Second generation cephalosporin antibiotic prophylaxis and *Clostridium difficile* infection in hip and knee arthroplasty

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ABSTRACT

INTRODUCTION The use of broad spectrum cephalosporin antibiotics has been discouraged by the Department of Health in England because of the link to increased *Clostridium difficile* infection rates. The aim of this study was to evaluate whether a local protocol that included the use of second generation cephalosporin (cefuroxime) antibiotics as a prophylactic agent was associated with increased risk of *C difficile* in elective hip and knee arthroplasty patients.

METHODS A retrospective intention-to-treat study was conducted. An infection control database of all cases of *C difficile* infection both in hospital and in the community was reviewed and cross-referenced against surgical records. A positive correlation was identified when a *C difficile* positive sample was documented within eight weeks of arthroplasty surgery.

RESULTS Only 1 case (0.02%) of *C difficile* positive diarrhoea was identified that correlated to the 8-week postoperative period following 4,488 arthroplasty procedures.

CONCLUSIONS The use of cephalosporin antibiotic prophylaxis in the elective hip and knee arthroplasty setting does not appear to be associated with increased *C difficile* infection rates, achieving surgical site infection rates that are comparable with the national average.

KEYWORDS

Total hip arthroplasty – Total knee arthroplasty – *Clostridium difficile* – Cephalosporin – Prophylaxis

Accepted 3 January 2017

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The use of prophylactic antibiotics has revolutionised elective and trauma orthopaedic surgery as one of the main factors for reducing infection rate, postoperative morbidity and return to normal function.^{1–3} In recent years, broad spectrum antibiotic prophylaxis has come under repeated scrutiny as resistant organisms have been recognised and linked with the widespread use of such antibiotics.⁴ Infection with these organisms has detrimental effects on patients and presents an economic burden for the National Health Service (NHS) owing to the need for treatment and isolation as well as the extended length of hospital stay and risk of spread.

In 2008 the Department of Health counselled trusts against the use of broad spectrum antibiotics, especially cephalosporins, for use in the prophylactic setting in surgery.⁵ This recommendation was made because of evidence suggesting that (in particular) second and third generation cephalosporins are associated with increased risk of *Clostridium difficile* infection.^{6,7} Meta-analyses have suggested that broad spectrum antibiotics (most notably cephalosporins and clindamycin) increase the risk of acquiring *C difficile* by up to 2–3 times.^{8–10}

One of these meta-analyses, which included only patients treated in the community, recommended cautious interpretation of the results, and indicated that patients who receive antibiotics and develop associated *C difficile* tend to possibly have poorer health in general.¹⁰ It also suggested that both duration and dosage of the antibiotic agent can play a role, and need to be evaluated further. In another meta-analysis, which evaluated patients in the hospital setting, the greatest risk of developing *C difficile* following antibiotic use was found to be within the first 30 days but risk remained increased for up to 90 days.⁸ The authors also highlighted that the number of antibiotics, dosage and duration of antibiotic use are all significant factors in developing *C difficile*.

C difficile infection is described as ‘one episode of diarrhoea, defined either as stool loose enough to take the shape of a container used to sample it or as Bristol Stool Chart types 5–7, that is not attributable to any other cause, including medicines, and that occurs at the same time as a positive toxin assay (with or without a positive *C difficile* culture) and/or endoscopic evidence of pseudomembranous colitis’.⁵

It has been proved that natural colonic flora is resistant to *C difficile* colonisation.^{11,12} In healthy adults, the normal

bacterial flora in the gut is significantly altered when broad spectrum antibiotics are administered, subsequently leading to an increased risk of *C difficile* colonisation. In addition, a number of other factors can lead to alteration in commensal flora. These include advanced age, nasogastric tubes, stool softeners, chemotherapy and reduction in gastric pH.^{13,14} The quality of immune response also plays an important role in the pathogenesis of *C difficile* as evidenced by the fact that approximately two-thirds of those colonised with *C difficile* become asymptomatic carriers.¹⁵

In 2007 surveillance of *C difficile* infections in England became mandatory in all patients aged 2 years and over. Since then, there has been a dramatic decrease in overall numbers, from 55,498 cases in 2007–2008 to 14,165 in 2014–2015.¹⁶ However, since this mandatory surveillance was introduced, 2014–2015 has been the first to show an increased incidence of *C difficile* (with a 6% rise from 2013–2014) despite widespread education, improved antibiotic prescribing and local hospital-based campaigns (Fig 1).¹⁶

The incidence of *C difficile* infection in the postoperative period following elective orthopaedic procedures has been reviewed in two retrospective case controlled studies, with the average incidence of *C difficile* postoperatively being between 0.16% and 0.17%.^{17,18} This is significantly greater than the total incidence in the NHS, which was 0.03% for 2014–2015.¹⁶ This demonstrates that elective orthopaedic patients are potentially high risk and it is therefore important to evaluate any interventions that may be causing this increased prevalence.

