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 among 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 a higher 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 BMI rate and thickness of subcutaneous tissue at the surgical site. Pharmokinetic 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 storable 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.

Results: Is 2 grams adequate?

- Grando et al (2004 commentary) reported an increase in SSI rate from 1% to 2.8% following discontinuation of gentamicin when originally used in combination with cefazolin (Fig 1). In this study, the highest MICs in the range of BMI appear to decrease with increasing BMI. As BMI increases, cefazolin levels are "straddled" on the various MIC thresholds. *Error bars represent 95% confidence intervals.

- Interestingly, studies show that microdialysis of cefazolin in subcutaneous adipose tissue appear to exceed well over the highest MIC thresholds 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.

- Evidence for inadequacy of cefazolin and enterobacteriaceae (22). Cefazolin is known safety of beta-ccephalosporins used for surgical prophylaxis including cefazolin (9). 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 (23). Determining optimal target MIC threshold is important. There are hundreds of S. aureus strains with a normal-distribution of MICs. Cefazolin is 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. Literature tends to show a trend of increased SSI rate with 2 gram 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. Systematic review of SSI rates 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. 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. If 3 grams is more efficacious in obese patients, determining the threshold (as long as there is one) for 3 grams may be a true trial given safety of cefazolin. Major guidelines furthered this notion and established a threshold based on weight, not BMI. A number of benefits to cefazolin 3 grams versus combination antibiotic prophylaxis. Easier to implement with a new antibiotics and no new modes of delivery. Known safety of beta-lactams. Further safeguard with an obesity threshold for 3 grams. Increased re-dosing interval. This is significant as intraoperative re-dosing is one of the harder interventions to implement.

Conclusion

- Reports of inadequate prophylaxis dosing in obese patients with a number of cephalosporins used for surgical prophylaxis including cefazolin (9). 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 (23). Determining optimal target MIC threshold is important. There are hundreds of S. aureus strains with a normal-distribution of MICs. Cefazolin is 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. Literature tends to show a trend of increased SSI rate with 2 gram 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. Systematic review of SSI rates 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. 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. If 3 grams is more efficacious in obese patients, determining the threshold (as long as there is one) for 3 grams may be a true trial given safety of cefazolin. Major guidelines furthered this notion and established a threshold based on weight, not BMI. A number of benefits to cefazolin 3 grams versus combination antibiotic prophylaxis. Easier to implement with a new antibiotics and no new modes of delivery. Known safety of beta-lactams. Further safeguard with an obesity threshold for 3 grams. Increased re-dosing interval. This is significant as intraoperative re-dosing is one of the harder interventions to implement.

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References

- Grando, C., DiPiro, J., Truffa, P., et al. Determining optimal target MIC thresholds is important. There are hundreds of S. aureus strains with a normal-distribution of MICs. Cefazolin is 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. Literature tends to show a trend of increased SSI rate with 2 gram 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. Systematic review of SSI rates 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. 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. If 3 grams is more efficacious in obese patients, determining the threshold (as long as there is one) for 3 grams may be a true trial given safety of cefazolin. Major guidelines furthered this notion and established a threshold based on weight, not BMI. A number of benefits to cefazolin 3 grams versus combination antibiotic prophylaxis. Easier to implement with a new antibiotics and no new modes of delivery. Known safety of beta-lactams. Further safeguard with an obesity threshold for 3 grams. Increased re-dosing interval. This is significant as intraoperative re-dosing is one of the harder interventions to implement.

Characteristics of cefazolin in the obese patient

- Obesity is a risk factor for surgical site infection among many surgical disciplines including colorectal surgery (9). Beta-lactam antibiotics for surgical prophylaxis are given as standard doses in adults regardless of weight or BMI due to safety of beta-lactam antibiotics. Cefazolin was initially given as a 1 gram IV dose in 1980s following reports of significantly decreased SSI with surgical prophylaxis (10,11). Currently, 2 grams cefazolin IV is the standard dose following 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 median database was searched. A focused internet search was done in addition to the medline search. Articles from reference list were also used to find original articles on the topic. Keywords used include but were not limited to: cefazolin, obesity, laparoscopic, enterobacteriaceae, antibiotic prophylaxis. 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.

Table 1. Selection of recent guidelines for cefazolin prophylaxis.

<table>
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<th>1 gram</th>
<th>2 grams</th>
<th>3 grams</th>
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<tr>
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<td>All BMI</td>
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<td>n/a</td>
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<td>18.5 - 24.9</td>
<td>80 kg</td>
<td>110 kg</td>
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<td>&gt; 25</td>
<td>&lt; 120 kg</td>
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