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Clostridium Difficile Bibliography – Guidelines, Economical and Clinical Impact

Literature Review

- Guideline (ESCMID)
- Economic Burden
- Performance
- PCR+ Toxin EIA Algorithm
- One-and-Done Approach
- Clinical Impact/POCT
- Cost-Effectiveness
- Importance of Binary Toxin

PUBLICATIONS

1 Guideline (ESCMID)

Crobach MJ, Planche T, Eckert C, Barbut F, Terveer EM, Dekkers OM, Wilcox MH, Kuijper EJ. **European Society of Clinical Microbiology and Infectious Diseases: update of the diagnostic guidance document for *Clostridium difficile* infection.** Clin Microbiol Infect. 2016 Aug;22 Suppl 4:S63-81. doi: 10.1016/j.cmi.2016.03.010. Epub 2016 Jul 25. PMID: 27460910. (2016)

- Unformed stool samples from patients 3 years or older should be tested for CDI. We recommend against the use of a single rapid test as a stand-alone test due to inadequate PPV in an endemic situation. Repeated testing after a first positive sample during the same diarrheal episode is not recommended in an endemic situation. A test of cure is not recommended.
- Neither GDH EIA nor toxin A/B EIA or NAAT can reliably be used as a stand-alone test to diagnose CDI. We recommend the use of a 2-step algorithm: first test should have a high NPV (GDH EIA or NAAT), second test should have a high PPV (Toxin A/B EIAs).
- The use of a two-step algorithm is recommended. Recommended algorithms for CDI testing:
  (a) GDH or NAAT-Tox A/B algorithm
  (b) GDH and Tox A/B-NAAT/TC algorithm

2 Economic Burden

van Beurden YH, Bomers MK, van der Werff SD, Pompe EAPM, Spiering S, Vandenbroucke-Grauls CMJE, Mulder CJJ. **Cost analysis of an outbreak of *Clostridium difficile* infection ribotype 027 in a Dutch tertiary care centre.** J Hosp Infect. 2017 Apr;95(4):421-425. doi: 10.1016/j.jhin.2016.12.019. Epub 2016 Dec 30. PMID: 28169013. (2017)

- The economic impact of Clostridium difficile infection (CDI) on the healthcare system is significant. In this retrospective analysis, the financial burden of a CDI outbreak in a Dutch tertiary care hospital was evaluated. The attributable costs of the one-year-long *C. difficile* ribotype 027 outbreak were estimated to be 1.222.376 EUR.
- The main contributing factor was missed revenue due to increased length of stay of CDI patients and closure of beds to enable contact isolation of CDI patients (36%). A second important cost component was extra surveillance and activities of the Department of Medical Microbiology and Infection Control (25%).
- To avoid unnecessary expense during an outbreak, it is important to follow evidence-based recommendations on control measures in order to limit pathogen spread at the earliest possible stage.

Heister T, Wolkewitz M, Hehn P, Wolff J, Dettenkofer M, Grundmann H, Kaier K. **Costs of hospital-acquired *Clostridium difficile* infections: an analysis on the effect of time-dependent exposures using routine and surveillance data.** Cost Eff Resour Alloc. 2019 Aug 1;17:16. doi: 10.1186/s12962-019-0184-5. PMID: 31388335; PMCID: PMC6670202. (2019)

- CDI is associated with sizeable in-hospital costs. In this cost-calculation analysis from Germany, CDI is associated with €9000 of extra costs, €7800 of higher reimbursements, and 6.4 days extra length of stay.
- On average, €1200 of the additional costs of CDI are not covered by additional reimbursements from insurance companies.
- Cases with CDI present on admission (N = 112) had average total costs of hospitalization of €5700 with a LOS of 12 days compared to €35,000 and 34 days for nosocomial cases.

