Table B.26: Clostridioides *difficile*, Testing–Single Studies

Note: Full references are available in the [Section 4.5 reference list](#Section4point5refs).

| Author, Year | Description of Patient Safety Practice | Study Design;Sample Size;Patient Population | Setting: | Outcomes: Benefits | Outcomes: Harms | Implementation Themes/Findings | Risk of Bias (High, Moderate, Low) | Comments |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Aichinger et al., 200830** | Not repeating negative CDI tests within 7 days of initial result | Retrospective review of stool testing for C. difficile from June 2006 through December 2007. 5,788 patients tested by enzyme immunoassay (EIA) and 2,827 patients tested by polymerase chain reaction (PCR).  | An unspecified healthcare facility | The group of EIA patients tested only twice consisted of 792 subjects (13.7% of patients tested with EIA). Twenty (2.5%) patients had a negative result on the first test with subsequent positive results on the following tests. Thirty-eight (4.8%) went from positive to negative. For PCR, 351 were tested twice; 2% (7) went negative to positive and 2.9% (10) went positive to negative.  | Not provided | The researchers concluded that the diagnostic gains of repeat testing are equally low for PCR and EIA and that repeat testing for C. difficile should not be routine. Several authors have suggested that it may be useful to test more than one stool specimen for C. difficile toxin by use of an immunoassay. Nevertheless, there are limited data supporting this practice.  | Not provided | None |
| **Archbald-Pannone et al., 201560** | Clinical factors to predict mortality following *C. difficile* infection (CDI) | A parsimonious predictive model was chosen using Akaike information criterion (AIC) and a best subsets model selection algorithm. Area under the receiver operating characteristic (ROC) curve was used to assess the model’s comparative, with AIC as selection criterion for all subsets to measure fit and control for over-fitting. 362 inpatients diagnosed with CDI who did not have chronic diarrhea. Followed them for 30 days after CDI diagnosis or until death. | U.S. academic hospital/ University of Virginia clinical laboratory | The area under the ROC curve was 0.804. The bootstrap estimate of optimism was -0.034; suggesting that this model applied to a novel cohort is expected to have an area under the curve (AUC) of 0.770. With this model, 1 point corresponds to approximately an 11% increase in the odds of death within 30 days. The selected model included Charlson comorbidity index (CCI), white blood cell count (WBC), blood urea nitrogen (BUN), intensive care unit, and delirium. The logistic regression coefficients were converted to a point scale and calibrated so that each unit on the CCI contributed 2 points, ICU contributed 5, unit of WBC (natural log scale) contributed 3, unit of BUN contributed 5, and delirium contributed 11. | Not provided | Clinicians could use this tool to enhance the early recognition of high-risk patients with CDI, implement a more intensive treatment regimen, and aid in the decision for earlier surgical consultation. The predictive model was directly calculated from the five retained variables: Charlson score, ICU at diagnosis, WBC, BUN, and delirium. Patients who were admitted from a long-term care facility, who were diagnosed in the ICU, and who developed delirium were at highest risk of dying within 30 days of CDI diagnosis. | Moderate | Background: According to article, current models to define severe CDI lack either sensitivity or specificity.  |
| **Bogaty et al., 201741** | Different CDI testing strategies (and their association with CDI incidence rates): EIA, glutamate dehydrogenase (GDH), GDH plus toxigenic cultures, nucleic acid amplification tests (NAATs) | Cross-sectional study of 95 hospitals by surveys conducted in 2010 and in 2013 to 2014. The association between testing strategies and institutional CDI incidence rates was analyzed via multivariate Poisson regressions. | 95 hospitals in Quebec, Canada | Between 2010 and 2014, 35 institutions (37%) modified their algorithm. Institutions detecting toxigenic *C. difficile* instead of *C. difficile* toxin increased from 14 to 37 (p<0.001). Institutions detecting toxigenic *C. difficile* had higher CDI rates (7.9 vs 6.6 per 10,000 patient-days; p=0.01). Institutions using single-step NAATs, GDH plus toxigenic cultures, and GDH plus cytotoxicity assays had higher CDI rates than those using an EIA-based algorithm (p<0.05). | Not provided | Infection control professionals should be aware that local CDI incidence rates may be influenced by the local choice of diagnostic test. The research found that laboratory detection of CDI has changed since 2010 and there is an association between diagnostic algorithms and CDI incidence.The heterogeneity of available tests can pose a significant threat to the validity of surveillance systems regarding interinstitutional comparisons.  | Low to moderate | Background: Many surveillance programs, including Quebec’s, provide no recommendations regarding the choice of laboratory tests to use, and CDI incidence rates are not adjusted to take this variable into consideration. |
