et al, 2007). However, studies which investigated the effects of acid suppression treatment on disease severity found no association (Kyne et al, 1999; Moshkowitz et al, 2007; Bishara et al, 2008).

Immunosuppressants

Although it is expected to influence disease severity, the impact of immunosuppression remains controversial. Both Rubin et al (1995) and Morris et al (2002) demonstrated an association between immunosuppression and adverse outcome in *C. difficile* colitis, while Lungulescu et al (2011) and Kyne et al (1999) found no association between immunosuppressive therapy and severe disease.

Other medications

The use of steroids (Dudukgian et al, 2010) and antiperistaltic medication (Rubin et al, 1995) have also been shown to be associated with severe *C. difficile*-associated disease. However, these findings have been challenged in other studies (Bishara et al, 2008; Lungulescu et al, 2011). Laxatives and anti-diarrhoeals have also been shown to have no association with disease severity (Kyne et al, 1999; Bishara et al, 2008).

Gastrointestinal interventions

Gastrointestinal endoscopy

Gastrointestinal endoscopy has been identified as a risk factor for *C. difficile* colitis in previous studies (Brown et al, 1990; Bignardi, 1998). Kyne et al (1999) found gastrointestinal instrumentation (oesophagogastroduodenoscopy, sigmoidoscopy and colonoscopy) to be associated with more severe disease. This study showed that patients who underwent endoscopy were four times more likely to develop severe disease than those who did not undergo this procedure.

Nasogastric tube feeding

Moshkowitz et al (2007) showed pre-hospitalization nasogastric feeding to be associated with increased mortality in *C. difficile* infection. A similar observation was made by Kyne et al (1999), demonstrating a near-significant association between nasogastric or percutaneous endoscopic gastrostomy feeding and severe *C. difficile*-associated disease. However, Dharmarajan et al (2000) and Bishara et al (2008) found no relationship between nasogastric feeding and disease severity and outcome.

The role of gastrointestinal interventions (endoscopy, nasogastric tube insertion and feeding) as predisposing factors for severe disease is being questioned. Some argue that current decontamination practices used on endoscopes are not effective in eradicating spores, although they are sufficient to inactivate the vegetative form of *C. difficile* (Kyne et al, 1999). Other proposed mechanisms include:

- Exposure to organisms via hands of personnel
- Contaminated enteral nutrition, especially that containing low fibre which promotes bacterial colonization
- Alteration of the faecal flora by gastrointestinal manipulation and hence loss of colonization resistance
- Interference with the acid barrier of the stomach especially in cases of post-pyloric nasogastric feeding (Kyne et al, 1999; Moshkowitz et al, 2007).

It is also possible that patients who require gastrointestinal interventions have a 'vulnerable' gastrointestinal tract, and as a consequence are predisposed to severe *C. difficile*-associated disease (Kyne et al, 1999).

Clinical signs

A number of physical signs are of value as predictors of severe disease. Abdominal distension, abdominal tenderness (also abdominal pain) and signs of peritonitis were predictors of severe *C. difficile* infection (Rubin et al, 1995; Lungulescu et al, 2011). APACHE II score, which includes blood pressure, heart rate and temperature measured within 24 hours of admission, has been shown to be important in predicting mortality in *C. difficile*-associated disease (Dudukgian et al, 2010). However, in other studies, temperature and heart rate on their own were not associated with disease severity (Dharmarajan et al, 2000; Andrews et al, 2003; Gujja and Friedenberg, 2009).

Laboratory parameters

A number of laboratory parameters such as raised white cell count, low albumin and raised creatinine or urea levels have been shown to be associated with severe disease and adverse outcome in *C. difficile*-associated disease.

Several studies have shown markedly increased or suppressed leukocyte counts to be associated with more severe disease and adverse outcome (Rubin et al, 1995; Lamontagne et al, 2007; Moshkowitz et al, 2007; Ali et al, 2008; Gujja and Friedenberg, 2009; Henrich et al, 2009; Pepin et al, 2009; Dudukgian et al, 2010; Lungulescu et al, 2011). The cut off for raised white cell count varied from >20 000 to >50 000 cells/mm^3 in these studies. On univariate analysis, Bishara et al (2008) found raised white cell count to predict 28-day mortality and long-term mortality. However, this did not reach statistical significance on multivariate analysis. Other studies have also failed to show a relationship between white cell count and disease severity (Nair et al, 1998; Andrews et al, 2003; Arora et al, 2011).

