


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.
confirming that CDI is responsible for substantial morbidity and presumably mortality in Australia.

There is clear evidence that CD RT027 causes more severe disease and also has a reduced cure rate and an increased risk of relapse. Other emergent strains of CD have contributed to the increasing burden of disease and also the changing the pattern of CDI. CD RT078, for example, shares genetic virulence characteristics with CD RT027, has been shown to cause severe disease and is associated with community-acquired infection.

Australia was forewarned of the possibility for arrival of CD RT027, although the fact that routine diagnostics are based on toxin detection, and isolates are not routinely cultured, hampered surveillance efforts. The first CD RT027 strain identified in Australia occurred in a patient returned from hospitalisation in North America but did not apparently result in secondary cases. Locally acquired infection was then reported in Melbourne in early 2010, although subsequent surveys of Australian CD isolates indicate that RT027 has not become endemic within Australia.

In this setting of heightened awareness and understanding of the potential for outbreaks of severe CDI, two patients at Monash Health developed clinically severe CDI in mid-2011. While not unusual, we were actively surveilling for the appearance of RT027 using the Xpert C. difficile PCR (Cepheid, Sunnyvale, CA, USA) as the confirmatory diagnostic test for CDI. This assay includes a detection probe for the tcdC nucleotide 117 deletion (tcdCA117) characteristic of CD RT027 strains, although this deletion is present in some other CD non-R027 strains. Faecal samples from both patients signaled strains, although this deletion is present in some other CD

Genomic analysis of CD RT027 isolates from around the world has identified two distinct epidemic lineages with evidence of intercontinental transmission, including repeated introductions from North America to the United Kingdom. Australian CD RT027 isolates were shown to have been imported from North America and the transmission of the Australasian RT244 clone found in a patient who developed CDI on return to the UK emphasises the potential for rapid international dissemination of virulent clones.

To further emphasise the potential for CDI to pose new challenges, we found that RT244 produces a variant Toxin B that has an altered N-catalytic domain more similar to C. sordellii lethal toxin and produces atypical cytotoxicity on Vero cells in vitro. This was the first report of this variant toxin being associated with a severe CDI cluster, but the role this variant toxin may play in the virulence of RT244 CDI has not yet been established.

A particular challenge for clinicians is the identification and treatment of relapses that occur in 20–25% of patients following the initial episode, but increase following each relapse and exceeds 50% following multiple recurrences. In the USA, 83,000 (21%) of CDI patients experienced first recurrences in 2011 and the high associated morbidity and costs associated with relapses have lent strong impetus to the development of new therapeutics that may prevent their occurrence. Fidaxomicin is a non-absorbable macrolide antibacterial recently licensed for CDI. Although substantially more expensive and no more effective than oral vancomycin, fidaxomicin reduces relapse rates in non-RT027 CDI and has therefore found a role in some CDI treatment guidelines. A number of new antibacterials are currently in Phase III trial including the quinolone cedazolid, and the lipopeptide analogue of Daptomycin, CB-183,315 as well as repurposed agents such as the non-absorbable rifamycin, rifaximin and nitazoxanide.

CDI is associated with antibacterial induced alteration in the gut microbiome and recurrent disease is associated with persistent gut dysbiosis. Restoration of the gut microbiome by administration of donor-derived faecal suspension is highly effective in preventing recurrence and restoration of gut microbial diversity. Theoretical concerns as to the lack of knowledge of long-term effects, transmission of pathogens and lack of standardisation of donor bacterial flora as well as the logistic difficulties have hampered access to this treatment. Efforts to define a minimal set of bacterial strains that could provide standardised on-demand treatment seem likely to be the way forward. A recent Phase II study offers the prospect of highly targeted bacteriotherapy using non-toxigenic CD for prevention of recurrent infection and another current study in a mouse model found that Clostridium scindens offered protection from...
CDI by altering bile acid metabolism in the gut so as to inhibit CDI spore germination.30

Further hope is offered by immune mediated protection to CDI. Absence of anti-toxin antibody is associated with disease and recurrence and passive immunisation by administration of bivalent monoclonal anti-Toxin A and anti-Toxin B antibodies reduced CDI recurrence from 25% to 7%30. A Phase III study examining the relative protective effect of anti-Toxin A, anti-Toxin B or the bivalent combination has been completed and results are anticipated shortly.31

Intensively applied control measures including anti-microbial stewardship, enhanced identification and reporting of cases and implementation of mandated infection control measures can reduce CDI, however, the huge burden of CDI, and the emergence of community acquired disease, challenges how further CDI control is to be achieved. An international Phase III placebo-controlled vaccine trial with a bivalent Toxin-A and Toxin-B toxoid vaccine is now underway in immunocompetent at-risk patients over 50 years of age, including at a number of Australian sites and if successful, offers an alternative and complementary strategy to reduce the global problem presented by CDI.32

References


Biography

Grant Jenkin is a physician and Director of the Mycobacterial Infection Service at Monash Infectious Diseases. His research interests include the genetic virulence determinants and immunity of mycobacterial and clostridial infections.