Risk of AKI with Gentamicin as Surgical Prophylaxis

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ABSTRACT

In 2009, the Scottish government issued a target to reduce *Clostridium difficile* infection by 30% in 2 years. Consequently, Scottish hospitals changed from cephalosporins to gentamicin for surgical antibiotic prophylaxis. This study examined rates of postoperative AKI before and after this policy change. The study population comprised 12,482 adults undergoing surgery (orthopedic, urology, vascular, gastrointestinal, and gynecology) with antibiotic prophylaxis between October 1, 2006, and September 30, 2010 in the Tayside region of Scotland. Postoperative AKI was defined by the Kidney Disease Improving Global Outcomes criteria. The study design was an interrupted time series with segmented regression analysis. In orthopedic patients, change in policy from cefuroxime to flucloxacillin (two doses of 1 g) and single-dose gentamicin (4 mg/kg) was associated with a 94% increase in AKI (P=0.04; 95% confidence interval, 93.8% to 94.3%). Most patients who developed AKI after prophylactic gentamicin had stage 1 AKI, but some patients developed persistent stage 2 or stage 3 AKI. The antibiotic policy change was not associated with a significant increase in AKI in the other groups. Regardless of antibiotic regimen, however, rates of AKI were high (24%) after vascular surgery, and increased steadily after gastrointestinal surgery. Rates could only be ascertained in 52% of urology patients and 47% of gynecology patients because of a lack of creatinine testing. These results suggest that gentamicin should be avoided in orthopedic patients in the perioperative period. Our findings also raise concerns about the increasing prevalence of postoperative AKI and failures to consistently measure postoperative renal function.

J Am Soc Nephrol 25: 2625–2632, 2014. doi: 10.1681/ASN.2014010035

Reported rates of postoperative AKI vary because of the heterogeneity of the populations studied. Uncomplicated AKI is associated with a mortality of 10%, rising to 50% in the context of multiorgan failure and up to 80% if RRT is required.[1,2] It was thought that the presence of AKI was a marker of coexisting pathology that increased mortality risk, but recent reports demonstrate AKI as an independent risk factor for mortality.[3,4] The increasing incidence of AKI and its long-term consequences have significant socioeconomic and public health effects globally.[5]

Clostridium difficile infection (CDI) is an important healthcare-associated infection. Antibiotic use increases the risk of CDI for at least 3 months[6] and short courses of perioperative antibiotic prophylaxis have also been associated with an increased risk of CDI, particularly in the context of an established outbreak.[7]

Received January 9, 2014. Accepted March 10, 2014.

Published online ahead of print. Publication date available at www.jasn.org.

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In 2009, the Scottish government issued a new target for all health boards to reduce CDI by at least 30% over 2 years.[8] The Scottish Antimicrobial Prescribing Group also produced recommendations for all National Health Service (NHS) boards to restrict the use of antibiotics associated with a high risk of CDI.[9] As part of a widespread antibiotic policy change at NHS Tayside, orthopedic antibiotic prophylaxis was changed from cefuroxime to gentamicin and flucloxacillin. After concerns raised by nephrologists and a small uncontrolled study in the Dumfries and Galloway region of Scotland that described an increased rate of AKI in patients after orthopedic surgery after this policy change,[10] it was felt that further investigation was required.

This study aimed to use robust methodology, in a larger, population-based study of adult patients undergoing orthopedic implant surgery, to evaluate the effect of the policy change on postoperative AKI. It is noteworthy that patients who underwent repair of a neck of femur (NOF) fracture received coamoxiclav as antibiotic prophylaxis after the policy change because of concerns raised by orthopedic surgeons with regard to administering gentamicin in this particular patient group. This analysis was then extended to evaluate postoperative AKI in other surgical specialties (urology, vascular, gastrointestinal, and gynecology) that had changed to a gentamicin-based regimen.

RESULTS

Descriptive Data

In total, 12,482 patients were included in the analysis from October 1, 2006, to September 30, 2010. Table 1 describes the baseline characteristics of the population. Of note, within the orthopedic patient group, 36% of patients were prescribed a nonsteroidal anti-inflammatory drug (NSAID) in the year before their operation and 38.5% were prescribed a diuretic. A comparison of the patients with and without AKI in the orthopedic group showed that only an increasing Charlson Comorbidity Index (CCI) score was associated with an increased risk of AKI on multivariate analysis (95% confidence interval [95% CI], 1.03 to 1.22; $P<0.001$). In urology patients, there was no difference between individuals with or without AKI. In vascular patients, an increasing CCI was associated with an increased risk of AKI on multivariate analysis (95% CI, 1.08 to 1.42; $P=0.03$). In gastrointestinal patients, older age (95% CI, 1.03 to 1.07; $P<0.001$) and male sex ($P=0.02$; 95% CI, 0.39 to 0.91) were associated with an increased risk of AKI. In gynecology patients, older age was associated with an increased risk of AKI (95% CI, 1.02 to 1.15; $P=0.02$).

