Clostridium difficile report: new challenges and developments

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Abstract

The European Congress of Clinical Microbiology and Infectious Diseases, the annual meeting of the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) is the most attended infectious disease conference worldwide. This year, more than 10,000 clinicians and scientists attended the congress to present and share the latest research breakthrough in infectious diseases. This article reviews the sessions on *Clostridium difficile* infections.

Key words: *Clostridium difficile* (*C. difficile*), diarrhea, guidelines, community, susceptibility, children

Update of ESCMID diagnostic guidelines for CDI

Clostridium difficile infection (CDI) is the leading cause of infective nosocomial diarrhoea worldwide. CDI also is associated with high rates of morbidity and mortality. The European Society of Clinical Microbiology and Infectious Diseases (ESCMID) has updated the diagnostic guidance document for CDI. Speaking at ECCMID 2015, Monique Crobach (Leiden, the Netherlands) presented the update to the 2009 guidelines and explained the aim of the new diagnostic document is to standardise CDI diagnosis for surveillance purposes across Europe (Crobach et al. 2015).

The authors have formulated the new CDI guidance based on the need to evaluate the new diagnostic tests that have become available since 2009, specifically nucleic acid amplification tests (NAATs) and the importance of free toxin detection in faeces to differentiate patients with CDI from those colonised.

Crobach and her expert colleagues performed a meta-analysis of 57 studies, which evaluated 25 different commercial laboratory tests including 4 GDH EIAs, 10 Tox A/B and 11 NAATS. GDH and NAATS were the most sensitive tests while Tox A/B EIAs were the most specific tests. The new guidance recommends the use of a two-step algorithm: the first step should be a sensitive test (NAAT or GDH EIA). Crobach explained that samples with a negative first test can be reported as negative for CDI, those with a positive test should be retested using the second stage assay. Because there are published data on the importance of free toxin detection, the authors of the guidance recommended that the second test should be a toxin detection method.

Unmet needs in diagnostic and management

Speaking at ECCMID 2015, Mark Wilcox (University of Leeds, Leeds Teaching Hospitals, & Public Health England, United Kingdom) discussed issues around current CDI treatment and new therapeutic options. He emphasised the need to identify patients with severe infection and those at risk of recurrence, and to be aware of the detrimental effects of using concomitant antibiotics (Wilcox et al. 2015). He acknowledged that while there are multiple drugs and interventions under investigation, there is a need to improve the evidence base for new drugs, whether antibiotics or other options. Wilcox commented on the weak evidence for the use of the probiotics in CDI and the new positive data for the "ultimate probiotic" - faecal transplantation. Currently, there is an inadequate choice of therapeutics in CDI; those available often have a poor sustained response or cure. There is an increased dependence on vancomycin, noting the poor efficacy of metronidazole. Wilcox discussed the management of CDI recurrence, including the results of fidoxamicin trials, which showed a 50% reduction in CDI recurrence. He recommended that, after a discussion with microbiology, clinicians should consider the use of fidaxomicin; vancomycin tapering/pulse therapy, IV immunoglobulin and lastly, donor stool transplant, are options for the treatment of multiple recurrences of CDI.

Challenges in diagnostic and management

The epidemiology of *C difficile* needs further investigation, especially recurrent CDI, as patients are underdiagnosed due to the absence of clinical suspicion and suboptimal laboratory methods. Speaking at ECCMID 2015, Carl Erik Nord (Stockholm, Sweden) discussed the recent epidemiological findings on CDI in Europe, namely the EUCLID study, which included 482 hospitals across 20 European countries (Nord 2015). Nord emphasised that in the EUCLID study, 80 patients with CDI had a missed CDI diagnosis every day, resulting in 40,000 patients with CDI being underdiagnosed every year in the 482 participant hospitals. He explained that while the risk factors for hospital-acquired CDI are well known, there are no risk factors yet known for community-acquired CDI.