A low serum albumin level (cut off varies from <25 to <30 g/litre) has been shown to predict severe *C. difficile*-associated disease or death (Rubin et al, 1995; Ramaswamy et al, 1996; Dharmarajan et al, 2000; Andrews et al, 2003; Moshkowitz et al, 2007; Bishara et al, 2008; Pepin et al, 2009; Lungulescu et al, 2011). In addition to low albumin level at the time of admission as a risk factor for increased mortality, Ramaswamy et al (1996) also showed a greater fall in serum albumin level (by >10 g/litre) with the onset of *C. difficile* colitis in those who died. Nair et al (1998) identified hypoalbuminaemia as a predictor of treatment failure, thus leading to a prolonged disease. However, other studies found no association between serum albumin level and disease severity or outcome (Lamontagne et al, 2007; Gujja and Friedenberg, 2009; Arora et al, 2011). It is suggested that malnutrition and poor metabolic status before the onset of *C. difficile* infection, which cause hypoalbuminaemia, could be the reasons for poorer outcome (Dharmarajan et al, 2000; Moshkowitz et al, 2007). In addition, hypoalbuminaemia itself may cause the immune system to be compromised, subsequently leading to severe disease. On the other hand, a fall in serum albumin levels could be the consequence of a severe protein-losing enteropathy and depressed hepatic synthetic function as a result of severe sepsis from *C. difficile*-associated disease. Likewise, significantly raised or depressed white cell count could simply be a feature of overwhelming sepsis and hence indicate severe disease.

Raised creatinine and/or urea levels have also been investigated extensively as markers of severe *C. difficile* infection. Raised creatinine level or a rise in creatinine level during the course of *C. difficile*-associated disease reliably predicts disease severity and complications (Dubberke et al, 2007; Bishara et al, 2008; Gujja and Friedenberg, 2009; Dudukgian et al, 2010; Lungulescu et al, 2011). Elevated serum urea and/or creatinine levels are also strong predictors of short- and long-term mortality following *C. difficile* infection (Bishara et al, 2008). Interestingly, Dharmarajan et al (2000) showed blood urea nitrogen levels to be a predictor of mortality, but found no appreciable association between serum creatinine level and death in *C. difficile*-associated disease. Similarly, Lamontagne et al (2007) also found no relationship between raised creatinine levels and 30-day mortality in *C. difficile*-associated disease.

Low haemoglobin has also been looked at for its role as a predictor of severe disease. Haemoglobin level is a valuable parameter in predicting complications including colectomy and *C. difficile*-associated disease-related death (Gujja and Friedenberg, 2009). However, Andrews et al (2003) found no association between haemoglobin level and severity of *C. difficile*-associated disease.

Both Lamontagne et al (2007) and Pepin et al (2009) showed a raised serum lactate level to be associated with increased mortality in *C. difficile*-associated disease patients. Alanine transaminase and serum bilirubin levels were among the laboratory parameters which attracted attention, but failed to show any significant association with disease severity in *C. difficile*-associated disease (Dubberke et al, 2007; Gujja and Friedenberg, 2009).

Interestingly, despite its predictive role in severe ulcerative colitis (Mowat et al, 2011), C-reactive protein has not been studied adequately for its potential use as a marker of severe disease in *C. difficile* infection. So far, a single retrospective study has identified C-reactive protein as an independent predictor of severe *C. difficile*-associated disease (Hardt et al, 2008).

Radiological findings

Few data exist regarding radiological markers of disease severity in *C. difficile*-associated disease. Boland et al (1995) looked at abdominal computed tomography scans from 64 patients with *C. difficile* infection performed within 3 days of diagnosis of *C. difficile*-associated disease. The only radiological finding that correlated with clinical severity was nodular mucosal thickening, which was found more frequently in those with raised white cell count. This study concluded that computed tomography changes correlated poorly with clinical severity.

