DIAGNOSIS OF *CLOSTRIDIUM DIFFICILE* INFECTIONS: WHEN and HOW?

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Burden of CDI in Europe and US

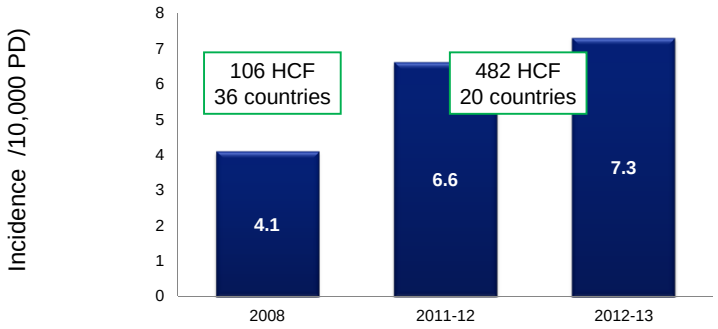
- US
  - 453 000 CDI/year[1]
  - 29 500 deaths
  - 1st agent responsible for HAI (12.5%) [2]
  - Urgent threat (CDC)

- Europe[3]
  - 172 000 CDI /year
  - 9% mortality (direct or indirect)
  - 8th agent responsible for HAI (5.4%)

[1]Lessa , NEJM 2015, 372, 825; [2] Magill SS, NEJM 2014; 370, 1198-208:
http://www.ecdc.europa.eu/en/publications/publications/healthcare-associated-infections-antimicrobial-use-pps.pdf

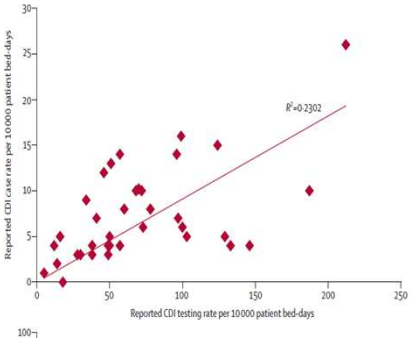
The changing epidemiology of CDI

- The incidence of CDI has increased in many countries worldwide [1–4, 6-7]
  - This trend coincided with the emergence of the hypervirulent NAP1/027/BI clone
  - In some countries (e.g. the UK) the incidence of CDI and prevalence of the hypervirulent strain NAP1/027BI have decreased over the last few years[5]

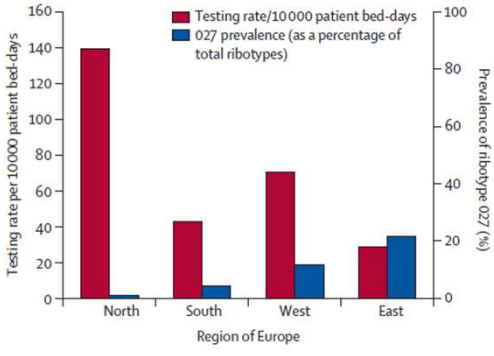


1. Lyytikäinen et al. Emerg Infect Dis 2009;15:761–5;
2. Søes et al. Euro Surveill 2009;14:pii19176;
3. Soler et al. Infect Control Hosp Epidemiol 2008;29:887–9;
4. Vonberg et al. Emerg Infect Dis 2007;13:179–80;
5. Health Protection Agency. 2011;
6- Bauer et al. Lancet 2011;377:63–73.
7. Davies, Lancet Inf. Dis 2014, 14, 1208-19

Association between testing rates and CDI incidence or prevalence of 027 across Europe



48-fold variation was noted in country specific testing rates



An inverse correlation was noted between the rate of testing and prevalence of ribotype 027

. Davies, Lancet Inf. Dis 2014, 14, 1208-19

Cases of community-acquired (CA)-CDI are increasingly common

- 12 714 diarrheal stools (prescribed by GP)[1]
  - 1.5% positive for toxigenic *C. difficile* (0.67/10 000 pts/y)
  - 7% were requested by GP → 40% CDI detected
- Performance of algorithm for testing diarrheal samples from patients in general practice

Test algorithm in diarrheal samples from the community	Setting	Patients tested (% of all unformed stools)	Positive results (% of all tested samples)	Detection of CDI (% of all tested positives)
> 65 y, after AB use or hospitalization	UK 2012	31	3.5	72
After AB use or hospitalization	NL (advice)	18	5	61

1. Hensgens et al CID 2014, 2014 Dec;20(12):O1067-74

Current challenges for CDI diagnosis

- Diagnosis has changed over the last 10 years
- Rapid and accurate diagnosis is crucial for:
  - Patient management
  - Prevention of nosocomial transmission
  - Epidemiology of the disease
- Ideal criteria for a diagnostic method are:
  - Specificity
  - Sensitivity
  - Rapid turnaround time
  - Cost-effectiveness
  - Technical simplicity (minimum hands on time)

