Surgical site infection rate is higher following hip and knee arthroplasty when cefazolin is underdosed

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Running title: Cefazolin dose and SSI

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Abstract

Purpose. While many guidelines recommend higher doses of cefazolin for those with higher body weight there are scant outcome data showing the benefit of higher doses. The surgical site infection (SSI) rate following hip or knee arthroplasty were analyzed by the dose of cefazolin used for surgical prophylaxis.

Methods. Analysis of the New Zealand national prospective surveillance and quality improvement SSI Improvement Programme data base for the period July 2013 to December 2017. The CDC National Healthcare Safety Network SSI definitions were used and patients were followed for 90 days after surgery. Under dosing was defined as 1g cefazolin for those weighing ≥80kg and <3g for those weighing ≥120kg.

Results. There were 38,288 procedures where cefazolin was used for prophylaxis; the weight was known for all these procedures. Of the 1840 patients receiving 1g of cefazolin 676 (37%) weighed ≥80kg. Of the 2,011 patients weighing ≥120kg, 1,464 (73%) were underdosed. After multivariable analysis male gender, higher total surgical risk scores, revision and hip arthroplasties, and cefazolin under dosing were associated with higher SSI rates. For the 2,106 underdosed patients the OR for SSI was 2.19 (95% CI 1.61-2.99, p<0.0001). The number of higher weight patients needed to treat to prevent one SSI was 83; a cost of <$500 to prevent an infection costing ~$40,000.

Conclusion. Patients undergoing hip or knee arthroplasty and weighing ≥80kg or ≥120kg should receive 2g or ≥ 3g of cefazolin respectively for SSI prophylaxis. The question of whether ≥4g is needed for those ≥120kg, or above a given BMI of >35kg/m^2 or >40kg/m^2, remains unanswered.

Word count: 259

Index terms: Bacterial infections; Cefazolin; Cephalosporins; Obesity; Surgical site infection; Weight

Key points:

1. Weight based recommendations for cefazolin used for surgical prophylaxis have been made without substantive correlation between weight-based dose and the risk of subsequent SSI.
2. 2,106 patients underdosed with cefazolin had a higher SSI rate, OR 2.2, following hip or knee arthroplasty.
3. Patients weighing ≥80kg or ≥120kg should receive 2g or ≥3g of cefazolin respectively for SSI prophylaxis.

Word count: 60

Introduction

The global obesity epidemic continues to expand. One of obesity's many adverse health effects is increased risk for surgical site infection (SSI).[1,2] While obese patients have equivalent health gain following arthroplasty than the non-obese they have higher complication rates, including SSI.[3-5] In New Zealand for those with a BMI of >40kg/m^2 the odds ratio for SSI following primary hip arthroplasty is 5.6 and 1.9 following primary knee arthroplasty.[6]

New Zealand's national SSI Improvement Programme (SSIIP), a prospective surveillance and quality improvement programme, started in 2013 with the aim of reducing SSI following hip and knee arthroplasty by improving adherence to interventions known to reduce SSI risk.[7,8] With increased adherence to the recommended interventions the median SSI rate has reduced from 1.36% to 0.96%.[9] The SSIIP recommended all patients undergoing arthroplasty receive ≥2g of cefazolin before surgery. It was unclear from the literature if those weighing >120kg should receive ≥3g because of the dearth outcome data showing that higher cefazolin doses for those with higher weight resulted in a reduced SSI rate.[10-14]

The SSIIP data includes body weight and dose of the antibiotic used for prophylaxis. The SSIIP data were analyzed to see if there was any relationship between weight, cefazolin dose and the SSI rate.