Characteristics of Patients with Missing Data

Table 2 shows the percentage of available data for each specialty. Biochemistry data were available in only 35% of gynecology patients and 58% of urology patients before the intervention and in 47% of gynecology patients and 52% of urology patients after the intervention. The majority of missing data were missing postoperative serum creatinine measurements, rather than preoperatively. Supplemental Table 3 shows multivariate analyses of the characteristics of patients included in the study versus patients excluded because of missing data. An examination of the characteristics of included patients compared with patients who were excluded due to missing data showed that the included orthopedic patients were older men with higher CCI comorbidity scores, as were the gastrointestinal patients.

Results of Interrupted Time Series Analysis

Orthopedic Patients

Figure 1A shows the percentage of AKI stages 1, 2, and 3 for each study month. Interrupted time series (ITS) analyses showed that there was a significant increase in AKI after the change in prophylactic regimen. After adjustment for age, sex, and use of other nephrotoxic drugs, only the change in policy was significantly associated with an increase in AKI, with a significant change in all levels of severity of AKI after the policy change ($\beta=0.30$; 95% CI, 0.01 to 0.59; $P=0.04$) for the highest serum creatinine postoperatively (Table 3).

Patients who underwent repair of the NOF received coamoxiclav throughout the study period. An analysis of these patients alone showed that the changes in slope for before and after the policy change were virtually zero ($\beta=-0.106$; 95% CI, -0.69 to 0.48, $P=0.77$) (Figure 1B).

Other Surgical Specialties

Results of ITS analyses are shown in Tables 4 and 5 for urology, vascular, gastrointestinal, and gynecologic surgery patients. There was no significant increase in the rates of AKI in these surgical specialties related to the policy change. However, the baseline rates of AKI in vascular surgery were high at 23.2% but did not increase significantly after the policy change. In gastrointestinal surgery, there was a 1.2% monthly increase in AKI ($P=0.29$) before the policy change, with a 0.6% monthly increase after the change in policy, indicating rates that were already increasing and slowing after the policy changed.

Orthopedic Outcome Data

A higher proportion of orthopedic patients with AKI died within 1 year of surgery compared with patients without AKI (20.8% versus 8.2%, respectively). The median length of hospital stay was 8 days (interquartile range [IQR], 5–13) in patients with AKI compared with 7 days (IQR, 4–10) in patients without AKI. There were 25 patients with persistent stage 2 or stage 3 AKI at 7 days postoperatively. None of these patients underwent a renal biopsy. Five patients died during the admission without receiving RRT and six patients received RRT. All surviving patients recovered their renal function to baseline.

DISCUSSION

In this large population-based study of >12,000 patients, we found that increased rates of AKI were associated with a change

Table 1. Descriptive data for other surgical specialties

Characteristic	Orthopedics		Urology		Vascular Surgery		Gastrointestinal Surgery		Gynecology	
	Before Intervention	After Intervention	Before Intervention	After Intervention	Before Intervention	After Intervention	Before Intervention	After Intervention	Before Intervention	After Intervention
Recommended antibiotics (dose)	Cefuroxime (1.5 g)	Flucloxacillin (1 g)×2 plus gentamicin (4 mg/kg)	Coamoxiclav (1.2 g)	Gentamicin (4 mg/kg)	Coamoxiclav (1.2 g)	Flucloxacillin (1 g)×2 plus metronidazole (500 mg)± gentamicin (4 mg/kg)	Coamoxiclav (1.2 g)	Metronidazole (500 mg) plus gentamicin (4 mg/kg)	Coamoxiclav (1.2 g)	Metronidazole (500 mg) plus gentamicin (4 mg/kg)
Patients (*n*)	3674	3992	421	402	358	362	1599	1672	176	227
Age (yr)	71.2 (13.5)	70.7 (13.9)	71.4 (12.5)	70.0 (13.1)	70.0 (11.3)	69.0 (12.9)	62.1 (15.9)	61.8 (16.3)	54.9 (13.7)	53.5 (13.7)
Baseline SCr (μmol/L)	79.0 (66.0, 94.0)	75.0 (62.0, 90.0)	92.0 (77.0, 114.0)	90.0 (74.0, 114.0)	89.5 (75.0, 113.0)	84.0 (67.0, 108.0)	75.0 (62.0, 89.0)	71.0 (60.0, 85.0)	71.0 (61.0, 83.0)	65.0 (58.0, 75.0)
Sex (%)										
Women	2359 (64.2)	2451 (61.4)	101 (24.0)	87 (21.6)	117 (32.7)	241 (67.3)	953 (57.0)	902 (56.4)	176 (100)	227 (100)
Men	1315 (35.8)	1541 (38.6)	320 (76.0)	315 (78.4)	241 (67.3)	234 (64.6)	719 (43.0)	697 (43.6)	0	0
SIMD (%)										
1–3	706 (19.4)	788 (20.0)	88 (21.2)	108 (27.2)	111 (31.2)	104 (29.0)	402 (24.4)	352 (22.4)	40 (23.0)	59 (26.0)
4–7	1616 (44.5)	1716 (43.6)	176 (42.4)	161 (40.6)	143 (40.2)	151 (42.1)	682 (41.4)	676 (43.1)	70 (40.2)	100 (44.1)
8–10	1311 (36.1)	1429 (36.3)	151 (36.4)	128 (32.2)	102 (28.7)	104 (29.0)	565 (34.3)	541 (34.5)	64 (36.8)	68 (30.0)
CCI (%)										
Low (0 or 1)	3494 (95.1)	3774 (94.5)	206 (48.9)	230 (57.2)	244 (68.2)	236 (65.2)	951 (59.5)	1040 (62.2)	122 (69.3)	152 (67.0)
Medium (2)	121 (3.3)	145 (3.6)	185 (43.9)	128 (31.8)	68 (19.0)	73 (20.2)	432 (27.0)	425 (25.4)	45 (25.6)	65 (28.6)
High (≥3)	59 (1.6)	73 (1.8)	30 (7.1)	44 (10.9)	46 (12.8)	53 (14.6)	216 (13.5)	207 (12.4)	9 (5.1)	10 (4.4)

