Perioperative antibiotic prophylaxis in the gastric bypass patient: Do we achieve therapeutic levels?

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Background. Perioperative surgical antibiotic prophylaxis requires that therapeutically effective drug concentrations be present in the tissues.

Methods. Patients undergoing Roux-en-Y gastric bypass for morbid obesity were given 2 g cefazolin preoperatively, followed by a second dose at 3 hours. Thirty-eight patients were each assigned to 1 of 3 body mass index (BMI) groups: (A) BMI = 40-49 (N = 17); (B) BMI = 50-59 (N = 11); (C) BMI ≥ 60 (N = 10). Multiple timed serum (baseline; incision, 15, 30, 60 minutes; prior to second prophylactic dose; and closure) and tissue (skin, subcutaneous fat, and omentum) specimens were collected and cefazolin concentration analyzed by microbiological assay.

Results. No significant difference was observed in intraoperative fluid replacement or blood loss among BMI groups. Serum antimicrobial concentrations exceeded resistance breakpoint (32 μg/mL) in 73%, 68%, and 52% of BMI groups A, B, and C, respectively. No significant difference in cefazolin concentration was observed in mean incisional skin and closure tissue specimens in groups A, B, and C. A significant decrease in cefazolin concentration was noted in closure adipose (p = .04), initial (p = .03) and closure omentum (p = .05) tissues in groups B and C compared with A. Over 90% of serum samples exhibited therapeutic concentrations covering 53.8% of gram-positive and 78.6% of gram-negative surgical pathogens. However, therapeutic tissue levels were achieved in only 48.1%, 28.6%, and 10.2% of groups A, B, and C, respectively.

Conclusions. Pharmacokinetic analysis suggests that present dosing strategies may fail to provide adequate perioperative prophylaxis in gastric bypass patients. (Surgery 2004;136:738-47.)

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The tenets of surgical prophylaxis require that the antimicrobial agent be administered in a timely fashion such that the maximal tissue concentration occurs at the time of incision, with therapeutic antimicrobial activity persisting throughout the duration of the surgical procedure.1,2 This premise is derived from the classical study by Burke, selected clinical trials, and pharmacokinetic data derived from healthy, non-obese individuals.3,5 Unfortunately, there is limited pharmacologic data available on the distribution of anti-infectives in the obese patient population. Limited pharmacokinetic studies in obese patients using vancomycin and the aminoglycosides have revealed that obesity is associated with complex alterations in both the volume of distribution (Vd) and total body clearance (Ct).6 The major factors influencing antimicrobial tissue levels and Vd include body composition, regional blood flow, and the affinity of the therapeutic agent for plasma proteins and selected tissue compartment.7,8 Under normal conditions and weight, blood flow in fat is poor and accounts for approximately 5% of cardiac output, whereas in the lean tissues it is 22%. In morbid obesity the percentage of fat per kilogram of total body weight is increased relative to lean tissue mass. Therefore blood flow per gram of fat is greatly reduced in the morbidly obese patient compared with moderately overweight or lean individuals.9

Two studies conducted in the 1980s measured serum and selected tissue concentrations of
Cefazolin in patients undergoing gastric bypass surgery for morbid obesity. One study reported that a 2 g parenteral dose of cefazolin resulted in higher adipose tissue levels at wound incision and closure compared with a 1 g dose. Mann found that preoperative administration of a 2 g dose of cefamandole was required to achieve intraoperative therapeutic tissue levels in the morbidly obese patient. Currently, in our institution patients undergoing elective Roux-en-Y gastric bypass receive 2 g of cefazolin 1 hour before incision with a second (2 g) dose delivered in the third hour of the operation. In previous prophylaxis pharmacokinetic studies, the mean body mass index (BMI) reported for patients undergoing elective gastric bypass was approximately 47. This value has risen significantly since these initial reports. It is now common for patients to present for Roux-en-Y gastric bypass with BMIs greater than 50. The mean BMI for patients undergoing gastric bypass for morbid obesity at our institution is approximately 55. Because of the paucity of tissue pharmacokinetic data in patients with high BMIs (> 50), the following investigation was undertaken to determine whether therapeutic serum and tissue levels are present in these patients undergoing elective gastric bypass.

