

The Vale of Leven Hospital Inquiry

Expert Witness Report: Professor Ian R Poxton

To cover:

1. An outline of what *Clostridium difficile* is, how it is acquired, and its presentation.
2. Experience of and data on *Clostridium difficile* outwith the UK, drawing upon those areas which I am in a position to report.
3. Future developments in the treatment and prevention of *Clostridium difficile* infection.

1.1. What is *Clostridium difficile*?

C. difficile is a bacterium belonging to the genus *Clostridium*. The species belonging to this genus are Gram-positive, rod-shaped, anaerobic and spore forming. It is the latter two features, especially the ability to form spores, that are crucial in considering the role of *C. difficile* as a pathogen. Of the hundred or so species of *Clostridium* only a handful are common pathogens of humans, with a few others affecting animals. The pathogens include such infamous species as *C. tetani* (causes tetanus), *C. botulinum* (botulism) and *C. perfringens* (gangrene and food poisoning). A few others are rare pathogens, while the majority are involved in the decay and recycling of organic matter of animal and plant origin. These are found in the environment and also in the gut of man and other animals. Those that are pathogenic invariably produce potent exotoxins, which are the major determinants of their virulence.

Pathogenic strains of *C. difficile* normally produce two toxins (A and B; some only produce B) which are responsible for the symptoms of *Clostridium difficile* infections (CDI). The symptoms are the result of damage to the cells lining the gut and the induction of inflammation, with diarrhoea of varying severity being the outcome. In the last decade at least one hypervirulent strain has evolved. This is known as PCR ribotype 027 (also known as BI or NAP1 in North America). One of its properties, which is connected to its increased virulence, is that it produces higher levels of toxins than other commonly encountered strains. This is due to one of the genes which control toxin production being naturally "knocked out". However, it should be stressed that any toxin-producing strain of *C. difficile* has the potential to cause severe disease, and just because the 027 strain appears to be more dangerous, its specific detection, to the possible exclusion of other strains of perceived lower virulence, is a "blinkered" approach and should be avoided.

1.2. How is *C. difficile* acquired?

This is very simple. To acquire the organism i.e. for a patient to become colonised, spores must enter by the mouth and are usually transmitted there by fingers. [In the past there have been reports of acquisition by the rectal route by means of contaminated endoscopes or rectal thermometers. However, this should now never happen]. As vegetative bacteria (the form that grows in the gut and produces the toxin) are rapidly killed in air, it is only the spores that are infectious. The usual sources of spores are surfaces that have been contaminated with faeces – usually from a symptomatic patient. The diarrhoea is often described as “explosive” and it is easy to imagine how spores become airborne. Spores are also present in many environments – presumably originating from contamination with human or animal faeces/sewage. Note that many young animals, including human babies, commonly carry the organism harmlessly. The spores are extremely resistant to physical and chemical agents (including heat, dryness and alcohol), and can only be readily killed by means of chlorine-containing disinfectants (at least 1000 ppm chlorine) or removed (but not killed) by traditional thorough washing with detergents.

Many people are exposed to spores of the organism but few healthy individuals become colonised. Figures quoted for healthy people in the community are that up to 4% may carry the bacterium harmlessly. However, as mentioned above babies are commonly colonised (50-70%), and up to 50% of elderly people in hospital can carry the organism without symptoms. It is thought that healthy carriers are protected from developing symptoms by their ability to mount a protective immune response, but the mechanisms are still poorly understood. The normal healthy bacterial populations of the gut (gut microbiota or “flora”) usually prevent colonisation by their simple presence: out-competing the pathogen, and for true colonisation to take place this protective microbiota must be disturbed in some way. This is usually by administration of antibiotics – to treat an infection in the patient – thus opening a niche for *C. difficile* to colonise. As the spores are effectively biologically inert, they can only colonise after they germinate into vegetative cells. This occurs once they are in a favourable anaerobic (oxygen-free) environment without competition from normal components of the gut microbiota. It is thought that exposure to bile in the small intestine helps trigger germination so that when they reach the colon (large bowel) they are able to multiply and consolidate there.

1.3. What are the presentations of *C. difficile* infections?

As described above it is possible for *C. difficile* to colonise the gut and to produce toxins yet not cause any symptoms. Such carriers do pose a theoretical risk to other patients. However, as they are asymptomatic, they should not pose a major risk as long as they follow good personal hygiene especially when using toilet facilities. Screening of asymptomatic patients is not currently done anywhere as far as I know – mainly because of the unknown risks they pose and there are no methods of treating such patients

to “cure” them of the carried *C. difficile*. We only know such asymptomatic patients exist from research studies.

