Clinical Kidney Journal

ckj

OXFORD

era edta
LEADING EUROPEAN NEPHROLOGY

Clinical Kidney Journal, 2021, vol. 14, no. 4, 1114–1119

doi: 10.1093/ckj/sfaa059
Advance Access Publication Date: 17 May 2020
Original Article

ORIGINAL ARTICLE

Acute kidney injury following prophylactic flucloxacillin and gentamicin in primary hip and knee arthroplasty

Judi Graham[1], Emma Borthwick[1], Christopher Hill[1], Janine Blaney[2], Nicola Gallagher[2], Lynne Armstrong[3] and David Beverland[2]

[1]Nephrology Department, Belfast City Hospital, Belfast, UK, [2]Primary Joint Outcomes Unit, Musgrave Park Hospital, Belfast, UK and [3]Wither's Department, Musgrave Park Hospital, Belfast, UK

Correspondence to: Judi Graham; E-mail: judimgraham@gmail.com

ABSTRACT

Background. Following concerns regarding the emergence of *Clostridium difficile* infection in 2010, we changed antibiotic prophylaxis in patients undergoing primary hip and knee arthroplasty from cefuroxime to flucloxacillin and single-dose (SD) gentamicin. A subsequent perceived increase in the incidence of post-operative acute kidney injury (AKI) led us to evaluate the AKI incidence between different prophylactic antibiotic regimes used at our centre.

Methods. We examined the incidence of AKI as defined by Kidney Disease: Improving Global Outcomes criteria in 1588 patients undergoing primary hip or knee arthroplasty from January 2010 to January 2015. Patients received the following prophylactic antibiotic regimes: 8 g flucloxacillin in four divided doses and SD gentamicin 1.5 mg/kg ideal body weight (IBW; maximum dose 120 mg; $n = 400$), 8 g flucloxacillin alone in four divided doses ($n = 400$), SD cefuroxime ($n = 400$), triple-dose (TD) cefuroxime ($n = 188$) and teicoplanin with SD gentamicin 1.5 mg/kg IBW ($n = 200$).

Results. The incidence of AKI was as follows: flucloxacillin and gentamicin (13%); flucloxacillin alone (8.5%); SD cefuroxime (2%); TD cefuroxime (0.5%); and teicoplanin and gentamicin (3%). Of the six patients who developed Stage 3 AKI, all were in the flucloxacillin and gentamicin group. The odds ratio for the development of AKI derived from a binary logistic regression model was highest in the flucloxacillin and gentamicin group [7.79 (95% confidence interval 3.54–17.14), $P < 0.0001$].

Conclusions. Our findings suggest that the use of prophylactic high-dose flucloxacillin and gentamicin should be used with caution in patients undergoing primary hip or knee arthroplasty without a clear advantage in reducing surgical site infections given the association with increased rates of AKI.

Keywords: acute kidney injury, flucloxacillin, gentamicin, periprosthetic joint infections, primary arthroplasty

Received: 3.10.2019; Editorial decision: 16.3.2020

INTRODUCTION

Within an ageing population and rising obesity rates, requirements for primary hip and knee arthroplasty are increasing. Periprosthetic joint infection (PJI), aseptic loosening and instability are now the most common reasons for revision following primary hip and knee arthroplasty [1], with considerable associated morbidity and cost [2]. Perioperative antibiotic prophylaxis has long been recognized as an unchallenged standard of care that is known to decrease the incidence of this potentially devastating complication [3].

The most common organisms associated with PJIs are staphylococci, with *Staphylococcus aureus* and *Staphylococcus epidermis* being the most frequently isolated pathogens [4]. Currently, there is no UK consensus on the timing, dose, duration or choice of antibiotic prophylaxis, with regional variation influenced by guidance from local policymakers. Cephalosporins have been widely used worldwide because of their broad-spectrum cover [5]; however, concerns regarding the emergence of *Clostridium difficile* (CD) infection in the UK in 2010 led to a change in practice in many centres to alternative antibiotic regimes.