Data are presented as the mean (SD) or median (IQR). SCr, serum creatinine; SIMD, Scottish Index of Multiple Deprivation.

Table 2. Completeness of creatinine data

Operation	Before Policy Change	After Policy Change	Chi Square	*P* Value	Preoperative	Postoperative	Preoperative and Postoperative
All orthopedic NOF	3674 (81)	4009 (82)	3.68	0.05	8883 (94.5)	7917 (84.2)	7698 (81.9)
Urology	421 (58)	402 (52)	4.38	0.04	1396 (92.9)	828 (55.1)	823 (54.8)
Vascular	358 (89)	362 (86)	2.00	0.16	798 (96.8)	727 (88.2)	720 (87.4)
Gastrointestinal	1599 (78)	1672 (78)	0.50	0.48	4089 (97.6)	3315 (79.2)	3271 (78.1)
Gynecology	176 (35)	227 (47)	12.76	<0.001	927 (94.2)	423 (43.0)	403 (41.0)

Data are presented as *n* (%) of patients with creatinine data.

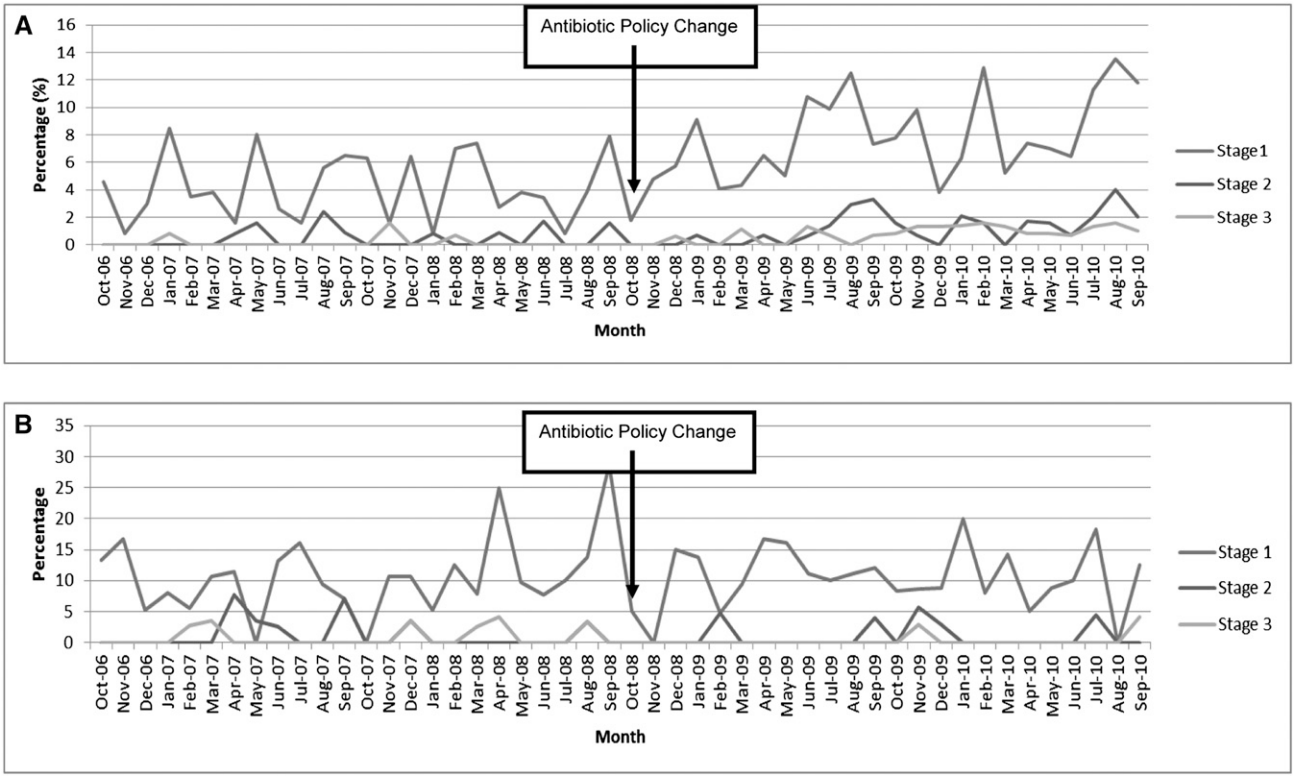

Figure 1. (A) Increase in percentage of AKI (adjusted) stages 1, 2, and 3 for each month (excluding NOF) following policy change. (B) No increase in percentage of AKI stage 1, 2, and 3 for each month in patients with a NOF fracture.