| **Casari et al., 201842** | Use of NAAT plus clear sampling criteria (unformed stool)  | Prospective, pre/post study. Analyses of sample numbers, numbers of positive results, and proportion of cases assessed as healthcare acquired over a 6-year period during which the testing method was changed from a toxin A/B immunoassay to a standalone commercial nucleic acid test after the first 2 years (2012) | A 750-bed tertiary care university hospital in Milan | Sample numbers and numbers of cases assessed as healthcare-acquired CDI fell after the introduction of the NAAT and sampling guidance, while infection rates in other hospitals in the same region remained relatively stable. A total of 8,680 samples were tested for CDI over the study period: 2,841, 2,746, 677, 768, 805, and 843 tests in 2010, 2011, 2012, 2013, 2014, and 2015, respectively. For the corresponding years, the total number of positive samples and those categorized as healthcare acquired was 106/105 for 2010, 108/104 for 2011, 92/79 for 2012, 95/75 for 2013, 93/76 for 2014, and 91/78 for 2015, respectively.  | Not provided | This study showed that moving from a toxin EIA to a standalone NAAT resulted in fewer samples tested and lower positivity rates, largely due to a reduction in the number of healthcare-associated cases. According to the authors, the reasons for these findings are likely to be multifactorial. 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. | Low | None |
| **Cooper et al., 201344** | An electronic screening tool to help identify patients at risk of CDI | Logistic regression was used to weigh six variables, and then a predictive model was devised to help identify which patients may be at risk for developing CDI. A retrospective review of 29,453 records of hospitalizations was conducted, including 274 cases of *C. difficile* toxin-positive patients, to retrieve data for the model. | A 255-bed, community hospital located in Virginia’s Shenandoah Valley | The final model resulted in an area under the curve of 0.929, which suggests that the electronic screening tool will be an accurate predictor of predisposition to the disease. Model testing suggests a positive relationship between the total weight or score and the probability of developing the disease. | The impact of the tool to the prevalence and control of the disease itself may be difficult to ascertain in isolation from other infection control measures. Further studies are warranted on the economic benefits of the electronic screening tool and how it affects physician decision making. | This study suggests that an electronic screening tool for CDI can be devised locally and result in reasonably accurate screening of patients at risk of developing the disease. This model could be applied to the electronic medical record to automatically generate updated lists of patients who may need monitoring for prompt testing, isolation, or treatment. Being alerted that a patient is at high risk for CDI may help the clinician to consider prompt isolation and empiric treatment in cases when the laboratory test (especially EIA) is negative or is still pending. | Low to moderate  | None |
| **Cruz-Betancourt et al., 201645** | A predictive preventive model for prevention of *Clostridium* *difficile* infection in patients in ICUs | A predictive screening tool was developed based on risk factors identified in the literature and validated by retrospective analysis of all HA-CDI cases occurring in critically ill patients during 2013. The tool was used to screen all patients admitted to an intensive care unit. Evidence-based interventions (bundle) were implemented for patients identified as being at high risk for HA CDI. Effectiveness of the model was measured by reduction of the HA-CDI rate during the intervention period compared with the pre-intervention period. | A vascular-thoracic ICU, a 20-bed unit providing care to patients following vascular surgery as well as to patients with chronic ventilator dependency | During the study period, 1,066 patients were screened using the predictive screening tool; 217 high-risk patients were identified as infected with *Clostridium difficile*. Sixty-two of these met exclusion criteria, resulting in a study population of 157 patients.During the pre-intervention phase, 10 cases of HA CDI occurred (overall incidence rate, 14.7). During the 12-month study period, two cases of HA CDI were identified (incidence rate, 3.12). The reduction was statistically significant. | Not provided | The combination of a predictive screening tool with preventive interventions in the vascular-thoracic ICU appeared effective in reducing HA-CDI rates. The two patients who developed CDI during the implementation period did not have the preventive bundle measures instituted due to procedural deviation. The major pharmacologic interventions related to adjustment or discontinuation of acid suppression therapy. Improved environment cleaning to reduce transmission in addition to improved hand hygiene rates also likely played a role in reducing HA-CDI rates, according to the authors. | Low to moderate | This study describes both the use of a predictive model and its integration into daily practice of interdisciplinary efforts at CDI reduction to demonstrate a method of clinical use of a predictive model. |
| **Figh et al., 201763** | Two published clinical prediction tools (CPTs): the Velazquez-Gomez Severity Score Index (VGSSI) and ATLAS scores | A retrospective review of the charts of 271 hospitalized patients with CDI. VGSSI and ATLAS scores were assigned. Means and correlations of these scores with mortality were evaluated. Multivariate logistic regression analysis was performed on 32 known potential mortality predictor variables. The review included 271 patient charts. | A hospital | Mortality was overall strongly associated with VGSSI and ATLAS scores with poor correlation within the intermediate ranges. Mean scores for nonsurvivors indicated poor calibration. | Although both CPTs revealed the ability to discriminate patients at greater risk for mortality, precision and overall calibration were lacking. | An external validation of VGSSI and ATLAS scoring systems showed that these two CPTs are inaccurate in stratifying patients into the appropriate severity index score for severe CDI. In the application of the VGSSI and the ATLAS score, it is clear that there is an overall correlation of these models with mortality. | Low to moderate  | These tools are used to predict the *severity* of CDI.There is a wide range of CDI severity. Approximately 25% will progress to pseudo-membranous colitis, and in this high-risk group, another 1–8% will become fulminant CDI.  |
