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How to: Surveillance of Clostridium difficile infections

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Abstract

Background: The increasing incidence of Clostridium difficile infections (CDI) in healthcare settings in Europe since 2003 has affected both patients and healthcare systems. The implementation of effective CDI surveillance is key to enable monitoring of the occurrence and spread of C. difficile in healthcare and the timely detection of outbreaks.
Aims: The aim of this review is to provide a summary of key components of effective CDI surveillance and to provide some practical recommendations. We also summarize the recent and current national CDI surveillance activities, to illustrate strengths and weaknesses of CDI surveillance in Europe.
Sources: For the definition of key components of CDI surveillance, we consulted the current European Society of Clinical Microbiology and Infectious Diseases (ESCMID) CDI-related guidance documents and the European Centre for Disease Prevention and Control (ECDC) protocol for CDI surveillance in acute care hospitals. To summarize the recent and current national CDI surveillance activities, we discussed international multicentre CDI surveillance studies performed in 2005e13. In 2017, we also performed a new survey of existing CDI surveillance systems in 33 European countries.
Content: Key components for CDI surveillance are appropriate case definitions of CDI, standardized CDI diagnostics, agreement on CDI case origin definition, and the presentation of CDI rates with well-defined numerators and denominators. Incorporation of microbiological data is required to provide information on prevailing PCR ribotypes and antimicrobial susceptibility to first-line CDI treatment drugs. In 2017, 20European countries had a national CDI surveillance system and 21 countries participated in ECDC-coordinated CDI surveillance. Since 2014, the number of centres with capacity for C. difficile typing has increased to 35 reference or central laboratories in 26 European countries.
Implications: Incidence rates of CDI, obtained from a standardized CDI surveillance system, can be used as an important quality indicator of healthcare at hospital as well as country level.

Background

Clostridium difficile, recently reclassified as Clostridioides difficile, is a Gram-positive spore-forming ubiquitous bacterium[1]. Toxigenic strains can cause C. difficile infection (CDI) with diverse clinical manifestations ranging from mild diarrhoea to life-threatening conditions. The most important modifiable risk factor for CDI is previous antibiotic treatment [2]. European data on CDI epidemiology in acute healthcare derive from a few limited studies with significant differences in their study design and number of participating healthcare facilities [3-7]. In response to an increased CDI incidence and spread of epidemic C. difficile strains belonging to ribotype (RT) 027 in Europe since 2003 [2-4], the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) published guidance documents for CDI diagnostics, treatment and infection control [8-10].

In May 2015, the European Centre for Disease Prevention and Control (ECDC) published a protocol for hospital-based CDI surveillance, to support the implementation of standardized CDI surveillance in Europe [11], in advance of the start of ECDC-coordinated surveillance of CDI on 1 January 2016.

The objectives of standardized CDI surveillance are to estimate the incidence and burden of CDI and to acquire information on the outcome of CDI, including deaths.

The purpose of this review is to provide a summary of key components of effective CDI surveillance and to provide some practical suggestions. We also summarize the recent and current national CDI surveillance activities, to illustrate strengths and weaknesses of CDI surveillance in Europe.

How to define a CDI case?

The alertness of clinicians to CDI and the availability of laboratory diagnostics with appropriate algorithms fundamentally affect CDI surveillance data. ESCMID currently recommends the systematic testing of patients with antibiotic-associated or healthcare-associated diarrhoea [8]. CDI surveillance is commonly restricted to hospitalized patients in the acute healthcare setting, even though several studies have highlighted the importance of CDI in long-term non-acute care, nursing homes and in the community [12, 13].

According to available guidance, microbiology laboratories should consider performing tests for CDI on all unformed stools (i.e. those that take the shape of the container) from healthcare settings such as acute care hospitals, irrespective of the request from the physician [5,8]. Solid stool samples should not be tested because of the absence of diarrhoea and the possibility of detecting asymptomatic C. difficile carriage. Rectal swabs should be used to acquire laboratory samples from patients with ileus due to reduced peristalsis [8]. Unless there is a strong clinical indication, unformed stool samples from children<2 years of age should not be tested, because asymptomatic gastrointestinal carriage is relatively common in this age group [14,15]. Test-of-cure should be discouraged, as it is possible to have prolonged carriage of C. difficile, despite the resolution of diarrhoea [8].