**PATIENTS AND METHODS**

The study protocol was reviewed and approved by the Medical College of Wisconsin-Froedtert Memorial Lutheran Hospital Human Subjects Institutional Review Board. All patients participating in the study were enrolled as per institutional informed-consent guidelines. Sixty patients scheduled for Roux-en-Y gastric bypass for morbid obesity were enrolled in the study initially; 22 patients were excluded (failure to achieve vascular access, 12; partial sample collection, 10), and 38 met all enrollment criteria. Patients were assigned to one of 3 groups on the basis of BMI values: Group A: BMI 40 to 49 (N = 17), Group B: BMI 50 to 59 (N = 11), and Group C: BMI ≥ 60 (N = 10). Two grams of cefazolin was parenterally administered to all patients approximately 30 to 60 minutes before wound incision. A baseline serum was collected before cefazolin administration, and 6 additional serum samples were collected post-prophylaxis: at wound incision; at 15, 30, and 60 minutes; before the second prophylactic dose (2 g); and at wound closure. The mean time differential between end of infusion and collection of the incisional serum sample was approximately 63, 42, and 49 minutes for groups A, B, and C, respectively. In addition to the serum samples, initial (postprophylaxis) and preclosure incisional skin, subcutaneous fat, and omentum tissues were obtained from each patient. A study nurse was involved in the timing and collection of all intraoperative serum and tissue specimens.

Upon collection, blood and tissue specimens were placed on ice and transported to the Surgical Microbiology Research Laboratory. The blood was...
allowed to clot and centrifuged for 10 minutes at 1,500 rpm, and serum and tissues were stored at −70°C until analysis. A cefazolin microbiological plate assay was performed by dispensing (in triplicate) 20 μL of serum into wells cut in Antibiotic Medium #1 (Difco, Detroit, Mich) seeded with *Streptococcus sanguis* reference strain A597-9, on 243 mm × 243 mm × 43 mm assay plates. The plates were incubated at 37°C for 24 hours in ambient air and zones of inhibition measured in millimeters. Tissue samples were blotted to remove residual blood, weighed, and homogenized in 0.2 mol/L phosphate-buffered saline (pH 7.8) for 5 minutes. After homogenization, tissue fractions were sonicated on ice for 10 minutes and centrifuged at 2,500 rpm for 5 minutes. Tissue homogenates were inoculated (20 μL) to the assay plates as per serum samples and incubated for 24 hours at 37°C before reading of the zones of inhibition. Calibration (cefazolin) standards were prepared daily in human serum, ranging from 0.25 to 128 μg/mL. The coefficient of linearity (correlation coefficient) for the standard curve ranged from 0.993 to 0.997. The between-assay variation for internal controls was 7%.

Descriptive statistical analysis, ANOVA, and chi-square tests were performed on selected data sets using the Minitab Statistical Program, release 13 (State College, Pa).

**RESULTS**

Patient demographic data for the 38 subjects who completed all enrollment criteria are presented in Table I. The mean BMIs for groups A, B, and C were 47.0, 53.9, and 69.2, respectively. Although females outnumbered males in all study groups, there were no significant differences in mean age, operative time, or blood loss among the three groups. In group C, a significant difference in fluid replacement (crystalloid) was noted compared with groups A and B. However, when fluid replacement was expressed as a function of body weight (kg), no significant difference was observed among the three groups. One patient in Group B received 2 units of packed red blood cells. Most operations (85%) were performed laparoscopically, and no significant difference was observed in the incidence of diabetes or postoperative SSIs among patient groups.

**Figure 1** documents the mean intraoperative serum concentrations of cefazolin at incision, at 15, 30, and 60 minutes, before second dosing, and at wound closure in groups A, B, and C. The mean serum values of cefazolin exceeded the resistant
breakpoint of 32 μg/mL at incision and at 15, 30, and 60 minutes in group A and group B patients (Table II). In group C, the cefazolin serum concentrations exceeded 32 μg/mL at incision and in the 15-minute and 30-minute samples. The mean cefazolin concentrations measured in serum collected before administration of the second dose fell below the resistant breakpoint in all three groups. After administration of a second 2 g dose of cefazolin, mean closure concentrations exceeded the resistance breakpoint in all groups. Analysis of individual group A, B, and C samples revealed that 82.3%, 72.7%, and 70%, respectively, of initial incisional serum samples exceeded the resistant therapeutic breakpoint, but in the pre-second-dose specimens, only 41.1% and 18.2% of samples from groups A and B, respectively, achieved concentration exceeding the resistant breakpoint. No pre-second-dose serum samples obtained from group C patients exceeded the resistant breakpoint for cefazolin. Although comparison of the mean from each of the three BMI groups revealed no significant difference, overall individual antimicrobial concentrations of cefazolin equaled or exceeded the resistant breakpoint value of 32 μg/mL in 73%, 68%, and 51% of serum specimens from groups A, B, and C, respectively ($p \leq .025$).

