RATIONAL TESTING

Diarrhoea after broad spectrum antimicrobials

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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.

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

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.[1] The perception that *C difficile* infection is exclusively a "hospital problem" persists, perhaps leading to underdiagnosis of this infection in community settings.[2] 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,[2] 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).[3]

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*.[4] 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).[4]

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.[4-6] 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.[7] These techniques are 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.[4]

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

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 ≥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

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- Postural hypotension (*BMJ* 2011;342:d3128)
- Investigation of diarrhoea in a traveller just returned from India (*BMJ* 2011;342:d2978)
- Investigation of an incidental finding of eosinophilia (*BMJ* 2011;342:d2670)
- Investigating hyponatraemia (*BMJ* 2011;342:d1118)

should instead use a combination of tests to increase specificity and sensitivity.[7 8] 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°C, peripheral white blood cell count of $>15\times10^9$/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.[4-6] 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.[4] 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.[9]

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).[4-6] 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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10-MINUTE CONSULTATION

Otitis media with effusion ("glue ear")

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A mother brings her 5 year old son to your practice, concerned about his difficulty hearing her and his poor attentiveness in school. She is worried that his speech is not developing as quickly as his peers'. He recently had severe earache, which resolved when the ear started discharging. He was treated on that occasion with oral antibiotics. On examination the tympanic membrane appears grey with an absent light reflex.

What you should cover

- Focus on the duration of the child's symptoms and the impact on the child's life and schooling. A history of recurrent ear infections or upper respiratory tract infections is important. Ask about any aural discharge, particularly persistent foul smelling discharge
- Elicit key elements about disability, such as:
  - -Poor listening skills, especially in noisy environments such as classrooms. Parents often report having to repeat themselves and the child watching television at a very loud volume
  - -Indistinct speech or delayed language development
  - -Inattention, behaviour problems, and slow educational progress
  - -Hearing impairment, fluctuating over days or weeks
  - -Clumsiness or poor balance.
- Otitis media with effusion (OME) in children can be asymptomatic; if you see children regularly, consider this diagnosis if you identify any of the hearing, behavioural, or developmental features above. The following groups are also at increased risk of OME: those in day care; those with older siblings; those whose parents smoke; those with cleft palate, cystic fibrosis, or Down's syndrome; and those who bottle feed, or feed while supine.
- Examine the child's upper respiratory tract and ears: the tympanic membrane typically appears dull and grey. The stapes bone may appear more prominent, as the low pressure behind it retracts the drum. An air-fluid level may be visible behind the drum. OME often coexists with large adenoids, and therefore the child may be seen to mouth-breathe.
- Look out for two "red flag" features: *(a)* atypical otoscopy with persistent foul smelling discharge suggestive of cholesteatoma; and *(b)* excessive hearing loss or examination findings that may suggest an additional sensorineural hearing deficit. Both warrant urgent referral for specialist ear, nose, and throat assessment.
- Try to gain an impression of the child's speech and language developmental status during the initial consultation, although time pressures and the child's nervousness may prevent this. At age 2-3 years a child should be able to form very short sentences, name common objects, speak intelligibly most of the time, and follow two-stage commands. By age 4-5 years, children should understand most things that are said to them, construct long sentences about definite topics, and speak in an easily intelligible voice (difficulties with some sounds are normal).

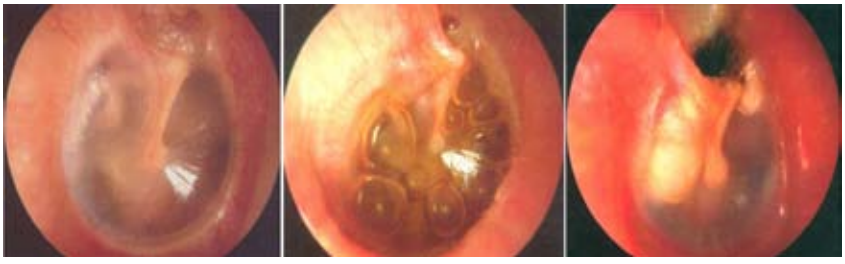
OTITIS MEDIA WITH EFFUSION ("GLUE EAR")

Eighty per cent of children under 10 years old will have had at least one episode of otitis media with effusion (OME) (figure). Bimodal peaks occur at age 2 and 5 years. The condition is often relapsing and remitting: an episode usually lasts for 6-10 weeks. In severe and persistent cases, permanent retraction and atrophy of the tympanic membrane can occur, occasionally leading to retraction pockets and ultimately cholesteatoma. However, the main concern in OME is the associated conductive hearing impairment, and the repercussions this can have for a child's education and speech and language development. The exact cause of the condition is not clearly understood , but it arises from eustachian tube dysfunction, causing chronically low pressure in the middle ear. This then leads to an inflammatory response in the middle ear mucosa, with production of fluid or "glue."

