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Reduction in postoperative Acute Kidney Injury following a change in antibiotic prophylaxis policy for orthopaedic surgery – an observational study

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Short running title: Reduced AKI in orthopaedic surgery

Abstract

Objectives: Evidence has shown that a prophylactic antibiotic regimen of flucloxacillin and gentamicin for orthopaedic surgery was associated with increased rates of post-operative acute kidney injury (AKI). This resulted in changes in national antibiotic policy recommendation for orthopaedic surgical prophylaxis. This study aimed to assess whether this change from flucloxacillin and gentamicin to co-amoxiclav was associated with changes in the rates AKI and *Clostridium difficile* infection (CDI).

Methods: An observational study and interrupted time series analyses were used to assess rates of post-operative AKI separately in patients undergoing neck of femur (NOF) repair and other orthopaedic operations which required antibiotic prophylaxis. Incidence rate ratios were used to evaluate changes in CDI rates.

Results: Following the change in policy, from flucloxacillin and gentamicin to co-amoxiclav, there was a relative change in rates of post-operative AKI of -63% (95% CI -77% to -49%) at 18 months in the other orthopaedic surgeries group. In the NOF repair group, there was no change in the rate of post-operative AKI -10%, (95% CI -35% to 15%) at 18 months. The incident rate ratio for CDI in other orthopaedic operations was 0.29 (95%CI 0.09 to 0.96) and for NOF repair patients was 0.76 (95%CI 0.28 to 2.08).

Conclusions: The use of co-amoxiclav for antibiotic prophylaxis in orthopaedic surgery was associated with a decreased rate of post-operative AKI compared to flucloxacillin and gentamicin and was not associated with increased rates of CDI.

Introduction

Surgical site infections (SSI) are a preventable healthcare associated infection. They are associated with a significant increase in morbidity, mortality, length of hospital stay and both socioeconomic and health related costs.[1, 2] Prophylactic antibiotics have been shown to reduce the rate of SSI in patients undergoing joint replacement surgeries[3] and are recommended for orthopaedic implant surgeries.[4] However, their use can also have associated adverse effects and unintended consequences, such as allergy,[5] the development of antibiotic resistance among organisms,[6] acute kidney injury (AKI)[7-10] and *Clostridium difficile* infection (CDI).[11, 12]

AKI is reported to be an independent risk factor for mortality, as well as being a marker of co-existing pathologies,[13-16] and is a predictor of poor prognosis in hospitalised patients.[17-19] AKI is associated with increased risk of the development and progression of chronic kidney disease (CKD), increased risk of readmission,[20] longer hospital stays and higher long term mortality rates,[19] even in patients with transient changes in renal function.[20] AKI therefore has associated important long term socioeconomic and public health effects.

CDI is a healthcare-associated infection with significant associated morbidity and mortality[21] that has been under mandatory surveillance in Scotland since 2006,[22] and in England since 2004.[23] Antibiotic use is associated with an increased risk of CDI for at least 3 months following administration.[24] In order to restrict the use of antibiotics associated with high risk of CDI[25] NHS Tayside orthopaedic antibiotic prophylaxis was changed from cefuroxime to gentamicin and flucloxacillin in October 2008. Following this, several studies indicated that prophylaxis with flucloxacillin and gentamicin in orthopaedic patients was associated with a significant increased rate of post-operative AKI.[7-10] Most of these were uncontrolled before and after studies, but one was a robust quasi-experimental analysis that found the same

effect.[7] In June 2012 within NHS Tayside, policy was changed from flucloxacillin and gentamicin to co-amoxiclav.

This study aimed to assess whether the change in orthopaedic antibiotic prophylaxis policy from flucloxacillin and gentamicin to co-amoxiclav was associated with changes in the rates of post-operative AKI and CDI in adult patients undergoing orthopaedic surgery. The study also aimed to assess the effect of post-operative AKI on length of hospital stay and one year post-operative mortality.

Ethical Approval

Anonymised record linkage was conducted according to the Health Informatics Centre (HIC) standard operating procedure. The Tayside Research Ethics Committee does not require submission of individual studies that follow this standard operating procedure.

Methods

This study included all adults aged ≥18 years who resided, or died, in the NHS Tayside region and, who underwent an orthopaedic surgical procedure requiring antibiotic prophylaxis, between 1st October 2008, and 31st December 2013. Patients were identified by the Office of Population, Censuses and Surveys Classification of Surgical Operations and Procedures 4th revision (OPCS-4) codes[26] from hospital admissions data (Supplementary Material, Table 1).