Methods

The SSIIP follows all publicly funded hip and knee arthroplasties in New Zealand. Full details of the methods, data collection, definitions and interventions have been previously published.[7-9] In brief all procedures have a standard information data set recorded, including patient gender, weight, procedure type, ie. hip or knee, primary or revision procedure, ASA score, duration of procedure, timing and dose of the antimicrobial prophylaxis used, and use of alcohol-based skin preparation. The CDC National Healthcare Safety Network (NHSN) SSI definitions were used and patients were followed for 90 days after surgery.[15-16] Only SSIs identified during the patient's initial admission or readmission were recorded.

The Programme's three promoted interventions are: administration of prophylaxis in the hour before incision; ≥2g of cefazolin or ≥1.5g cefuroxime; and the use of an alcohol-based skin preparation containing either povidone iodine or chlorhexidine.[7-9,17]

Cefazolin underdosing was defined as 1g for those weighing ≥80kg and <3g for those weighing ≥120kg. Other doses were defined as recommended dosing, ie. 1g for <80kg, 2g for 80-120kg and ≥3g for ≥120kg.

The univariable associations between demographic, clinical and surgical features and recommended cefazolin dosing and SSI were summarized as odds ratios (ORs) with 95% confidence intervals. Those variables showing significant associations with SSI were entered into a multivariable logistic regression to determine the independent associations with SSI. For multivariable analysis weight was entered into the analysis in preference to BMI as this had the stronger univariate association and was most directly associated with the weight-based underdosing As there was an association between weight and recommended cefazolin dose the multivariable model was re-calculated with and without weight as an independent variable and a single measure was generated which combined the weight and cefazolin underdosing groups to allow comparisons of the effect of underdosing within individual weight groups. A two-tailed p-value <0.05 was taken to indicate statistical significance.

The number of higher weight patients needed to treat (NNT) to prevent one SSI was calculated by the formula; absolute risk reduction (ARR) = 100/NNT. We used the previously published increased cost of arthroplasty related SSI, ~NZ$40,000, to compare the additional cost of prophylaxis.[18] The cost of a 1g vial of cefazolin is ~NZ$0.70. An all up cost of drug, other materials and time was estimated to be ~NZ$5.

Under New Zealand Health and Disability Ethics Committee guidelines formal Ethical Committee review is not needed for this type of quality improvement related audit analysis.

Results

From 1 July 2013 through 31 December 2017 46,360 hip and knee arthroplasties were covered by the SSIIP. There were 38,288 procedures where cefazolin was used for prophylaxis; the weight was known for all these procedures. There were 407 SSI; 141(34.6%) superficial, 161(39.5%) deep and 105(25.8%) organ/space. There was no difference in the proportion of types of SSI in patients underdosed vs. patients receiving recommended doses (p=0.64, data not shown). Patients weighing ≥120kg had a higher SSI rate than those <120kg 2.9% (95%CI 2.2-3.7) vs. 0.96% (95%CI 0.86-1.07), OR 3.1 (95%CI 2.3-4.1), p<0.001.

Of the 1,840 patients receiving 1g of cefazolin 676 (37%) weighed ≥80kg, including 34 weighing >120kg. Of the 2,011 patients weighing ≥120kg, 1,464 (73%) were underdosed. There were 2,106 patients who were underdosed; 642 weighing ≥80kg who received only 1g of cefazolin and 1464 weighing ≥120kg who received <3g of cefazolin. Only 18 patients received >3g of cefazolin. Underdosed patients were younger, more likely to be male and, predictably, heavier and with higher BMI, Table 1.

Univariable analysis showed a number of characteristics associated with higher SSI rates, Table 2. After multivariable analysis male gender, higher total surgical risk scores, revision and hip arthroplasty procedures, and cefazolin underdosing were all independently associated with higher SSI rates, Table 2. The percentage of those weighing >120kg increased over patient risk scores from 3% for score 0, to 8% for score 1 and 13% for ≥2, p<0.001 and the association between risk and SSI was significant within each of the three weight groups (<80kg, 80-<120kg, ≥120kg: p<0.001, p<0.001 and p=0.026 respectively). After multivariable analysis (excluding weight) the 2,106 underdosed patients had an increased OR for SSI of 2.19 (95% CI 1.61-2.99, p<0.0001), Table 2. For the two weight groups 80-120kg and ≥120kg there was no statistical difference in the SSI rate between those underdosed and those receiving recommended dose, Figure 1. When all underdosed patients were compared to those getting a recommended dose the SSI rate was higher, Table 2 and Figure 1. When weight was added to this same model the OR for the effect of underdosing was no longer significant, OR=1.17 (95% CI 0.73-1.86).