PUBLICATIONS

3 Performance

Azrad M, Tkhawkho L, Hamo Z, Peretz A. **The diagnostic performance and accuracy of 3 molecular tests for the detection of *Clostridium difficile* in stool samples, compared with the Xpert® C. difficile test.** J Microbiol Methods. 2020 Jan;168:105784. doi: 10.1016/j.mimet.2019.105784. Epub 2019 Nov 20. PMID: 31758952. (2020)

- Prospective performance and diagnostic accuracy evaluation of 3 molecular tests (BDmax™ *C. difficile*, Simplexa™ *C. difficile* Direct, and GenomEra™ *C. difficile*) compared to Xpert® *C. difficile*
- Xpert *C. difficile* is the most advantageous test in matter of total turnaround time (50 mins). Also, no multiple preparatory steps are required before sample loading to the instrument.
- Furthermore, it has the advantage of identifying the hyper virulent *C. difficile* strain NAP1/Ribotype 027.

4 PCR+ Toxin EIA Algorithm

Crone AS, Wright LM, Cheknis A, Johnson S, Pacheco SM, Skinner AM. **Characteristics and outcomes of *Clostridioides difficile* infection after a change in the diagnostic testing algorithm.** Infect Control Hosp Epidemiol. 2024 Jan;45(1):57-62. doi: 10.1017/ice.2023.145. Epub 2023 Jul 18. PMID: 37462099. (2024)

- Adopting Xpert *C. difficile* + toxin EIA is a reasonable strategy for diagnosis of CDI. The addition of toxin EIA testing provides clinicians with critical data on the severity of infection. Treatment was initiated 25.6% less frequently for toxin-negative encounters compared to toxin-positive encounters, with no significant changes in recurrence.
- A testing strategy of PCR+ toxin EIA helped predict recurrent CDI.

Hilt EE, Vaughn BP, Galdys AL, Evans MD, Ferrieri P. **Impact of the Reverse 2-Step Algorithm for *Clostridioides difficile* Testing in the Microbiology Laboratory on Hospitalized Patients.** Open Forum Infect Dis. 2024 Apr 27;11(5):ofae244. doi: 10.1093/ofid/ofae244. PMID: 38756762; PMCID: PMC11097206. (2024)

- PCR testing has a superior sensitivity than GDH antigen testing and is therefore a potentially better initial test. The implementation of a toxin EIA to a clinical microbiology laboratory using an existing PCR platform is feasible and has minimal impact on the laboratory space and workflow.
- Discordant results are the most common outcome of reflex *C. difficile* testing. In this study, 65% had discordant PCR and toxin EIA results with 15% having discordant PCR and GDH results and 50% having discordant GDH and toxin results.
- The authors advocate for a multistep algorithm that starts with Xpert *C. difficile* and reflexes to GDH/toxin EIA. In their study, 15% of tcdB PCR+ patients were GDH negative, which could be missed with the current 2 step algorithm (GDH-toxin EIA).

5 One-and-Done Approach

Bettger CC, Giancola SE, Cybulski RJ Jr, Okulicz JF, Barsoumian AE. **Evaluation of a two step testing algorithm to improve diagnostic accuracy and stewardship of *Clostridioides difficile* infections.** BMC Res Notes. 2023 Aug 14;16(1):172. doi: 10.1186/s13104-023-06398-9. PMID: 37580824; PMCID: PMC10426052. (2023)

- A two-step testing algorithm (Xpert *C. difficile* followed by Tox A/B II EIA 96-T) was implemented in a tertiary care center in an effort to improve diagnostic accuracy for CDI.
- While discordant laboratory results may have helped providers distinguish between colonization in the untreated minority of cases, the majority of discordant cases in this study were deemed clinically significant and were treated. Given suboptimal sensitivity of EIA, some discordant samples will likely represent true CDI and may lead to missed diagnoses.
- Identification of toxin positivity is less relevant in patients with clinically significant disease. Additionally, this further supports the recommendation in the U.S. for PCR testing alone when pre-test probability is improved with stool submission criteria.