Symptomatic patients present with:

- Mild, self-limiting diarrhoea/simple colitis which can often be managed simply by removing the precipitating antibiotic
- More serious diarrhoea requiring treatment – usually with metronidazole (treatments will be discussed in 3 below)
- Pseudomembranous colitis
- Fulminant colitis, including toxic megacolon and a risk of perforation – which are life-threatening

The latter two require treatment with the best drug currently available – which is vancomycin, and assessment to see if surgical intervention is needed. If it is, it is best done as early as possible as surgical resection is often done too late.

All symptomatic cases require isolation, or cohort nursing in the case of multiple cases in an outbreak.

Several descriptions of the symptoms of CDI to define severity and prognosis have been published, but have been criticised for being over-complicated. Currently simplified definitions are being formulated so that a clinician can readily determine the severity of the disease. This has implications for treatment/patient management.

Health Protection Scotland has the following definitions

(<http://www.documents.hps.scot.nhs.uk/about-hps/hpn/clostridium-difficile-infection-guidelines.pdf>):

- Mild CDI is not associated with a raised white blood cell count (WBC); it is typically associated with mild diarrhoea (3 loose or liquid stools per day or more frequently than is normal for the person) and no systemic symptoms.
- Moderate CDI is associated with a raised WBC that is $<15 \text{ cell/mm}^3$; it is typically associated with moderate diarrhoea (typically 3 or more loose or liquid stools per day or more frequently than is normal for the person) and some systemic symptoms.
- Severe CDI is when a patient has two or more severity markers, e.g., temperature $> 38.5^\circ\text{C}$, WBC $> 15 \text{ cells/mm}^3$, creatinine $> 1.5 \times$ baseline.
- Life-threatening CDI includes hypotension, partial or complete ileus or toxic megacolon, or CT evidence of severe disease.

A real problem is that of recurrent disease:

Currently about 20% of patients suffer a relapse of symptoms following an initial cure to their primary episode of disease. In about half of these it appears that they may have been infected with a different strain of *C. difficile*. Infection with the hypervirulent 027/NAP1/BI strain appears to result in higher levels of relapse (~30%).

A patient who has already had one relapse will have a higher chance (45%) of suffering another or multiple relapses. Management of such patients is often extremely difficult.

2. The situation locally and elsewhere in the world

This section is based on both published and unpublished (confidential sources).

The UK is not alone in experiencing massive problems with CDI. Wherever it is looked for it is found, and it is a major healthcare-associated infection problem throughout the developed world.

The UK has led the field in surveillance. In both England & Wales (PHLS/HPA) and Scotland (SCIEH/HPS) voluntary schemes have been running since the early 1980s. Reporting became mandatory in 2006, and from April 2007 all acute NHS Trusts in England are required to report all cases of CDI in patients aged 2 years and over. In Scotland we now gather data for all those aged over 15 years and results are stratified between 15-64 and 65 and older.

Comparing data between countries is difficult as some simply measure total cases per country, while others use hospital admissions or patient days as the denominator. Of the countries doing active surveillance in Europe it is estimated that overall there is a mean of around 0.5-0.6 cases per 1000 patient days, but with levels of up to 10 per 1000 patient days reported. However, it is highly variable with generally lower figures from countries in southern Europe compared to northern ones. It is perceived that numbers of cases are stable or increasing, but with an acknowledged high level of under-reporting. Currently in Scotland the levels have decreased markedly from a high of almost 1.6 per 1000 patient days in 2007/8 to about 0.4 cases presently. Similar changes have been reported in the rest of the UK with a decrease of at least 50%, but levels appear to be plateauing. This decrease is the result of increased awareness with better infection control, cleaning and judicious use of antibiotics.

In our own studies in Lothian we have compared different medical specialties to see which patients are at most risk. We found that some groups e.g. renal patients and patients in intensive care, had rates of between 6 and 7 cases per 1000 occupied bed days, and these were higher than patients in medicine of the elderly wards, with rates of about 2 cases per 1000 occupied bed days [Reddy S, Taori S, Poxton IR (2010). Changes in laboratory and clinical workload for *Clostridium difficile* infection from 2003-2007. *Clinical Microbiology and Infection*. 16: 340–346].

It was in Canada and certain NE States in the US that the appearance of the hypervirulent 027/BI/NAP1 strain was first recognised. This was the strain that was subsequently shown to have caused problems in Stoke Mandeville and

other hospitals throughout England, Wales, Ireland, some parts of Scotland (notably at the Vale of Leven) and throughout much of NW Europe. It is now being found throughout the world. Unexpectedly some regions have not seen this strain; for example in SE Scotland/Edinburgh there has only been a single case back in the summer of 2008).