Table 1 shows the recommended antibiotics and doses in NHS Tayside before and after the 2012 policy change. Patients who underwent repair of a neck of femur (NOF) fracture received co-amoxiclav as antibiotic prophylaxis throughout the period of observation described here because of concerns raised by orthopaedic surgeons with regard to administering gentamicin in this particular patient group.

This study period encompassed 63 months between October 2008 and December 2013. The study design was an interrupted time series (ITS) with segmented regression analysis[27] using 44 monthly time points before and 19 monthly time points after the intervention in June 2012.

Definitions

The definition of postoperative renal impairment used the Kidney Disease Improving Global Outcomes (KDIGO) criteria.[28] (Supplementary Material Table 2) Patients with postoperative AKI were classified according to their most severe degree of AKI. This was applied using baseline serum creatinine as the pre-measurement (most recent in the year prior to surgery) and maximal serum creatinine during the first 7 post-operative days as the post-measurement.

The definition of post-operative CDI was any case with a *Clostridium difficile* toxin positive stool sample and/or polymerase chain reaction (PCR) for *Clostridium difficile* positive result within 12 weeks post-operatively. Cases were excluded if there had been another positive sample for *Clostridium difficile* toxin or PCR in the 12 weeks prior to this, due to the possibility of this being a recurrence of CDI.

Data Sources

Data were provided by HIC[29] at the University of Dundee. Data were linked between the following datasets: Community Health Index (CHI) register, Scottish Morbidity Record of hospital admissions (SMR01), OPCS-coded procedures, laboratory results database, medicines dispensed by community pharmacies, General Register Office death database and Scottish Care Information – Diabetes Collaboration (SCI-DC).

Age, to the nearest year in the year of surgery, sex and social deprivation, the Scottish Index of Multiple Deprivation (SIMD) which is linked to residential postal code, were obtained from the CHI register. A Charlson Comorbidity Index (CCI)[30] score was calculated for each

patient from hospital discharge codes and the number of medication types dispensed from community pharmacies in the previous three months was applied as an additional measure of comorbidity.

Exposure to medicines that predispose to renal impairment (NSAIDs, cyclooxygenase-2 inhibitors, angiotensin-converting enzyme inhibitors (ACE I), angiotensin II receptor antagonists (ARB), diuretics, β-blockers, metformin, other hypoglycaemics and lipid regulating medications), in the three months prior to the operation was ascertained from dispensed prescribing data.

Baseline renal function was obtained from the laboratory database. This was the most recent preoperative serum creatinine measurement in 12 months prior to and including the date of operation, which could include preoperative samples taken during the current admission. The median was calculated if there was more than one serum creatinine measurement taken on the same day. Only patients with both preoperative and postoperative creatinine measurements could be included. The completeness of creatinine data in each group was measured and reported (Table 2). Patients already established on renal replacement therapy pre-operatively were excluded from the analysis. In cases where a patient had a subsequent operation within 7 days of another operation, the second operation was excluded from the analysis.

Statistical Analysis

Monthly rates of AKI were defined by the number of patients with AKI as a proportion of all patients aged ≥18 years undergoing orthopaedic 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 for linearity with splines. Kolmogorov - Smirnov test[31] and the Shapiro – Wilk test[32] were used to check data were normally distributed. Segmented regression analysis of ITS data was used to assess intervention effects on total AKI at 1, 6, 12

and 18 months after the policy change, with 95% confidence intervals (95%CI)[27, 31] and models were assessed for first order autocorrelation using the Durbin–Watson statistic,[33] with adjustment for autocorrelation using lag terms as required. The effect size at each time point was converted to a relative percentage difference between the observed and predicted (if the intervention had not happened) AKI rate.

To assess for the effect of factors other than policy change on total AKI rates multiple linear regression was used to determine the effects of exposure to medicines that predispose to renal disease, age, sex and CCI on all rates of AKI in the time periods before and after policy change.

The monthly rates of CDI were too small to undergo ITS analysis. Due to there being no or few cases in some months, rates of CDI were calculated using incidence rate ratios[34] (IRR) and 95% CIs.

The median length of stay with IQR was calculated from data extracted from SMR01 data.

Death within 1 year of surgery was calculated as a percentage of all patients who had undergone operations within each group, in patients with and without post-operative AKI.