PUBLICATIONS

Casari E, De Luca C, Calabrò M, Scuderi C, Daleno C, Ferrario A. **Reducing rates of *Clostridium difficile* infection by switching to a stand-alone NAAT with clear sampling criteria.** Antimicrob Resist Infect Control. 2018 Mar 12;7:40. doi: 10.1186/s13756-018-0332-2. PMID: 29564088; PMCID: PMC5848539. (2018)

- Lack of confidence in the sensitivity of the toxin tests meant that clinicians often repeated the test up to three or more times before declaring the patients free from *C. difficile* infection and releasing them from isolation, resulting in a poor use of isolation facilities.
- Moving from a toxin EIA to a stand-alone NAAT resulted in fewer samples tested and lower positivity rates, largely due to a reduction in the number of healthcare associated cases. Two- or three-step algorithms can cause confusion with interpretation for clinicians and may introduce delays in initiating management of patients because of the longer time to results, especially where batching of some tests is required.
- The use of rapid and highly sensitive Xpert *C. difficile* together with clear sampling guidance offers the optimal approach to patient management and best use of isolation facilities.

Iffland A, Zechel M, Lewejohann JC, Edel B, Hagel S, Hartmann M, Löffler B, Rödel J. **Experience with PCR Testing for Enteric Bacteria and Viruses of Emergency Department Patients with Acute Gastroenteritis: Are There Implications for the Early Treatment of *Clostridioides difficile* Infection?** Antibiotics (Basel). 2024 Mar 6;13(3):243. doi: 10.3390/antibiotics13030243. PMID: 38534678; PMCID: PMC10967468. (2024)

- The most common gastrointestinal pathogen in the emergency department (ED) detected was *C. difficile*, with 20 cases out of 133 patients (15%), and as expected, the majority of cases were in the older patient group. The median time to report PCR results was 6.17 h compared to 57.28 h for culture results for bacterial pathogens. Timely reporting of positive PCR results may also increase attention to basic hygiene measures like hand hygiene and pathogen-specific measures, such as isolation and personal protective equipment.
- The guidelines state that a positive PCR screening test in combination with a negative toxin antigen test needs to be clinically evaluated. However, this strategy may lead to excessive repeat testing. PCR testing for ED patients with acute gastroenteritis (AGE) has the greatest impact on the early detection of CDI in the elderly patient population.
- The introduction of PCR for the diagnosis of AGE infection in patients presenting to the ED may have the greatest impact on the rapid identification of *C. difficile* and the timely administration of antibiotics if necessary. *C. difficile* diagnosis based on PCR testing alone in the context of clinical symptoms is acceptable for therapeutic decisions.

6 Clinical Impact/POCT

Dewar S, Vass D, MacKenzie FM, Parcell BJ. **Point-of-care testing by healthcare workers for detection of meticillin-resistant *Staphylococcus aureus, Clostridioides difficile,* and norovirus.** J Hosp Infect. 2019 Dec;103(4):447-453. doi: 10.1016/j.jhin.2019.08.002. Epub 2019 Aug 9. PMID: 31404566. (2019)

- The feasibility of introducing three separate Cepheid GeneXpert tests was assessed: Xpert SA Nasal Complete, Xpert *C. difficile*, and Xpert Norovirus for point-of-care testing (POCT) on a ward in a district general hospital. The tests significantly reduced hands-on time, process steps, and time to result for identification of all three micro-organisms. Overall agreement with central laboratory testing was >98% for all three tests. Staff members fed back that POCT had a positive impact in terms of clinical utility.
- Xpert *C. difficile* can be used as POCT solely by healthcare workers in a ward setting throughout a seven-day/24 h period. It could be used as an alternative screening test to laboratory GDH for *C. difficile* detection. The study showed good agreement with laboratory testing (99.0% agreement) and the use of Xpert *C. difficile* test reduced clinical TAT (84h to 3h), thus allowing for more effective bed management and improved patient care.