In August 2010, we changed our antibiotic prophylaxis from cefuroxime to flucloxacillin in combination with gentamicin. Unexpectedly, we observed a rise in the incidence of post-operative acute kidney injury (AKI) at our centre, which we initially attributed to the use of gentamicin. Following consultation with our local nephrology and microbiology colleagues, the hospital protocol was changed from gentamicin 3 mg to 1.5 mg/kg ideal body weight (IBW) in September 2013. However, in retrospect even prior to September 2013, the maximum dose had never been >1.5 mg/kg IBW. Therefore, this led us to question whether it was actually flucloxacillin or both these antibiotics in combination that was responsible for the high incidence of AKI.

Several studies have reported an association between the use of prophylactic flucloxacillin and gentamicin and subsequent kidney impairment. Challagunda *et al.* evaluated the incidence of AKI in 198 patients undergoing primary hip and knee arthroplasty. Patients were divided into four groups according to what antibiotic prophylaxis they received, with two groups receiving cefuroxime monotherapy and the remaining two groups receiving gentamicin (160 mg for patients weighing >60 kg and 120 mg if weight was <60 kg) in combination with either low-dose flucloxacillin (4 g/day) or high-dose flucloxacillin (8 g/day). They found that the highest rates of AKI occurred in patients treated with high-dose flucloxacillin in combination with gentamicin [6]. In this group, 27 of 52 (52%) patients developed AKI, with 3 patients requiring temporary dialysis compared with 10 of 46 (22%) in the low-dose flucloxacillin and gentamicin group and 4 of 48 (8%) and 7 of 52 (14%) in the two groups who were administered prophylactic cefuroxime. The lower rate of AKI incidence in the low-dose flucloxacillin group compared with the high-dose group suggested that the higher dose flucloxacillin rather than gentamicin may be responsible for the rise in AKI incidence. Similar cases of AKI secondary to dicloxacillin and gentamicin in 163 patients with hip fractures have also been reported in the literature [7]. Bailey *et al.* also reported significantly increased rates of AKI following a change from cefuroxime antibiotic prophylaxis to single-dose (SD; 2 g) flucloxacillin in combination with gentamicin in patients undergoing elective hip and knee replacements. In their study, 24 of 254 (9.45%) patients developed AKI in the flucloxacillin and gentamicin group compared with 4 of 238 (1.69%) in the cefuroxime group [8]. While these studies supported our observations that flucloxacillin and gentamicin prophylaxis may lead to increased rates of AKI, patient numbers were relatively small and it remained unclear if one or both of these antibiotics were responsible.

There have been two larger observational studies examining AKI in joint replacement that led directly to a national change in the prophylactic antibiotic policy for orthopaedic surgery in Scotland. Bell *et al.* investigated AKI rates following a policy change from cefuroxime to gentamicin (4 mg/kg) and flucloxacillin (two doses of 1 g) in 2009. Interrupted time series (ITS) analyses showed a significant increase in AKI following this change in prophylactic regimen in orthopaedic patients. After adjustment for age, sex and use of other nephrotoxic drugs, change in policy was the only factor that remained significantly associated with an increase in AKI. The antibiotic policy change was not significantly associated with a change in AKI in the other surgical groups including urology, vascular, gastrointestinal and gynaecology [9]. Due to the increased AKI rate following this policy change, in 2012, policy was changed again from flucloxacillin and gentamicin to amoxicillin–clavulanic acid. Walker *et al.* [10] investigated this policy change in relation to the AKI rate in patients who underwent orthopaedic surgery. They found that this change in antibiotic prophylaxis was associated with decreased rates of post-operative AKI using ITS analysis [10].

AKI, formerly known as acute kidney failure, is a both common and serious problem among hospitalized patients. It is associated with increased morbidity and mortality, length of hospital stay and subsequently, cost [11]. The aim of this article was to investigate the association between prophylactic antibiotic regime and subsequent development of post-operative AKI in a relatively large group of patients undergoing primary hip and knee arthroplasty. In addition, we evaluated the severity of the AKI, impact on length of hospital stay and factors influencing the development of AKI within our unit.