All analyses were carried out in IBM SPSS (version 21) and SAS (version 9.2.1) software. A p-value of <0.05 was considered statistically significant.

The analysis plan included information that addressed the common risks of bias in ITS studies (Supplementary Material, Table 3).

Results

Data were provided for 14,563 potentially eligible orthopaedic operations in the study period of October 1, 2008 to December 31, 2013. Of these, five duplicate cases were excluded.

Cases were split into two groups, Group 1 (n=12707): patients who underwent orthopaedic operations other than NOF repair, as identified by the International Statistical Classification of Diseases and Related Health Problems ICD9/10 main condition codes, and Group 2 (n=1851): patients who underwent a NOF repair operation. Patients were excluded if they were on the renal replacement register (Group 1 n=33 (0.26%), Group 2 n=8 (0.43%)), if the operation was within 7 days of a previous operation (Group 1 n=22 (0.17%), Group 2 n=0) or if creatinine data were missing (Group 1 n=3410 (26.8%), Group 2 n=81 (4.38%)). In total, 11,004 cases were included (Figure 1).

Compared to patients in the other orthopaedic operation group, patients in the NOF group were older, were more likely to be female and had higher CCI scores (Table 1). However, baseline creatinine was no worse in NOF patients compared with the other orthopaedic operation group, median creatinine 69 µmol/L (IQR 53-94) versus 68 µmol/L (IQR 57-80) respectively.

Table 1 includes the percentage of missing creatinine data within each sub-group. The majority of missing creatinine measurements were post-operative. There were fewer missing creatinine data for patients with NOF repair operations. An examination of the characteristics of patients included *versus* patients who were excluded due to missing data showed that the included patients were, on average, older patients with higher CCI comorbidity scores (Supplementary Material, Table 4).

Acute Kidney Injury

The majority of AKI was mild (Stage 1) AKI (Table 2). Overall, AKI was more common in the NOF repair patients (Group 2) and affected a slightly higher proportion overall in the second study period, while Group 1 had a slightly lower proportion of patient with AKI in the second study period (after prophylaxis changed).

All other orthopaedic surgeries (Group 1)

The monthly proportion of patients with any stage of post-operative AKI in Group 1 fell following the intervention (Figure 2A) and interrupted time series analysis indicated a relative change of -63% (95% CI -77% to -49%) 18 months after the policy change (Table 3).

Multiple linear regression analyses were performed to assess for the effects of sex, age, CCI and the use of other nephrotoxic drugs. In addition to the policy change only ACE I/ARB were significantly associated with an increase in rates of post-operative AKI (β=0.186; 95% CI, 0.03 to 0.342; p=0.02).

Neck of Femur repair (Group 2)

Over the whole period of observation AKI rates in this group were highest, and they had most variation in the year preceding the change in antibiotic policy for the other group (Figure 2B). From interrupted time series analysis, there were statistically significant reductions in AKI rates in the following year but these were much smaller relative changes than in Group 1 and there was no significant change at 18 months after the policy change -10%, (95% CI -35% to 15%, Table 3).

Multiple linear regression analyses were performed to assess for the effects of sex, age, CCI and the use of other nephrotoxic drugs. Only ACE I/ARB were significantly associated with an increase in rates of post-operative AKI (β=0.2520; 95% CI, 0.04 to 0.464; p= 0.02).

Other outcomes

Death within 1 year of surgery

A higher proportion of patients with AKI died within 1 year of surgery compared with patients without AKI in both the NOF operations group 36.63% (n=89) versus 25.15%

(n=382), respectively (chi-square=14.09 df=1 p<0.001) and the other orthopaedic operations group 10.48% (n=108) versus 5.18% (n=425), respectively (chi-square=47.33 df=1 p<0.001).

Length of hospital stay

In the other orthopaedic operations group the median length of hospital stay was 6 days (IQR 11-3) in patients with post-operative AKI compared with 5 days (IQR 9-3) in patients without post-operative AKI. In the NOF repair operation group was 7 days (IQR 11-4) in patients with post-operative AKI compared with 6 days (IQR 10-3) in patients without post-operative AKI.

Clostridium difficile infection and SSI Rates

There was no change in the rate of CDI before and after the policy change in either group. The CDI IRR (95% CI) for the NOF repair group was 0.76 (0.28 to 2.08) and for other operations was 0.29 (0.09 to 0.96).