PUBLICATIONS

Salmona M, Jolivet S, Duprilot M, Akpabie AC, Fourati S, Decousser JW. **Laboratory-based strategy using a new marketed polymerase chain reaction test to manage diarrheic episodes among patients from rehabilitation and long-term care facilities.** Am J Infect Control. 2016 Jun 1;44(6):716-8. doi: 10.1016/j.ajic.2015.12.027. Epub 2016 Feb 24. PMID: 26921013. (2016)

- *C. difficile* and norovirus are the two main agents responsible for extensive gastroenteritis outbreaks in rehabilitation care facilities (RCFs) and long-term care facilities (LTCFs). The availability of a rapid and sensitive nucleic acid amplification test (Xpert *C. difficile*, Xpert Norovirus) could limit the risk of cross-transmission. This 2-step laboratory-based strategy seems to be economical and efficient to adequately implement isolation precautions for diarrheic patients from RCFs and LTCFs.
- *C. difficile* and norovirus were successively identified from 17% and 23% of 52 episodes of diarrhea, respectively, during the winter season, leading to 100% adequate isolation measures. In patient populations with numerous risk factors for diarrhea, a combined laboratory-based approach could improve infection control.

Jazmati N, Hain O, Hellmich M, Plum G, Kaasch A. **PCR based detection of tcdCΔ117 in *Clostridium difficile* infection identifies patients at risk for recurrence - A hospital-based prospective observational study.** Anaerobe. 2019 Jun;57:39-44. doi: 10.1016/j.anaerobe.2019.03.010. Epub 2019 Mar 13. PMID: 30878603. (2019)

- This study from a tertiary care hospital in Germany shows that the detection of tcdCΔ117 by real-time PCR at the time of diagnosis is associated with an increased all-cause mortality and further episodes of CDI. Its potential use for clinical prediction rules should be considered and explored on a larger scale. From 1121 tested stool samples, 107 patients with CDI were included in the study. TcdCΔ117 was detected in 18 (16.8%) of these patients.
- Patients with detection of tcdCΔ117 are much more likely to have recurrent CDI and have a higher 30-day all-cause mortality rate. Thus, the detection of tcdCΔ117 could be used to stratify patients according to the risk of recurrence at the time of diagnosis.

Alnimr A, Alwazzeh MJ, Al-Ameer A. **The Clinical and Laboratory Impact of Upgrading *Clostridioides* (formerly *Clostridium*) *difficile* Infection Testing from Routine to Molecular Based-Algorithm: an Observational Case-Study from the Eastern Province, Saudi Arabia.** Clin Lab. 2019 Aug 1;65(8). doi: 10.7754/Clin.Lab.2019.181252. PMID: 31414736. (2019)

- Xpert *C. difficile* testing is a supportive tool for diagnosing CDI with rapid turnaround time that is helpful for patient management and initiating effective infection control measures.
- In terms of workflow and time to results, Xpert *C. difficile* was superior to EIA, with a shorter turnaround time of 50 minutes, including 5 minutes of sample preparation. Also, there was less metronidazole and vancomycin therapy initiated for patients with a negative *C. difficile* test observed with molecular testing.
- In addition, a reduction was noted in the number of tests ordered per patient for presumptive CDI after shifting to the Xpert *C. difficile* test.

7 Cost-Effectiveness

Lim VW, Tomaru T, Chua B, Ma Y, Yanagihara K. **Budget Impact Analysis of Adopting a One-Step Nucleic Acid Amplification Testing (NAAT) Alone Diagnostic Pathway for *Clostridioides difficile* in Japan Compared to a Two-Step Algorithm with Glutamate Dehydrogenase/Toxin Followed by NAAT.** Diagnostics (Basel). 2023 Apr 18;13(8):1463. doi: 10.3390/diagnostics13081463. PMID: 37189564; PMCID: PMC10137341. (2023)