Since 2009, ESCMID has recommended a two-step algorithm for microbiological diagnosis of CDI [8]. The first step should be a sensitive test with a high negative predictive value. These should either be an enzyme immunoassay for the detection

of glutamate dehydrogenase, or a nucleic acid amplification test for the detection of C. difficile toxin gene(s). When this screening test is positive, stool samples should be tested using a sensitive enzyme immunoassay or a cell cytotoxicity neutralization assay in a second step, to confirm the presence of free toxins in the stool samples. The use of stand-alone enzyme immunoassays for toxins should be discouraged because of their insufficient sensitivity. Stand-alone nucleic acid amplification tests, which detect the presence of toxin genes, can overestimate the incidence of CDI, because they do not detect in vivo toxin production [8,16].

Patients who have had pseudomembranous colitis diagnosed by lower gastrointestinal endoscopy, or who have characteristic colonic histopathology, should also be considered to be a CDI case, without any further requirement for stool sample testing [11,17,18]. However, pseudomembranous colitis is not entirely specific for CDI. Other pathogens (e.g. cytomegalovirus, Entamoeba histolytica, Shigella species, Shiga-toxin producing Escherichia coli) and medication (e.g. cisplatin, cyclosporine A) can cause similar pathology [19].

A decision algorithm for application of the CDI case definition using ESCMID-recommended diagnostic algorithm [8] is shown in Fig. 1a.

CDI case origin

The designation of case origin is determined by the time and place of the onset of CDI symptoms[2,11,17,18,20], (Fig. 1b).

Cases of‘ healthcare-associated CDI’(HA CDI) either had an onset of symptoms in a healthcare facility on day three or later, following admission to a healthcare facility on day one; or they had onset in the community within 4 weeks of discharge from a healthcare facility (the current facility or any other facility).

‘Community-associated CDI’(CA CDI) cases have had no discharge from a healthcare facility within the 12 weeks before the onset of symptoms. In addition, their onset of symptoms either took place outside healthcare facilities, or took place in a healthcare facility on the day of admission or on the following day.

If a CDI case has been discharged from a healthcare facility in the4e12 weeks before the onset of their CDI symptoms, their case origin is designated as ‘unknown’.

The designation of a CDI case as ‘recurrent’ is independent of the designation of CDI case origin. Recurrent CDI cases are individuals who meet the CDI case definition (including return of diarrhoeal stools with a positive laboratory test) after completion of CDI treatment, who had new onset of symptoms between 2 and 8 weeks after the onset of symptoms from a previous episode of CDI.

Fig. 1.Decision algorithms for (a) application of Clostridium difficile infection (CDI) case definition using ESCMID-recommended diagnostic algorithm [8] and (b) designation of the origin of CDI cases.

CDI rates

Presentation of CDI rates as incidence density (cases/10 000patient-days) or incidence (cases/10 000 admissions) facilitates comparison of hospitals of different sizes with different surveillance periods. If data on the number of patient-days or number of admissions are unavailable, suitable alternative denominators include bed-days (cases/10 000 bed-days) and discharges (cases/10 000 discharges). Patient-days are calculated by summing the number of days in which a bed is occupied overnight by patients hospitalized during the surveillance period. Bed-days are calculated by multiplying the number of hospital beds by the length of the surveillance period of that hospital.

All hospitalized patients should be included in the denominator, including patients on long-term care wards and children aged2 years. Day patients should be excluded, i.e. hospital patients who arrive and leave without an overnight stay, such as day cases, emergency room patients and dialysis patients [11,17,18].

The numerator is the number of hospitalized patients who meet the CDI case definition who had their onset of CDI symptoms during the surveillance period, plus the number of CDI cases who were admitted during the surveillance period with CDI symptom present at admission. C. difficile-positive children aged2 years should only be included in the numerator if there is a compelling clinical evidence to diagnose them as a CDI case [11,17,18].

