Dentists, antibiotics and *Clostridium difficile*-associated disease

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IN BRIEF

- Provides an update on *Clostridium difficile*-associated disease in the context of antimicrobial drug prescribing.
- Highlights *Clostridium difficile*-associated disease as a primary care phenomenon in addition to hospital acquisition.
- Addresses the important role of all healthcare workers, including dentists, in reducing the incidence of *Clostridium difficile*-associated disease through improved prescribing practice.

EDUCATION

Dentists prescribe significant volumes of antimicrobial drugs within primary care settings. There is good evidence that many of the prescriptions are not justified by current clinical guidance and that that there is considerable misuse of these drugs in dentistry. One of the risks associated with antibiotic administration is *Clostridium difficile*-associated disease (CDAD), an entity of which many healthcare workers, including dentists, have little knowledge or understanding. This review seeks to identify the extent and nature of the problem and provides an up to date summary of current views on CDAD, with particular reference to community acquired disease. As for all healthcare workers, scrupulous attention to standard infection control procedures and reducing inappropriate antibiotic prescribing are essential to reduce the risks of CDAD, prevent emergence of further resistant strains of microorganisms and maintain the value of the arsenal of antibiotics currently available to us.

INTRODUCTION

Dentists are responsible for a significant volume of antibiotic prescribing. In the year 2013, dentists in England prescribed 5.6 million items, representing 0.5% of all the items prescribed throughout the healthcare services.[1] The majority (68.2%) of these dental prescriptions were for antibacterial drugs.[1] A Welsh study found 9% of all antibacterial drugs dispensed in primary care were prescribed by dentists.[2] This may be viewed as unsurprising, since most of the dental pathology treated by dentists has an infective origin. However, the role of antibiotics in dentistry is a vexed subject.[3] The fact that most oral and dental infections are caused by biofilms militates against their use in many clinical situations.[4,5] Furthermore, there have been many publications that have demonstrated poor adherence by dentists to prescribing guidelines.[6–11]

In recent times, public and professional attention has been focused on the international problem of antibiotic resistance, following publication by the World Health Organisation of its global report on surveillance of antibiotic resistance,[14] which has been heavily reported in the media and to which politicians have reacted. Profligate misuse of antibiotics is a major contributing factor to antimicrobial drug resistance, and clinical problems caused by organisms such as MRSA[15] are well recognised, prompting all healthcare workers, including dentists, to reflect carefully on their prescribing habits. Unfortunately, recent evidence from primary care prescribing in the UK suggests that there has been little recent improvement, despite the range of strategies that have been launched to promote better antimicrobial prescribing.[16] One additional complication of antibiotic use with which many dentists may be less than familiar is the potential for *Clostridium difficile*-associated disease (CDAD).[17] There is evidence of a general lack of knowledge of CDAD among healthcare professionals.[18] A recent structured literature review of factors that impact on health care professionals' risk perceptions and responses towards *C. difficile* revealed that technical knowledge and understanding of risk factors were poor, especially among doctors and nurses.[19] In view of the significant morbidity and mortality caused by this organism, and the major financial burden (estimated for the USA to be $1.1 billion per year[20]) there is an urgent need for healthcare worker education.

This paper reviews the issue in the context of the broadening spectrum of CDAD within the community and the need to educate and inform dentists about this particular risk.

ANTIBIOTIC PRESCRIBING IN DENTISTRY

Antibiotic prescribing practices by dentists have been examined in detail in a recent study and reveal significant room for improvement.[9] Prescription of an antibiotic should be based on accurate diagnosis and is only indicated for the management in a limited number of bacterial infections in dentistry.[21] Unless there are clinical signs of spreading infection or the patient is becoming systemically unwell, antibiotics should not be a first line measure where local surgical actions are required.[22] In such cases, primary treatment is surgical debridement, removal of the cause of the infection, and drainage of pus.[21] On occasions, antibiotics may be required as an adjunct to local surgical measures in the treatment of purulent orofacial infections, though in many cases drainage alone is sufficient for the immunocompetent host.[22]