What you should do

- The role of primary care staff is to make the correct diagnosis, observe the patient, provide appropriate advice, and refer to an ear, nose, and throat specialist as indicated. When red flag symptoms are detected, we recommend that children referred as "urgent" cases are seen within two to three weeks. Many ear, nose, and throat departments offer a paediatric service that allows rapid access in such cases.
- Antibiotics, topical and systemic steroids, decongestants, mucolytics, and antihistamines are not recommended in the routine management of OME; there is no clearly effective medical treatment.[1] Surgical treatment in the form of insertion of a ventilation tube (grommet) is effective in some cases.[2]

This is part of a series of occasional articles on common problems in primary care. The *BMJ* welcomes contributions from GPs.



Appearances of the tympanic membrane. Left to right: normal; otitis media with effusion; cholesteatoma

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Should you or shouldn't you prescribe antibiotics for otitis media in children? http://bit.ly/hqTOhF

USEFUL RESOURCES

Medical Research Council Multicentre Otitis Media Study Group. Surgery for persistent otitis media with effusion: generalizability of results from the UK trial (TARGET). Trial of Alternative Regimens in Glue Ear Treatment. *Clin Otolaryngol Allied Sci* 2001;26:417-24

Information for patients

Glue ear (Patient UK)
—www.patient.co.uk/health/Glue-Ear.htm

Glue ear (ENT UK)
—www.entuk.org/patient_info/ear/glueear_html

Glue ear (National Deaf Children's Society)
—www.ndcs.org.uk/family_support/glue_ear/

- In deciding whether to refer to an ear, nose, and throat specialist a child in whom you have diagnosed OME, take into account the duration of symptoms, the impact of the child's hearing impairment on his or her daily life, and the parent's wishes. Encourage the child (if old enough) to express his or her feelings about the treatment options. Consider also concerns raised by the school or health visitor.
- The guidelines from the National Institute for Health and Clinical Excellence (NICE) on the management of OME recommend a period of "active monitoring" for three months to check that the symptoms are persistent.[2] Ideally, this would entail two objective measurements (pure tone audiometry) three months apart. However, a child with a suspected conductive hearing loss who has had audiometry on two separate occasions during a period of at least three months and has been observed for this period by their general practitioner can be referred for surgery without further delay.
- Reassure the parents that hearing loss caused by OME often resolves spontaneously and that the period of active observation should not affect this. Give advice for maximising the child's functional hearing—for example, the child should sit at the front of the class at school, people should speak directly to the child to enable lip reading, and background noise should be minimised as far as possible. If relevant, warn parents that exposure to cigarette smoke worsens the outlook.
- If you are greatly concerned about the child's development, an early referral for a hearing aid may be appropriate during the observation period and while on the waiting list for surgery. Hearing aids are used in children with Down's syndrome and OME or when surgery is contraindicated or declined.

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2 National Institute for Health and Clinical Excellence. Surgical management of children with otitis media with effusion (OME). (Clinical guideline 60.) 2008. www.nice.org.uk/CG060.

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Emergency in the cowshed

It is said that *prarabdha* (that part of your *karma* that cannot be altered) follows you wherever you go. Being an obstetrician, I tried to escape from my hectic medical practice to my guru's ashram, the Swami Rama Sadhak Grama in Rishikesh. But guess what? The mother of all mothers, a beloved cow named Kapila, was in trouble. She had delivered a female calf and had pushed the uterus out too.

I had never seen anything like this. A 20 kg mass that looked like a watermelon turned inside out lay beside her tail. Its surface bore large rounded bodies (cotyledons) covered with the membranes, which I removed. Two capable veterinarians drove up on their motorbike, and I felt reassured. Dr Sati drew up 4 mL of adrenaline (enough to kill four humans) and injected it locally to reduce blood loss and shrink the mass. An epidural was given in the coccygeal space. Then we rubbed ice over the uterus to reduce its size, so that we could replace it. The three of us struggled: one held the mass, while the others tried slowly to push the vaginal sleeve in. Two or three young yogis restrained the cow. We were almost halfway through when she gave a huge heave, and it was all out again.

Her bladder was full, so we evacuated it using a small needle, but there was no change in the size of the mass. We tried again and again, but in vain. The chief vet, Dr Joshi, struggled on despite having ankylosing spondylitis. Being the most experienced, he hit on another plan—this time he decided to replace the fundus first, contrary to medical (human) teaching. Sugar was sprinkled over the mass for its hygroscopic effect, while we waited to catch our breath more than anything else.

We called out to our guru, Swami Rama, to help us help poor Kapila. I had started to feel desperate. It had been over two hours, and we were all near exhaustion. The chief vet held the fundus and pushed his entire fist in. With all our skill, we slowly tried sliding the adjoining areas in. A good 20 minutes later, with careful pushing, we managed it. Jai Gurudev.

We placed three sutures to narrow the vulva, using a needle as thick as a pen. We quickly milked the cow to release the hormone oxytocin, which would help contract the uterus. Then we pushed and prodded her to stand, so that gravity could keep the uterus in place. The cow passed a huge amount of urine, and I knew we had made it. The calf quickly latched on, and all was well.

At the 6 pm post-op round, Kapila gave me a loving glance, as if to say, "Thank you, doctor."

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