CDI is almost always associated with antibiotics, Stuart Johnson (Loyola University, Maywood, USA) reminded the ECCMID 2015 audiences (Johnson 2015). Alternative therapies should be considered as strategies for treating patients with

recurrent CDI. Johnson suggested the use of agents that are not antibiotics, whether immune approaches or toxin binding proteins such as tolevamer. However, he remarked on the results of the 3 arms phase 3 trial of tolevamer in CDI vs vancomycin vs metronidazole in a 2:1:1 ratio, in which tolevamer was inferior to antibiotic treatment of CDI, and metronidazole was inferior to vancomycin. Johnson then advised on alternative fidoxamicin treatment regimens and caution for using standard treatment dosing in patients with multiple CDI recurrences. He described the taper, post-vancomycin fidaxomicin chaser regimens and advised that patients should have careful follow-up. Well-designed clinical trials of recurrent CDI are needed, concluded Johnson.

Spores have a key role in the acquisition and transmission of *C. difficile*, explained David Jenkins (Leicester, United Kingdom) (Jenkins et al. 2015). There is a risk of acquiring *C. difficile* from previous room occupants. In a recent study described by Jenkins, a substantial number of patients had acquired *C. difficile* from sources other than symptomatic patients. Jenkins also explained the effects of exposure to fidaxomicin or vancomycin on sporulation by *C. difficile*. Fidaxomicin targets RNA polymerase and completely inhibited outgrowth throughout the experiment, while vancomycin targets the cell wall synthesis and only inhibits the later stages of outgrowth. Leicester local service evaluated the use of fidaxomicin for primary episode of CDI and recurrence. Jenkins discussed the results, which showed the rate of recurrence in patients treated with fidaxomicin was more than 50% lower than the rate of recurrence in non-fidaxomicin treated patients. A further seven-centre study that collected data on CDI episodes before and after the introduction of fidaxomicin found that fidaxomicin could be a cost-effective treatment option when used first-line in a real-world setting.

Pharmacoeconomic considerations play an increasing role in assessing the value of an anti-CDI drug, especially if it reduces recurrent episodes, according to Christian Eckmann (Hanover, Germany) (Eckmann 2015). Speaking at ECCMID 2015, he discussed cost-effective approaches to treating severe and recurrent CDI based on the changing epidemiology of *C. difficile* in Europe. Interestingly, the incidence of CDI has increased since 2000 in Austria, Denmark, Finland, Germany and Spain, while in Belgium, Finland and the UK, the incidence of nosocomial CDI has decreased over the past few years. CDI places a significant burden on hospitals, explained Eckmann. He recommended hospitals use a cost-efficacy strategy in setting of high fixed costs through shortening the length of stay in hospitals.

Eckmann presented the ‘Early switch and early discharge criteria’ that helped to design the cost model structure of CDI and the results of the Cologne case-control study that measured cost of CDI and CDI recurrence. He applied the cost-effectiveness matrix to a study on the cost-effectiveness analysis of fidaxomicin versus vancomycin in CDI, which showed that fidaxomicin is cost-effective in patients with severe CDI and in patients with first CDI recurrence versus vancomycin.

CDI in transplant recipients

The incidence and severity of CDI is increasingly reported in liver transplant (LT) recipients. The results of a study that looked at modifiable and non-modifiable risk factors and graft survival outcomes associated with CDI in LT recipients were

presented by Shilpa Chaudhari (Drexel University, Philadelphia, USA) (Chaudhari et al. 2015). Researchers conducted retrospective chart reviews in patients with a positive *C. difficile* test result within one year post-discharge from LT; they evaluated 65 consecutive patients, of which 15 (23%) developed CDI. CDI occurred after a median of 65 days (IQR 13-248) post-transplant, and more than half (53%) had severe infection according to Zar classification. Chaudhari explained that there was an increased incidence of CDI with the use of third generation cephalosporins, carbapenems or fluoroquinolones, regardless of temporal relationship to LT. Patients with a prolonged length of stay prior to LT were more likely to become infected with *C. difficile*. There was no significant difference on graft survival at 6 and 12 months follow-up.