in prophylactic antibiotic policy from cefuroxime to flucloxacillin and gentamicin in patients undergoing orthopedic surgery (excluding repair of a NOF fracture) in the Tayside region of Scotland. The majority of patients had transient stage 1 AKI but there were patients with persisting stages 2 and 3. This association with the antibiotic policy change is strengthened because there was no increase in AKI rates in patients with a NOF fracture who received coamoxiclav as prophylaxis after the policy change. CDI rates fell in both of these groups, suggesting that the orthopedic antibiotic prophylaxis policy change was not responsible for this reduction. We did not find any association between the change in prophylactic antibiotic policy to include gentamicin with AKI in urology, vascular, gastrointestinal, and gynecology surgical patients.

Table 3. ITS of monthly percentage of AKI in orthopedic surgery patients using preoperative versus highest postoperative creatinine measurement, excluding patients with a NOF fracture

Variable	β (95% Confidence Interval)	*P* Value
Time	0.08 (−0.12 to 0.28)	0.40
Intervention (0, before policy change; 1, after policy change)	−1.65 (−5.45 to 2.16)	0.39
Time after intervention	0.30 (0.01 to 0.59)	0.04
Percentage of men (+1%)	−0.07 (−0.30 to 0.16)	0.52
Mean age (+1 year)	0.09 (−0.69 to 0.88)	0.81
Percentage of β-blockers (+1%)	−3.85 (−8.24 to 0.54)	0.08

Table 4. Summary of results in all surgical specialties

Variable	Fracture NOF	Other Orthopedic Implant Surgery	Urological Surgery	Vascular Surgery	Gastrointestinal	Gynecology
Postoperative AKI before the policy change (%)[a]	104 (15.0)	186 (6.2)	49 (11.6)	83 (23.2)	118 (7.4)	8 (4.5)
Postoperative AKI after the policy change (%)[a]	94 (14.8)	361 (10.8)	63 (15.7)	91 (25.1)	204 (12.2)	9 (4.0)
Percent change in AKI (after versus before the policy change) (95% CI)	−9.6 (−10.2 to −9.1)	+94 (93.8 to 94.3)	+28.6 (26.8 to 30.4)	+9.6 (8.9 to 10.3)	+72.9 (72.2 to 73.6)	+12.5 (4.4 to 20.6)
IRR after versus before the policy change[b]	0.99 (0.75 to 1.30)	1.72 (1.43 to 2.05)	1.35 (0.93 to 1.95)	1.08 (0.80 to 1.45)	1.65 (1.32 to 2.07)	0.87 (0.34 to 2.26)

Data are presented as *n* (%), percent change (95% CI), or IRR (95% CI). IRR, incidence rate ratio.

[a]Percentage of patients with Acute Kidney Injury Network stages 1–3 (at least 150% increase in serum creatinine).

[b]The incidence rate ratio is calculated as follows: C-post/T-post or C-pre/T-pre, where C-post is number of patients in the postoperative period, T-post is number of person-years at risk in the postoperative period, C-pre is the number of patients in the preoperative period, and T-pre is the number of person-years at risk in the preoperative period

In addition, we identified three areas of concern. First, rates of postoperative AKI in vascular surgery were especially high, at 23% before the intervention and 25% after the intervention. Second, rates of postoperative AKI steadily increased in gastrointestinal surgery patients throughout the study period. Finally, rates of postoperative AKI data could only be ascertained in 52% of urology patients and 47% gynecology of patients because of missing postoperative serum creatinine data.

The strengths of our study are that we addressed risks of bias for ITS studies in our analysis plan (Supplemental Table 2), defined the operations using operation procedure codes (OPCs) (Supplemental Table 1), and used the Kidney Disease Improving Global Outcomes (KDIGO) definition of AKI. The limitations of our study are common to all nonrandomized studies, including potential ascertainment and selection biases. Randomized controlled trials are often not appropriate and/or are too expensive to assess the effects of global policy change. The ITS is the strongest quasi-experimental design to assess intervention effects in nonrandomized settings. It controls for trends existing before the intervention by using multiple points before and after the intervention.[11,12] A specific limitation of this study was missing preoperative or postoperative serum creatinine measurements in a large proportion of urology and gynecology patients. The patients who were included were older and had greater comorbidity compared with patients who were excluded because of missing creatinine data. This could bias the results in these groups in either direction in estimating the rates of AKI. In addition, we were unable to adjust for potential effects of medication and intraoperative events on AKI rates because these data are not collected electronically.