| **Islam et al., 201332** | Cohorting patients—recognize risk of reinfection | Data describing patient demographics, comorbidity, CDI severity, and treatment were collected for 248 CDI patients between October 2008 and June 2011. The primary outcome was symptomatic recurrence within 30 days of diagnosis. | A single hospital ward | A total of 158 (55.6%) CDI patients was admitted to the cohort ward. On multivariate analysis, cohorting (3.94; 95% CI 1.23 to 12.65; p=0.021) and urinary infection (4.27; 1.62 to 11.24; p=0.003) were significant predictors of recurrence. | Not provided | Patients admitted to a *C. difficile* cohort ward may be at increased risk of recurrence because they are at increased risk of reinfection. Study suggests that hospitals using cohort wards to control *C. difficile* should manage patient flow through the cohort to minimize this risk. | Low to moderate  | None |
| **Kassam et al., 201661** | CDI-related mortality prediction tool to prevent CDI mortality: *C. difficile* Associated Risk of Death Score (CARDS) | Retrospective analysis of United States 2011 Nationwide Inpatient Sample (NIS) database. All CDI-associated hospitalizations were identified using discharge codes (ICD-9-CM, 008.45). Predictive properties of model discrimination were assessed using the c-statistic and validated in an independent sample using the 2010 NIS database. | A large U.S. database, 374,747 cases with an associated diagnosis of CDI | The overall risk score in the cohort ranged from 0 to 18. Mortality increased significantly as CARDS increased. CDI-associated mortality was 1.2% with a CARDS of 0 compared with 100% with a CARDS of 18. The model performed similarly in the validation cohort. The severity scoring system had a comparable performance with a c-statistic of 0.77. | Not provided | The CARDS model displayed good discriminative ability, which was validated in an independent CDI cohort. Age has been identified as a risk factor of initial CDI development and CDI-associated mortality. ICU admission was also a strong independent predictor of CDI-associated mortality (odds ratio 5.23, 95% CI, 4.79 to 5.72). A number of chronic comorbidities are important predictors of CDI-associated mortality. Inflammatory bowel disease, malignancy, and liver disease were all independently identified to increase the odds of CDI-associated death in the model. | Low | None |
| **Koo et al., 201438** | Taking into account false positives for real-time PCR for *Clostridium difficile*-associated disease (CDAD) detection  | CDAD rates were compared before and after real-time PCR implementation. After real-time PCR introduction, all hospitalized adult patients were screened for *C. difficile* by testing a fecal specimen by real-time PCR, toxin enzyme-linked immunosorbent assay, and toxigenic culture. The study included 199 enrolled hospital subjects.  | A 600-bed university hospital in Houston, TX | CDAD hospital rates significantly increased after changing from cell culture cytotoxicity assay to a real-time PCR assay; 199 hospitalized subjects were enrolled, and 101 fecal specimens were collected*. C. difficile* was detected in 18 subjects (18%), including 5 subjects (28%) with either definite or probable CDAD and 13 patients (72%) with asymptomatic *C. difficile* colonization. | The difficulty in interpreting the clinical significance of *C. difficile* detected by NAATs is emphasized by recent studies describing the importance of confirmation of *C. difficile* toxin production. In spite of the high sensitivity of NAATs for *C. difficile* detection, PCR assays cannot distinguish asymptomatic colonization from symptomatic disease; i.e., there are false positives | Study reports that most healthcare-associated diarrhea is not attributable to CDAD, and the prevalence of asymptomatic *C. difficile* colonization exceeds CDAD rates in healthcare facilities. PCR detection of asymptomatic *C. difficile* colonization among patients with non-CDAD diarrhea may be contributing to rising CDAD rates and a significant number of CDAD false positives. PCR may be useful for CDAD screening, but further study is needed to guide interpretation of PCR detection of *C. difficile* and the value of confirmatory tests. A gold standard CDAD diagnostic assay is needed. | Moderate  | Most subjects identified with *C. difficile* were asymptomatic, irrespective of the detection method, including 8 of 12 (67%) *C. difficile-*positive subjects by PCR. The only significant difference between subjects with CDAD and *C. difficile-*colonized patients was the mean number of stools passed in the previous 24 hours. Limitations of this study include enrollment of 51% of eligible patients and fecal specimen collection from only half of enrolled subjects. |