C. difficile isolate characterization for surveillance purposes

Laboratory methods to characterize C. difficile isolates include PCR ribotyping, detection of the presence of toxin genes or toxin production and antimicrobial susceptibility testing. Preferably, typing should be performed at a national reference or central laboratory.

Polymerase chain reaction (PCR) ribotyping is a molecular typing method based on variability in a length and number of copies of intergenic spacer region between genes encoding 16S and 23S ribosomal RNA. Capillary electrophoresis-based PCR ribotyping has higher discriminatory power, which enables inter-laboratory data exchange, than conventional agarose-based ribotyping [21].Four national reference centres in Europe and North America recently validated a published laboratory protocol for capillary electrophoresis PCR ribotyping, which has high inter-laboratory reproducibility [22].

Different C. difficile RTs (strains) may produce different spectra of toxins (toxin A, toxin B and binary toxin), whereas non-toxigenic RTs (strains) do not encode the genes for toxin production. Current protocols for multiplex PCR determine the presence of such C. difficile virulence factors (e.g .tcdA, tcdB, cdtA and cdtB) [23,24], although ultimately such data should also be obtainable from whole genome sequencing. For the purpose of CDI surveillance, determination of antimicrobial susceptibility to metronidazole, vancomycin and moxifloxacin is recommended, using European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoints[11,17,18,25]. Fidaxomicin susceptibility testing should also be considered, especially in countries that include fidaxomicin in their CDI treatment

recommendations. EUCAST specifies that the MIC breakpoints for metronidazole and vancomycin are 2 mg/L, whereas the MIC for moxifloxacin is 4 mg/L. These EUCAST break-points are based on epidemiological cut-off values that distinguish wild-type isolates from those with reduced susceptibility [25]. Noepidemiological cut-off value has been determined for fidaxomicin yet, but two European studies suggest a MIC of 0.25 mg/L [26,27].Agar dilution is recommended for antimicrobial susceptibility testing [25], particularly if it is performed by a national or central reference laboratory. Other methods, such as E-test and CLSI agar incorporation, may not recognize isolates with reduced susceptibility to metronidazole [28].

Incorporation of whole genome sequencing data into CDI surveillance could markedly improve epidemiological investigations of CDI transmission. Whole genome sequencing data have already been applied to the analysis of transmission chains of C. difficile between patients [29-31]and between humans and animals[32].In addition, genomic data have been used for phylogenetic studies of epidemic RT017 and RT027[33,34].

Summary of CDI epidemiology in Europe until 2017

Several European multicentre studies have been performed to describe CDI epidemiology and to estimate CDI prevalence and incidence in Europe. In 2000, CDI incidence was estimated to be 1.1cases per 1000 patient admissions [35]. In 2005, the incidence density was estimated at 2.5 cases per 10 000 patient-days [3]. In 2008, CDI incidence was estimated at 4.1 cases per 10 000 patient-days [4]. In 2011-13, a prospective, multicentre, biannual, point prevalence study of CDI in hospitalized patients with diarrhoea (EUCLID) estimated an incidence density of 7.0 cases per 10 000 patient-days [5]. The increased CDI incidence rates reported in theEUCLIDstudyareprobablyassociatedwiththestudydesignusinganoptimal testing algorithm. This study also provided strong evidence that CDI incidence was underestimated in Europe, due to a lack of awareness for C. difficile testing among physicians [5]. The 2011/12ECDC point prevalence survey of healthcare-associated infections and antimicrobial use in European acute care hospitals included data from >230 000 patients in 33 European countries. The prevalence of HACDI was 3.7%. It estimated that the burden of HACDI was 123 997 (95% CI 61 018-284 857) cases annually in the European Union and European Economic Area (EU/EEA) countries [36].

The observed increase in CDI incidence has been concomitant with changes in the prevailing C. difficile RTs in Europe. The pre-dominance of RT001 (13%) and RT014/020 (16%) in 2005 and 2008,respectively [3,4], was displaced by a predominance of RT027 (19%) by 2012/13 [6]. The emergence of RT027 significantly influenced CDI surveillance policy worldwide, due to its outbreak potential and association with notable morbidity and mortality[2,37,38]. For an overview of results from international multicentre CDI studies in Europe see Supplementary material (Table S1).