AKI occurs in 5%–7.5% of acute care hospital inpatients. Of these patients, 30%–40% of AKI incidences occur perioperatively depending on the surgical setting.[13,14] The incidence of AKI varies according to the surgical specialty, with the majority of the epidemiologic literature in cardiac and vascular surgery.[15]

We have shown that rates of AKI vary depending on the surgical setting, ranging from 6% in orthopedic surgery to 25% in vascular surgery. This suggests that patients undergoing vascular surgery are already at risk of developing AKI. Factors that may contribute to this predisposition include age, comorbidity, use of intravenous contrast for vascular imaging and intervention, renovascular disease, and presence of sepsis. Although gentamicin is included in the vascular surgery policy, it is optional and many patients may not receive it because they are deemed to be at high risk for developing AKI, which may account for the results in vascular patients. In gastrointestinal patients, rates of AKI were increasing before the policy change, with a slower increase after the policy change. Therefore, although rates of AKI are higher in the postintervention period, this increase cannot be attributed to the policy change and thus requires investigation into other causes. The large amount of missing data in urology and gynecology patients with a difference in testing before and after intervention threatens the validity of these data. It is, however, important to note that a large number of patients who are attending for major surgical procedures are not having their renal function checked in the preoperative or postoperative period, particularly as the evolving literature indicates an increase in short- and long-term consequences of AKI in this population. The KDIGO AKI guidelines state that major surgery is an exposure for AKI; thus, these patients should have their serum creatinine and urine output measured, according to their clinical status.[16]

Patients who receive gentamicin prophylaxis are generally undergoing major surgery and we thus suggest that a minimum standard of care should be that they have their blood levels checked preoperatively and at least 24 hours postoperatively.

The development of AKI is associated with longer hospital inpatient stays and increased mortality[13,14,17] as well as a greater risk of readmission, development and progression of CKD, and poorer long-term survival.[18] Epidemiologic data have shown that survivors of AKI have higher long-term mortality rates than those patients who survive hospitalization without AKI.

Table 5. Segmented regression analysis, point estimates (β), and *P* values for all surgical specialties

Variable	Fracture NOF		Other Orthopedic Implant Surgery		Urological Surgery		Vascular Surgery		Gastrointestinal		Gynecology	
	β	P Value	β	P Value	β	P Value	β	P Value	β	P Value	β	P Value
Preintervention slope	0.17 (−0.24 to 0.58)	0.41	0.08 (−0.12 to 0.28)	0.40	−0.00 (−0.01 to 0.02)	0.99	0.02 (−0.01 to 0.04)	0.18	0.01 (−0.01 to 0.04)	0.29	−0.04 (−0.13 to 0.05)	0.35
Change in level	−3.68 (−11.74 to 4.37)	0.36	−1.65 (−5.45 to 2.16)	0.39	−0.01 (−0.24 to 0.22)	0.91	−0.03 (−0.50 to 0.45)	0.92	−0.14 (−0.52 to 0.25)	0.49	−0.48 (−2.42 to 1.46)	0.63
Change in slope	−0.11 (−0.69 to 0.48)	0.77	0.30 (0.01 to 0.59)	0.04	0.01 (−0.01 to 0.03)	0.16	−0.03 (−0.07 to 0.01)	0.11	0.01 (−0.02 to 0.03)	0.68	0.04 (−0.09 to 0.16)	0.55

Data are presented with 95% CIs.

This association becomes stronger as the severity of AKI increases but is present in patients with small reversible rises in serum creatinine.[18] There is a lack of therapeutic intervention available once AKI is established. The need for RRT is associated with mortality rates of up to 80%, increased hospital stay, and significantly increased cost. Earlier detection and recognition of AKI to prevent progression and the need for RRT are therefore imperative both for reducing short- and long-term morbidity and mortality as well as economic benefits.

It remains unclear whether gentamicin or flucloxacillin in the doses described, or indeed the combination of both, increased the incidence of AKI in this patient group. None of the patients in our study underwent renal biopsy, so we cannot ascertain the exact mechanism of renal injury. Flucloxacillin is associated with acute interstitial nephritis[19] but this is a relatively uncommon adverse effect. Gentamicin is a direct tubular toxin, and toxicity during gentamicin therapy is more commonly observed. After glomerular filtration, some gentamicin remains in the lysosomes of the renal proximal tubular epithelium. With either prolonged dosing or supratherapeutic levels, the accumulation of the drug increases; it leaks from the lysosomes entering and damaging mitochondria. This leads to tubular epithelial cell death and the acute tubular necrosis–like picture that is typical of gentamicin toxicity.[20] It has been shown that the nephrotoxic potential of gentamicin varies according to the population studied. Factors potentially relevant to our population include age, dehydration, preexisting renal impairment, and concomitant diuretics and NSAIDs.[21] Several recent meta-analyses have shown that the risk of AKI as a result of aminoglycosides is high when used for the empirical treatment of severe Gram-positive or Gram-negative bacterial infections.[22–25] Therefore, the KDIGO AKI guideline recommends that aminoglycosides should not be used for the treatment of infection unless no suitable, less nephrotoxic therapeutic alternatives are available.[16] However, concerns regarding antimicrobial resistance as well as increasing rates of CDI have led to continued widespread gentamicin use. In Scotland, the relatively low levels of resistance to aminoglycosides among key pathogens in the therapeutic context described make them attractive agents.

The orthopedic population was older, with a mean age of 71 years, but the median baseline serum creatinine was 77 μmol/L (IQR, 64–92), indicating that preoperative renal function was preserved. Our results showed that 36% of the orthopedic patients were prescribed a NSAID in the year before surgery and 39% were prescribed a diuretic. However, we adjusted for these factors in our analysis.