| **Kuntz et al., 201448** | Tool to predict risk of CDI after an outpatient visit | Developed and validated a prognostic risk score to predict CDI risk for individual patients following an outpatient healthcare visit. A cohort of Kaiser Permanente Northwest (KPNW) patients with an index outpatient visit between 2005 and 2008, and identified CDI in the year following that visit. Researchers applied Cox regression and synthesized a priori predictors into a CDI risk score, which was validated among a Kaiser Permanente Colorado (KPCO) cohort. They calculated and plotted the observed 1-year CDI risk for each decile of predicted risk for both cohorts. | Cohort of 356,920 patients from a health system | Among 356,920 KPNW patients, 608 experienced CDI, giving a 1-year incidence of 2.2 CDIs per 1,000 patients. The Cox model differentiated between patients who do and do not develop CDI: there was a c-statistic of 0.83 for KPNW. The simpler points-based risk score, derived from the Cox model, was validated successfully among 296,550 KPCO patients, with no decline in the area under the receiver operating characteristic curve: 0.785 (KPNW) vs. 0.790 (KPCO).  | Not provided | The predicted risk for CDI agreed closely with the observed risk. The CDI risk score used data collected during usual care to successfully identify patients who developed CDI, discriminating them from patients at the lowest risk for CDI. The prognostic CDI risk score provides a decision-making tool for clinicians in the outpatient setting. The patient characteristics that contributed >30 points to the risk score, indicating an approximate doubling of risk, were: age 55 years and older (38 to 100 points, depending on age category); hospitalization of 7 days (37 points); liver disease (47 points); inflammatory bowel disease (43 points); and cephalosporin use (38 points) or clindamycin use (58 points). | Low | None |
| **Lanzas and Dubberke, 201420** | Screening patients at admission to detect asymptomatic *C. difficile* carriers and placing positive patients into contact precautions | An agent-based transmission model for *C. difficile* that incorporates screening and contact precautions for asymptomatic carriers in a hospital ward.Simulation of scenarios that vary according to screening test characteristics, colonization prevalence, and type of strain present at admission. | Electronic data were collected retrospectively from six medicine wards at Barnes-Jewish Hospital in St. Louis, Missouri | On average, testing for asymptomatic carriers reduced the number of new colonizations and hospital-onset (HO)-CDI cases by 40% to 50% and 10% to 25%, respectively, compared with the baseline scenario. Test sensitivity, turnaround time, colonization prevalence at admission, and strain type had significant effects on testing efficacy. | Not provided | Screening patients at admission to detect and isolate asymptomatic carriers could decrease the number of new colonizations and HO-CDI cases at the ward level. Simulations indicated that tests with a sensitivity greater than 90% and turnaround times less than 2.5 days could reduce the number of secondary new colonizations (and subsequent CDIs) caused by asymptomatic carriers. Additional research is needed to determine the costs, feasibility, and impact of screening on patient outcomes. | Low to moderate  | Simulation: “The contribution of symptomatic cases to transmission and new infection is likely to be lower than previously thought, and the likelihood of transmission and infection appears to also be *strain specific.*” |
| **Longtin et al., 201619** | Detecting and isolating *C. difficile* asymptomatic carriers at hospital admission | Controlled quasi-experimental study between November 19, 2013, and March 7, 2015; 7,599 patients screened at admission.  | A 354-bed Canadian acute care facility | During the intervention, 38 patients (3.0 per 10,000 patient-days) developed an HA CDI compared with 416 patients (6.9 per 10,000 patient-days) during the pre-intervention control period (p<0.001). The researchers estimated that the intervention had prevented 63 of the 101 (62.4%) expected cases. By contrast, no significant decrease in HA-CDI rates occurred in the control groups. |  Not provided | The cost-benefit of this strategy is unknown, but preliminary estimates suggest that the intervention may be cost effective. The intervention cost U.S. $130,000 over 17 periods and prevented approximately 63 cases. Because each case costs U.S. $3,427 to $9,960, the savings in averted CDI (U.S. $216,000 to $627,000) are greater than the costs of the intervention. | Low | Context: “Present guidelines do not recommend screening and isolating asymptomatic carriers.” |
| **Maghdoori and Moghadas, 201721** | Screening at the time of hospital admission, and screening in-hospital patients with potential exposure to *C. difficile*, to detect colonized/ asymptomatic patients (in the context of imperfect patient isolation) | Stochastic modeling for the transmission dynamics of CDI in a hospital ward. Simulation of various scenarios for detection and isolation of colonized patients. Model incorporated several parameters representing the level of patient screening, effectiveness of isolation, treatment failure, and level of susceptibility to infection. | A hospital ward with 50 beds (simulation) | When the effectiveness of patient isolation was 100%, the daily incidence of *C. difficile* was reduced by over 79% (95% CI, 78% to 79.6%) as a result of 92.5% *rapid* screening *at the time of hospital admission*. For isolation with less than 100% effectiveness, the benefits of screening and detection of colonized patients were reduced as a result of within-ward transmission.Compared with the results for rapid testing, results that take 2 days (without patient isolation) significantly lowered the effect of admission screening on reducing the prevalence of CDI.When screening 90% of *in-hospital patients starting on day 100*, there was an increasing trend in the percentage reduction of *C. difficile* incidence over time, reaching levels over 76%. | Findings indicate that if infection control measures are implemented inefficiently, within-ward transmission can potentially offset the benefits of patient screening. | The analysis found that if rapid screening of patients at the time of hospital admission and screening of in-hospital patients are implemented individually, then the former would always outperform the latter in terms of reducing the prevalence and incidence of CDI irrespective of the reproduction number, time delay in the release of laboratory tests, or effectiveness of patient isolation. Model shows that impact of screening at admission or day 100 is dramatically reduced when test results take 2 days.  | Moderate  | Study is based on several simulations.Addresses the issue of asymptomatic carriers in CDI transmission and suggests screening for asymptomatic carriers may be effective under certain conditions.  |