MATERIALS AND METHODS

We conducted an observational service evaluation using a prospectively maintained database of all patients undergoing primary hip or knee arthroplasty in a large elective orthopaedic unit from January 2010 to January 2015. Patients undergoing revision surgery or trauma-related surgery were excluded. Patients were categorized into five different groups according to which antibiotic prophylaxis they received: flucloxacillin and gentamicin for patients receiving cementless implants; flucloxacillin alone in patients receiving a cemented implant; SD cefuroxime; triple-dose (TD) cefuroxime; or teicoplanin and gentamicin. During the period that flucloxacillin-based regimes were in use, patients with a documented penicillin allergy or known colonization with methicillin-resistant *S. aureus* were alternatively administered teicoplanin and gentamicin if they had a cementless implant. In cemented procedures, Palacos® cement containing gentamicin was routinely used. Patients within each of the groupings were a consecutive sample.

Antibiotics were administered as follows (Table 1): 2 g flucloxacillin prior to skin incision followed by 2 g at 6 h, 12 h and 18 h with or without 1.5 mg/kg IBW gentamicin (maximum dose 120 mg) at induction; 1.5 g cefuroxime at induction with or without further 750 mg doses at 8 h and 18 h in both cementless and cemented procedures and 10 mg/kg teicoplanin and 1.5 mg/kg IBW gentamicin at induction in cementless procedures.

All patients had their kidney function checked at baseline pre-operatively and at least once in the first 48 h post-operative

Table 1. Dosing regimes according to antibiotic group

Antibiotic prophylaxis	Dose	Timing of doses	Time period
FlucloxacillinGentamicin	2 g	0, 6, 12, 18 h	1 March 2014–17 June 2014
	1.5 mg/kg IDW (max dose 120 mg)		
Flucloxacillin	2 g	0, 6, 12, 18 h	3 January 2014–20 August 2014
SD cefuroxime	1.5 g	0 h	1 October 2014–27 November 2014
TD cefuroxime	1.5 g	0 h	4 January 2010–1 February 2010
	750 mg	8, 18 h	
TeicoplaninGentamicin	10 mg/kg	0 h	2 February 2011–30 January 2015
	1.5 mg/kg IBW (max dose 120 mg)	0 h	

0 h = induction immediately prior to skin incision; h = time in hours post-induction.

period. AKI was defined and staged as per the Kidney Disease: Improving Global Outcomes criteria [12]. Stage 1 was defined as an increase in serum creatinine by 26.5 μmol/L within 48 h or an increase to 1.5 times baseline creatinine presumed to have occurred within the previous 7 days. Stage 2 was defined as a serum creatinine rise by 2–2.9 times from the baseline value and Stage 3 was a rise three times the baseline serum creatinine or if dialysis was required.

Data were collected on the following variables: gender, age, American Society of Anaesthesiologists (ASA) grade, nature of operation (primary hip or knee), mode of anaesthesia (spinal or non-spinal), use of cement, pre-operative creatinine and estimated glomerular filtration rate (eGFR), maximum post-operative creatinine and length of hospital stay.

Statistical analysis

Statistical analysis was carried out using IBM SPSS for Windows, Version 22 (IBM Corp., Armonk, NY, USA) All relevant data were assessed for normal distribution (Shapiro–Wilk) and are presented and analysed accordingly. Categorical data between antibiotic groups were analysed using Chi-squared tests. Kruskal–Wallis test was used to explore creatinine levels by antibiotics grouping at the pre-operative stage, post-operative stage and the difference between the two (pre- and post-operative). Binary logistic regression analysis was performed to determine the factors that influence the development of post-operative AKI. Statistical significance was set at the $P \leq 0.05$ level.

Ethical approval

This work was performed as an audit project which was registered with the Trust Standards, Quality and Audit Department.

RESULTS

The study cohort consisted of a total of 1588 patients. The overall median [interquartile range (IQR)] age of patients was 69 (61–76) years and 56.9% were female. More patients (54.8%) had primary hip arthroplasty and 60.5% of the joint replacements were cementless. Baseline differences existed between the groups in relation to gender, ASA grade and surgery type, and whether cement was used. There were no significant differences in length of stay, pre-operative eGFR or creatinine between antibiotic regimes. Baseline characteristics of the groups are presented in Table 2.

