Clostridium difficile-associated diarrhoea (CDAD): new and contentious issues

The last decade has seen the prevention of healthcare-associated infections (HAIs) become a public and NHS priority [1, 2]. The resultant local and national targets have started to reap some benefits, with a fall in the rate of methicillin-resistant Staphylococcus aureus (MRSA) bacteraemias [3] and a decline in the rate of Clostridium difficile-associated diarrhoea (CDAD) [4]. Despite this, CDAD remains one of the most frequent nosocomial infections (annual incidence >50,000 cases in 2007) [4].

PCR ribotype 027 (also known as BI/NAP1), a previously uncommon strain, has been associated with recent outbreaks in North America [5], Europe and the UK [6]. Ribotype 027 has emerged as the dominant strain in England representing 41% of isolates (up to 60% in certain regions) [7]. Strains of this ribotype are believed to be linked to increased disease severity often manifested with leucocytosis, raised creatinine, hypoalbuminaemia, toxic megacolon, need for colectomy, shock, death and higher rates of relapse. However, this is not always the case. A recent study comparing matched cases of CDAD caused by 027 versus non-027 strains showed that severity as defined by shock, paralytic ileus, pseudomembranous colitis or toxic megacolon was not linked to ribotype 027 and can occur with any strain [8]. Enhanced molecular fingerprinting, which enables strain subtyping to a greater extent than ribotyping, may provide further clues about the epidemiology and possible association of ‘hypervirulent’ strains with disease severity.

Community-acquired CDAD is emerging as a previously unrecognised entity. A recent case-control study demonstrated that community-acquired CDAD may be...
underdiagnosed with at least one-third of the cases unrelated to recent hospitalisation or antibiotic use [9]. Further studies are needed to elucidate the epidemiology and risk factors associated with community-acquired CDAD. Admitting teams must therefore consider the possibility of CDAD in anyone with a recent onset diarrhoeal illness.

Recent American and British treatment recommendations emphasise the importance of assessing disease severity to stratify patients to the most appropriate antibiotic [2, 10]. Oral vancomycin is recommended in patients with severe CDAD based on randomised controlled trial data which showed improved cure rates compared to metronidazole [11]. There is a lack of consistency in the criteria used to define severe CDAD; the UK guidance includes a temperature of >38.5°C, the presence of an acute rise in creatinine (>50% from baseline value), leukocyte count >15 × 10⁹/L and symptoms/signs of colitis or shock. A prospectively derived and validated severity score is lacking.

Metronidazole is still effective in mild CDAD. Recent reports of isolates with reduced in vitro susceptibility to metronidazole [12, 13] have unclear clinical significance. Microbiology laboratories in the UK do not routinely culture C. difficile and the emergence of resistance may not be detected in a timely fashion. Hence, it is particularly important to be vigilant for increased rates of treatment failure with either metronidazole or vancomycin.

Prevention

The current strategies for the prevention of CDAD are based on infection control procedures including isolation and hand washing, antimicrobial stewardship and environmental decontamination [2].

Prompt isolation of patients with CDAD in a side room or a cohort bay is an established intervention [2]. The use of isolation wards, whilst not a new concept, has spread following recent publicised outbreaks [6] and contributed to the decrease in the rate of CDAD in a number of trusts. Isolation wards could confer advantages besides infection control, e.g. through a multidisciplinary team approach to the management of CDAD between microbiologists, infectious diseases physicians, gastroenterologists, surgeons, dieticians and geriatricians. Such an approach could also stimulate research. Whilst there is a lack of published data, an early report from University Hospitals of Leicester NHS Trust found a significant reduction in mortality rates in unmatched patients with CDAD managed in an isolation ward compared to patients managed in other medical wards [14].