| **Moehring, et al., 201340** | Change from nonmolecular to molecular testing techniques—impact on surveillance | Comparison of the relative change in incidence rate (IRR) of healthcare facility-associated (HCFA) CDI among hospitals in the Duke Infection Control Outreach Network before and after the date of switch from nonmolecular tests to polymerase chain reaction (PCR) using prospectively collected surveillance data from July 2009 to December 2011. Data from 10 hospitals that switched and 22 control hospitals were included. Individual hospital estimates were determined using Poisson regression. 1,805 cases of CDI over 4,038,447 patient days. | 32 hospitals in the Duke Infection Control Outreach Network | For those hospitals that switched to PCR, mean incidence rate of HCFA CDI before the switch was 6.0 CDIs per 10,000 patient-days compared with 9.6 CDIs per 10,000 patient-days after the switch. After adjustment in the mixed-effects model, the overall IRR comparing CDI incidence after the switch to before the switch was 1.56 (95% CI, 1.28 to 1.90). Time-trend variables did not reach statistical significance.Hospitals that switched from nonmolecular to molecular tests experienced an approximate 56% increase in the rate of HCFA CDI after testing change. | Improved test sensitivity because of the change to molecular diagnostic testing can produce both positive and negative effects. A molecular test is more expensive to implement, may cause confusion among ordering providers, and may be overused because of its novelty. Also, the more sensitive test may be “too good” at identifying patients who are colonized but not truly infected with *C. difficile*.  | Study shows that increase in CDI rates in the United States up to 2009 were due at least in part to “surveillance bias” (e.g., changing definitions and new testing methods). The purpose of this study was to adjust for time-dependent factor and isolate the impact of the change in testing method. All 10 hospitals that switched to PCR testing used the Cepheid Xpert *C. difficile* assay (Xpert CD assay; Cepheid).In the context of testing for potentially transmittable diseases within the hospital setting, the improved sensitivity of molecular tests allows infected and colonized patients to be rapidly and reliably identified.,. | Low to moderate  | Centers for Disease Control and Prevention (CDC) National Healthcare Safety Network surveillance definitions were used to identify incident cases of community-onset HCFA and HO HCFA CDI. The study period corresponds with introduction of the 2008 change in CDC surveillance definitions for CDI, which included source type interpretations. should be noted. In fact, two hospitals in the study saw a numerical decrease in their incidence rates after the switch. |
| **Mostafa et al., 201829** | Factors for conversion from negative to positive PCR CDI test | A retrospective chart review of 20,866 laboratory test orders (2 years) for *C. difficile* PCR was conducted. The test result, clinico-pathologic patient features, and previous test results were recorded. Univariate and multivariate analysis were conducted to compare patients with initial and repeat negative results (n=248) with a group of patients with conversion from negative to positive results within 7 days. | Medical college and diagnostic laboratory | Among these charts, 1,637 (8.0%) were tests repeated within 7 days of previously valid test result. Based on only single repeat test orders, 970 (59.3%) followed an initial negative and 554 (33.8%) followed an initial positive test result. An additional 113 (6.9%) tests were repeated more than once within 7 days of the original test. Patients with a history of *C. difficile* confirmed by PCR within the 60 days prior to initial test were 19 times more likely to have a repeat positive result within 7 days of a negative result (95%, CI, 6.64 to 54.17, p<0.001). Conversely, patients with history of any antibiotic therapy within 14 days prior to initial test were 3.9 times more likely to have a repeat negative result (95% CI, 1.6 to 10.0, p=0.003). | Not provided | Identification of prior *C. difficile* infection as the only factor significantly correlated with conversion from negative to positive *C. difficile* test result within 7 days aids in selective test use and reduces the costs associated with unnecessary laboratory testing. The study demonstrates a potential for cost savings. Over a 2-year period, they found that 8% of tests were repeated within 7 days of a valid result, with an estimated cost of $61,537.50. Limiting repeat testing within 7 days to only those patients with a history of CDI within the previous 60 days would reduce this cost by ~90%. | Low to moderate | None |
| **Napierela et al., 201324** | PCR testing | Pre/post. The 20-month interval of *C. difficile* toxin A/B EIA testing that directly preceded commencement of *C. difficile* tcdB PCR was reviewed, as well as the first 20 months of PCR testing. | Three hospitals with 166, 538, and 260 beds | All three hospitals experienced significant reductions in healthcare-associated CDI upon introduction of molecular diagnostics (p≤0.05). Site-specific *C. difficile* testing volume decreased by 32.5–53.9% following implementation of tcdB PCR. | Not provided | These data suggest a strong influence of *C. difficile* toxin testing modality on healthcare-associated CDI. Conversion from *Clostridium difficile* toxin A/B EIA to tcdB PCR for diagnosis of CDI resulted in significant decreases in laboratory testing volume, reducing the workload. There were generally unchanged *C. difficile* toxin detection rates.  | Low  | None |