We have demonstrated that a change in prophylactic antibiotic policy to flucloxacillin (two doses of 1 g) and single-dose gentamicin (4 mg/kg) was associated with increased rates of AKI in patients undergoing orthopedic implant surgery. We postulate that this is because they are a high-risk population for developing AKI. Therefore, greater attention to all modifiable risk factors, including prophylactic antibiotic choice, is vital in the perioperative period in order to reduce

AKI risk in this vulnerable patient group. Our findings have led to a change in the national antibiotic policy recommendation for orthopedic surgical prophylaxis in Scotland and thus demonstrate the importance of measuring unintended consequences of healthcare interventions. Consequently, it is planned that this study will be repeated across other health boards in Scotland. We have also highlighted that rates of AKI in vascular surgery are high and AKI is rising in gastrointestinal surgery. Furthermore, it is concerning that there was a lack of testing for AKI in urology and gynecology surgery patients. Greater awareness and increased testing for this potentially reversible condition is vital.

CONCISE METHODS

Study Design

This study included all adults aged>18 years who resided in or died in the NHS Tayside region and who underwent surgical procedures in which the revised surgical prophylaxis policy included gentamicin as part of a prophylactic antibiotics regime (Table 2) between October 1, 2006, and September 30, 2010. This study period encompassed 2 years before and after the change in the antibiotic policy. Patients were identified by the OPCs from hospital admissions data (Supplemental Table 1). Table 1 shows the recommended antibiotics and doses before and after the policy change. The primary definition of postoperative renal impairment used was the KDIGO criteria.[16] This was applied using baseline serum creatinine as the premeasurement (most recent before surgery) and maximal serum creatinine during the first 7 postoperative days as the postmeasurement. Patients with postoperative AKI were classified according to their most severe degree of AKI. Stage 1 was defined as increase in serum creatinine of $\geq$26.4 μmol/L or an increase to 150%–200% of baseline. Stage 2 was an increase in serum creatinine to 200%–300% of the baseline value. Stage 3 was an increase in serum creatinine to >300% of baseline or a serum creatinine of $\geq$354 μmol/L or initiation of RRT.

Data were linked using the Health Informatics Centre (HIC)[26] at the University of Dundee. The HIC enables anonymized health record linkage from the population of Tayside, Scotland (n=400,000), using a unique identifying Community Health Index (CHI) number. Data were linked between the following relevant data sets: Scottish Morbidity Record of hospital admissions and OPC-coded procedures, and laboratory results and medicines dispensed by community pharmacies.

Anonymized record linkage was conducted according to HIC standard operating procedure. The Tayside Research Ethics Committee does not require submission of individual studies that follow this standard operating procedure. We obtained permission from NHS Tayside's Caldicott Guardian to identify patients who had severe postoperative AKI so that their case notes could be reviewed.

Data on age, to the nearest year in the year of surgery, and sex were obtained from the CHI register and social deprivation was obtained from the Scottish Index of Multiple Deprivation, linked to the postal code from the CHI register.

A CCI[27] was calculated for each patient from hospital discharge codes and the number of dispensed prescriptions from community pharmacies in the previous year was applied as an additional measure of comorbidity. Exposure to medicines in the previous year that predispose to renal impairment (NSAIDs, cyclooxygenase-2 inhibitors, angiotensin-converting enzyme inhibitors, angiotensin II receptor antagonists, diuretics, and β-blockers) was ascertained from dispensed prescribing data.

Baseline renal function was obtained from the laboratory database. This was the most recent, preoperative serum creatinine measurement and could include preoperative samples taken during the current admission for elective surgery; however, patients undergoing emergency surgery may have AKI on admission to the hospital as a result of trauma. We therefore used the most recent serum creatinine measurement before admission for emergency patients to distinguish CKD from AKI. Only patients with preoperative and postoperative creatinine measurements could be included, so we measured and reported the completeness of data in each group. Patients on RRT were excluded from the analysis.

Statistical Analyses

Data from each surgical specialty (orthopedics, urology, vascular surgery, and obstetrics and gynecology) were analyzed separately. The design was an ITS study with segmented regression analysis[28] using 24 monthly time points before and after the intervention in October 2008. The analysis plan included information that addressed the common risks of bias in ITS studies (Supplemental Table 1). The monthly rates of AKI were defined by the number of patients in each AKI stage as a proportion of all patients aged$\geq$18 years undergoing surgery in each month. Rates were plotted over time for descriptive purposes and the functional form of the relationship before and after the intervention was assessed with splines. Rates were analyzed using multiple linear regression if the functional form was linear. Where monthly rates were not normally distributed, log transformation was used in the linear regression models to conform to the statistical criterion of normal distribution of residuals. All models were tested for autocorrelation using the Durbin–Watson statistic.[29] Multivariate analyses including age, sex, nephrotoxic drugs, and comorbidity were carried out only when there was a significant change in AKI postintervention. Data for chronic nephrotoxic medication use were adjusted at an aggregate level. Poisson regression analysis was used when there were no or few patients for certain months. In Poisson regression, the outcome variable is in the form of counts or number of patients, and the natural log of the denominator (total number of operations) was included in the model as an offset. Analyses were carried out in IBM SPSS (version 21) and SAS (version 9.2.1) software.