Post-operatively, patients in the flucloxacillin and gentamicin group had a significantly greater increase in creatinine compared with any of the other groups ($P \leq 0.0001$) with a median (IQR) increase of 4.0 (−4 to 15) μmol/L (Supplementary data, Table S1). In the flucloxacillin and gentamicin group, significantly more patients went on to develop post-operative AKI (13%) compared with the other regimes, with patients in the TD cefuroxime regime having the lowest (2%) incidence (Table 3). Of the 52 (13.0%) patients in the flucloxacillin and gentamicin group who did develop AKI, 41 patients (78.9%) had Stage 1, with 5 patients (9.6%) having Stage 2 and 6 patients (11.5%) developing Stage 3. This was the only group to have an incidence of Stage 3 AKI. None of the patients required dialysis. As expected, patients who developed AKI had a significantly longer length of hospital stay ($n = 6$ days, IQR 4–9) than those who did not ($n = 4$ days, IQR 3–5; $P \leq 0.0001$; Supplementary data, Table S2).

Binary logistic regression analysis was carried out to determine the factors that influence AKI post total hip and knee arthroplasty (Table 4) while controlling for existing baseline group differences in gender, ASA grade, surgery type and cemented/cementless implants. The overall model was highly significant ($P \leq 0.0001$) and was able to predict 93.7% of the cases of AKI. Variables that were not significant included ASA grade, cemented/cementless joint, baseline eGFR and baseline creatinine values. The most significant influencing predictor of AKI was prophylactic antibiotic regime. Using SD cefuroxime as the reference category, patients that received flucloxacillin and gentamicin were 7.8 times more likely to develop AKI [odds ratio (OR) = 7.79, 95% confidence interval (CI) 3.54–17.14], while patients that received flucloxacillin alone were 4.4 times more likely to develop AKI (OR = 4.44, 95% CI 1.88–10.47). Females were 1.78 times (95% CI 1.02–2.94) more likely to develop AKI than males, as were patients undergoing knee arthroplasty (OR = 1.96, 95% CI 1.19–3.22). Each increase in 1 year of age was associated with a statistically significant increase in odds of development of AKI (OR = 1.07, 95% CI 1.04–1.09). Baseline eGFR and creatinine levels had no significant influence within this model.

DISCUSSION

This work demonstrates that in our unit, the choice of 8 g of flucloxacillin in four divided doses in combination with a single 1.5 mg/kg IBW of gentamicin for antibiotic prophylaxis is associated with a significantly increased likelihood of post-operative AKI. In addition, patients who develop AKI are more likely to have a prolonged hospital stay by an estimated 2 days. This has significant implications for cost and morbidity.

The majority of patients (78.8%) in the flucloxacillin and gentamicin group who developed AKI had small creatinine rises and were classified as Stage 1. Despite this rarely causing

Table 2. Comparison of baseline characteristics and length of hospital stay across prophylactic antibiotic group