| **Planche et al., 201314** | Toxin (cytotoxin assay) testing as a CDI reference method | Prospective, observational multicenter study, cytotoxigenic culture and cytotoxin assays on 12,420 fecal samples in four U.K. laboratories. Also performed tests that represent the three main targets for CDI detection: bacterium (glutamate dehydrogenase), toxins, or toxin genes. Use of routine blood test results, length of hospital stay, and 30-day mortality to clinically validate the reference methods. Data were categorized by reference method result. | Four U.K. laboratories | A multivariate analysis accounting for potential confounders confirmed the mortality differences between groups 1 and 3 (odds ratio 1.61, 95% CI, 1.12 to 2.31). Multistage algorithms performed better than did standalone assays. In more than 6,000 patients with diarrhea, no increase in mortality occurred when a toxigenic *C. difficile* strain alone was present (cytotoxigenic culture positive, cell cytotoxin assay negative). By contrast, toxin (cell cytotoxin assay) positivity was associated with clinical outcome. Other clinical indicators were worse for cell cytotoxin assay-positive cases, but no difference was noted between cytotoxigenic culture-positive, cell cytotoxin assay-negative cases, and negative controls. | Not provided | Researchers found that toxin (cell cytotoxin assay) positivity was associated with clinical outcome and state that this reference method (of the three groups) best defines true cases of *C. difficile* infection. A positive cell cytotoxin assay indicates that the diarrhea was probably caused by CDI infection, whereas a positive cytotoxigenic culture indicates that a patient could be infectious even though the diarrhea might have resulted from another cause. A new diagnostic category of potential *C. difficile* excretor (cytotoxigenic culture positive but cytotoxin assay negative) could be used to characterize patients with diarrhea that is probably not due to *C. difficile* infection. | Low  | Highly technical.Article looks at predictor of disease severity.Background: Cytotoxigenic culture detects toxigenic CDI and gives a positive result more frequently (because of colonization, which means that individuals can have the bacterium but no free toxin) than does the cytotoxin assay, which detects preformed toxin in feces. |
| **Reigadas et al., 201527** | Systematic testing of diarrheal stool for CDI regardless of clinician request | Prospective study in which systematic testing for toxigenic *C. difficile* on all diarrheic stool samples was performed regardless of the clinician’s request. A total of 3,673 unformed stool samples from patients age >2 years was processed for detection of toxigenic *C. difficile*. | A 1,550-bed hospital | Testing found 249 episodes of CDI. Of these, 45 episodes (18.1%) were excluded because they did not fulfill the criteria for diarrhea (3 unformed stools/24 h). Therefore, 204 CDI episodes met the inclusion criteria (CDI episodes in patients age >2 years); of these, 178 had raised clinical suspicion and 26 (12.7%) had no clinical request for toxigenic *C. difficile* testing. Community-acquired cases and young age were risk factors for clinical underdiagnosis. | Not provided | The introduction of a systematic search for toxigenic *C. difficile* in all diarrheic stools arriving at a microbiology laboratory reveals a significant proportion of unsuspected cases and provides a more complete picture of the situation of CDI in a nonselected population. The main risk factors for lack of clinical suspicion were community-associated CDI and young age. In this study, 31.4% of CDI patients had not previously received antibiotics.  | Low to moderate | None |
| **Saab et al., 201533** | CDI screening of hospitalized patients with cirrhosis | A Markov model was used to compare costs and outcomes of two strategies for the screening of CDI. The first strategy consisted of screening all patients for CDI and treating if detected (screening). In the second strategy, only patients found to have symptomatic CDI were treated (no screening).  | Hospital simulation | The results of the model showed that screening for CDI was consistently associated with improved healthcare outcomes and decreased healthcare use across all variables in the one- and two-way sensitivity analyses. Using baseline assumptions, the costs associated with the no-screening strategy were 3.54 times those of the screening strategy. Moreover, the mortality for symptomatic CDI was lower in the screening strategy than the no-screening strategy. | Not provided | Evidence demonstrated that cirrhotic patients may be particularly affected by CDI. The results of the study showed that screening and treating *C. difficile* in asymptomatic patients are not cost effective but cost saving. | Moderate | None |