In 2011/12 in Europe, the emergence of reduced susceptibility to metronidazole and vancomycin and almost 40% resistance to moxifloxacin was observed among the most prevalent European RTs of 953C. difficile isolates tested [26]. A recent study suggests that variations in the rate of fluoroquinolone prescription may have been a

major factor in the emergence, and later for the control, of CDI due to fluoroquinolone-resistant C. difficile RTs including RT027in England [39].

ECDC-coordinated CDI surveillance in the EU/EEA

The ECDC surveillance protocol for European surveillance of CDI derives from the protocol produced as part of the ECDC-funded 'European CDI Surveillance Network' (ECDIS-Net) project [7]. The protocol specifies three options for surveillance intensity: the 'minimal option 'that only collects hospital-level aggregate numerators and denominators, the 'light option 'that also collects case-based numerators including mortality, and the 'enhanced option' that also collects microbiological data on at least the first ten cases with a unique identifier linking the case-based data [11], (Table 1).

Fourteen European countries pilot tested the ECDC protocol, including five countries that did not have on going national CDI surveillance. Thirty-seven hospitals participated and collected data for 90-92 days between 13 May and 1 November 2013. Thirty-six hospitals included all wards and one hospital excluded the neonatal ward. All hospitals used the minimal and light surveillance options; the enhanced option was used by 33 hospitals. Data were collected for 1152 individuals, of which 1078 also had case-based data collected using the light or enhanced option. CDI origin and infection outcome data were available for 1013 (94%) and1056 (98%) of these individual, respectively. Of the 317 individuals for whom enhanced data were collected, 291 (92%) had a successful match of their microbiological and epidemiological data. Additionally, the coordinating laboratory could assign an RT to 268(92%) of the 291 isolates collected from these individuals [7].

A post-pilot survey regarding the feasibility of the three surveillance options was completed by 26 (79%) of 33 hospitals. They reported that data collection was 'not difficult' for both the light option (88% hospitals) and the enhanced option (enhanced case-based data: 88%; microbiological data collection: 92%). The median times required for the minimal, light and enhanced protocols were 1.1, 2.0 and 3.0 person-days per 10 000 discharges, respectively [7].

ECDC coordination of CDI surveillance in EU/EEA countries started on 1 January 2016. During the first year of surveillance, hospitals in at least 21 (70%) of 30 EU/EEA countries used the common protocol to acquire comparable CDI surveillance data [40,41].

As of 6 December 2017, 19 countries had submitted CDI surveillance data to ECDC, for 579 hospital surveillance periods in2016. Of these hospital surveillance periods, 294 (50.8%) had used the enhanced surveillance option, 54 (9.3%) had used the light surveillance option and 231 (39.9%) had used the minimal surveillance option.

The current protocol (version 2.3 from April 2017) requests microbiological data (enhanced option) from at least five consecutive CDI cases, whereas previous protocol versions (versions 2.1and 2.2) had requested data from ten consecutive isolates [11,17,18].There is currently no evidence base for the minimum number of isolates; rather the recommendations were designed to promote feasibility. Notably, a study in 21 hospitals in the Czech Republic in2015 identified a difference in the

distribution of RTs detected in the first ten and the second ten consecutive C. difficile isolates within each hospital [42]. Some countries, such as the Netherlands, perform comprehensive surveillance of all CDI cases, collecting epidemiological, clinical and microbiological data. This supports early recognition of outbreaks due to new C. difficile RTs and the distribution of certain RTs in specific populations [43, 44]. As the ECDC protocol links microbiological data to case data, the hospitals' collection and reporting of microbiological data from all their cases will permit faster identification of new strains with increased morbidity or mortality, thus facilitating initiation of appropriate control measures.

To support the microbiological aspects of ECDC CDI surveillance, the Leiden University Medical Centre, the Netherlands, provides reference typing of C. difficile isolates that are not typeable at national level in EU/EEA countries, in close collaboration with the C. difficile reference laboratory in Leeds, UK (open call for tender OJ/05/11/2015-PROC/2015/029, framework service contract ECDC/2016/016).