- Evaluation of the budgetary impact of a one-step NAAT alone pathway in Japan, by comparing it with a two-step CDI diagnostic algorithm initially with GDH/toxin EIA, followed by NAA.
- When the sensitivity of NAAT was above 91.6%, the NAAT alone pathway would lead to cost saving, because it could accurately capture 753 more patients using a model of 100,000 symptomatic, hospitalized adult patients suspected with CDI requiring a CDI diagnostic test. However, the NAAT alone pathway resulted in 1749 more patients accurately diagnosed with CDI and 91 fewer deaths. With a higher NAAT sensitivity of 100%, cost savings of JPY 32,809 (USD 352) per CDI accurately diagnosed was achieved with the NAAT alone pathway.
- Although the NAAT alone pathway was more costly from the test costs alone compared to the two-step algorithm, it resulted in a greater number of CDI diagnosed accurately and fewer CDI-related deaths. The findings of this study support the adoption of the NAAT alone pathway from the economic value perspective.

PUBLICATIONS

8 Importance of Binary Toxin

Androga GO, Hart J, Foster NF, Charles A, Forbes D, Riley TV. **Infection with Toxin A-Negative, Toxin B-Negative, Binary Toxin-Positive *Clostridium difficile* in a Young Patient with Ulcerative Colitis.** J Clin Microbiol. 2015 Nov;53(11):3702-4. doi: 10.1128/JCM.01810-15. Epub 2015 Sep 9. PMID: 26354812; PMCID: PMC4609731. (2015)

- Binary toxin (CDT) is beginning to receive attention due to its increasing prevalence in human and animal isolates of *C. difficile*. In this case study, toxin A- toxin B- CDT+ *C. difficile* RT033 was isolated during recurrent episodes of severe diarrhea in the absence of other enteric pathogens.
- Although *C. difficile* was isolated, it was considered nontoxigenic due to the lack of fecal cytotoxin. *C. difficile* ribotype 033 (RT033), negative for the toxin genes tcdA and tcdB but positive for binary toxin genes (cdtAB), was identified from the specimens.
- Importance to use *C. difficile* test, which is able to detect CDT from patients with clinically significant *C. difficile* infection (CDI), because such strains are not detected by most diagnostic methods.

Riedel T, Neumann-Schaal M, Wittmann J, Schober I, Hofmann JD, Lu CW, Dannheim A, Zimmermann O, Lochner M, Groß U, Overmann J. **Characterization of *Clostridioides difficile* DSM 101085 with A-B-CDT+ Phenotype from a Late Recurrent Colonization.** Genome Biol Evol. 2020 May 1;12(5):566-577. doi: 10.1093/gbe/evaa072. PMID: 32302381; PMCID: PMC7250501. (2020)

- *C. difficile* strain with toxin A- toxin B- CDT+ phenotype led to a recurrent infection in a patient with severe comorbidities and very susceptible for CDIs.
- Analysis of the toxin repertoire revealed the presence of a complete binary toxin locus and an atypical pathogenicity locus consisting of only a tcdA pseudogene and a disrupted tcdC gene sequence.
- This study highlights the potential role of the binary toxin in this recurrent colonization and possibly further in a host dependent virulence.

Young MK, Leslie JL, Madden GR, Lyerly DM, Carman RJ, Lyerly MW, Stewart DB, Abhyankar MM, Petri WA Jr. **Binary Toxin Expression by *Clostridioides difficile* Is Associated With Worse Disease.** Open Forum Infect Dis. 2022 Jan 10;9(3):ofac001. doi: 10.1093/ofid/ofac001. PMID: 35146046; PMCID: PMC8825761. (2022)

- Binary toxin (CDT) expression by *C. difficile* is associated with worse disease (measured by increased rates of ICU admissions and higher mortality). Additionally, these patients had longer stays in the hospital and ICU, causing increased burden to health care systems.
- Utilization of PCR and testing for *C. difficile* toxins A and B may not reveal the entire picture when diagnosing CDI; detection of CDT-expressing strains is valuable in identifying patients at risk of more severe disease.
- Characterizing *C. difficile* infection with CDT-expressing strains may be beneficial in clinical disease diagnosis and treatment.

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