| **Schroeder et al., 201443**  | PCR or GDH plus on-demand PCR as most cost-effective diagnostic strategies | Decision analysis from the hospital perspective to compare multiple CDI testing algorithms for adult inpatients with suspected CDI, assuming patient management according to laboratory results; 10,000 symptomatic adults | Hospital simulation | A cost-benefit analysis (including estimated costs of missed cases) favored standalone on-demand PCR (vs. batch PCR) in most settings but favored on-demand PCR preceded by lateral-flow testing if a missed CDI case resulted in less than $5,000 of extended hospital stay costs and <2 transmissions, if lateral-flow GDH diagnostic sensitivity was >93% or if the symptomatic carrier proportion among the toxigenic culture-positive cases was >80%. These results can aid guideline developers and laboratory directors who are considering rapid testing algorithms for diagnosing CDI. | Not provided | This economic evaluation found that rapid testing is likely to be cost saving and more effective relative to the other technologies. Under most reasonable scenarios, standalone on-demand PCR as a one-step test is the strategy that minimizes false-negative results and costs to the healthcare system. However, where costs of a missed CDI diagnosis are minimal, where lateral-flow GDH/on-demand PCR or lateral-flow GDH-Tox/on-demand PCR can be performed with high diagnostic sensitivity, or where the symptomatic carrier proportion is high, testing with lateral-flow GDH or lateral-flow GDH-Tox before on-demand PCR is a justifiable option. | Moderate | None |
| **Silva et al., 201728** | PCR testing *plus* clinical assessment to diagnose CDI | A matched case-control study was conducted on inpatients in a tertiary care center. The first 50 patients with diarrhea and a positive PCR were identified as cases. Control patients were hospitalized patients receiving antibiotics, but with no diarrhea, housed in a room as close as possible to each case during the same admission time. A convenience sample of healthcare workers who cared for *C. difficile*-infected patients was also tested. | A tertiary care center. a 670-bed facility in the city of Sao Paulo, Brazil | There were two positive PCR results for *C. difficile* in controls (4.1%). None of the healthcare workers were positive for *C. difficile* by PCR. There was no difference between groups with respect to overall antibiotic use before the requested PCR for *C. difficile* (p=0.359). Most cases had a high proportion of gastrointestinal disorders (71.4%) compared with control (8.2%), p<0.001. | Not provided | The only non-antimicrobial predictor for CDI was gastrointestinal symptoms (p<0.001). Recommend assessing patients for diarrhea and interpreting laboratory results considering the clinical setting and the likelihood of other etiologies. The significance of a positive PCR result creates difficulties for clinical interpretation, due to the large number of positive tests from individuals without disease. According to the study, the use of molecular tests alone to diagnose CDI, without the toxin or host response tests, will likely lead to an excessive number of positively diagnosed cases, excessive treatment, and increased healthcare costs. | Low to moderate | Background: The diagnosis of CDI increases concern that asymptomatic carriers of toxigenic *C. difficile* may be diagnosed with CDI.  |
| **Stites et al., 201646**  | A predictive model that identifies patients at high risk for CDI at the time of hospitalization.This approach to early identification was evaluated to determine if it could improve upon a pre-existing antimicrobial stewardship (AMS) program.The hospital’s AMS program was administered as part of routine care, consistent with the guidelines of the Infectious Diseases Society of America. | Logistic regression and ROC curve analyses were used to develop an analytic model to predict risk for CDI at the time of hospitalization in a retrospective cohort of inpatients. The model was validated in a prospective cohort. Concurrence between the model’s risk predictions and a pre-existing AMS program was assessed. This cohort study analyzed electronic medical record (EMR) data from 42,120 patient admissions retrospectively in 2014, and prospectively for 10,990 admissions between July and September 2015.  | A large safety-net hospital in Philadelphia, PA (inner city) | The model identified 55% of patients who later tested positive as being at high risk for CDI at the time of admission. One in every 32 high-risk patients with potentially modifiable antimicrobial risk factors tested positive for CDI. Half (53%) tested positive before meeting the risk criteria for the hospital’s AMS program (c-statistic 0.77, 95% CI, 0.69 to 0.84). The model was faster than the AMS program. One in four patients in the highest risk category at the time of admission later experienced one or more of the AMS program antimicrobial risk factors during hospitalization. Approximately half (53%) tested positive after being identified by the PIPAR model but before meeting the criteria for the AMS program. All results were similar in the prospective cohort. | Over half of the patients who tested positive (55%) were identified at the time of admission by the PIPAR model as “very high risk” (highest of six categories). Approximately 2 in every 100 of these patients tested positive for CDI while hospitalized. (Thus, almost half were not identified as the highest risk, although still more accurate and timely than the existing system.) | Identification of patients predisposed to CDI at the time of admission would allow the AMS program to target high-risk patients earlier than current standard practice, which relies on retrospective chart reviews, and to use multiple strategies. By using the risk data to identify patients proactively, the AMS program could implement a prospective control system to ensure that antimicrobial therapy is appropriate at the time of initiation, including choice of agent, dose, and duration. | Low | Testing criteria: The laboratory only tested samples from patients with more than three liquid stools within a 24-hour period. |