Survey of current CDI surveillance systems in Europe

In August 2017, to update the current knowledge on CDI surveillance in Europe, the ESCMID study group for C. difficile (ESGCD)conducted a survey by sending a questionnaire to selected subject-matter experts from EU Member States, Iceland, Norway and Switzerland. For the UK, representatives from England, Northern Ireland, Wales and Scotland were contacted separately. The questionnaire requested information on existing CDI surveillance systems and availability of reference laboratories for C. difficile in their country. The survey was completed by 33 out of 34 countries (see Supplementary material, Table S2).

In this ESGCD survey, 20 of 33 countries reported 24 national CDI surveillance systems (Fig. 2). This is more than was reported in a similar survey in 2011, when a CDI surveillance system was in place in only 14 of the 31 responding European countries [20].

Many of the 24 national surveillance systems report data on only HA CDI, even though CA CDI and ‘unknown origin’ CDI constituted 16% of CDIs detected in hospitalized patients during the pilot survey of European CDI surveillance in 2013 [7]. National surveillance systems in the Netherlands and Hungary changed in2011 and 2015, respectively, to provide data on the origin of CDI cases in hospitalized patients, rather than solely reporting data on HA CDI.

In 2017, 26 of 33 countries reported the existence of a national reference or central laboratory for C. difficile in their country, indicating the availability of support for the enhanced option of the ECDC CDI surveillance protocol (Fig. 2). The reference laboratories of 11 countries produced an annual CDI report.

Polymerase chain reaction ribotyping was available for CDI surveillance in 20 of 31 countries in 2011 and 23 of 32 countries in2014 [45]. The current survey indicates that two of nine countries that did not have any ribotyping available in 2014 have acquired capacity for capillary electrophoresis PCR ribotyping (Slovakia and Greece). In our 2017 survey,13 countries reported the availability of multilocus

variable-number tandem-repeats analysis, which is particularly suitable for outbreak investigation[46e48].

Table 1Data collected in the three different Clostridium difficile infection (CDI) surveillance options in the ECDC CDI surveillance protocol [11,17,18]

Fig.2. The presence of Clostridium difficile infection surveillance system and reference or central laboratories for C. difficile in 2017, by country

Future perspectives

The incidence of HA CDI is an important quality indicator of healthcare at hospital as well as country level, reflecting the quality of both infection prevention and control as well as antimicrobial stewardship. Results from this ESGCD survey indicate progress across Europe towards comprehensive monitoring and reporting of CDI, including provision of detailed microbiological data on circulating C. difficile strains.

There are still options to improve the epidemiological and microbiological aspects of CDI surveillance. For example, linkage of CDI surveillance data to antimicrobial and proton pump inhibitor consumption data at hospital or national level, using existing national and European databases, may be useful to assess the impact of antimicrobial use and proton pump inhibitor use on CDI incidence [49]. Additionally, CA CDI is usually only detected if the patient attends healthcare and is tested for CDI. Monitoring of CA CDI at national and European level should permit the determination of CDI incidence in community and identification of prevailing RTs.

Availability of CDI surveillance data in ‘real time’ could be achieved by implementation of electronic surveillance. Linkage of hospital administrative information systems to microbiological information systems will eventually permit automated reporting of CDI data, enabling rapid identification of outbreaks. Until electronic surveillance is achievable, frequent reporting of CDI surveillance data at national and European level should be promoted, in close collaboration with ECDC.

Published data suggest an increase in CDI incidence in Europe and rapid changes in the distribution of the most prevalent RTs [5, 6, 34, 40-42]. This calls for the strengthening of national and European centres to provide up-to-date diagnostic, prevention and treatment advice for CDI. Such centres could also provide molecular typing support for CDI outbreaks in healthcare facilities. Typing (e.g. PCR ribotyping and eventually whole genome sequencing) data should optimally be shared within a European network, to enable early identification of emergent RTs with public health relevance.

Transparency declaration

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Appendix A. Supplementary data

Supplementary data related to this article can be found at
See sheet

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