Characteristics	Flucloxacillin/ gentamicin ($n = 400$)	Flucloxacillin ($n = 400$)	SD cefuroxime ($n = 400$)	TD cefuroxime ($n = 188$)	Teicoplanin/ gentamicin ($n = 200$)	Total ($n = 1588$)	P-value
Gender, *n* (%)							<0.0001
Male	160 (40.0)	195 (48.8)	175 (43.8)	91 (48.4)	63 (31.5)	684 (43.1)	
Female	240 (60.0)	205 (51.2)	225 (56.2)	97 (51.6)	137 (68.5)	904 (56.9)	
Age, median (IQR), years	69 (62–76)	68 (59–76)	69 (60–75)	68 (60–75)	71 (62–79)	69 (61–76)	0.13
ASA grade, *n* (%)							
1	32 (8.0)	51 (12.8)	25 (6.3)	15 (8.0)	11 (5.5)	134 (8.4)	≤0.0001
2	326 (81.5)	297 (74.3)	298 (74.5)	146 (77.7)	150 (75.0)	1217 (76.6)	
3	39 (16.7)	52 (13.0)	77 (19.3)	27 (14.4)	39 (19.5)	234 (14.75)	
4	3 (0.8)	0	0	0	0	3 (0.2)	
Surgery type, *n* (%)							
Primary knee	248 (62.0)	67 (16.7)	206 (51.5)	79 (42.0)	118 (59.0)	718 (45.2)	≤0.0001
Primary hip	152 (38.0)	333 (83.3)	194 (48.5)	109 (58.0)	82 (41.0)	870 (54.8)	
Spinal anaesthesia, *n* (%)							
Yes	386 (96.5)	389 (97.3)	385 (96.3)	183 (97.3)	191 (95.5)	1534 (96.6)	0.79
No	14 (3.5)	11 (2.8)	15 (3.8)	5 (2.7)	9 (4.5)	54 (3.4)	
Cemented joint, *n* (%)							
Yes	40 (10.0)	355 (88.8)	141 (35.3)	70 (37.2)	22 (11.0)	628 (39.5)	≤0.0001
No	360 (90.0)	45 (11.2)	259 (64.8)	118 (62.8)	178 (89.0)	960 (60.5)	
Pre-operative eGFR, *n* (%)							
≥60 mL/min/1.75 m^2	330 (82.5)	333 (83.3)	336 (84.0)	162 (86.2)	158 (79.0)	1319 (83.1)	0.41
<60 mL/min/1.75 m^2	70 (17.5)	67 (16.8)	64 (16.0)	26 (13.8)	42 (21.0)	269 (16.9)	
Pre-operative creatinine, median (IQR), μmol/L	79 (65–92)	80.5 (69–94)	80 (67–92)	79.5 (67–91)	77.5 (66–94)	80 (67–92)	0.46
Length of stay, median (IQR), days	4.00 (3–6)	4.00 (3–5)	4.00 (3–6)	4.00 (3–5)	4.00 (3–6)	4.00 (3–6)	0.56

Table 3. Incidence of AKI by prophylactic antibiotic regime

		Prophylactic antibiotic regime					
AKI and AKI stage	Sex	Flucloxacillin/ gentamicin ($n = 400$), *n* (%)	Flucloxacillin alone ($n = 400$), *n* (%)	SD cefuroxime ($n = 400$), *n* (%)	TD cefuroxime ($n = 188$), *n* (%)	Teicoplanin/ gentamicin ($n = 200$), *n* (%)	P-value*
AKI (all stages)	ALL	52 (13.0)	34 (8.5)	8 (2.0)	1 (0.5)	6 (3.0)	≤0.0001
	F	28 (53.8)	11 (32.4)	3 (37.5)	1 (100)	3 (50)	
	M	24 (46.2)	23 (67.6)	5 (62.5)	0	3 (50)	
Stage 1	ALL	41 (78.9)	30 (88.2)	8 (100)	1 (100)	5 (83.3)	
	F	24 (58.5)	11 (36.7)	3 (37.5)	1 (100)	2 (40)	
	M	17 (41.5)	19 (63.3)	5 (62.5)	0	3 (60)	
Stage 2	ALL	5 (9.6)	4 (11.8)	0	0	1 (6.7)	
	F	3 (60)	0			1 (100)	
	M	2 (40)	4 (100)			0	
Stage 3	ALL	6 (11.5)	0	0	0	0	
	F	1 (16.7)					
	M	5 (83.3)					

*Chi-squared analysis. F = female, M = male.

concern among clinicians, epidemiological evidence supports that even mild reversible AKI has important clinical consequences including an increased risk of death [11, 13]. For instance, patients with Stage 1 AKI with a rise in creatinine of 26.5 μmol/L have been shown to have a 2-fold increase in terms of in-hospital mortality [14]. In addition, it is now recognized that an episode of AKI has important implications for the long-term development of cardiovascular disease, chronic kidney disease and mortality even if there has been resolution [15, 16]. As the severity of AKI increases, the risk of requiring dialysis and death rises, particularly with Stage 3 AKI [14]; however, it is worth noting that we observed relatively low numbers of patients in this category, with 11.5% of AKI cases being classified as Stage 3 and no patients requiring dialysis.