362 procedures (1%) lasted longer than 4 hours and 20 (1% of the underdosed total) were underdosed.

To calculate the NNT the ARR was 1.21% [2.19% (SSI rate in those underdosed) - 0.98% (SSI rate for recommended doses)], 1.21 = 100/NNT, the NNT= 83. The cost of the additional cefazolin prophylaxis for 83 patients, at ~NZ$5/patient, was ~$415 vs. the $40,000 cost of an orthopedic SSI following arthroplasty.[18]

Discussion

Recent guidelines on reducing SSI or surgical prophylaxis differ in their recommendations for weight-based dosing. Some do not make specific recommendations at all.[19,20] In the most widely referenced 2013 multi-society authored guidelines Bratlzer et al state that conclusive recommendations for weight based dosing in obese patients cannot be made because clinically relevant decreases in SSI rates based on higher doses over standard doses have not been published.[21] However, considering the low cost and safety profile of cefazolin these practice guidelines concluded that increasing the dose to 2g for >80kg and 3g for >120kg was easily justified.[21] Others either reference Bratzlter et al or have the same weight based recommendations.[22,23] The Medical Letter concurs but notes that morbidly obese patients may need higher doses.[24] Others recommend increasing the dose to 3g for those >160kg.[25] The Australian Therapeutic Guidelines recommend 2g without a specific dose for >120kg but note that antibiotic pharmacokinetics are altered in obesity so dose adjustment may be necessary.[26] The 2018 International Consensus Meeting on musculoskeletal infection recommends to consider 3g for ≥ 120kg.[27] The multi-Society sponsored French prophylactic guideline recommends doubling the recommended cefazolin dose for those with a BMI of >35kg/m^2.[28] The 2017 CDC guideline makes no recommendation on adjusted dosing for lack of trials evaluating the benefits and harms of weight-adjusted prophylaxis and its effect on the risk of SSI.[29]

To have the best chance of reducing SSIs prophylaxis should be given in an appropriate dosage and time to ensure adequate serum and, more importantly, free tissue concentrations during the period of contamination.[21] As noted by others, the literature on higher dosing is clouded because of reporting results by BMI rather than weight,[21] although some reports do provide weight ranges for the BMI groups analysed.[10-14] Interpretations of the likely clinical efficacy of prophylactic antibiotics based on tissue homogenate concentrations and likely MICs for expected pathogens has been criticized as it often generates misleading conclusions.[30] Unbound drug concentrations are preferred and unbound serum concentrations is considered a useful surrogate marker.[30] Several reports have looked at free serum or tissue concentrations, none of which could make correlations to SSI rates.[11,14,31,32] In a sample of patients undergoing aortic aneurysm repair, where only 3 of 12 were obese and none were morbidly obese, a single 2g dose of cefazolin given 30 minutes before incision provided adequate interstitial concentrations.[31] Monte Carlo simulations showed a reduced probability of target attainment for morbidly obese patients receiving a 2g cefazolin dose.[32] Others have reported adequate free serum concentrations of cefazolin and suggested that a single 2g dose is sufficient for morbidly obese patients.[11,14] However earlier reports found that cefazolin tissue concentrations are between 5-10% of serum concentration[10,12] meaning that on the free serum concentrations observed in these two studies, ~ 25-35 µg/mL at 30 minutes,[11,14] tissue concentrations may not be sufficient to be above relevant MICs for long enough. Hites et al measured free serum cefazolin concentrations and analyzed patients buy both BMI, <35kg/m^2 and ≥35kg/m^2, and weight, <120kg and ≥120kg, using a target concentration of free serum cefazolin of 4µg/mL to indicate the likelihood of adequate prophylaxis.[33] They found no factor associated with insufficient free serum cefazolin and concluded that current BMI and weight cut-offs are poor indicators of which patients could benefit from increased cefazolin dose regimens.[33] In addition