Much of the existing literature related to antibiotic prescribing in dentistry focuses on microbial resistance. However, it is clear that prescribing practice in the profession does not uniformly correspond with current guidance.[23] English data from 2013 showed the majority of antibacterial drugs prescribed in dentistry to be penicillins or metronidazole. However, clindamycin or cephalosporins were prescribed in over 35,000 cases.[1] As the two forms of antibiotic most commonly associated with CDAD, the prescribing of such agents by dentists must take into account the potential risk of this significant negative outcome.[24]

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Further studies are currently being undertaken to gain greater insight into the prescribing practice of primary care dentists, focusing on the issue of antibiotic resistance.[25,26] Data collected will shed light on current prescribing behaviours, which can be extrapolated to enhance our understanding of the use of drugs associated with CDAD within dentistry. Based on existing qualititative data, it is evident dentists are altering their choice of antibiotic drug regime from the available armamentarium due to clinical ineffectiveness.[27] This suggests the potential for a future increase in the use of second line antibiotics, multiple courses of antibiotics and increased length of antibiotic treatment by dentists, all factors increasing the risk of CDAD.

NICE published guidelines in 2008, indicating that antibiotic prophylaxis to prevent infective endocarditis was no longer necessary due to a lack of substantial evidence and that regular tooth brushing was as likely to cause a bacteraemia as a dental procedure.[12] A subsequent epidemiological follow-up study was unable to identify an increased number of cases of infective endocarditis following this change to guidance.[28] A more recent study by the same group has cast some doubt on the decision and NICE is once again reviewing the guidance.[29]

It should be pointed out that antibiotic prescribing is, in general, empirical within dentistry. Special investigations involving the expertise of a microbiologist are not utilised to any great extent by the dental profession, so that there is no guidance for treatment from culture and sensitivity reports.[30] This also results in a lack of surveillance of potential emerging resistance in the organisms that cause odontogenic infections[31,32] a problem compounded by the biofilm lifestyle.[33] The risk of repeated blind prescribing of ineffective courses of antibiotics is self-evident.

In summary, the number of occasions on which prescription of antibiotics is required in routine dentistry is relatively small if current guidance is followed.

THE RELATIONSHIP BETWEEN ANTIBIOTICS AND *C. DIFFICILE*–-ASSOCIATED DISEASE

When an antibiotic is administered, it has a major impact on the bacteria which form the balanced ecosystem of the gut microflora. The colonisation of the gut is a staged process subject to microbial, internal and external factors which influence its development to a climax community, taking up to a week to stabilise.[34] The extent to which an antibiotic will alter the gut flora depends upon several factors including spectrum of action, degree of absorption, elimination route and any inactivation through enzymes or becoming bound to body fluids or intestinal material.[35] One potential effect of destabilisation of this microflora is establishment of the opportunistic spore-forming pathogen *C. difficile*, which may result in *C. difficile*- associated disease (CDAD).[36]

Clostridium difficile is a Gram positive, anaerobic, motile rod-shaped bacterium with the ability to form spores.[17] It was first isolated in the gut microflora from the stools of infants by O'Toole and Hall in 1935.[37] Interestingly, research from as early as the 1950s, using experimental animal models, implicated clostridia in antibiotic-associated colitis.[38] However, it was not until the late 1970s that researchers began to publish work linking the use of antibiotics and presence of *C. difficile* to the gastrointestinal system disease known as pseudomembranous colitis (PMC).[39–44] In particular, the disease appeared to be linked to the use of the antibiotic clindamycin.[45] Since then, various antibiotics have been implicated in CDAD including the fluoroquinolones, cephalosporins and, of importance to dentists, the commonly used amoxicillin.[46]

C. difficile produces and releases two toxins which cause inflammatory changes in the gastrointestinal system and are responsible for PMC. Toxin A (TcdA) is an enterotoxin and Toxin B (TcdB) is a cytotoxin.[36,47] At a cellular level both toxins have cytotoxic effects which result in cell mortality by altering the gut cell's cytoskeleton. This is achieved by the toxin catalysing a conformational change in the guanosine triphosphate (GTP) - binding proteins in the process of glycosylation. The GTP – binding proteins are known as Rho proteins and are responsible for cell structure and movement.[48] The inflammatory changes seen in this form of colitis appear to be due mainly to TcdA, resulting in haemorrhagic fluid secretion, inflammation and necrosis of the gut mucosa.[49]