It is well recognized that gentamicin can induce tubular toxicity, particularly with cumulative doses [17]. Flucloxacillin-associated kidney impairment is less frequently described but associations with interstitial nephritis have been reported [18, 19]. Our results suggest the combination of flucloxacillin and gentamicin appears to act synergistically in precipitating AKI in

Table 4. Binary logistic regression analysis of factors influencing AKI

Covariates	OR (95% CI)	P-value
ASA grade		
1 (Ref)	1.0 (Ref)	–
2	1.5 (0.58–4.00)	0.87
3	1.5 (0.50–4.38)	0.40
4	0	0.99
Gender		
Male (Ref)	1 (Ref)	
Female	1.78 (1.02–2.94)	0.0300
Age	1.07 (1.04–1.09)	≤0.0001
Primary surgery		
THR (Ref)		–
TKR	1.96 (1.19–3.22)	0.008
Antibiotic regime		
SD cefuroxime (Ref)	1 (Ref)	–
TD cefuroxime	4.17 (0.52–33.33)	0.1800
Flucloxacillin and gentamicin	7.79 (3.54–17.14)	≤0.0001
Flucloxacillin alone	4.44 (1.88–10.47)	0.001
Teicoplanin and gentamicin	1.28 (0.43–3.86)	0.66
Joint cement		
Cementless (Ref)	1 (Ref)	–
Cemented	2.94 (1.49–4.17)	0.24
Baseline eGFR		
≥60 mL/min/1.73 m^2	1 (Ref)	–
<60 mL/min/1.73 m^2	1.45 (0.71–2.96)	0.30
Baseline creatinine	1.01 (0.99–1.02)	0.38

THR = total hip replacement; TKR = total knee replacement.

this group of patients given that the rate of AKI was 7.8-fold higher when compared with another group using a similar dose of gentamicin (teicoplanin and gentamicin group) and 4.4-fold higher when compared with the flucloxacillin alone group. The exact mechanism of kidney impairment remains unclear but given that both drugs are primarily renally excreted, reduced clearances when given concomitantly may lead to increased tubular toxicity and subsequent acute tubulointerstitial nephritis [20].

As previously discussed, Challagunda *et al.* reported similar findings of increased rates of AKI following flucloxacillin and gentamicin prophylaxis in patients undergoing primary hip or knee arthroplasty. They also found the incidence of AKI fell significantly when the dose of flucloxacillin was reduced from 8 to 4 g daily [6]. Despite this study having relatively small sample numbers and length of follow-up, the OR (14.5, 95% CI 4.2–49.7) linking high-dose flucloxacillin with SD gentamicin to AKI was considerable and supports our own findings. Currently, there is wide variation across UK centres with regards to the dose of flucloxacillin used as antibiotic prophylaxis for primary hip or knee arthroplasty with some UK centres using much lower doses of 2 g/day [8]. Further studies are required to determine what dose of flucloxacillin is optimal in terms of efficacy in reducing PJI rates along with incidence of AKI.

There is currently no consensus on the use of antibiotic laden bone cements (ALBCs) for preventing PJIs. A meta-analysis of seven randomized controlled trials involving 6381 cases of hip or knee arthroplasties found the use of ALBC had no difference on the rates of superficial infection but did have a lower incidence of deep infection when compared with plain cement or systemic antibiotic administration alone [21]. Within our regression analysis model, taking all other variables into account, we found that cemented or cementless joints did not significantly contribute to the development of AKI.

The estimated cost of treating PJIs in total hip and knee replacements is currently around £100 000 per patient [2]. Patients are often required to return to hospital for more challenging operations, incurring longer hospital stays, requirement for antibiotics and costly revision implants [22]. Patients may be left with devastating outcomes including death and amputation, and incur more pain and disability compared with their pre-operative state [23]. One study by Zmistowski *et al.* [24] showed a significant increase in 1 year mortality in patients who developed PJIs. In our local experience, while flucloxacillin and gentamicin were associated with an increased incidence of AKI, our rates of PJIs appeared to be lower.