C difficile spreading between animals and humans

While the causes of the increase in human CDI remain poorly understood, farm animals are considered as a potential reservoir for human CDI. Wilco Knetsch (Leiden University Medical Center, Leiden, Netherlands) and his colleagues applied whole genome phylogenetic single-nucleotide polymorphism (SNP) analysis to compare 280 *C. difficile* PCR type 078/126 isolates and its close relatives, types 033 (n = 16), 045 (n= 13), collected from human, animal, environment and food sources and diverse geographical locations (Europe, North-America, Asia and Australia) (Knetsch W et al. 2015). Four clusters for types 033, 045, 066/127 and 078/126 and a more diverse mixed cluster of various *C. difficile* types were found. In total 25.641 SNPs were identified, of which 22.223 SNPs belonged to a small group of eight diverse *C. difficile* isolates. Three clusters for types 033, 045 and 078/126 share the same observation that human and animal isolates are mingled; no separate clusters were found with either human or animal isolates solely. In several cases, human and animal isolates had identical SNP genotypes, meaning there were zero SNP differences. In addition, Knetsch and his group observed identical antimicrobial resistance determinants for tetracycline (tet40, tetO, tet44 en tetM) and streptomycin (Aph3-III, Ant6-Ia, Sat4A and Ant6-Ib) present in human and animal *C. difficile* isolates. The researchers concluded that *C. difficile* is capable of spreading between animals and humans although there may be an unidentified common (environmental) source.

Immunosuppression in CDI

Immunosuppression is a known risk factor for CDI. Stefano Di Bella (National Institute for Infectious Diseases "L. Spallanzani", Rome, Italy) and his colleagues conducted a retrospective case-control (1:2) study on HIV positive hospitalized patients with CDI, and controls (Di Bella S et al. 2015). Only healthcare facility (HCF)-onset, and HCF-associated (HO-HCFA) CDI were included. A CDI episode was considered as a positive *C. difficile* toxin assay. The researchers found an increasing incidence in CDI cases among HIV-infected patients admitted from 2008 to 2013. Low serum immunoglobulin G levels at admission are associated with an increased risk of developing CDI among HIV-infected patients. A deficiency in humoral immunity appears to play a major role in the development of CDI among HIV-infected patients.

Clostridium difficile-associated disease

Tigecycline might be a useful alternative for treating patients with *Clostridium difficile*-associated disease (CDAD), according to a prospective cohort study presented at ECCMID 2015 by Thais Larrainzar-Coghen (Hospital Universitari Vall d'Hebron, Barcelona, Spain)

(Larrainzar-Coghen 2015). The researchers defined a CDAD case as a patient with diarrhoea (≥3 loose stools/day) or toxic megacolon associated with a positive testing for CD toxin A and/or B. Cure was defined as resolution of the symptoms of CDAD in the following 8 weeks and recurrence, as a new episode of CDAD that occurs ≤8 weeks after the onset of a previous one, provided that CDAD symptoms from the earlier episode resolved with or without therapy. Tigecycline (alone or in combination with other *C. difficile* therapies) was used for the treatment of CDAD and the concomitant infection in all 9 cases. Eight out of these 9 episodes of CDAD treated with tigecycline were first episodes while only 1 was a recurrence. Length of tigecycline treatment was 6.78 ± 4.02 days. Overall 6/9 (66.7%) patients were cured, 2 (22.2%) recurred, and 1 (11.9%) died within first 30 days after diagnosis. It should be noted that treatment of CDI is not a licensed indication for tigecycline.

C difficile susceptibility

C. difficile isolates from across the UK collected within a 12 year time period appear sensitive to a number of alternative antimicrobial agents including fidaxomicin. MIC_{90} values for FDX differed according to ribotype, but as no breakpoints currently exist for this agent, it is unclear as to whether this will affect clinical efficacy, according to Sarah Copsey-Mawer (Public Health Wales, Cardiff, United Kingdom) (Copsey-Mawer et al. 2015). In this UK study, 384 *C. difficile* isolates from 47 PCR ribotypes that were submitted to the UK Anaerobe Reference Unit (UKARU) between 2001- 2012 were tested. All isolates were susceptible to metronidazole and vancomycin. MICs were obtained by agar dilution according to CLSI guidelines for fidaxomicin, nitazoxanide, rifampicin, rifaximin, and teicoplanin. Copsey-Mawer explained that the majority of isolates were susceptible to all agents, regardless of ribotype. For fidaxomicin, 47 isolates had slightly raised MIC values of 0.5 mg/l, the majority of which were 027 isolates. Raised MIC values were also observed for type 106. She described that the majority of isolates were more sensitive to rifampicin that rifaximin; four isolates (001,012 and two 027 strains) were resistant to rifampicin, two of which were also resistant to rifaximin (001 and 027).

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