A particular strain of *C. difficile*, PCR ribotype 027, has been associated with increased morbidity and mortality rates. This strain was isolated in significant outbreaks of CDAD in Quebec in Canada[50] and the UK.[51] Other areas of Europe have also reported outbreaks associated with this strain[52] and further worldwide spread is inevitable with the ongoing risk of a CDAD pandemic.[53] It appears to produce particularly potent TcdA and TcdB in addition to a further toxin, *Clostridium difficile* transferase (CDT), which is believed to contribute to virulence by targeting the cytoskeleton development through prevention of actin polymerisation.[54] CDT also contributes to virulence by enhancing clostridial cell adherence to the gut mucosal cells.[55] The 027 strain is not alone in being hypervirulent, as previous research samples were assumed to be the 027 strain when in fact they belonged to other strains such as 176, 198 and 244, indicating the potential for numerous strains to display heightened pathogenicity.[56] Moreover, the incidence of the 027 strain has significantly reduced, with emergence of ribotypes 078, 002, 005, 014/20 and 015.[57]

Furthermore, evidence is beginning to emerge which indicates that the ribotype of *C. difficile per se* may be less important in predicting the severity of the potential infection than previously thought and that other factors may play a significant role, such as the white cell and albumin counts.[58]

Concern is now growing with regard to resistance in *C. difficile* as the PCR ribotype 027 has also begun to show a resistance profile to the standard catalogue of drugs.[59] A recent paper describing a recombinant bacteriophage-derived endolysin that lyses *C. difficile in vitro* suggests a novel alternative bactericide.[60]

EPIDEMIOLOGY

In the year 2012, deaths associated with CDAD in England and Wales totalled 1,646,[61] following a climax in reported cases of disease within the same population between March 2007 and April 2008, when a total of 55,499 cases was recorded.[62] In light of the heavy burden of CDAD, major changes were made at government, health board and clinical levels to reduce the number of CDAD cases.[63] The number of cases has dropped steadily over the subsequent years since these changes, but it remains a serious clinical problem.[61] While in its infancy as a recognised pathogen, *C. difficile* was reported as being primarily a hospital acquired infection.[63] However, its presence in the community is now recognised as a significant problem and the number of cases of CDAD outwith hospitals is increasing.[64] A recent study showed that community-acquired cases accounted for 41% of 385 cases of *C. difficile* infection and that these individuals were younger, more likely to be female, had lower comorbidity scores, and were less likely to have severe infection or to have been exposed to antibiotics.[65] Nevertheless, 78% of those with the community-acquired form had received antibiotics (compared with 94% of those with hospital-acquired infection), reflecting the importance of antibiotics in both groups and highlighting the relevance to dental practice.[65]

TRANSMISSION OF *C. DIFFICILE*

Transmission of *C. difficile* is via the faecal-oral route. The organism has been isolated from objects surrounding hospital patients with CDAD and also from patients who are asymptomatic carriers. Contaminated areas included the floors, sink basins, blankets

Table 1 The spectrum of CDAD and suggested management. Adapted from Public Health England, Updated guidance on the management of *C. difficile* infection[86]

Disease severity	Defined by	Suggested management
Mild	Not associated with a raised WCC; it is typically associated with 3 loose stools per day	Oral metronidazole 400-500 mg tds for 10-14 days
Moderate	Associated with a raised WCC and 5-7 loose stools per day	Oral metronidazole 400-500 mg tds for 10-14 days
Severe	WCC >15 × 109/L, or an acute rising serum creatinine (that is, >50% increase above baseline), or a temperature of >38.5 °C, or evidence of severe colitis (abdominal or radiological signs). The number of stools may be a less reliable indicator of severity.	Oral vancomycin 125 mg qds for 10–14 days. Fidaxomicin should be considered for patients with severe CDI who are considered at high risk for recurrence; these include elderly patients with multiple comorbidities who are receiving concomitant antibiotics.
Life threatening	Includes hypotension, partial or complete ileus or toxic megacolon, or CT evidence of severe disease.	Oral vancomycin up to 500 mg qds for 10-14 days via naso-gastric tube or rectal installation plus iv metronidazole 500 mg tds
Recurrent	Recurrence of diarrhoea at least 3 consecutive loose stools within 30 days of a previous CDI episode AND positive *C. difficile* toxin test	Oral fidaxomicin 200 mg bd is recommended; Oral vancomycin 125 mg qds is an alternative.
Multiple recurrences	As above with evidence of wasting and malnutrition	1. Review ALL antibiotic and other drug therapy (consider stopping PPIs and/or other GI active drugs) 2. Consider supervised trial of anti-motility agents alone 3. Fidaxomicin (if not received previously) 200 mg 12-hourly for 10-14 days 4. Vancomycin tapering/pulse therapy (4-6 week regimen) 5. IV immunoglobulin, especially if worsening albumin status 6. Donor stool transplant