Generally surveillance schemes elsewhere in the world are in their infancy, and this is particularly true of the USA.

3. Prevention and Treatment – present and future

3.1. Prevention of CDI: current measures to prevent CDI include:

Adherence to good infection control measures:

- Isolation of symptomatic patient or cohort nursing during outbreaks
- Perform good hand hygiene – hand washing with soap and water
- Use appropriate personal protective equipment- gloves and gowns/aprons
- Cleaning of the patient environment with chlorine-based disinfectants (or H₂O₂ vapour for empty isolation wards)
- Use of care equipment dedicated to individual patient – BP cuffs, stethoscopes, thermometers, commodes
- Endoscopes to be cleaned in sporocidal disinfectants

Antibiotic stewardship to avoid undue exposure of patients to main risk factor:
Specific Health Protection Scotland Recommendations
(<http://www.documents.hps.scot.nhs.uk/about-hps/hpn/clostridium-difficile-infection-guidelines.pdf>)

- Stop any non-clostridial antimicrobial treatment in patients with CDI as soon as possible.
- Review frequency, duration and type of antimicrobial used, and avoid the use of high-risk agents (e.g. cephalosporins, broad-spectrum penicillins, fluoroquinolones and clindamycin) in patients at risk. Use these agents only when medically needed.
- Audit and feedback are efficient tools in changing the prescribing habits of medical and nursing staff.
- Antimicrobial prophylaxis should not be continued beyond 24 hours following an operative procedure. AMTs should audit administration of surgical prophylaxis.

Education of all healthcare workers in CDI is essential. There is an online tutorial with self assessment (written by the author of this report) now available from NHS Scotland Education (NES) at their HAI Learning Resources website. Patients and their visitors should also be offered basic education on hygiene.

3.2. Prevention of CDI: future measures

As well as strict adherence to the above there are several new measures that may be introduced in the future – but certainly not imminently. These include:

- The development of a vaccine to prevent CDI. It is being developed by Sanofi-Pasteur in France. It is likely to enter Phase 2 clinical trial in the next year or so.
- Various antibody-based passive immunotherapeutic measures are being developed. The most promising has completed Phase 2 trials and is now owned by Merck Inc who expect to put it through Phase 3 trials soon. It is based on two monoclonal antibodies that target the main virulence factors of *C. difficile* – toxins A and B. In the first instance, it is likely to be used to prevent recurrent disease rather than primary episodes. Other similar approaches are being designed which employ antibodies produced in animals, including egg and milk antibodies.

3.3. Treatment of CDI: Current

At present the only two fully recommended treatments for CDI are with the antibiotics metronidazole and vancomycin, and the FDA have only licensed the latter. The current European treatment guidelines are summarised below [Bauer MP, Kuijper EJ, van Dissel JT. European Society of Clinical Microbiology and Infectious Diseases (ESCMID). Treatment guidance document for *Clostridium difficile* infection (CDI). *Clin. Microbiol. Infect.* 2009; 15, 1067-1079].

1. Anti-peristaltic agents and opiates should be avoided.
2. In general, strive to use antibiotics covering a spectrum no broader than necessary and narrow the antibiotic spectrum of treatment after results of cultures and/or susceptibility tests become known.
3. Mild CDI (stool frequency < 4 times daily; no signs of severe colitis), clearly induced by the use of antibiotics, may be treated by stopping the inducing antibiotic. Observe patients closely for any signs of clinical deterioration and place on therapy immediately if this occurs.
4. Treatment for an initial episode and a first recurrence of CDI:
If oral therapy is possible:
 - non-severe: metronidazole 500 mg tid orally for 10 days
 - severe: vancomycin 125 mg qid orally for 10 days
 If oral therapy is impossible:
 - non-severe: metronidazole 500 mg tid intravenously for 10 days
 - severe: metronidazole 500 mg tid intravenously for 10 days + intra-colonic vancomycin 500 mg in 100 mL of normal saline every 4–12 h and/or vancomycin 500 mg qid by nasogastric tube
5. Colectomy should be performed to treat CDI in any of the following situations:
 - perforation of the colon
 - systemic inflammation and deteriorating clinical condition not responding to antibiotic therapy; this includes the clinical diagnoses of toxic megacolon and severe ileus. Colectomy should preferably be performed before colitis is very severe. Serum lactate may, inter alia, serve as a marker for severity (operate before lactate exceeds 5.0 mmol/L).
6. Treatment for a second recurrence of CDI and later recurrences:
If oral therapy is possible:

- vancomycin 125 mg qid orally for at least 10 days
 - consider a taper (for example, decreasing daily dose with 125 mg every 3 days)/pulse (for example, a dose of 125 mg every 3 days for 3 weeks) strategy
- If oral therapy is impossible:
- metronidazole 500 mg tid intravenously for 10–14 days plus retention enema of vancomycin 500 mg in 100 mL of normal saline every 4–12 h and/or vancomycin 500 mg qid by nasogastric tube
7. In all the above-mentioned cases, oral vancomycin may be replaced by teicoplanin 100 mg twice daily, if available.