Despite the potential benefits of isolation in respect of infection control, moving frail older people (those most likely to get CDAD) increases their risk of delirium and its associated adverse effects on morbidity, mortality, institutionalisation rates and length of stay [15]. No randomised trials have assessed the value of isolation measures in the control of CDAD, and a systematic review of existing studies is lacking. A systematic review of studies evaluating isolation for the control of MRSA, despite highlighting the methodological weaknesses of these studies, suggested that isolation was effective in controlling MRSA when used as part of a broader infection control strategy [16]. Guidelines quote this as indirect evidence for the value of isolation in CDAD [2]. It is certainly not clear what the relative merits of adequate nurse staffing levels, hand washing, adherence to strict antibiotic policies, good cleaning standards and adequate space around the bedside may be for reducing CDAD, as opposed to isolation. Consequently, some geriatricians have voiced their concerns, particularly in relation to the use of isolation wards [17]. High-quality studies that adhere to published standards [18] and define delirium as a potential harm are indicated to address these concerns.

Another major concern about the use of an isolation ward, particularly one based on cohorting rather than side rooms, is the lack of robustness of the current diagnostic tests used for C. difficile. Newer toxin detection tests, which provide a same day result, have a suboptimal sensitivity and specificity compared to the gold standard method which requires 48 h. A recent meta-analysis and a head-to-head comparison of the main current rapid assays predict unacceptably low positive predictive values for low incidence populations such as patients admitted from the community [19, 20]. This could result in the allocation of uninfected patients to an isolation ward where they would be at risk of cross infection. Better diagnostic tests are needed, possibly combining a rapid screening test with a second confirmatory test coupled with a two-tier isolation procedure for suspected and confirmed cases. Yet again, the risks of multiple moves on incident delirium or prolonging prevalent delirium need to be considered.

Current guidelines recommend de-isolation of patients who have been diarrhoea free for 48 h and have passed a formed stool [2]. A significant proportion of patients will continue to shed C. difficile in their stool even after the diarrhoea has settled. Recent studies indicate that asymptomatic carriers and patients recovering from CDAD continue to contaminate their environment and are likely to harbour C. difficile on their skin, which can then be transmitted onto healthcare workers’ gloves [21, 22]. The effect this has on CDAD transmission has not been evaluated. Moreover, the risk of CDAD recurrence after treatment is 20%, irrespective of the antibiotic used, and rises sharply in patients who have already had one episode of recurrence [5]. Most initial episodes of recurrence have been shown to be due to reinfecction rather than true relapse [23]. A prospectively derived and validated prediction score for recurrent CDAD was recently described [24]. It is not known whether more aggressive isolation or decontamination policies would be indicated in the above groups of patients, i.e. patients with persistent shedding or those at high risk of recurrence.

Antimicrobial stewardship has a key role in the prevention of CDAD. Geriatricians led the way in demonstrating that antibiotic policies restricting cephalosporin use were effective in reducing CDAD rates [25–27]. Data from prospective trials are needed to eludicate the CDAD risk associated with...
different antibiotics. Furthermore, the use of narrow spectrum empirical antibiotics remains a challenge in the face of rising bacterial resistance. Consequently, outcome data for the treatment of sepsis should be collected where such empirical policies exist.

C. difficile remains a major healthcare challenge with some early indication that we may be turning the tide. With a concerted effort and the emergence of new evidence, we should be able to achieve further gains against this evolving pathogen. However, we must ensure that whilst ‘being seen to be doing something’ we are not exchanging one iatrogenic disease (CDAD) for another (delirium).

Conflict of interest

The authors report no conflict of interests

Theodoros Gouliouris1,*, Duncan R. Forsyth2, Nicholas M. Brown3
1Specialty Registrar in Microbiology and Infectious Diseases, Clinical Microbiology and Public Health Laboratory, Addenbrooke’s Hospital, Cambridge University Hospitals NHS Foundation Trust, Hills Road, Cambridge CB2 0QQ, UK, Email: theo.gouliouris@doctors.org.uk
2Consultant Geriatrician, Department of Medicine for the Elderly, Addenbrooke’s Hospital, Cambridge University Hospitals NHS Foundation Trust, Hills Road, Cambridge CB2 0QQ, UK
3Consultant Medical Microbiologist, Clinical Microbiology and Public Health Laboratory, Addenbrooke’s Hospital, Cambridge University Hospitals NHS Foundation Trust, Hills Road, Cambridge CB2 0QQ, UK

To whom correspondence should be addressed

References


