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Eyes on Evidence

expert commentary on important new evidence

Antibiotics and community-associated *Clostridium difficile* infection

A meta-analysis finds that recent use of antibiotics is associated with an increased risk of *Clostridium difficile* infection in adults who have not been admitted to a healthcare facility. Some classes of antibiotic are associated with a greater risk than others.

Overview: *Clostridium difficile* is an anaerobic bacterium that is present in the gut of up to 3% of healthy adults and 66% of infants. *C difficile* rarely causes problems in healthy people because it is kept in check by the normal bacterial population of the intestine. However, certain antibiotics – especially broad spectrum antibiotics – can disturb the balance of bacteria in the gut, which allows *C difficile* to multiply rapidly and produce toxins. The symptoms of *C difficile* infection include diarrhoea, fever and abdominal cramps. In more serious cases, infection can cause severe inflammation of the bowel (pseudomembranous colitis) and may be life-threatening.

In 2012–13, 14,687 cases of *C difficile* infection in children and adults were reported in England, a rate of 27.7 cases per 100,000 population (Public Health England 2013). This rate reflects a year-on-year decrease in the number of cases, from 108.6 cases per 100,000 population in 2007–8 when mandatory reporting began.

See the NICE Evidence Services topic page on *C difficile* for a general overview of this condition.

Current advice: Public Health England guidance states that supportive care should be given to people with *C difficile* infection, including hydration, electrolytes and nutrition. Antiperistaltic agents should be avoided in people with acute infection. The precipitating antibiotic should be stopped wherever possible; agents with less risk of inducing *C difficile* infection can be substituted if an underlying infection still requires treatment. Consideration should be given to stopping or reviewing the need for proton pump inhibitors (PPIs) in people with or at high risk of *C difficile* infection.

People with mild infection may not require specific *C difficile* antibiotic treatment. Mild or moderate disease can be treated with oral metronidazole, but oral vancomycin is preferred for severe infection. Fidaxomicin should be considered for people with severe *C difficile* infection who are at high risk for recurrence. Fidaxomicin may also be considered in severe cases that have not responded to oral vancomycin (see the NICE Evidence summary: new medicine on fidaxomicin). The addition of oral rifampicin or intravenous immunoglobulin may also be considered in such cases. In life-threatening disease, high dose oral vancomycin plus intravenous metronidazole is recommended.

New evidence: Deshpande et al. (2013) conducted a meta-analysis of studies on the risk of community-associated *C difficile* infection in adults using antibiotics. The authors identified papers and conference abstracts on comparative, observational, community-based studies in any language. Eight high quality case–control studies (n=30,184) from the UK, the USA and Canada were included in the meta-analysis. Cases had been exposed to antibiotics in the 30–180 days before diagnosis, and neither cases nor controls had been admitted to a healthcare facility in the previous 8 weeks to 1 year.

Antibiotic exposure was associated with a significantly higher risk of *C difficile* infection than no exposure to antibiotics (odds ratio [OR]=6.91, 95% confidence interval [CI] 4.17 to 11.44, p<0.00001). The risk of infection was greatest with clindamycin (OR=20.43, 95% CI 8.50 to 49.09; 2 studies), followed by fluoroquinolones (OR=5.65, 95% CI 4.38 to 7.28; 3 studies), cephalosporins (OR=4.47, 95% CI 1.60 to 12.50; 3 studies), penicillins (OR=3.25, 95% CI 1.89 to 5.57; 4 studies), macrolides (OR=2.55, 95% CI 1.91 to 3.39; 3 studies) and sulphonamides or trimethoprim (OR=1.84, 95% CI 1.48 to 2.29; 3 studies). Tetracyclines were not associated with a significantly increased risk of infection (OR=0.91, 95% CI 0.57 to 1.45; 3 studies).

The authors noted that their findings should be interpreted with caution given that significant heterogeneity was present among the studies included, fewer than 10 studies were analysed and all the studies were observational, so cannot prove causation. However, they suggested that patients and healthcare professionals should be aware of the risk of *C difficile* infection associated with antibiotic prescriptions in outpatient settings and should, where possible, select drugs associated with a lower risk.

Commentary: "In 2007–08, non-hospital cases of *C difficile* infection reported in patients aged 2 years and over comprised approximately 40% of the total cases in England. In 2012–13, this proportion had risen to approximately 60% (Public Health England 2013). This increase in community-associated cases coincides with likely increased awareness and ascertainment of community cases, due to the introduction of national testing guidelines, increasing use of PPIs (which are a risk factor for *C difficile* infection [Cunningham et al. 2003]) and better control of hospital-acquired *C difficile* infection. Therefore, the use of lower risk antibiotics in the community, particularly among elderly patients on PPIs, is likely to be of increasing importance.

"Antibiotic use also drives the development of resistance. Inter-country (as well as within-country) variations in prescribing suggest that the total quantities of antibiotics prescribed could be reduced, particularly for infections likely to be of viral aetiology. Set against this is the need to treat promptly and appropriately to avoid morbidity and mortality from *C difficile* infection and reduce the likelihood for the need for hospital admission.

"The findings of Deshpande et al. (2013) are consistent with previous papers showing that clindamycin, fluoroquinolones and cephalosporins are the highest risk antibiotics for *C difficile*, with commonly used antibiotics such as penicillins and macrolides also a risk. Bearing in mind the limitations expressed by the authors, this article provides useful additional knowledge for practitioners trying to select the best antibiotics to treat infection in those at risk of *C difficile*." ***– Dr Philippa Moore, Consultant Medical Microbiologist, Gloucestershire Hospitals NHS Foundation Trust***

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