In the UK in the last 6 years, antibiotic choice in many units has been driven more by concern about CD and AKI than PJI. Luo *et al.* performed a meta-analysis to compare the efficacy of cefuroxime prophylaxis and flucloxacillin/gentamicin prophylaxis in preventing post-operative wound infections and their associations with post-operative CD infection and kidney impairment. They found that while flucloxacillin/gentamicin was associated with a significantly lower risk of CD when compared with cefuroxime, it was associated with a significantly higher risk of post-operative AKI, particularly in orthopaedic surgery [25]. Furthermore, efficacy rates in terms of preventing post-operative wound infections were similar, although this did not specifically apply to PJIs. Clearly, preventing these infections is of fundamental importance while also avoiding undue harm to patients from AKI. Further large multicentre trials are required to determine efficacy of regime, dose and timing of antibiotic prophylaxis.

We acknowledge that our findings must be interpreted with caution given that this was not a randomized controlled trial. We did not have data on comorbidities, but instead, used ASA grade as a surrogate, which is based on severity of disease and may result in inconsistent application across patients. Furthermore, considerable variation in the ASA classification allocation has been reported given that it does not consider age, sex, weight, nature of the operation, anaesthetic or surgical skill, degree of pre-surgical preparation or the facilities for post-operative care [26]. While the study period was 5 years, the majority of data were collected in 2014, with some of the data being collected 4 years previously. While there were no other major services or quality improvements during the 5-year period, the older data may be less contemporary and subject to other confounders. There were also some potential unmeasured confounders associated with the development of post-operative AKI that we were unable to account for such as intraoperative hypotension. These aside, we had a reasonable sample size and the abrupt decline in AKI following a change in antibiotic prophylaxis from flucloxacillin and gentamicin to cefuroxime suggests that other confounders for AKI were less likely.

With the demand in orthopaedic services increasing, patient safety must be upheld in addition to trying to reduce greater overall costs to the National Health Service. While seemingly mild cases of AKI are less apparent to clinicians compared with severe AKI requiring dialysis, the impact of non-dialysis-requiring AKI is still significant in terms of post-operative morbidity, length of stay and increased mortality risk after what is, in essence, an elective procedure. Prevention and effective treatment of post-operative AKI should be a priority in addition to preventing PJIs. Our findings suggest that the use of

prophylactic high-dose flucloxacillin and gentamicin should be used with caution in patients undergoing primary hip or knee arthroplasty given the association with increased likelihood of AKI. Further randomized trials should investigate the risk of AKI versus risk of surgical site infection with different antibiotic combinations.

SUPPLEMENTARY DATA

Supplementary data are available at ckj online.

CONFLICT OF INTEREST STATEMENT

None declared. The results presented in this article have not been published previously in whole or part. Each author certifies that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest and patent/licensing arrangements) that might pose a conflict of interest in connection with the submitted article.

This work was performed as an audit project, which was registered with the Trust Standards, Quality and Audit Department.

This work was performed at the Primary Joint Outcomes Unit, Musgrave Park Hospital, Belfast.