The aim of this study was to evaluate whether the use of broad spectrum cephalosporin (cefuroxime) as a prophylactic agent is associated with an increased risk of *C difficile*, as proposed by the Department of Health guidance.⁵ Surgical site infection (SSI) rates were also examined.

Methods

In conjunction with the microbiology department, a list of all *C difficile* cases identified both in the community and in hospital for the period January 2010 to December 2014 was compiled from the departmental *C difficile* database. The cases of *C difficile* that were positively identified by the microbiology department were cross-referenced with the picture archiving and communication system to look for postoperative hip or knee radiography indicating a total hip or knee replacement. The trust infection control policy is to

send a sample for any episode of diarrhoea for *C difficile* analysis and isolate the patient until the result is available.

Using the National Joint Registry, all primary hip and knee arthroplasty patients (including those with neck of femur fractures) were identified. All arthroplasty procedures were undertaken at Colchester General Hospital under the care of ten consultant orthopaedic surgeons. Local orthopaedic department policies (drawn up in conjunction with the microbiology department) for all total hip and knee arthroplasties are summarised in Table 1.

Identified cases of *C difficile* infection occurring within eight weeks of arthroplasty were cross-referenced with microbiology case root cause analysis. If this showed no other primary contributory factors, the infection was marked as having a positive arthroplasty correlation/causation. All total knee and hip arthroplasties over this period were also assessed for SSI rates using data collected for the National Joint Registry.

Table 1 Local prophylactic antibiotic policies for total hip and knee arthroplasty

	At induction	8h postoperatively	16h postoperatively
Standard	Cefuroxime 1.5g, IV	Cefuroxime 750mg, IV	Cefuroxime 750mg, IV
Penicillin / cephalosporin allergy	Teicoplanin 400mg, IV Gentamicin, IV	Nil	Nil
IV = intravenous			

Table 2 Indications for total hip and knee arthroplasty

Indication	n
Osteoarthritis	4,263 (95.0%)
Acute neck of femur fracture	123 (2.7%)
Avascular necrosis	13 (0.3%)
Inflammatory arthropathy	3 (0.07%)
Congenital dysplasia	2 (0.04%)
Other	84 (1.8%)

Table 3 Distribution of ASA (American Society of Anesthesiologists) grades for patients undergoing total hip and knee arthroplasty

ASA grade	n
1	505 (11.3%)
2	2,816 (62.7%)
3	1,094 (24.4%)
4	69 (1.5%)
5	4 (0.1%)

Results

Between January 2010 and December 2014, a total of 4,488 total knee and hip arthroplasties were undertaken; of these, 2,272 were total hip replacements and 2,216 were total knee replacements. The mean age of those undergoing arthroplasty was 71 years (range: 19–98 years). The indications are shown in Table 2. ASA (American Society of Anesthesiologists) grades of patients varied significantly, with the majority of patients being ASA grade <3 (Table 3).

The overall SSI rate for all knee and hip arthroplasties undertaken during this period in our department was 0.6%. This is comparable with the national figures reported by Public Health England for 2009–2014, with knee arthroplasty SSI rates at 0.6% and hip arthroplasty at 0.7%.¹⁹

Root cause analysis

After cross-referencing these 4,488 cases with the *C difficile* database, only 1 case (0.022%) was found to have occurred within 8 weeks of lower limb arthroplasty. This single case of *C difficile* diarrhoea underwent root cause analysis. There were significant confounding factors, which may have propagated *C difficile* infection.

