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Improving *C. difficile* Diagnosis: Why Two-Step Algorithm Testing Makes a Difference

The two-step algorithm for *C. diff* improves diagnostic accuracy, reduces unnecessary treatments, supports antimicrobial stewardship, and helps avoid overdiagnosis-related penalties

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Clostridioides difficile (*C. diff*) infections (CDI) are among the most prevalent hospital-acquired infections, but accurately diagnosing them continues to be a challenge. Nucleic acid amplification testing (NAAT) methods frequently result in overdiagnosis, leading to unwarranted treatments and possible penalties for healthcare providers.

A two-step algorithm approach presents a solution that greatly enhances diagnostic accuracy and provides operational and financial advantages.

Current guidelines: Two-step algorithm to include screening and toxin testing

To ensure patients receive appropriate diagnosis and treatment for *C. diff* infection, the 2021 American College of Gastroenterology (ACG) Clinical Guidelines and the 2018 Infectious Diseases Society of America (IDSA)/Society for Healthcare Epidemiology of America (SHEA) Guidelines emphasize the importance of a multistep algorithmic approach comprised of a sensitive screening test, such as glutamate dehydrogenase (GDH) or NAAT, combined with the specific toxin EIA.

GDH vs NAAT: Clinically equivalent sensitivity

Researchers have compared the results of GDH screening, NAAT, and algorithm methods to laboratory reference standards and clinical symptoms and found that GDH and NAAT demonstrated clinically equivalent sensitivity and are equally appropriate as an initial screening test to rule out CDI. NAAT testing methods detect the presence of *C. diff* toxin genes but cannot distinguish between asymptomatic carriers and patients with active disease.

This fundamental limitation leads to overdiagnosis and subsequent overtreatment when NAAT is used alone and underscores the need to include the sensitive toxin test as part of a CDI testing algorithm.

NAAT testing alone overdiagnoses CDI by approximately 58 percent, and among hospitalized adults, although 21 percent tested positive by NAAT, only 44.7 percent of these patients had toxins detected by clinical toxin tests. Most telling, virtually all CDI-related complications and deaths occurred in patients with positive toxin immunoassay results, while patients with positive NAAT but negative toxin tests had outcomes comparable to patients without *C. diff* by either method.

Failed approaches: NAAT alone or with institutional criteria

Many facilities have attempted to address overdiagnosis by implementing institutional criteria for sample acceptance or by relying on NAAT testing alone. Unfortunately, these approaches continue to result in overdiagnosis.

NAAT testing alone, while offering rapid results (typically less than one hour), cannot differentiate between colonization and active infection. This speed comes at the cost of clinical accuracy, leading to unnecessary treatments and inflated infection rates.

Institutional criteria for sample acceptance (such as requiring liquid stool) help somewhat but still fail to address the fundamental limitation of NAAT testing: its inability to distinguish

between carriers and truly infected patients.

Two-step algorithm testing: Better patient care and reduced penalties

Two-step algorithm testing combines sensitive GDH screening testing with specific toxin enzyme immunoassay (EIA) results to confirm active infection rather than merely detecting the presence of *C. diff* bacteria.

Using a complete standalone two-step *C. diff* algorithm in a single EIA test device, actionable results can be provided simultaneously in 30 minutes. This ensures that only patients with active infections receive treatment, reducing unnecessary antibiotic use and potential side effects.

When using this two-step approach, one facility reported a 28 percent decrease in anti-CDI antibiotics after implementing improved testing.

Another concern for facilities is National Healthcare Safety Network (NHSN) penalties for reportable infections. Due to improved diagnostic accuracy, one academic medical center reported a 70 percent decrease in reportable CDI events after implementation.

Across multiple healthcare facilities, conversion to two-step testing was also associated with a 47 percent reduction in hospital-onset CDI incidence and a 37 percent reduction in CDI-specific antibiotic utilization.

The two-step approach effectively balances resource utilization with clinical accuracy, creating sustainable improvements in both infection control practices and healthcare economics, all while maintaining appropriate clinical care standards for patients. By implementing this testing methodology, healthcare facilities can significantly improve diagnostic accuracy, reduce unnecessary treatments, and enhance antimicrobial stewardship while avoiding regulatory penalties associated with overdiagnosis.

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