and toilet seats of the patients and the hands of nurses who had changed the bedding of patients.[66–70] Person to person spread through hand transfer is a key mode of transmission,[71] exemplified by the isolation of *C. difficile* from the hands of 59% of healthcare workers caring for CDAD patients.[72] *C. difficile* spores are capable of surviving for up to five months in the environment.[73] Upon entering the gastrointestinal system the spores are able to resist the defence mechanisms of the body and lie dormant. Alteration of the gut flora, notably through antibiotic administration, allows the spores to germinate and return to a vegetative state in which they are pathogenic through toxin production.[74] Although the details of the germination process remain unclear at present, greater understanding may contribute to treatment and prevention of CDAD in the future. *C. difficile* has also been found in animals and in meat products consumed by humans, and although there is no substantial evidence to date, it is proposed that there is a possible route of transmission from animals to humans,[75] with potential for global spread of the organism through livestock and foodstuff transfer.[53]

Thus, person to person spread is an important mode of transmission in CDAD.[71] Little is currently known about the transmission of *C. difficile* within dental settings and further research should be undertaken to address this. The dental surgery may act as a reservoir for spores through hand contact contamination by the asymptomatic patient. The fundamental processes of infection control are central to breaking the chain of infection, including hand hygiene and appropriate cleaning and disinfection of the clinical environment. Compliance with hand hygiene continues to be a source of concern within the dental profession.[76] Although alcohol-based hand rubs are of use in clinical settings they do not remove or inactivate *C. difficile* spores and therefore hand washing carried out with soap and water is required.[62,77] Appropriate cleaning of the dental surgery should also be reinforced. As with biofilms, mechanical disruption is of great importance in the removal of *C. difficile* spores from the environment.[78] It is also of relevance to note that chlorine based agents are significantly more effective than detergents in destroying *C. difficile* spores.[73,79]

RISK FACTORS

The major risk factors associated with CDAD include antibiotic exposure, severe underlying disease, older age and immune suppression.[80] Patients attend for dental treatment throughout life and dentists will undoubtedly encounter patients with these risk factors on a regular basis. However, it is important to recognise that fit and healthy patients who display none of the risk factors may also succumb to CDAD with potentially serious outcomes.[81]

Cases of CDAD have been reported in conjunction with a wide spectrum of different antibiotics.[80] Traditionally clindamycin was regarded as the main culprit, but the fluoroquinolones and cephalosporins, in particular the third generation cephalosporins, have become increasingly implicated.[24] It is believed that the broad spectrum activity and historic profligate use of these agents has led to a significant resistance pattern developing for *C. difficile*, unsurprisingly resulting in CDAD associated with their use.[82] The relevance of this to the dental practitioner is the potential for any antibiotic to cause the changes in gut flora necessary for CDAD. Clindamycin is occasionally prescribed in dentistry as a second line antibiotic and has a notable ability to penetrate bone.[83] Amoxicillin and co-amoxiclav have a relatively wide spectrum of action and are regularly prescribed by dental practitioners but they too have the potential to contribute to CDAD.[84]

PRESENTATIONS OF *CLOSTRIDIUM DIFFICILE*-ASSOCIATED DISEASE

The clinical presentation of patients who have been infected with *C. difficile* varies considerably, from the asymptomatic patient who acts as a carrier, to the systemically ill patient suffering from PMC, with potential for bowel perforation and ultimately death.[85] Its onset typically is within 49 days of starting the course of antibiotics. The spectrum of CDAD ranges from mild to severe and its clinical descriptors and evidence based management are summarised in Table 1.[86] The most common symptoms in patients with mild to moderate *C. difficile* infection are watery diarrhoea three or more times per day for two or more days, together with mild abdominal tenderness and cramps.