ACKNOWLEDGMENTS

This study was funded by the Scottish Government Healthcare Associated Infection Task Force.

DISCLOSURES

None.

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See related editorial, "The Seen and the Unseen: Clinical Guidelines and Cost-Effective Care," on pages 2390–2392.

This article contains supplemental material online at http://jasn.asnjournals.org/lookup/suppl/doi:10.1681/ASN.2014010035/-/DCSupplemental.

Supplemental Material

Table I OPCS codes for orthopaedic surgery requiring antibiotic prophylaxis

W15 1st Metatarsal Osteotomy, e.g. for Hallux Valgus	W19 Primary Open Reduction of Fracture with Intramedullary Fixation
W37 Total Hip Replacement, cemented	W20 Primary Open Reduction of Fracture with Extra medullary Fixation
W38 Total Hip Replacement, uncemented	W21 Primary Open Reduction of Intra-articular Fracture with Fixation
W39 Total Hip Replacement, other	W22 Other Primary Open Reduction of Fracture
W94 Total Hip Replacement, hybrid, cemented	W23 Secondary Open Reduction of Fracture
W95 Total Hip Replacement, hybrid, uncemented	W24 Closed Reduction of Fracture with Internal Fixation
W40 Total Knee Replacement, cemented	W25 Closed Reduction of Fracture with External Fixation
W41 Total Knee Replacement, uncemented	W46 Prosthetic Replacement of Head of Femur, cemented
W42 Total Knee Replacement, other	W47 Prosthetic Replacement of Head of Femur, uncemented
W43 Total Prosthetic Replacement of Other Joint, cemented	
W44 Total Prosthetic Replacement of Other Joint, uncemented	
W49 Humeral Head Replacement, cemented	
W50 Humeral Head Replacement, uncemented	
W59 Fusion of Toe Joint	
W60 Fusion of Other Joint	
W96 Total Shoulder Replacement, cemented	
W97 Total Shoulder Replacement, uncemented	
O06 Hybrid Total Shoulder Replacement, cemented humerus	
O07 Hybrid Total Shoulder Replacement, cemented glenoid	
O08 Hybrid Total Shoulder Replacement, both components cemented	
O21 Total Elbow Replacement, cemented	
O22 Total Elbow Replacement, uncemented	

GASTROINTESTINAL SURGERY
J02 Partial excision of liver
J03 Extirpation of lesion of liver
J04 Repair of liver
J18 Excision of gall bladder and exploration of common bile duct
J27 Excision of bile duct
J28 Excision of lesion of bile duct
J29 Connection of hepatic duct
J30 Connection of common bile duct
J31 Open introduction of prosthesis into bile duct (if stones but not if cancer)
J32 Repair of bile duct
J33 Incision of bile duct
J34 Plastic repair of sphincter of Oddi using duodenal approach
J35 Incision of sphincter of Oddi using duodenal approach
J36 Other operations on ampulla of Vater using duodenal approach
J55 Total excision of pancreas
J56 Excision of head of pancreas
J57 Other partial excision of pancreas
J58 Extirpation of lesion of pancreas
J59 Connection of pancreatic duct
J60 Other open operations on pancreatic duct
J61 Open drainage of lesion of pancreas
UPPER GI
G01 Excision of oesophagus and stomach (oesophagogastrectomy)
G27 Total excision of stomach (total gastrectomy)
G28 Partial excision of stomach (partial gastrectomy)
G31 Connection of stomach to duodenum
G32 Connection of stomach to transposed jejunum
G33 Other connection of stomach to jejunum
G35 Operations on ulcer of stomach
G36 Other repair of stomach
G38.5 Incision of stomach not elsewhere classified
G41 Repair of perforation of pylorus
LOWER GI
H04 Total excision of colon and rectum
H05 Total excision of colon
H06 Extended excision of right hemicolon
H07 Other excision of right hemicolon
H08 Excision of transverse colon
H09 Excision of left hemicolon
H10 Excision of sigmoid colon
H11 Other excision of colon
H12 Extirpation of lesion of colon
H13 Bypass of colon
H14 Exteriorisation of caecum
H15 Other exteriorisation of colon
H16 Incision of colon
H29 Subtotal excision of colon and rectum
H33 Excision of rectum
G49 Excision of duodenum
G50 Open extirpation of lesion of duodenum
G52 Operations on ulcer of duodenum
G53 Other open operations on duodenum
G58 Excision of jejunum
G59 Extirpation of lesion of jejunum
G60 Artificial opening into jejunum

