Evidence for inadequacy of 2 gram cefazolin for surgical prophylaxis in obese patients

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Abstract

Obesity is a risk factor for surgical site infection across many surgical disciplines including colorectal surgery. Cefazolin is a widely-used surgical prophylaxis given as a 2 gram standard dose in adults due to the safety of beta-lactam drugs. Reports have emerged suggesting inadequate surgical site protection conferred with this dose in obese patients. This may be due to differential distribution of cefazolin along the surgical tract as it shows poor penetration into subcutaneous fat. Penetration further decreases with increasing subcutaneous fat. Preliminary evidence show increased SSI rate in heavier patients with a single 2 gram cefazolin prophylaxis versus combination with gentamicin. A number of reports indicate a direct relationship between SSI rate and thickness of subcutaneous tissue at the surgical site. Pharmacokinetic studies show much lower cefazolin concentrations in adipose tissue compared to serum. Given the same IV dose, cefazolin concentrations in adipose tissue show an inverse relationship with BMI and straddle clinical breakpoints and other MIC thresholds for common SSI isolates at higher BMI values. No trend is apparent with cefazolin concentrations in serum over a wide range of BMI. Serum concentrations exceed well over the highest MIC thresholds over a wide range of BMI. There is currently no evidence directly comparing SSI rate in obese patients after 2 gram versus 3 gram cefazolin prophylaxis. Clinical trials are ongoing to answer this question with published results expected in the next few years. There is evidence suggesting no difference in related toxicity or adverse event between 2 gram and 3 gram cefazolin prophylaxis. There is no evidence against empirical use of 3 gram cefazolin prophylaxis and this may confer a number of benefits including increased intraoperative re-dosing interval.

Methods

To address the topic of cefazolin dosing in obese patients for surgical prophylaxis, the medline database was searched. A focused internet search was done in addition to the medline search. Articles from reference list of review/guideline articles were also used to find original articles on the topic. Keywords used include but were not limited to prevent* or prophyla*, obesity, surg* or colorectal, cefazolin or antibiotic*. Articles not written in English were excluded. Full-length articles were read unless they were neither freely accessible nor accessible via the UBC online library. In this case, only the abstracts were read.

Background

- Obesity is a risk factor for surgical site infection across many surgical disciplines including colorectal surgery[1-3].
- Beta-lactam antibiotics for surgical prophylaxis are given as standard doses in adults regardless of weight or BMI due to safety of beta-lactams[4-7].
- Cefazolin was initially given as a 1 gram IV dose in 1980's following reports of significantly decreased SSI with surgical prophylaxis[8,11,12].
- Currently, 2 grams cefazolin IV is the standard dose following reports of further decreased SSI rates[4,13].
- Obesity remained a risk factor for SSI; reports of altered pharmacokinetics in the obese patient emerged and emphasized the importance of body composition[9,10,13,18,19].

Characteristics of cefazolin in the obese patient

- First-generation cephalosporin in the beta-lactam class of antibiotics.
- Recommended agent across most surgical discipline due to cost-effectiveness, coverage of gram-positive cocci and enterobacteriaceae[4,7,21].
- Hydrophilic; stays in serum and does not distribute into adipose tissue well[19].
- Physiologically, adipose tissue is poorly perfused. Perfusion further decreases with increasing adipose tissue[22].
- Thus, cefazolin is not expected to penetrate into adipose tissue well in obese patients.
- Displays time-dependent killing and very short post-antibiotic effect; zero post-antibiotic effect against gram-negative rods, one of the most common pathogens isolated from SSI of gastrointestinal surgery patients[6,9,23,24].
- Thus, cefazolin levels must exceed minimal inhibitory concentration for the duration of potential contamination across various tissue types along the surgical tract. This corresponds to the time of incision to closure[23-26].
- Displays inoculum effect; larger inoculum of bacteria can increase MIC. This is a concern in colorectal surgery (clean-contaminated) as inoculum size can vary considerably[27].

Results: Is 2 grams adequate?

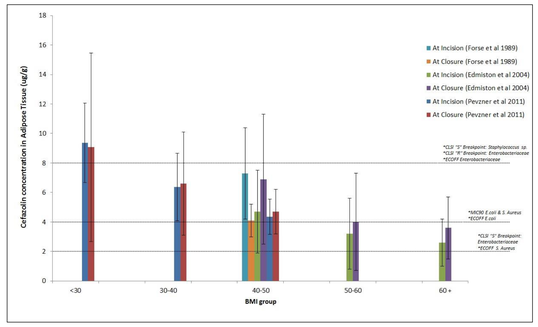

Fig 1. Cefazolin concentration in adipose tissue by BMI group after 2 grams cefazolin IV[8-10]. Cefazolin concentration in adipose tissue appear to decrease with increasing BMI. As BMI increases, cefazolin levels "straddle" on the various MIC thresholds.
*Error bars represent 95% confidence intervals

