The complex factors that contribute to *Clostridium difficile* infection

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Over the past decade *Clostridium difficile* has emerged as a serious public health issue, causing both hospital-based epidemics and community-associated disease. The most commonly recognised cause of antibiotic-associated diarrhoea in the human population, *C. difficile* was initially seen as a nuisance pathogen causing limited disease in the hospital setting. However, the emergence of ‘hypervirulent’ strain types, associated with an increase in both morbidity and mortality, has made it a pathogen of great concern worldwide. Infection with *C. difficile* is also being increasingly documented in animals, with suggestions that animals destined for human consumption may provide a reservoir for disease. The use of antibiotics is considered the main risk factor for the development of human infection; however, many other factors such as strain type, patient age, and host immune response all contribute to disease caused by *C. difficile*.

A Gram-positive, spore-forming, anaerobic rod, *C. difficile* was first identified as causing disease in 1978. Disease arising from *C. difficile* infection (CDI) may range from mild and self-limiting diarrhoea through to pseudomembranous colitis; in some cases CDI may progress to toxic megacolon, perforation of the bowel, sepsis and death. Extra-intestinal cases of CDI are rare. While nearly half of all infections are in those younger than 65, more than 90% of deaths occur in people aged 65 or older. *C. difficile* can be isolated from about 3% of healthy adults, while up to 35% of hospital patients can be carriers. Children under the age of two years are commonly asymptomatic carriers of *C. difficile*; however, disease can occur in the paediatric population as well.

Disease is caused by the production of two major toxins, toxin A and toxin B, which are produced by strains that encode the Pathogenicity Locus (PaLoc); strains that do not contain PaLoc are non-toxigenic and considered unable to cause disease. All toxigenic strains produce toxin B; however, not all of them produce toxin A. Both toxins are monoglucosyltransferases that inactivate host cell Rho-family GTPases, resulting in disruption of the host cell actin cytoskeleton and cell death. This, in turn, leads to the loss of tight junction integrity in the gut, and movement of fluid into the intestinal lumen, causing diarrhoea. Toxins A and B also induce inflammatory responses, which contribute to host tissue damage during infection.

Aside from the two major toxins, the virulence factors of *C. difficile* are still poorly characterised. Sporulation and germination are important in the disease process, as the infectious particle ingested by patients is the spore. Once in the gut, germination occurs and the vegetative cell expresses factors required for survival and pathogenesis in the host. *C. difficile* may produce a number of these factors, which include fibronectin-binding proteins, S-layer, capsule, type IV pili, and flagella. Some strains also produce an additional toxin termed binary toxin, or CDT (*C. difficile* transferase). An ADP-ribosylating toxin, CDT does not appear essential for disease; however, it has been suggested that this toxin may promote colonisation in the host.

Antibiotic use is the most important risk factor for developing CDI, as exposure to antibiotics disrupts the normal gut microbiota, thus reducing the normal ‘colonisation resistance’ of the large intestine and allowing *C. difficile* to colonise. Antibiotic use is associated with both carriage of *C. difficile* and with diarrhoea, and the duration...
of an antibiotic course is also a risk factor for CDI\textsuperscript{14}. Most antibiotics have been implicated in the development of CDI in patients\textsuperscript{22}, which is often associated with acute care hospitals\textsuperscript{19} and with the elderly\textsuperscript{21}. Decreased host defences, common in the elderly population, may also play a role in the development of infection. A predisposition to recurrent disease is associated with an inadequate immune response\textsuperscript{25}. Relapses of CDI are common, and may lead to a cascade of interrelated complications, which can ultimately be fatal\textsuperscript{24}. Relapses may follow an initial infection in about 20% of cases\textsuperscript{25}, and rates of subsequent relapses can rise to 40–60\%\textsuperscript{26}. While these recurrences may be caused by relapsing infection with the same strain, it has been suggested that between 33–75\% of cases may be due to infection with a new strain\textsuperscript{25}.

The epidemiology of CDI has changed over the last decade. The rise of ‘hypervirulent’ ribotype 027 strains has seen an increase in the morbidity and mortality associated with \textit{C. difficile}\textsuperscript{27,28}. Prior to the outbreaks in 2002 and onwards, ribotype 027 strains were not commonly isolated\textsuperscript{29}, but are now considered to be one of the most clinically important strain types of \textit{C. difficile}. This strain type is now well established worldwide, including in Australia\textsuperscript{50}. However, other strain types are also becoming a cause for concern, with ribotype 017 and ribotype 078 strains associated with more severe disease in human patients\textsuperscript{31,32}. These strain types have been identified locally\textsuperscript{33}, highlighting the need for epidemiological vigilance when it comes to \textit{C. difficile}. New variants will also continue to emerge, as recently seen in Australia with ribotype 244 strains\textsuperscript{34}. The development of fluoroquinolone resistance has been linked to the global spread of ribotype 027 strains\textsuperscript{35}, but why other strain types become more or less prevalent is not always clear\textsuperscript{34}. Without ongoing monitoring, it will be difficult to ascertain changes in strain type within the local population.

Community-associated CDI is becoming increasingly important, with a greater awareness of cases occurring outside of the traditional hospital setting. The spectrum of disease seen in these patients is similar to that seen in healthcare-associated CDI. Mild and self-limiting disease is common, and many community-based patients may not seek medical attention\textsuperscript{56}. The infection source for community-acquired CDI is not known, and these cases cannot always be linked to the major risk factors associated with CDI\textsuperscript{17}. Animals and animal-derived food products have both been suggested as potential sources of \textit{C. difficile}\textsuperscript{20}, but this has not yet been clearly demonstrated.

Undoubtedly, \textit{C. difficile} has emerged as an important public health problem, no longer just confined to hospitals as a nuisance pathogen. As discussed elsewhere in this issue, \textit{C. difficile} is present in Australia and is found in human and animal populations. Multiple factors drive the disease process, including strain type, patient age, and host immune response. While the use of antibiotics and the development of resistance have selected for particular strain types associated with outbreaks of severe disease, other strain types are also emerging. For this reason, \textit{C. difficile} infection is of significant clinical and veterinary concern, and will continue to be so into the future.

References


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Biographies

Dr Kate Mackin is a Research Fellow in the Department of Microbiology at Monash University. She completed her PhD in 2014, exploring the diversity of Clostridium difficile clinical isolates, identifying important strain types in local hospitals. She also demonstrated that variant strain types regulate virulence factors differentially, through the master regulator Spo0A. Her current work extends on these themes, to identify other factors important in the pathogenesis of C. difficile.

The biography for A/Prof Dena Lyras is on page 103.

Clostridium difficile infection: an Australian clinical perspective