Audits of SSI rates were not done consistently for all types of surgery in the study population throughout the study period; however the SSI rates among the procedures audited were low throughout the study period with no apparent change in rate accompanying the policy changes

Discussion

This large observational study of >14,500 patients, found that a change in prophylactic antibiotic policy from flucloxacillin and gentamicin to co-amoxiclav was associated with decreased rates of post-operative AKI in patients undergoing orthopaedic surgeries (excluding NOF repairs) in the NHS Tayside Region of Scotland, with the majority of patients developing mild (Stage 1) AKI. The association with the change in antibiotic policy

is strengthened because there were much smaller reductions in monthly AKI rates among patients who underwent NOF repair, who received co-amoxiclav throughout the study period, and the change at 18 months post policy change was not significant in this group. There was no change in CDI rates associated with the change in antibiotic policy.

We have shown a reduction in all stages of post-operative AKI by -63% (95% CI -77%,-49%) at 18 months post antibiotic policy change statistically significantly associated with that change in policy. There are likely to be other factors also contributing to the change in rates of AKI, supported by the (smaller magnitude and not significant at 18 months) reduction in NOF patients who were not affected by the policy change. Such factors include anaesthetic practice and post-operative care, such as the Enhanced Recovery Programme, which aims to optimise pre- and post-operative care including reducing the physical stress of the operation, promoting effective analgesia and encouraging early mobilisation and oral nutrition. This programme may lead to an increase in rates of post-operative AKI, as patients may be exposed to more nephrotoxic analgesics and less fluid replacement in the post-operative period than before. There has also been ongoing work throughout our institutions, educating healthcare professionals around recognition, prevention and management of AKI.

The causes of AKI are multifactorial and reported incidence varies dependent on the definition used, as well variations in population groups and settings[35]. The incidence of AKI in acute hospitalised patients is 5-7.5%, with 30-40% of cases occurring in the surgical perioperative period.[36, 37] This is an important contributor to post-operative morbidity and mortality[35] and research suggests that up to 30% of AKI is iatrogenic and/or potentially preventable.[38] The KDIGO AKI guidelines state that major surgery and trauma are exposures for non-specific AKI, where there is no specific kidney disease causing AKI. [28] Therefore, it is important that these patients have their serum creatinine and urine output measured

alongside their clinical status. In line with previous recommendations[7] patients receiving surgical antibiotic prophylaxis are generally undergoing major surgery and, as a minimum, should have serum creatinine measured both pre-operatively and at least 24 hours post-operatively.

The unadjusted one year post-operative mortality was higher in patients who had undergone an NOF repair surgery when compared with those having undergone other orthopaedic surgeries. Within each subgroup crude 1 year post-operative mortality was higher among those with post-operative AKI than those without. This is consistent with the previous findings, including this cohort that AKI contributes to higher mortality.[16, 19, 36-38] We did not, however, find any difference in length of hospital stay, when comparing patients with and without AKI, which may be because the majority of AKI were stage 1and it is possible that AKI was not detected until after the patient was discharged so did not impact on inpatient management. The potential implications of reduced rates of AKI include reduced mortality, readmission to hospital, progression to CKD and the subsequent socio-economic costs, that have previously been identified in the literature.[20]

There was no change in CDI rates in either group, suggesting that this is not related to changes in surgical prophylactic antibiotic policy. Restrictions on the use of therapeutic antibiotics considered high-risk for CDI, which are used for longer durations, have contributed, alongside infection control procedures and a change in circulating strains and virulence of *Clostridium difficile*,[12, 39] to a reduction in rates of CDI.[40]

Effective restrictions on the use of therapeutic antibiotics associated with high risk for CDI have also been shown in the orthopaedic surgery population, without a subsequent effect on rates of deep SSI.[41] Rates of CDI across the UK have fallen. By 2013, in Scotland there had

been reductions in CDI of greater than 79% since 2007/08[42] and in 2013/14, England reported a reduction in CDI of 76% compared with 2007/08.[43]

Prophylactic antibiotics in orthopaedic implant surgery reduces the risk of SSI.[3] In an ageing population, it is likely that the number of orthopaedic operations is going to increase, exposing more individuals to prophylactic antibiotics. Any prophylactic antibiotic should aim to reduce SSI rates, providing cover for commonly implicated pathogens and considering local resistance patterns, while also minimising the associated risks of AKI, CDI, antibiotic resistance and allergies. SSI, AKI and CDI are interlinked. The management of SSI is antibiotic therapy. SSI in severe cases can lead to sepsis. Both exposure to certain antibiotics and sepsis have been identified as risk factors for non-specific AKI.[28] Further antibiotic exposure would also put patients at an increased risk of CDI,[24] which itself may result in a patient becoming dehydrated, another susceptibility for non-specific AKI.[28] It is therefore important to ensure that intended and unintended consequences of changes in policy are balanced.