the significantly lower adipose tissue blood flow in obese patients, potentially worsened if normothermia is not maintained in theatre, may further reduce free tissue concentrations of prophylactic antibiotics in obese patients.[34,35]

The only paper we are aware of showing a reduction in SSI rates was based on increasing the cefazolin dose in morbidly obese patients (BMI ≥40kg/m^2) undergoing banded gastroplasty from 1g to 2g. The infection rate fell to 5.6% from the 16.5% observed in historical controls receiving 1g.[10] All other studies analyzing serum or tissue levels based on dose have either not reported the SSI rate or have been too small in size to allow any comparison between cefazolin concentration(s), either free or total or serum or tissue, and SSI. To the best of our knowledge there is only one other report analyzing cefazolin dosing and weight with respect to the SSI rate. Using the same definitions for dosing Rondon et al reported on the outcome of 17,343 primary arthroplasties over a 13-year period.[36] Their results are similar to this study; most patients (96%) >120kg were underdosed. Patients weighing >120kg had a higher peri-prosthetic joint infection (PJI) rate at 1-year follow-up, 3.25% vs. 0.83%, and following multivariate analysis underdosed patients had a statistically higher OR for PJI of 1.67.[36] Taken together our findings suggest that underdosing of cefazolin is part of the reason why those with higher body weights, and BMI, have higher SSI rates. Taken together the results indicate that patients undergoing hip or knee arthroplasty and weighing ≥80kg or ≥120kg should receive 2g or ≥ 3g of cefazolin respectively for SSI prophylaxis. This is particularly important for those weighing ≥120kg who are most frequently underdosed. Future reports on SSI risk vs. patient weight or BMI should take dosing into account.

The analysis did show however that dose is only a part of the SSI risk equation because when weight is added into the multivariable analysis dose is no longer significant. We interpret this as indicating that other features of high weight or obesity adversely impacting the SSI risk are present in the underdosed group, particularly those ≥120kg. These factors were not overcome by the doses used in this cohort. The question of whether ≥4g is needed for those ≥120kg, or above a given BMI of >35kg/m^2 or >40kg/m^2, remains unanswered.

This study has a number of strengths as it includes prospectively collected data, used widely adopted SSI definitions, and only counted in-hospital SSIs where relevant information to decide on the presence of a SSI was available. The weight was known for all patients receiving cefazolin allowing for analysis of the entire cohort. Our study has a number of limitations. It is a retrospective analysis of prospectively collected data. Only SSIs detected during a hospital admission were recorded and SSIs managed in the community, or SSIs presenting after 90 days, were not recorded. As we did not record the presence of other comorbidities, eg. diabetes, smoking, immune compromise, we are unable to test their relevance in relation to the doses of cefazolin used. While redosing for long procedures was not analyzed, only 1% lasted longer than the recommended redosing time of 4 hours and underdosed patients were not overrepresented in this group.[21] We are unable to comment on other modifiable factors such as glucose control and normothermia in this cohort. While this analysis is limited to hip and knee arthroplasties our finding is probably generalizable to whenever cefazolin is used for SSI prophylaxis.

We agree with Bratzler et al that given the low cost of and safety of cefazolin higher doses can be justified.[21] In New Zealand the increased cost and length of hospital stay for arthroplasty related SSI are ~NZ$40,000 and 42 days respectively.[18] Given that the cost of giving cefazolin to 83 higher weight patients to prevent one SSI is under NZ$500 using higher doses is cost effective.