REFERENCES

1. Green M, Howard P, Porter M et al. National Joint Registry for England, Wales, Northern Ireland and the Isle of Man - 13th Annual Report. 2016. http://www.njrreports.org.uk/Portals/0/PDFdownloads/NJR%2013th%20Annual%20Report%202016.pdf (11 October 2016, date last accessed)
2. Briggs T. A national review of adult elective orthopaedic services in England. *Getting it Right First Time*. 2015. file:///C:/Documents%20and%20Settings/pcis/My%20Documents/Downloads/GIRFT-National-Report-Mar15%20.pdf (11 October 2016, date last accessed)
3. Albuhairan B, Hind D, Hutchinson A. Antibiotic prophylaxis for wound infections in total joint arthroplasty: a systematic review. *J Bone Joint Surg* 2008; 90-B: 915–919
4. Zimmerli W, Trampuz A, Ochsner PE. Prosthetic joint infections. *N Engl J Med* 2004; 351: 1645–1654
5. Parvizi J, Gehrke T, Chen AF. Proceedings of the international consensus meeting on periprosthetic joint infection. *Bone Joint J* 2013; 95-B: 1450–1452
6. Challagunda SR, Knox D, Hawkins A *et al*. Renal impairment after high-dose flucloxacillin and single-dose gentamicin prophylaxis in patients undergoing elective hip and knee replacement. *Nephrol Dial Transplant* 2013; 28: 612–619
7. Solgaard L, Tuxoe JI, Mafi M *et al*. Nephrotoxicity by dicloxacillin and gentamicin in 163 patients with intertrochanteric hip fractures. *Int Orthopaedics* 2000; 24: 155–157
8. Bailey O, Torkington MS, Anthony I *et al*. Antibiotic-related acute kidney injury in patients undergoing elective joint replacement. *Bone Joint J* 2014; 96-B: 395–398
9. Bell S, Davey P, Nathwani D *et al*. Risk of AKI with gentamicin as surgical prophylaxis. *J Am Soc Nephrol* 2014; 25: 2625–2632
10. Walker H, Patton A, Bayne G *et al*. Reduction in postoperative acute kidney injury following a change in antibiotic prophylaxis policy for orthopaedic surgery: an observational study. *J Antimicrob Chemother* 2016; 71: 2598–2605
11. Chertow GM, Burdick E, Honour M *et al*. Acute kidney injury, mortality, length of stay, and costs in hospitalized patients. *J Am Soc Nephrol* 2005; 16: 3365–3370
12. Kidney Disease improving Global Outcomes (KDIGO). Clinical Practice Guidelines for Acute Kidney Injury. 2012. http://www.kdigo.org/clinical_practice_guidelines/AKI.php/ (10 October 2016, date last accessed)
13. Lassnigg A, Schmidlin D, Moudieddine M *et al*. Minimal changes of serum creatinine predict prognosis in patients after cardiothoracic surgery: a prospective cohort study. *J Am Soc Nephrol* 2004; 15: 1596–1605
14. Thakar CV, Christianson A, Freyberg R *et al*. Incidence and outcomes of acute kidney injury in intensive care units: a Veterans Administration study. *Crit Care Med* 2009; 37: 2552–2558
15. Coca SG, Yusuf B, Shlipak MG *et al*. Long-term risk of mortality and other adverse outcomes after acute kidney injury: a systematic review and meta-analysis. *Am J Kidney Dis* 2009; 53: 961–973
16. Amdur RL, Chawla LS, Amodeo S *et al*. Outcomes following diagnosis of acute renal failure in U.S. veterans: focus on acute tubular necrosis. *Kidney Int* 2009; 76: 1089–1097
17. Rossert JA, Fischer EA. Acute interstitital nephritis. In: Feehally J, Floege J, Johnston RF (eds). *Comprehensive Clinical Nephrology*. 3rd edn. Philadelphia, PA: Mosby, 2007, 681–689
18. Pusey CD, Saltissi D, Bloodworth L *et al*. Drug associated acute interstitial nephritis: clinical and pathological features and the response to high dose steroid therapy. *Q J Med* 1983; 52: 194–211
19. Xu B, Murray M. Flucloxacillin induced renal failure. *Aust Fam Physician* 2008; 37: 1009–1011
20. Landersdorfer C, Kirkpatrick C, Kinzig M *et al*. Inhibition of flucloxacillin tubular renal secretion by piperacillin. *Br J Clin Pharmacol* 2008; 66: 648–659
21. Alijanipour P, Parvizi J. Infection post-total knee replacement: current concepts. *Curr Rev Musculoskelet Med* 2014; 7: 96–102
22. Kapadia BH, McElroy MJ, Issa K *et al*. The economic impact of periprosthetic infections following total knee arthroplasty at a specialised tertiary-care centre. *J Arthroplasty* 2014; 29: 929–932
23. Fedorka CJ, Chen AF, McGarry WM *et al*. Functional ability after above-the-knee amputation for infected total hip arthroplasty. *Clin Orthop Relat Res* 2011; 469: 1024–1032
24. Zmistowski B, Karam JA, Durinka JB *et al*. Periprosthetic joint infection increases the risk of one-year mortality. *J Bone Joint Surg Am* 2013; 95: 2177–2184
25. Luo S, Lai Y, Liu C *et al*. Prophylactic use of gentamicin/flucloxacillin versus cefuroxime in surgery: a meta-analysis of clinical studies. *Int J Clin Exp Med* 2015; 8: 17856–17867
26. Daabiss M. American Society of Anaesthesiologists physical status classification. *Indian J Anaesth* 2011; 55: 111–115