The strengths of our study are that we used a robust quasi-experimental study design to evaluate a real-world policy change, addressed risks of bias for ITS studies in our analysis plan (Supplementary Material, Table 2), defined operations using OPCS-4 operation procedure codes (Supplementary Material, Table 3), defined NOF cases using ICD9/10 codes, and used the KDIGO definition of AKI.

We addressed the issues common to all non-randomised studies, including potential ascertainment and selection biases. Data were prospectively entered into electronic databases and were not subject to manipulation or bias. ITS is the strongest quasi-experimental design to assess intervention effects in non-randomised setting. It allows for control of trends that

exist before the intervention being studied, by using multiple time points before and after the intervention.[44, 45]

A weakness of our study is that we were unable to adjust for potential effects of intraoperative events and other medications prescribed during in-patient stay on AKI rates because these data are not collected electronically. Furthermore, it is possible that the changes in diagnostic criteria and methods could have masked a true decrease in CDI incidence over the study period.

Rates of post-operative AKI were not assessed in 4% of the NOF repair surgery group and 27% of the other orthopaedic operations group because of missing pre-operative and post-operative creatinine data. These patients were younger and had less comorbidity when compared with patients who were included in the study. This could bias the results in either direction of estimating the rates of AKI. However, there were similar percentages of missing creatinine data in the pre-intervention and post-intervention groups.

Previous literature showed that a prophylactic antibiotic regimen of flucloxacillin and gentamicin in orthopaedic patients was associated with a significant increased rate of AKI. From the previous research carried out by our group it is not clear whether gentamicin or flucloxacillin or both antibiotics increased the risk of post-operative AKI, or by what mechanism.[7] However, this study has shown that using co-amoxiclav for antibiotic prophylaxis in orthopaedic surgery is associated with a decreased rate of post-operative AKI compared to flucloxacillin and gentamicin and is not associated with an increased rate of CDI. This study also raises the importance of monitoring the intended and unintended consequences of policy change within healthcare.

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Transparency declaration

None to declare.

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Table 1. Baseline characteristics and missing creatinine data

Characteristic	Operations other than NOF repair		NOF repair operations	
	Before 2012 policy change	After 2012 policy change	Before 2012 policy change	After 2012 policy change
Recommended antibiotics (dose)	Flucloxacillin (1g) x 4 doses + one dose Gentamicin (4mg/kg)	3 doses Co-amoxiclav (1.2g)	3 doses Co-amoxiclav (1.2g)	3 doses Co-amoxiclav (1.2g)
Patients (n)	6267	2975	1250	512
Mean Age (yr) (SD)	68.5 (14)	68.9 (13.6)	80 (11.4)	80.6 (10.2)
Median Baseline SCr (µmol/L) (IQR)	74 (62-88)	68 (57-80)	72 (57-94)	69 (53-94)
Sex n(%)				
Female	3619 (57.7)	1774 (59.6)	914 (73.1)	372 (72.7)
Male	2648 (42.3)	1201 (40.4)	336 (26.9)	140 (27.3)
SIMD n(%)				
1-3 (most deprived)	1212 (19.3)	573 (19.3)	244 (19.5)	113 (22.1)
4-7	2679 (42.7)	1299 (43.7)	545 (43.6)	217 (42.4)

8-10 (least deprived)	2269 (36.2)	1044 (35.1)	444 (35.5)	171 (33.4)
CCI n(%)				
Low (0)	5282 (84.3)	2317 (77.9)	789 (63.1)	303 (59.2)
Medium (1 or 2)	870 (13.9)	584 (19.6)	400 (32)	183 (35.7)
High (≥3)	115 (1.8)	74 (2.5)	61 (4.9)	26 (5.1)
Patients before missing creatinine exclusions n(%)*	8515	4137	1304	539
Missing pre-operative creatinine	453 (5.32)	192 (4.64)	7 (0.54)	4 (0.74)
Missing post-operative creatinine	1995 (23.43)	1039 (25.11)	49 (3.76)	22 (4.08)
Missing both pre and post-operative creatinine	405 (4.76)	173 (4.18)	4 (0.31)	2 (0.37)

