Clostridium difficile

The second international *Clostridium difficile* symposium was held in Maribor, Slovenia, from 6th – 9th June 2007. This followed the successful first meeting, also held in Slovenia, in May 2004. Approximately 150 delegates, including 50 young scientists funded under the Marie Curie Actions scheme, attended the meeting, who represented 24 countries from 5 continents. The organization committee was superbly led by Maja Rupnik and the secretariat smoothly run by Jacqueline Minton.

During the 3 years between the symposia, *C. difficile* has come out of relative obscurity to become well known worldwide as the latest superbug – largely as a result of the emergence of the hyper-virulent BI/NAP1/027 epidemic strain on both sides of the Atlantic and the resultant press coverage, especially in the UK and Canada. The 3 day symposium programme covered all of the important aspects of *C. difficile* research, and sessions included epidemiology; clinical aspects, and disease prevention and control; molecular characterization of strains; pathogenesis and molecular biology; toxins of *C. difficile*; antibiotic resistance and *C. difficile* in animals and food. All authors who presented papers at the meeting, either oral or poster, were invited to submit their work for this special issue of the *Journal of Medical Microbiology*. An additional paper not presented at the meeting was also considered. All submissions were handled by the normal peer review process through the existing editorial board and the papers in this issue are the 18 that were accepted.

The first two sessions on various aspects of molecular and clinical epidemiology included several presentations on the changing epidemiology of *C. difficile* infection and the epidemic strain, as well as the definition of risk factors. Papers in this issue covering these areas are those by Shin *et al.* (2008) and Indra *et al.* (2008), who introduced the epidemiology of *C. difficile* in Korea and Austria, respectively.

A paper by Van der Kooi *et al.* (2008) demonstrated how antibiotic use was a major risk factor for outbreaks of the 027 hypervirulent strain in the Netherlands. Studies on pathogenesis and host response were covered in these and following sessions, and papers in this issue relevant to these aspects include those by Sánchez-Hurtado *et al.* (2008) on the antibody response to *C. difficile* in cases and controls, and that by Brun *et al.* (2008) on the use of a surface layer protein SLP-36kDa to enhance the immune response to co-administered antigens.

Several of the pathogenesis studies investigated the effects of other agents on defined virulence factors. For example the study by Denève *et al.* (2008) showed how antibiotics increased colonization factor expression, and the study by Sánchez-Hurtado & Poxton (2008) showed that the cytotoxic activity of *C. difficile* toxin A could be enhanced by certain surface-associated antigens. Dawson *et al.* (2008) assessed the role of *p*-cresol – an agent produced by very few other bacteria and toxic to many microbes – in possible virulence mechanisms. Further immunological studies by Wright *et al.* (2008) used human sera to identify immunoreactive cell wall proteins. Stress responses by *C. difficile* were investigated by microarray analysis by Emerson *et al.* (2008). The major toxins of *C. difficile*, CdtA and CdtB, were the subject of several papers. Two review articles on this subject are included in this issue, that by Bruno Dupuy and colleagues (Dupuy *et al.*, 2008) describes how toxin synthesis is negatively regulated by TcdC, and that by Klaus Aktories' group (Giesemann *et al.* 2008) gives the latest information on the processing of the toxins once taken up by the cell. Gerhard *et al.* (2008) report on how CdtA triggers apoptosis in intestinal epithelial cells. Stabler *et al.* (2008) have used microarray analysis to identify a novel toxin B gene sequence in 027 strains, and they suggest it may affect binding of the toxin from this strain and may be related

to its increased virulence. A paper not presented in Maribor, but very relevant to our knowledge of toxin control in *C. difficile* when grown in the presence of sublethal concentrations of antibiotics has been included in this issue. This is the paper by Gerber *et al.* (2008) who have investigated the effects of sub-MIC levels of metronidazole, vancomycin, clindamycin and linezolid on toxin gene transcription and they describe a new method for transcriptomic analysis of toxin genes in *C. difficile*. Spigaglia *et al.* (2008) reported on fluoroquinolone resistance in *C. difficile* by analysing the *gyrA* and *gyrB* genes in strains collected in the prospective study performed by the European Study Group for *C. difficile* in 2005. One paper by Pirs *et al.* (2008) is included on the isolation of *C. difficile* from food animals in Slovenia, adding more evidence that the organism may have a zoonotic spread. Finally a paper by Sleator & Hill (2008) discusses the potential for a 'designer' probiotic for *C. difficile* – an important approach that is hopefully much better than previously reported studies using commercially available yoghurt-like drinks, and certainly more palatable than 'faecal transplants'.

The final session of the meeting was to discuss research priorities. Those agreed are listed below. Since June 2007 advances have been made on many of these, but for the record they are all included.

Agreed *C. difficile* research priorities (June 2007)

- Epidemiology – define and investigate:
 - new presentations/manifestations of *C. difficile*-associated disease
 - new populations at risk, e.g. peripartum women, neonates/children
 - community associated/acquired *C. difficile*-associated disease
 - food-borne/zoonotic *C. difficile*?
 - infection control measures
 - norovirus co-infections/associated infections

- new preventions and interventions
- Develop more methods for genetic modification
- Further work on mechanisms of pathogenesis and host susceptibility
- Antibiotic resistance
 - define breakpoints
 - investigate resistance mechanisms
- Use of microarrays for comparative genomics, typing, etc.
- There was agreement that nomenclature for a unified typing method should be established.
- In the short to medium term ribotyping should be retained – based on the UK (Cardiff Anaerobe Reference Unit) system – with agreed methodologies, software (Bionumerics) and a library of the most commonly encountered types made available to those requesting it. In the longer term multilocus variable-number tandem-repeat analysis and microarray-based systems should be investigated further. It was considered important that a culture collection be established and this be housed in an established culture collection of a country, such as the National Collection of Type Cultures in the UK.

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