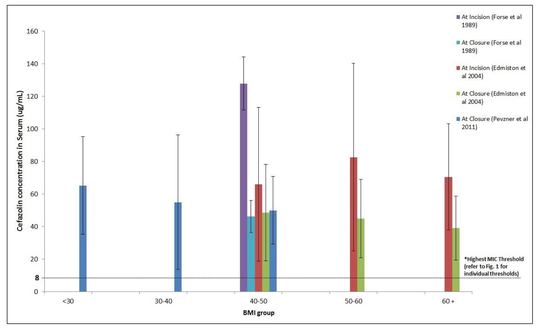

Fig 2. Cefazolin concentration in serum by BMI group after 2 grams cefazolin[8-10]. No trend is observed over the range of BMI. Cefazolin concentrations in serum appear to stay above the highest MIC thresholds over the range of BMI.
*Error bars represent 95% confidence intervals.

- Grando et al (2004 commentary) reported an increase in SSI rate from <1% to 2.8% following discontinuation of gentamicin when originally cefazolin 2 grams plus gentamicin 2 mg/kg was given in cardiac surgery where weight over 75 kg conferred greatest risk of SSI (OR = 21)[13].
- Cefazolin concentrations in adipose tissue show an inverse relationship with BMI (Fig.1) and begin to fall below various MIC thresholds above obese threshold (BMI > 30)[8-10].
- Cefazolin concentrations in serum show no trend with BMI (Fig.2) and stay well above the highest MIC threshold (8 µg/mL) at any BMI[8-10].
- Vermillion et al (2000), Mehta et al (2013), Kwaan et al (2013) reported direct relationship between SSI rate and thickness of subcutaneous tissue at the surgical site[40-42].
- No study available that directly compares 2 grams of cefazolin versus 2 grams plus another similar coverage antibiotic or 3 grams cefazolin in terms of SSI rate in obese patients.
- Studies comparing cefazolin concentrations versus MICs' (ex. clinical breakpoint) is an inexact in-vitro surrogate for in-vivo target concentration. Nonetheless, a concentration well above clinical breakpoint is expected and usually seen with therapeutic antibiotic dosing[28-32].
- Significant overlap between various MICs. Epidemiological cut-off or MIC90 of wild-type distribution may be a better threshold MIC than clinical breakpoint to keep prophylactic doses minimal since the few non-wildtype, resistance-acquired strains may have much higher MICs[28-32].
- Higher doses of cefazolin appear to be safe. Waltrip et al (2002) reported no difference in related toxicity or adverse events among 137 cardiac surgery patients randomized to receive either 2 grams IV, 2 grams IV plus 20 mg/min infusion, or 3 grams IV plus 15 mg/min infusion for surgical prophylaxis. Patients in group 2 and 3 received 3.1 to 6.9 grams and 4.6 to 5.8 grams respectively during the operation[5].

Table 1. Selection of recent guideline recommendations for cefazolin prophylaxis.

	1 gram	2 grams	3 grams
Blondel-Hill et al, 2011[4] (Interior Health BC Guideline)		All BMI	
Alexander et al, 2011[21] (cited 61 times as of Oct. 16, 2013)	< 80 kg	81 – 160 kg	> 160 kg
Bratzler et al, 2013[7] (cited 18 times as of Oct. 16, 2013)		< 120 kg	> 120 kg

Conclusion

- Reports of inadequate prophylaxis dosing in obese patients with a number of cephalosporins used for surgical prophylaxis including cefazolin[14-16].
- Consistent evidence for much lower cefazolin levels in adipose tissue compared to serum, which decreases further as BMI increases. Body composition, not weight seems to be the issue[8-10].
- Determining optimal target MIC threshold is important. There are hundreds of S. aureus strains with a normal-distribution of MICs[28-32].
- Currently, 2 grams cefazolin is the recommended dose in clean surgeries and clean-contaminated surgeries. In addition to obesity, the different bacterial exposure profile, inoculum size, and patient profile should be considered, especially with regards to colorectal surgery[4,5,9,10,20].
- Literature merely suggests lack of coverage with 2 grams cefazolin in obese patients. No evidence available at the moment demonstrating lower SSI rate with 3 grams of cefazolin compared to 2 grams in obese patients.
- Number of clinical trials ongoing at the moment testing this intervention. More conclusive evidence will likely emerge in the next few years[33-38].
- Currently, no evidence against empirically administering 3 grams of cefazolin for surgical prophylaxis in obese patients. Recent major guidelines recommend 3 grams for obese patients weighing over 120 kg based on pharmacokinetic data[7,21].
- If 3 grams is more efficacious in obese patients, determining the threshold (as long as there is one) for 3 grams may be a trivial issue given safety of cefazolin. Major guidelines furthered this notion and established a threshold based on weight, not BMI[5-7].
- A number of benefits to cefazolin 3 grams versus combination antibiotic prophylaxis.
- Easier to implement with no new antibiotics and no new modes of delivery.
- Known safety of beta-lactams. Further safeguard with an obesity threshold for 3 grams[5-7].
- Increased re-dosing interval. This is significant as intraoperative re-dosing is one of the harder interventions to implement[23].

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