Bacterial virulence factors

Little is known about *C. difficile* virulence factors and disease severity. McEllistrem et al (2005), in a study which included only 49 patients, found no association between binary toxin gene and adverse outcome. However, a much larger and more robust study by Loo et al (2005), involving over 1700 patients, demonstrated the presence of binary toxin genes and a partial deletion of the *tcdC* gene to be associated with severe disease and adverse outcome. *tcdC* is a regulatory gene that down-regulates expression of the *tcdA* and *tcdB* genes, which encode for toxins A and B respectively (Spigaglia and Mastrantonio, 2002). Polymorphisms or partial deletions of the *tcdC* gene are associated with high levels of toxin A and toxin B (Warny et al, 2005), which are the best-described virulence factors of *C. difficile* (Poxton et al, 2001).

Environmental factors

C. difficile spores are able to survive for several months in the environment (Vonberg et al, 2008), and are resistant to some commonly used hospital detergents and disinfectants (Fawley et al, 2007). Although studies have demonstrated a reduced incidence of *C. difficile*-associated disease with use of potent disinfectants (Mayfield et al, 2000), the relationship between environmental factors and disease severity is yet to be explored.

Discussion

This review highlights several risk factors for severe *C. difficile* infection, ranging from patient-based factors to medical interventions. Advanced age, comorbid illnesses involving major organ systems and laboratory parameters

such as leucocytosis, hypoalbuminaemia and raised creatinine level are predictors more commonly described to be associated with severe *C. difficile* infection and poor outcome. However, these findings are not universal across all studies.

A number of studies have used these risk factors to devise a severity scoring system to help identify those at risk of severe *C. difficile*-associated disease. For example, Lungulescu et al (2011) included a history of malignancy, white cell count at admission of >20 000/dl, serum albumin level <3.0 mg/dl and creatinine level at admission >1.5-fold the baseline to create the *C. difficile* infection Severity Index. The risk of developing severe *C. difficile*-associated disease increased almost three-fold for each 1-point increase in the *C. difficile* infection Severity Index score. In a prospective study, Drew and Boyle (2009) used white cell count, urea and serum albumin levels to devise the RUWA scoring system in order to predict complications in *C. difficile* infection. The negative predictive value of RUWA scoring system was 97%, and thus was shown to be useful in identifying patients at low risk of complications. However, these scoring systems need validation in large prospective studies.

Despite several studies, there is lack of consistency in all identified risk factors. A number of explanations may account for these conflicting results. One important factor is the difference in severity stratification. While some studies have used more robust criteria, such as *C. difficile*-associated disease-related death, colectomy or intensive care unit admission, others have included 'softer' criteria such as length of hospital stay and daily intestinal output. Most studies were retrospective and therefore the quality of data collected is questionable. There is also a wide variation in the sample size studied ranging from 30 to over 1000. In addition, the complex nature of *C. difficile*-associated disease (i.e. development of *C. difficile* infection in hospitalized patients who were admitted for other reasons) makes it difficult to interpret the parameters that were considered as risk factors for severe *C. difficile*-associated disease. For example, a high white cell count could be the result of an underlying chest infection rather than severe *C. difficile* infection or a combination of both. In addition, there was no consistency in the factors that were tested to predict severe *C. difficile*-associated disease.

Conclusions

Several factors have been identified as being associated with severe *C. difficile*-associated disease and increased mortality. Awareness of such factors allows early identification of patients at risk of adverse outcome, and thus those who warrant more intense monitoring and management, potentially limiting morbidity and mortality from *C. difficile*-associated disease. BJHM

Figure 1 *is reproduced from Poutanen and Simor (2004) by kind permission of the Canadian Medical Association.*

Conflict of interest: none.

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KEY POINTS

- *Clostridium difficile*-associated disease is the most common cause of nosocomial diarrhoea in hospitalized patients, and its incidence is increasing.
- Early identification of patients at risk of complications could reduce morbidity and mortality from *C. difficile*-associated disease.
- Factors helpful in identifying such patients include age >70 years, multiple comorbidities or comorbidities involving major organ systems, use of multiple and/or prolonged antibiotics and immunosuppressants, signs of peritonitis, and raised white cell count, low serum albumin level, raised or rise in creatinine level.

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