Guidelines

REVIEW

European Society of Clinical Microbiology and Infectious Diseases (ESCMID): Data review and recommendations for diagnosing *Clostridium difficile*-infection (CDI)

M. J. T. Crobach[1], O. M. Dekkers[2], M. H. Wilcox[3] and E. J. Kuijper[1]

2009
Updates in preparation

SHEA-IDSA GUIDELINE

Clinical Practice Guidelines for *Clostridium difficile* Infection in Adults: 2010 Update by the Society for Healthcare Epidemiology of America (SHEA) and the Infectious Diseases Society of America (IDSA)

Stuart H. Cohen, MD; Dale N. Gerding, MD; Stuart Johnson, MD; Ciaran P. Kelly, MD; Vivian G. Loo, MD; L. Clifford McDonald, MD; Jacques Pepin, MD; Mark H. Wilcox, MD

2010

A Practical Guidance Document for the Laboratory Detection of Toxigenic *Clostridium difficile*
September 21, 2010*

The American Journal of Gastroenterology **108**, 478-498 (April 2013) | doi

Guidelines for Diagnosis, Treatment, and Prevention of Clostridium difficile Infections

CLINICAL GUIDELINES

Australasian Society for Infectious Diseases guidelines for the diagnosis and treatment of *Clostridium difficile* infection

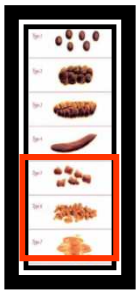
Allen C Cheng, John K Ferguson, Michael J Richards, Jennifer M Robson, Gwendolyn L Gilbert, Alistair McGregor, Sally Roberts, Tony M Korman and Thomas V Riley

2011

General considerations

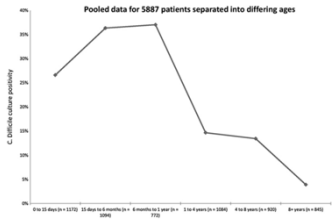
1. Only diarrheic stools should be processed

- Laboratory definition :
  - Stool taking the shape of the container
- Clinical definition :
  - Aspect 5, 6, 7 on Bristol scale
  - ≥ 3 stools in 24 or fewer consecutive hours or more frequently than is normal for the individual (definition WHO)



2. Do not test stool samples from neonates < 3 y.

- Asymptomatic colonisation is frequent in neonates (6 m -1 y).
- The carriage rate drops progressively
- With a physician's request only



Enoch ; A, Journal of Infection (2011) 63, 105e113; *; Schutze et cal. , Pediatrics 2013, 131, 1, 196-200.*

General considerations

3- Repeated diagnostic testing is not useful

- Repeat testing is a frequent and costly practice
- Stool samples tested twice (<7 days) following 13.7% of EIA, 12.4% of PCR tests[1]
- The frequency of test results converted from negative to positive (diagnostic gain) following repeat testing is low, whatever the method used

Authors	Technique	Patients (n)	Diagnostic gain
Aichinger et al. 2008[1]	EIA A + B, PCR	5,788 2,827	1.9% (7 days) 1.7% (7 days)
Renshaw et al. 1996[2]	CTA	2,009	1%

- Repeat testing may lead to false-positive result (lack of specificity)[3]

1. Aichinger et al. J Clin Microbiol 2008;46:3795–7;
2. Renshaw et al. Arch Pathol Lab Med 1996;120:49–52;
3. Litvin et al. Infect Control Hosp Epidemiol 2009;30:1166–71.

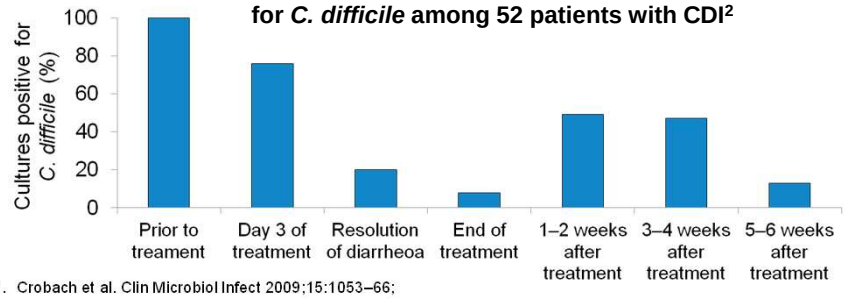
EIA, enzyme immunoassay;
CTA, cytotoxicity assay;
PCR, polymerase chain reaction

General considerations

4. Test-of-cure is not recommended[1]

- Spores detectable in **7%** (2/28) of patients at the end of treatment for CDI[2]
- Positive cultures found in **56%** (15/27) of patients 1–4 weeks after therapy[2]

Percentage of stool cultures positive for *C. difficile* among 52 patients with CDI[2]