Conclusion

The increased rates of SSI observed in higher weight, and higher BMI, patients is in part due to underdosing of cefazolin. More effort should be made to ensure doses recommended for patients with higher weights are administered. Patients undergoing hip or knee arthroplasty and weighing ≥80kg or ≥120kg should receive 2g or ≥ 3g of cefazolin respectively for SSI prophylaxis. The need for higher doses remains unknown.

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Table 1. Characteristics of patients receiving recommended or less than recommended cefazolin dose for surgical prophylaxis for hip and knee arthroplasty procedures.

	Recommended dose	Underdosed	P value
	N=36,183 (94.5%)	N=2106 (5.5%)	
Characteristic			
Mean, years (range)	68.7 (14-99)	62.8 (25-95)	
Age, ≥65 years	24,508 (67.7%)	914 (43.4%)	<0.0001
Gender, male	16,197 (44.8%)	1,394 (66.2%)	<0.0001
Weight (kg)			
<80	15,114 (41.8%)	-	
80-<120	20,522 (56.7%)	642 (30.5%)	
≥120	547 (1.5%)	1,464 (69.5%)	<0.0001
BMI (kg/m^2)			
>30	14,809 (40.9%)	860 (40.8%)	Not significant
>40	1,960 (5.4%)	967 (45.9%)	<0.0001
Total risk score; 0-1	33,827 (93.5%)	1,868 (88.7%)	<0.0001
Alcohol based skin preparation used	35,647 (98.5%)	2,063 (98%)	Not significant
Prophylaxis given <60 minutes before incision	34,786 (96.1%)	1,970 (93.5%)	<0.0001
Revision arthroplasty	2,584 (7.2%)	128 (6.1%)	Not significant

Table 2. Univariable and multivariable analysis of risk factors for SSI following hip and knee arthroplasty.

		Univariable	Analysis		Multivariable	Analysis *	
Variable	SSI rate % (95% CI)	Odds Ratio	95% CI	P value	Odds Ratio	95% CI	P value
Recommended dose	0.98% (0.88-1.09	Reference					
Underdosed	2.52% (1.91-3.31)	2.61	1.95-3.5	<0.0001	2.19	1.61-2.99	<0.0001
Female	0.94% (0.79-1.05)	Reference					
Male	1.24% (1.08-1.42)	1.37	1.13-1.67	0.0016	1.26	1.03-1.54	0.026
Age, <65 years	1.09% (0.92-1.29)						
Age, ≥65 years	1.05% (0.93-1.18)	0.97	0.79-1.19	0.73, NS			
Weight (kg)*							
<80	0.81% (0.68-0.97)	Reference					
80k-<120	1.07% (0.94-1.22)	1.31	1.06-1.64	0.015			
≥120	2.88% (2.21-3.73)	3.62	2.64-4.96	<0.0001			
BMI (kg/m^2)*							
<30	0.75% (0.63-0.89)	Reference					

30-<35	0.94% (0.77-1.15)	1.25	0.96-1.63	0.09,NS			
35-<40	1.39 (1.1-1.75)	1.85	1.4-2.45	<0.0001			
≥40	2.46% (1.94-3.11)	3.32	2.49-4.42	<0.0001			

	SSI rate % (95% CI)	Univariable	analysis		Multivariable	analysis	
		Odds ratio	95% CI	p	Odds ratio	95% CI	p
Total risk score							
0	0.71% (0.61-0.83)	Reference					
1	1.45% (1.25-1.68)	2.05	1.66-2.53	<0.0001	1.86	1.49-2.31	<0.0001
≥2	2.42% (1.81-3.22)	3.43	2.47-4.74	<0.0001	2.3	1.61-3.29	<0.0001
Alcohol based skin preparation used							
Yes	1.04% (0.94-1.15)	reference					
No	1.84% (0.68-4.48)	0.56	0.23-1.37	0.2, NS			
Prophylaxis given with 60 minutes of incision							
Yes	1.04% (0.94-1.15)	Reference					
No	2.02% (1.26-3.2)	0.53	0.33-0.85	0.008			NS