Other treatments that have been used include

- The use of other antibiotics, but those licensed seem no better than the two standard drugs.
- Biotherapies to restore or protect the normal gut microbiota. These have included the use of proprietary probiotics such as yoghurt-based drinks, but there is no proof that these do any good. However, instillation of normal donor faeces into the gut by either the naso-gastric route or the rectal route – so-called “faecal transplantation”, appears to work extremely effectively – but is not very aesthetic!
- Several attempts have been made to develop toxin-binding agents. However, the most promising to date: Genzyme’s “Tolvamer” is not being developed further due to its failure to show superiority over vancomycin in two recent, large Phase 3 clinical trials.
- Immunotherapy with intravenous immunoglobulin (unselected antibody preparation obtained from pooled serum from blood donors), issued in the UK by the Blood Transfusion Service. It has not been officially trialled and its efficacy is debated.

3.4. Treatment of CDI: Future:

- Perhaps the most promising drug to treat CDI is a new antibiotic: fidaxomicin (manufactured by Optimer Inc). It has recently completed two large Phase 3 trials and shows much promise when compared to vancomycin. It has a very narrow spectrum of activity and does not seem to disturb the normal gut microbiota very much and thus does not produce the same level of recurrences of CDI as its competitors. It is currently undergoing the final stages of licensing and is likely to be available in the next few months. No doubt its cost will determine how much it will be used – at least initially.
- Other than the above drug, and the treatments and preventions mentioned already, the only other promising treatment in the pipeline is a therapy/prevention being developed by ViroPharma Inc. This utilises a naturally-occurring strain of *C. difficile* that does not produce any toxin: the non-virulent, non-toxigenic *C. difficile* strain (NTCD). If this strain colonises a patient, it seems to prevent subsequent colonisation by toxigenic (virulent) strains. The initial intention of the therapy is purposely to colonise patients immediately after successful treatment with a conventional antibiotic with NTCD to prevent recurrence of disease. Successful colonisation studies have been completed and

Phase 2 trials are imminent. Eventually this may be “fed” to all at-risk patients to prevent primary episodes.

- As faecal transplantation is so effective, it is highly possible that a more “tasteful” biotherapy might be designed where the protective species of bacteria present in faeces are identified, grown in pure culture and then fed to patients in a palatable form.
- Finally the immunotherapeutic preventions described above might be used as a treatment, perhaps to lessen the severity of moderate and severe CDI, rather than a prevention of relapse.

DECLARATION OF EXPERT WITNESS

I, PROFESSOR IAN POXTON, DECLARE THAT:

I understand that my primary duty in furnishing written reports and giving evidence is to assist the Inquiry and that this takes priority over any duties I may owe to others. I confirm that I have complied and will continue to comply with this duty;

1. To the best of my knowledge I do not know any of the patients included in the Inquiry remit;
2. To the best of my knowledge I do not know any of the medical or nursing staff included in the Inquiry remit;
3. I have received a copy of the Vale of Leven Hospital Inquiry Terms of Reference. I have read those terms and in preparing this report, and in expressing my opinion I have been instructed to remain within to the Terms of Reference;
4. I have endeavoured in this report and in my opinion to be accurate and to have covered all relevant issues concerning the matters stated which I have been asked to address. The opinions expressed represent my true and complete professional opinion;
5. I have endeavoured to include in this report matters of which I have knowledge and of which I have been made aware which might adversely affect the validity of my opinion. I have stated any qualifications to my opinion;
6. I have included the sources of all information that I have used;
7. I will notify the Inquiry Team immediately and confirm in writing if, for any reason, my existing report or opinion requires any correction or qualification;
8. In forming an independent view, I have not included or excluded material at the suggestion of others, including those instructing me;
9. I understand that:
 - (a) My report, subject to any corrections before swearing or affirming as to its correctness, will form my evidence which I will give under oath or affirmation;
 - (b) I may be questioned on my report and by parties assisted by an expert; and
 - (c) I am likely to be the subject of public adverse criticism by the Inquiry if the Inquiry concludes that I have not taken reasonable care in trying to meet the standards set out above.
10. I confirm that I have not entered into any agreement whereby the amount or payment of my fees, charges or expenses is in any way dependent upon the outcome of the Inquiry

Signature:



Date:

3rd May 2011