G63 Other open operations on jejunum
G68 Allotransplantation of ileum
G70 Open extirpation of lesion of ileum
G74 Creation of artificial opening into ileum
G75 Attention to artificial opening into ileum
G78 Other open operations on ileum
GYNAECOLOGICAL SURGERY
Q07 Abdominal excision of uterus
Q08 Vaginal excision of uterus
Q09 Other excision of uterus
Q074 laparoscopic total hysterectomy
Q075 - laparoscopic subtotal hysterectomy
UROLOGICAL SURGERY
M651 TURP
M421 TURBT
M091 Fragmentation of kidney stone
M271 Fragmentation of ureteric stone
M273 Fragmentation of ureteric stone
M094 Removal of kidney stone
M263 Removal of ureteric stone
M343 Radical cystectomy
M612 Laparoscopic radical prostatectomy M612 AND Y752 (need to include)
Y752 Laparoscopic radical prostatectomy
VASCULAR SURGERY
L16 Extraanatomic bypass of aorta
L18 Emergency replacement of aneurysmal segment of aorta
L19 Other replacement of aneurysmal segment of aorta
L20 Other emergency bypass of segment of aorta
L21 Other bypass of segment of aorta
L22 Attention to prosthesis of aorta
L23 Plastic repair of aorta
L25 Other open operations on aorta
L28 Transluminal insertion of stent graft for aneurismal segment of aorta
L29 Reconstruction of carotid artery
L30 Other open operations on carotid artery
L37 Reconstruction of subclavian artery
L38 Other open operations on subclavian artery
L41 Reconstruction of renal artery
L42 Other open operations on renal artery
L45 Reconstruction of other visceral branch of abdominal aorta
L46 Other open operations on other visceral branch of abdominal aorta
L48 Emergency replacement of aneurysmal iliac artery
L49 Other replacement of aneurysmal iliac artery
L50 Other emergency bypass of iliac artery
L51 Other bypass of iliac artery
L52 Reconstruction of iliac artery
L53 Other open operations on iliac artery
L56 Emergency replacement of aneurysmal femoral artery
L57 Other replacement of aneurysmal femoral artery
L58 Other emergency bypass of femoral artery
L59 Other bypass of femoral artery
L60 Reconstruction of femoral artery
L62 Other open operations on femoral artery
L65 Revision of reconstruction of artery
L68 Repair of other artery

L70 Other open operations on other artery
L75 Other arteriovenous operations
L77 Connection of vena cava or branch of vena cava
L79 Other operations on vena cava

Table II: Cochrane EPOC (Effective Practice and Organisation of Care) Risk of Bias Criteria for Interrupted Time Series studies and analysis plan for addressing each risk

Cochrane Risk of Bias Criteria	**Analysis Plan**
Was the intervention independent of other changes? Low	This was a planned intervention and analysis. The stimulus for the analysis was concern about possible unintended consequences of the policy change; The policy was intended to reduce *C difficile* infection. Multivariate analysis was used to adjust for possible changes in demography, co-morbidity or risk factors for AKI
Was the shape of the intervention effect pre-specified? **Low**	The point of analysis was the point of intervention (introduction of the new antibiotic policy in October 2008). The anticipated shape of the intervention effect was an increase in post-operative renal impairment after the intervention
Was the intervention unlikely to affect data collection? **Low**	Analysis compared frequency of sampling for renal function tests in the risk window in the pre- and post-intervention phases in order to test whether the intervention may have affected data collection.There were slightly greater numbers of tests performed in the pre-intervention period which would have biased results towards the null as it may have led to cases of AKI being missed.
Was knowledge of the allocated interventions adequately prevented during the study? **Low**	The primary outcome (acute kidney injury) was objectively defined from serum creatinine tests
Were incomplete outcome data adequately addressed? **Low**	We included information about frequency of renal function tests in the pre- and post-intervention periods and were able to identify any patients with missing data that prevented assessment of post-operative renal impairment. We have only drawn conclusions from groups where there was a low incidence of missing data.
Was the study free from selective outcome reporting? **Low**	Our study only has one outcome and this was derived from routine data. There was a significant amount of missing data as serum creatinine testing was not done. We have reported the frequency of missing data.
Was the study free from other risks of bias? **Low**	We had 24 monthly time points pre- and post-intervention so were able to adjust for seasonal variation.

Table III. Multivariate Analysis of included versus excluded patients

Orthopaedic Surgery				
Variable	**B**	**Sig**	**B**	**95% CI**
Age at surgery	0.07	<0.001	1.08	1.07, 1.08
Gender	-0.40	<0.001	0.67	0.59, 0.76
Charlson comorbidity Index	0.11	0.04	1.12	1.01, 1.24
Urology				
Age at surgery	0.03	*<0.001*	1.03	1.02, 1.03
Gender	-0.28	*0.02*	0.76	0.60, 0.96
Charlson comorbidity Index	-0.03	0.43	0.98	0.92, 1.04
Vascular				
Age at surgery	0.06	*<0.001*	1.06	1.05, 1.08
Gender	-0.25	0.28	0.78	0.50, 1.22
Charlson comorbidity Index	0.02	0.75	1.03	0.89, 1.19
		Gastrointestinal		
Age at surgery	0.02	*<0.001*	1.02	1.01, 1.02
Gender	-0.53	*<0.001*	0.59	0.50, 0.70
Charlson comorbidity Index	0.49	*<0.001*	1.64	1.49, 1.80
Gynaecology				
Age at surgery	0.02	*<0.001*	1.02	1.01, 1.04
Gender	-	-	-	-
Charlson comorbidity Index	0.28	*<0.001*	1.32	1.15, 1.52