In severe cases, patients become dehydrated and frequently require hospitalisation. *C. difficile* causes inflammation of the colon and may result in patches of raw tissue that bleed and produce pus, the condition known as pseudomembranous colitis. Signs and symptoms of severe infection include watery diarrhoea 10 to 15 times a day, abdominal cramping and pain, blood or pus in the stool, fever, nausea, dehydration, loss of appetite, weight loss, swollen abdomen, kidney failure and increased white blood cell count.

DIAGNOSIS OF CDAD

In March 2012, the Health Protection Agency in the UK issued updated guidance on testing stool samples for identifying the presence of *C. difficile*.[87] *C. difficile* toxin enzyme immunoassays are not deemed suitable as stand-alone tests for the diagnosis of CDAD or detection of *C. difficile*. It recommends an initial test for toxin gene using a nucleic acid amplification test such as the polymerase chain reaction, or glutamate dehydrogenase test enzyme immunoassay, which should then be followed by a sensitive toxin enzyme immunoassay.[87]

Imaging of the colon through endoscopic examination is not normally indicated but may be used if other colonic pathologies may exist, laboratory studies are inconclusive or the clinical status worsens.[88]

THE DENTIST'S ROLE

Of the 'four principles' of medical ethics postulated by Tom Beauchamp and James Childress in their textbook *Principles of biomedical ethics*, two are of particular relevance to this paper. These are 'beneficence', namely that a practitioner should act in the best interest of the patient (*salus aegroti suprema lex*) and 'non-maleficence' also known as 'first, do no harm' (*primum non nocere*).[89] Reaching for the prescription pad in a clinical situation where the use of antibiotics is unfounded contravenes these fundamental principles, putting the patient at unnecessary risk of complications such as anaphylaxis and CDAD. The latter is vividly illustrated in the two case reports cited in the paper by Blossom and colleagues, one of which concerns a 48 year old woman who developed CDAD following the prescription of antibiotics after endodontic surgery.[81] The second case describes a 31-year-old pregnant woman who developed CDAD following a course of trimethoprim-sulphamethoxazole for a urinary tract infection and who ultimately died of pseudomembranous colitis and toxic megacolon.[81] Both of these cases concerned fit, healthy outpatients who were prescribed antibiotics and for whom such a serious outcome could not have been foreseen. The second case was presented by the authors to illustrate that it may well be the dental practitioner who is presented with the young otherwise healthy group of patients complaining of symptoms. Therefore the dental community must have some understanding of CDAD to provide holistic care and direct the patient to seek appropriate medical attention.

A further notable case of CDAD was recently reported following the routine administration of prophylactic antibiotics to a patient undergoing maxillofacial surgery. The patient, a young and healthy female, subsequently developed fulminant colitis. Significant life-altering surgical intervention was necessary to remove a large portion of the patient's colon to manage the disease.[90] Practitioners should bear these examples in mind every time there is a temptation to prescribe an antibiotic and to be absolutely clear that there is a real indication in line with clinical guidance.

The profession must also readdress the current existing discrepancies in prescribing patterns. The use of audit has been beneficial in improving prescribing within primary dental care and together with education may further increase adherence to best practice guidelines.[91,92] There is good evidence that antibiotic stewardship programmes can be a successful means of encouraging good antibiotic prescribing practice.[93] Such methodologies could be extremely helpful in dentistry to reinforce some of the good work already underway by many in the profession to enhance antibiotic prescribing practice further.

Within hospital settings, where patients who are colonised with *C. difficile* are being nursed, the importance of standard infection control precautions is paramount.[94] The risk of environmental contamination with *C. difficile* is less in a dental surgery setting and the standard infection control precautions recommended in modern dental practice will mitigate, providing they are followed.[95]

In summary, the dental community must work together with colleagues in all areas of healthcare to ensure the highest standards of infection control and adherence to antibiotic prescribing protocols if we are to retain the effectiveness of antibiotics and prevent complications such as CDAD in our patients.

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