***** Data are presented as n (%) of all patients after exclusion of duplicates, patients on RRT and subsequent operation within 7 days

Table 2. AKI rates by each stage

	Operations other than NOF repair		NOF repair operations	
AKI Stage n(%)	Before 2012 policy change	After 2012 policy change	Before 2012 policy change	After 2012 policy change
1	618 (9.86)	239 (8.03)	153 (12.24)	67 (13.09)
2	95 (1.52)	22 (0.74)	16 (1.28)	4 (0.78)
3	45 (0.72)	12 (0.4)	2 (0.16)	1 (0.2)
None	5509 (87.9)	2702 (90.8)	1079 (86.32)	440 (85.94)

Table 3. ITS analyses intervention effects at 1, 6, 12 and 18 months post-policy change for other orthopaedic operations and NOF repair operations, all AKI Stages (Rate per 100 patients)

	Operations other than NOF repair				NOF repair operations			
	1 month	6 months	12 months	18 months	1 month	6 months	12 months	18 months
Absolute difference	-6.1	-8.2	-10.6	-13.1	-4.7	-3.8	-2.8	-1.8
95% CI	(-9.7,-2.6)	(-11.2,-5.2)	(-13.9,-7.4)	(-17.3,-8.9)	(-8.8,-0.5)	(-7.3,-0.4)	(-6.5,0.8)	(-6.6,3.0)
Relative change	-36.0%	-45.2%	-54.8%	-63.2%	-28.7%	-22.8%	-16.1%	-10.0%
95% CI	(-54.6%,-17.4%)	(-57.7%,-32.6%)	(-65.3%,-44.3%)	(-77.3%,-49.1%)	(-52.2%, -5.3%)	(-40.8%, -4.8%)	(-34.6%, 2.3%)	(-34.7%, 14.8%)