| **Tabak et al, 201547**  | An HO-CDI predictive model using electronic health records clinical data present at time of admission | Retrospective data analysis of 78,080 adults discharged from six acute care hospitals between January 1, 2007, and June 30, 2008; 323 HO-CDI cases (including 310 nonrecurrent and 13 recurrent CDIs) were identified. A logistic regression model to predict the risk of HO CDI and validation of the model using 1,000 bootstrap simulations. | Six U.S. acute care hospitals | About 21% patients within the higher risk strata accounted for 65% of all HO-CDI cases. The logistic regression model yielded 14 independent predictors, including hospital community-onset CDI pressure, patient age ≥65, previous healthcare exposures, CDI in previous admission, admission to the ICU, albumin ≤3 g/dL, creatinine >2.0 mg/dL, bands >32%, platelets ≤150 or >420 109/L, and WBC >11,000 mm3. The model had a c-statistic of 0.78 (95% CI, 0.76 to 0.81) with good calibration. For 79% of patients with risk score of 0–7, there were 19 HO CDIs per 10,000 admissions; for patients with risk score of 20+, there were 623 HO CDIs per 10, 000 admissions (p<0.0001) | Not provided | Using clinical parameters available at the time of admission, this HO-CDI model displayed good predictive ability. It may have utility as an early risk identification tool for HO-CDI preventive interventions and outcome comparisons. Application of the risk score needs to be tested prospectively, preferably in hospitals with advanced electronic health records. The number needed to treat with an intervention to prevent one case of HO CDI will be required to determine the overall cost-effectiveness of the tool. | Low | There are risk factors due to the care process (e.g., hospital antimicrobial exposure) but also those present on admission. The researcher asserted that on-admission risk stratification may help with prevention. |
| **Van Beurden et al., 201762** | Three published prediction tools for patients at risk of a complicated course of CDI.The three models were from: Hensgens (2014), Na (2015), and Welfare (2011). A course of CDI was considered complicated if any of the following criteria were met within 30 days after the diagnosis of CDI: (1) death as a direct or indirect consequence of CDI, (2) admission to the ICU for treatment of CDI or its complications, (3) surgery (colectomy) for toxic megacolon, perforation or refractory colitis. | The validation cohort comprised 148 patients diagnosed with CDI between May 2013 and March 2014. During this period, 70 endemic cases of CDI occurred as well as 78 cases of CDI related to an outbreak of *C. difficile* ribotype 027. Model calibration and discrimination were assessed for the three prediction rules.To quantify how close predictions are to the actual outcome (calibration), the authors plotted the observed number of complicated cases against the predicted number of complicated CDI courses in the simplified risk categories provided by the original studies. | A 750-bed tertiary care center in Amsterdam | For those patients diagnosed with CDI due to nonoutbreak strains, the prediction model developed by Hensgens performed the best, with an AUC of 0.78. For entire cohort, AUC was 0.68. This prediction model can therefore be used in an endemic setting to identify patients at risk for CDI complications, aiding clinicians in deciding which patients to monitor closely for CDI-related complications. In conclusion, the study shows that a prediction rule can only be used in a cohort comparable with the derivation cohort. | The performance of all three prediction models was poor when applied to the total validation cohort with an estimated AUC of 0.68 for the Hensgens model, 0.54 for the Na model, and 0.61 for the Welfare model. | Early identification of patients at risk of a complicated course or death could help clinicians inform patients and might help doctors guide antibiotic treatment. All three prediction models performed poorly when validated using the total cohort, which included CDI cases from an outbreak as well as endemic cases. The prediction model of Hensgens performed relatively well for patients diagnosed with CDI due to nonoutbreak strains, and this model may be useful in endemic settings. | Low to moderate  | Search of PubMed and Embase for studies on prediction tools for a severe or complicated course of CDI up to February 2016 (Appendix A). Selected studies that (1) predicted at least one relevant outcome (i.e., severity, complications, mortality) and (2) developed a prediction model or risk score. |
| **Van der Wilden, 201449** | A risk scoring system (RSS) for patients at risk of developing fCDC (fulminant *C. difficile* colitis) | All patients (746) with *C. difficile* colitis admitted to Massachusetts General Hospital were prospectively enrolled in a specific database aiming to collect data on *C. difficile* infections. Various criteria/weighted risk factors were collected. Univariate analysis was performed to compare patients with and without fCDC. | Massachusetts General Hospital | The RSS successfully discriminates patients with *C. difficile* infection from those who have fCDC (AUC, 0.98). Calibration was low (Brier score of 0.019), indicating that the possibility of developing fCDC could be estimated accurately. A cutoff of 6 points was used to divide patients at high risk of developing fCDC, which classified 97.9% of patients correctly. In combination with a high specificity (88.4%) and excellent negative predictive value (99.8%), this scoring system proved it has the potential to be used at the bedside in order to safely rule out the possibility of fCDC. | The positive predictive value of 36.7% is low and should be considered against the background of its estimation in a low-prevalence setting (6.4% of total cohort was diagnosed with fCDC). | The researchers believe that the next step would be to externally validate the RSS to allow widespread implementation. | Moderate  | The RSS included four variables: Age >70 years, WBC ≥20.000/µL or ≤2,000/µL, cardiorespiratory failure (defined as CDC-related vasopressor and/or mechanical ventilation requirement), and diffuse abdominal tenderness on physical exam.  |