

## PRACTICE

## RATIONAL TESTING

## Diarrhoea after broad spectrum antimicrobials

*Clostridium difficile* infection needs prompt diagnosis to avoid risk of progression to colitis or to toxic megacolon. This article discusses which patients to test and how

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This series of occasional articles provides an update on the best use of key diagnostic tests in the initial investigation of common or important clinical presentations. The series advisers are Steve Atkin, professor, head of department of academic endocrinology, diabetes, and metabolism, Hull York Medical School; and Eric Kilpatrick, honorary professor, department of clinical biochemistry, Hull Royal Infirmary, Hull York Medical School. To suggest a topic for this series, please email us at [practice@bmj.com](mailto:practice@bmj.com).

A 60 year old man with advanced multiple sclerosis who lives in a nursing home presents with diarrhoea (watery stool five to seven times daily) and a temperature of 38.7°C. He has not vomited and is not constipated. He has no history of bowel disease but is prone to recurrent urinary tract infections and was recently treated with co-amoxiclav for another episode of diarrhoea. The diarrhoea started several days after the antibiotic finished. No other residents or staff members have had diarrhoea. Abdominal examination shows tenderness without distension, and active bowel sounds.

### What is the next investigation?

*Clostridium difficile* infection is an important cause of diarrhoea in patients who have recently received antimicrobials, irrespective of setting. *C difficile* has gained notoriety as a potentially fatal hospital acquired infection, but the overall number of cases in England has dropped substantially in the past two years, with most of the decline accounted for by cases in hospital patients.<sup>1</sup> The perception that *C difficile* infection is exclusively a “hospital problem” persists, perhaps leading to underdiagnosis of this infection in community settings.<sup>2</sup> A study of community onset *C difficile* infection conducted in a UK urban area reported an annual incidence of 29.5 cases per 100 000 population,<sup>2</sup> and in some UK areas cases of *C difficile* infection with onset in the community now outnumber those arising in hospitals (although some of the former will have been associated with recent admission to hospital).<sup>3</sup>

Broad spectrum agents, which include cephalosporins and fluoroquinolones such as ciprofloxacin, are more likely than narrower spectrum drugs to cause *C difficile* infection. Elderly patients are particularly at risk because immune function wanes as age increases and bowel organisms are highly complex, and antibiotic use further reduces the ability of commensal organisms to protect against colonisation by *C difficile*. Thus the Health Protection Agency in England recommends that microbiology laboratories should test all diarrhoeal stool specimens from patients ≥65 years for *C difficile*.<sup>4</sup> However, as the incidence of *C difficile* infection in patients younger than 65 years (most notably those aged 60-64 years) is increasing, this guidance also recommends testing stools from patients aged under 65 years if there is clinical suspicion (diarrhoea can begin after even a single antibiotic dose).<sup>4</sup>

If *C difficile* infection is not diagnosed promptly and treated appropriately, there is a risk of progression to colitis or to toxic megacolon and possible death. Additionally, failure to diagnose the infection may lead to inappropriate management of symptoms through use of antimotility drugs, which, according to current guidelines, should not be used in acute *C difficile* infection.<sup>4,6</sup> Furthermore, delay in a diagnosis can also increase the risk of additional cases developing in an institution such as a nursing home because introduction of appropriate precautions for infection control is hindered.

Clinicians should ask for a stool specimen from patients suspected of having *C difficile* infection as soon as is feasible and submit it promptly to the microbiology laboratory.

### Testing for *C difficile* toxin

Several techniques for the laboratory diagnosis of *C difficile* infection are available but the commonest methods rely on detection of *C difficile* toxin by using enzyme immunoassays and immunochromatographic assays.<sup>7</sup> These techniques are

### Learning points

*Clostridium difficile* infection in community settings may be underdiagnosed; consider this diagnosis in patients who develop diarrhoea while receiving, or after completing, a course of antibiotics

Although patients aged  $\geq 65$  years are at greatest risk of infection, the incidence in younger patients, especially in those aged 60-64, is increasing

If an initial toxin test for *C difficile* is negative but clinical features are still consistent with infection, then testing a second specimen is indicated

Sensitivity and specificity of individual tests for toxins are variable, and if you have a strong clinical suspicion of *C difficile* infection despite a negative toxin test, discuss with a microbiologist the possibility of using a combination of tests

Testing for cure after the resolution of symptoms and/or completion of antimicrobial treatment in *C difficile* infection is not indicated

rapid and easy to perform but are much more likely to yield false positive and false negative results. It is therefore important to consider submitting a second faecal specimen if clinical suspicion of *C difficile* infection remains in a patient who is still symptomatic and whose initial specimen was negative for the toxin.<sup>4</sup>

The risk of erroneous test results has led to recommendations that laboratories should not rely solely on a single, kit based assay for *C difficile* toxin testing and should instead use a combination of tests to increase specificity and sensitivity.<sup>7-8</sup> Nevertheless, the number and types of tests vary considerably among laboratories, as do diagnostic algorithms. If a patient is strongly suspected of having *C difficile* infection but their stools are negative for *C difficile* toxin on initial testing, a discussion with a microbiologist about further investigations would be valuable. These could include referral of the specimen to a laboratory that can test for *C difficile* toxin by examining its cytopathic effect on cell lines. This is a slower technique than the usual ones but is less likely to produce a false negative result. If the patient remains symptomatic it would be reasonable to start empiric antimicrobial treatment for *C difficile* infection pending the results of further investigations.

### Once *C difficile* infection is confirmed

Do an initial assessment of disease severity. There is no universally accepted definition of severe *C difficile* infection, although a temperature of  $>38.5^{\circ}\text{C}$ , peripheral white blood cell count of  $>15 \times 10^9/\text{L}$ , an acutely rising serum creatinine ( $>50\%$  above baseline), a raised serum lactate concentration, and severe abdominal pain have all been cited as indicators of severe *C difficile* infection.<sup>4-6</sup> Stool frequency is less reliable as an indicator in severe infection.

Review patients daily to check they are responding to treatment and receiving optimal supportive care.<sup>4</sup> Patients in the community whose symptoms are not improving or are worsening (especially if there are other complications such as a failure to maintain adequate hydration) may need to be admitted to hospital. Regular monitoring of the patient is particularly important given the emergence in Europe and North America of strains belonging to ribotype 027, which is considered to be associated with increased disease severity, slower response to treatment, and poorer overall outcome.<sup>9</sup>

Resolution of symptoms is sufficient to indicate therapeutic success; tests of cure for *C difficile* infection are not indicated, especially as toxin is often still detectable in the stools even after a patient becomes asymptomatic. However, if a patient recovers from infection but subsequently develops diarrhoea, test again for the toxin and other enteric pathogens as relapses or reinfections occur in as many as 20% of cases.

### Outcome

An initial faecal specimen was negative for *C difficile* toxin and other enteric pathogens. However, as the patient remained symptomatic a second specimen was submitted after discussion with a microbiologist. This specimen was examined using a combination of tests and was found to be positive for the *C difficile* toxin. As the patient had a high temperature, a marker for severe infection, he was treated with oral vancomycin according to guidelines (125 mg four times a day for 10-14 days). This drug was chosen in preference to the currently recommended treatment for non-severe *C difficile* infection: metronidazole (400-500 mg three times a day for 10-14 days).<sup>4-6</sup> He responded well to vancomycin. A specimen submitted to the laboratory to determine whether the patient was free of *C difficile* infection was not processed.

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