A 72-year-old patient was admitted initially as a trauma case with an extracapsular neck of femur fracture. The patient underwent proximal femoral nailing and had routine x-rays after the procedure, which revealed early metalwork failure and cut-out. The antibiotic protocol for trauma cases is intravenous (IV) co-amoxiclav (a single dose of 1.2g at

induction). In cases of penicillin allergy, a single dose of IV teicoplanin is administered instead.

The patient then underwent semielective single stage revision of primary fixation metalwork to the total hip replacement. Perioperatively, the patient received the standard cefuroxime regimen with added gentamicin (a single dose of 140mg at induction) owing to it being a complex primary case. Hip joint tissue samples were sent for microbiology analysis, which revealed evidence of coagulase negative staphylococci and enterococci on extended culture. After discussion with the microbiology department, the patient was given two weeks of IV teicoplanin (10mg/kg once daily), which was then converted to oral linezolid (600mg twice a day) for a further four weeks. The patient was discharged home three weeks after arthroplasty on oral antibiotics. Alongside the antibiotics, the patient was also discharged with laxatives as they were suffering from constipation due to significant analgesic requirements. After seven weeks following surgery, the patient was readmitted to hospital with abdominal pain, diarrhoea and confirmed *C difficile* toxin samples.

This more complicated patient underwent multiple procedures and had an extended hospital stay. The patient was also administered prolonged broad spectrum antibiotic prophylaxis, and it is quite legitimate to correlate the regime with subsequent *C difficile* infection and consider it may be causative. Medical co-morbidities and the fact that the patient was given prolonged laxatives during the admission may also have a role to play. The outcome of the root cause analysis, however, suggested that appropriate antibiotics were administered and in view of the complexity of the case, all antibiotic treatment and laxative use was deemed to be in the best interests of the patient and adherent to local microbiology guidelines. It is therefore difficult to attribute this positive *C difficile* case to the use of prophylactic cephalosporin as there are multiple strong confounding factors.

Discussion

It has been suggested in multiple studies that cephalosporin use is associated with an increased risk of developing *C difficile* infections.^{8–10} The most recent meta-analysis regarding antibiotic use and hospital acquired *C difficile* infection, by Slimings and Riley, found that patients taking second generation cephalosporins have a two to threefold increase in the risk of developing a *C difficile* infection.⁸ However, this did not specifically examine prophylaxis regimes but rather studied the effect of cephalosporin use in general. Some studies have also shown that moving away from cephalosporin regimes can decrease the risk of developing *C difficile* infections by up to four times, as described by Vernaz *et al* and Starks *et al*.^{20,21}

Contrary to the current published research, our study demonstrates a *C difficile* infection rate significantly lower than that described in the literature.^{17,22} There is also strong evidence in the literature that using multiple doses of perioperative antibiotics reduces long-term reoperation rates, for all reasons, as described by Engesaeter *et al*.²³

Despite the published data, there is still limited evidence regarding the use of cephalosporins in orthopaedic patients undergoing arthroplasty. There have been no randomised controlled trials investigating whether there is any association between the rate of *C difficile* infection and antibiotic prophylaxis. Given the large population required to carry out such a study, this is unlikely to change.¹⁷

Study limitations

It is acknowledged that our study did not measure the rate of penicillin allergy and therefore the use of second line prophylaxis (in the form of teicoplanin and gentamicin) instead of cefuroxime. However, based on figures in the literature for a penicillin allergy incidence in the general population of approximately 10%,^{24,25} it can be extrapolated that 449 patients were not given the cefuroxime prophylaxis. If we were to use this extrapolated figure, the rate of *C difficile* infection would still be a very low (0.024%), with a difference of only 0.002 percentage points.

The effect of cephalosporin on deep infection and revision rates was also not assessed in this study. The patients were not screened pre or postoperatively for *C difficile* and it is consequently not possible to draw conclusions regarding the potential asymptomatic colonisation with *C difficile* following cephalosporin use. In addition, there was no control group in the study but national *C difficile* infection data could be used as a baseline.

Conclusions

This study has demonstrated that the use of three doses of IV cephalosporin (cefuroxime) peri/postoperatively does not appear to be associated with increased *C difficile* infection rates and achieves SSI rates that are comparable with the national average. Its use in elective orthopaedic surgery for primary total hip and knee arthroplasty therefore seems safe. In view of our findings and the fact that cephalosporins have good broad spectrum action against the common microbes causing morbidity in arthroplasty, judicious use still has a strong role to play.

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