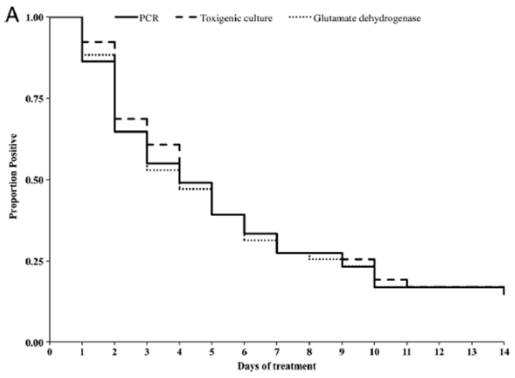


1. Crobach et al. Clin Microbiol Infect 2009;15:1053–66;
2. Sethi et al. Infect Control Hosp Epidemiol 2010;31:21–7.

General considerations

5. Stool samples should be taken prior initiation of CDI treatment

- Prospective study to determine the time to conversion of CDI test result
- 51 patients with CDI
- For PCR, 14%, 35%, and 45% of positive CDI tests converted to negative after 1, 2, and 3 days of treatment, respectively
- Increased age and infection with NAP1 strains were associated with persistent positive PCR results.



Sunkesula , CID 2013, 57, 494-500

Reducing inappropriate testing and treatment

- Inappropriate testing may lead to treat asymptomatic carriers
- Dubberke *et al.* (2011)
  - 36% of patients tested for CD did not meet criteria for testing because they did not have clinically significant diarrhea
- Kundrapu *et al.* (Idweek 2014)
  - 18% did not have clinically significant diarrhea or had a clear alternative explanation for diarrhea (eg laxatives)
- Ongoing education of physicians and nurses and feedback are successful to reduce inappropriate testing[2]

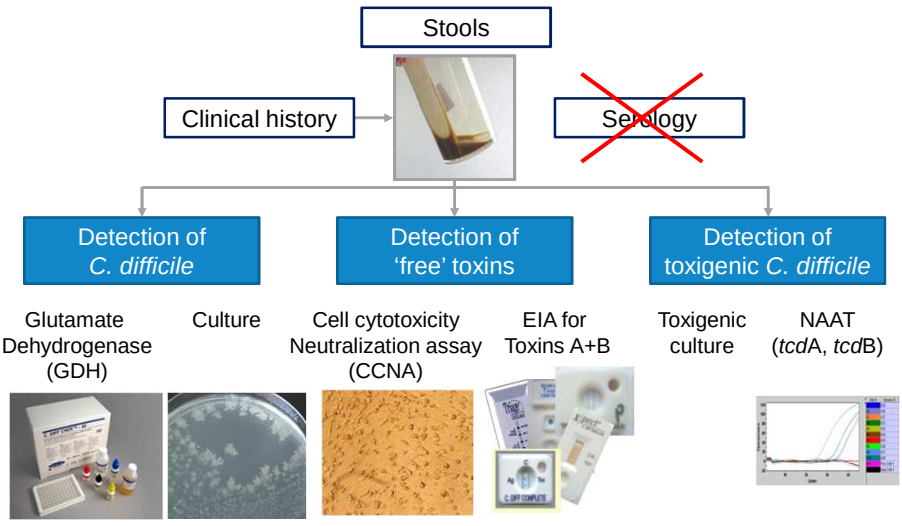
Dubberke E, J Clin Microbiol. 2011 Aug; 49(8): 2887–2893. Jury LA, Infect Control Hosp Epidemiol. 2013 Nov;34(11):1222-4

Laboratory diagnosis of CDI

- Current guidelines from different scientific societies (ESCMID, ASM, IDSA) highlight the importance of laboratory testing in the investigation of suspected CDI[1,2]
- The diagnosis of CDI is based on
  - a combination of signs and symptoms, confirmed by microbiological evidence of *C. difficile* toxin and toxin-producing *C. difficile* in stools, in the absence of another cause, or
  - colonoscopic or histopathological findings demonstrating pseudomembranous colitis
- Colonic imaging techniques
  - Radiography, computed tomography and endoscopy are sometimes used[2,3] especially if a faecal sample is not available
  - However, imaging techniques have been largely superseded by more sensitive laboratory tests because imaging can identify colitis, but not its cause

1. Debasth et al.; Clin Microbiol Infect 2014; 20 (Suppl. 2): 1–26
2. Cohen SH, Infect Control Hosp Epidemiol 2010; 31(5):431-455.

Testing methods: an overview



EIA, enzyme immunoassay;
GDH, glutamate dehydrogenase,,NAAT: nucleic acid amplification tests

Reference methods: current issues

- The two reference methods are the stool cell cytotoxicity neutralization assay and the toxigenic culture
- They detect different targets (free toxin or presence of a strain with the potential to produce toxins) and are not directly comparable
- Not frequently used in routine practice
- Not standardised
- Slow turnaround time (>48 hours) and time consuming
- Used as ‘gold standard’ for evaluation of other methods

Crobach et al. Clin Microbiol Infect 2009;15:1053–66.