Revision arthroplasty							
No	0.94% (0.79-1.05)	Reference					
Yes	2.69 (2.13-3.39)	2.92	2.26-3.77	<0.0001	2.13	1.59-2.83	<0.0001
Hip vs. knee arthroplasty							
Hip	1.2% (1.06-1.36)	Reference					
Knee	0.9% (0.79-1.07)	0.76	0.63-0.93	0.008	0.78	0.65-0.98	0.028

*Removing weight and BMI from the analysis, see text. NS= not significant.

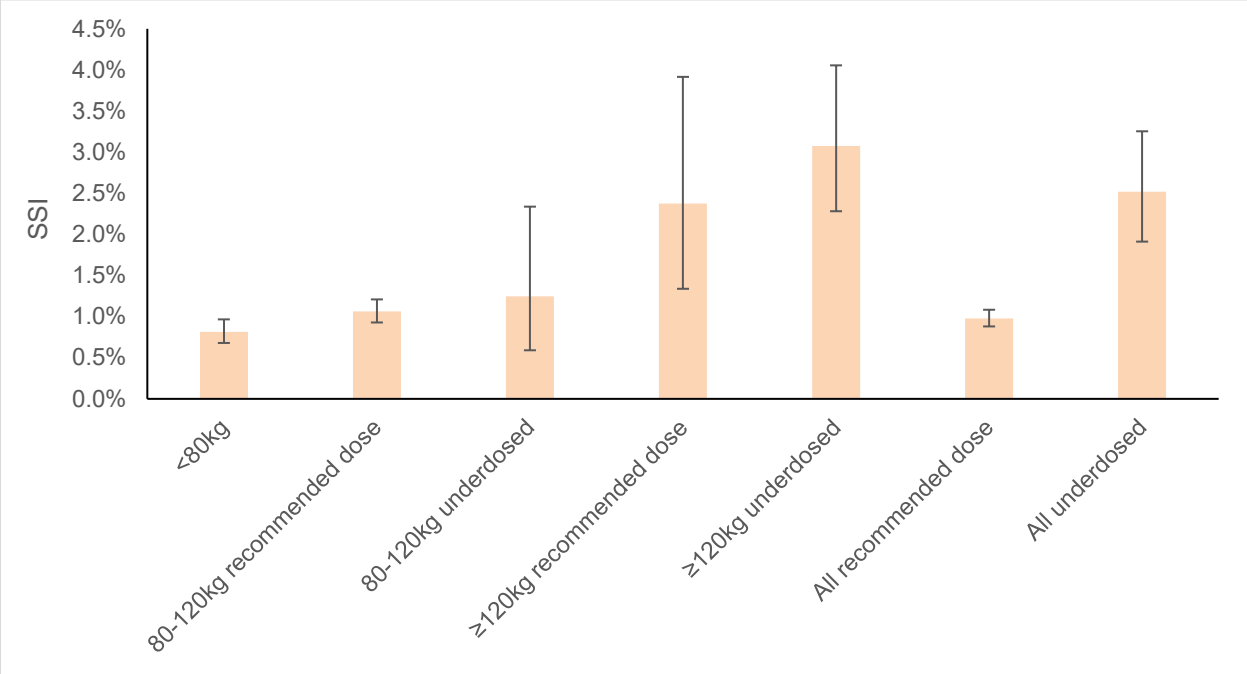

Figure 1. Surgical site infection rate by patient weight and cefazolin dose given as surgical prophylaxis. Underdosed defined as 1g for those ≥80kg and <3g for those ≥120kg. Recommended doses defined as 1g for <80kg, 2g for 80-<120kg and 3g for ≥120kg. Bars represent 95% confidence intervals.