Figure 1: Summary of case groupings and exclusions

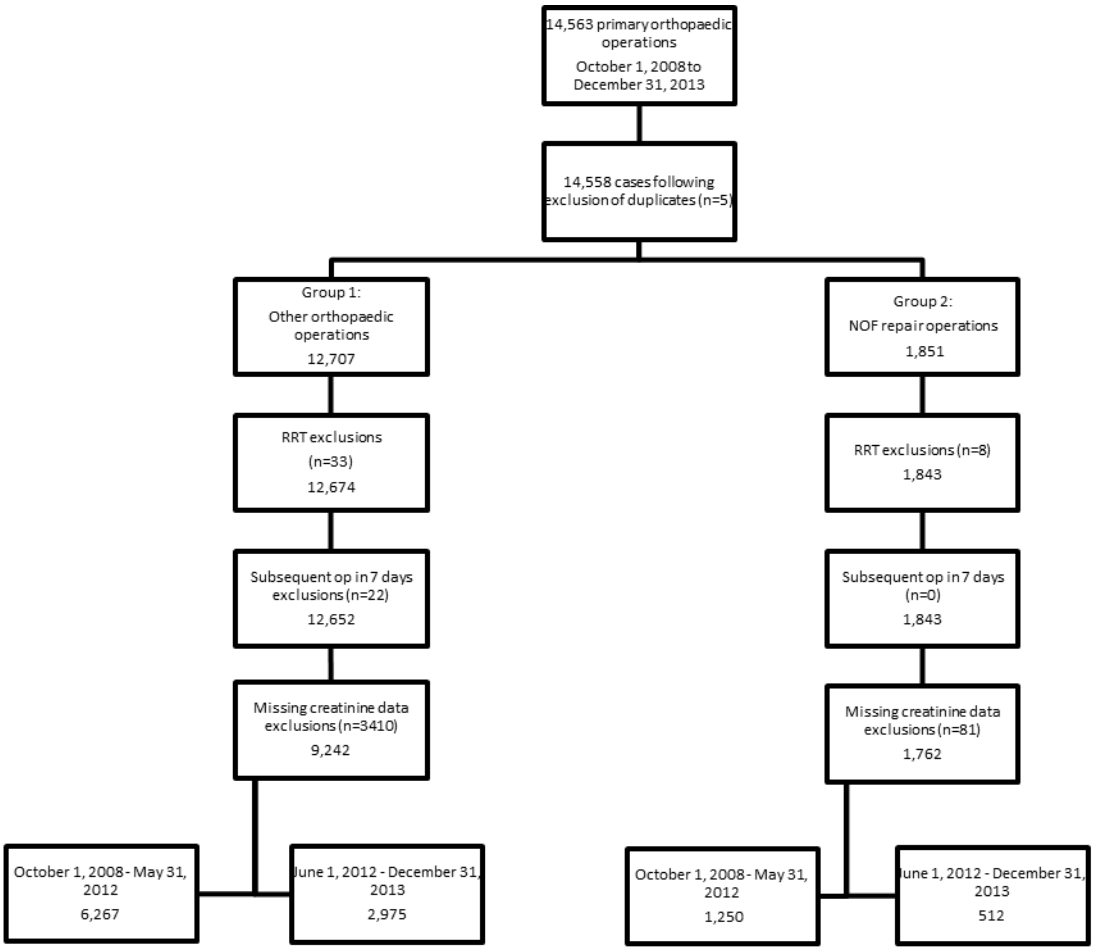

Figure 2A: AKI (Stages 1-3 combined) in orthopaedic operations other than NOF repair from October 2008 to December 2013. The Policy Change was from flucloxacillin plus gentamicin to co-amoxiclav for antibiotic prophylaxis.

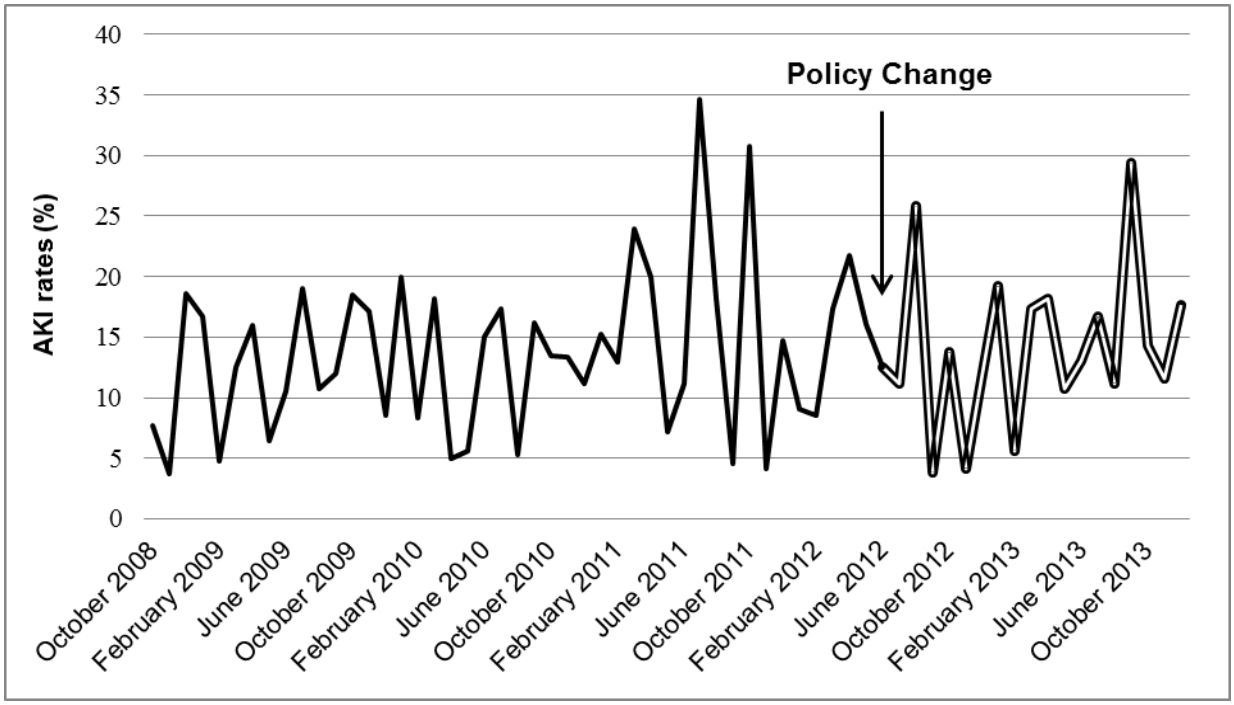

Figure 2B: AKI (Stages1-3 combined) in NOF repair operations from October 2008 to December 2013 with co-amoxiclav the recommended antibiotic prophylaxis throughout. The Policy Change was for operations other than NOF repair.