Figure 2 demonstrates the mean tissue concentration of cefazolin in skin, adipose, and omentum. The mean initial incisional skin concentrations recorded for groups A, B, and C were 3.3, 2.8, and 3.6 μg/g, respectively (Table II). Although the mean skin closure concentrations increased on average from 1.6 to 4.8 μg/g compared with initial incisional values, only group A skin closure specimens achieved values above 8 μg/g, the therapeutic breakpoint for susceptibility to cefazolin. No significant difference was observed in the mean initial incisional or closure skin concentrations in groups A, B, or C. In addition, no significant difference was seen in initial adipose cefazolin concentration among the three study populations. However, a significant difference was observed in the closure adipose ($p = .04$), initial omentum ($p = .03$), and closure omentum ($p = .05$) concentrations in groups B and C compared with group A. The mean adipose and omentum concentrations of cefazolin in initial and closure tissue samples ranged from a high of 6.9 μg/g (adipose closure—group A) to 1.9 μg/g (omentum initial—group B). The highest mean cefazolin tissue concentration was observed in group A patients compared with B and C, and the lowest mean tissue concentrations were generally observed in group C patients.

The potential relationship of in situ drug concentration to in vitro susceptibility of selected surgical pathogens is demonstrated in Fig 3, which documents the percent susceptibility of 320 gram-positive and gram-negative bacteria recovered over a 2-year period (2002-2003) from postoperative SSIs (9 surgical services). In total, 36% of the Staphylococcus aureus and 71% of the Staphylococcus epidermidis isolates recovered from SSIs recorded minimal inhibitory concentrations (MIC) $\geq$ 16 μg/mL. In general, gram-negative isolates were more sensitive to cefazolin than gram-positive isolates; 76.4% of Escherichia coli and 83.6% of Klebsiella pneumoniae exhibited MIC $\leq$ 8 μg/mL. Therapeutic breakpoints for cefazolin are limited to gram-positive rods and cocci and enteric gram-negative bacteria. Therapeutic breakpoints for nonenteric gram-negative bacteria or anaerobic bacteria have not been determined for the first-generation cephalosporins because of intrinsic β-lactamase resistance, limited spectrum of activity, and pharmacodynamic considerations. Regardless of BMI group, over 90% of serum samples exhibited cefazolin concentrations $\geq$ 8 μg/mL, sufficient therapeutic activity to cover 53.8% of gram-positive and 78.6% of gram-negative surgical pathogens. However, in comparison cefazolin tissue

### Table II. Comparative mean (± SD) serum and tissue pharmacokinetics in gastric bypass patients after 2 g cefazolin prophylaxis

<table>
<thead>
<tr>
<th>BMI Groups*</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>$p^1$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incisional</td>
<td>65.9 (±47.2)</td>
<td>82.5 (±57.7)</td>
<td>70.4 (±32.7)</td>
<td>NS</td>
</tr>
<tr>
<td>15 min</td>
<td>58.0 (±37.8)</td>
<td>79.6 (±63.8)</td>
<td>52.9 (±25.1)</td>
<td>NS</td>
</tr>
<tr>
<td>30 min</td>
<td>47.8 (±32.0)</td>
<td>61.2 (±49.5)</td>
<td>39.7 (±20.1)</td>
<td>NS</td>
</tr>
<tr>
<td>60 min</td>
<td>35.0 (±26.1)</td>
<td>37.4 (±25.9)</td>
<td>26.2 (±11.6)</td>
<td>NS</td>
</tr>
<tr>
<td>Before second dose closure</td>
<td>24.3 (±16.6)</td>
<td>18.9 (±10.9)</td>
<td>17.1 (±6.6)</td>
<td>NS</td>
</tr>
<tr>
<td>Tissues</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial skin</td>
<td>3.3 (±2.1)</td>
<td>2.8 (±2.2)</td>
<td>3.6 (±1.1)</td>
<td>NS</td>
</tr>
<tr>
<td>Closure skin</td>
<td>8.1 (±5.8)</td>
<td>6.7 (±4.3)</td>
<td>5.2 (±1.1)</td>
<td>NS</td>
</tr>
<tr>
<td>Initial adipose closure</td>
<td>4.7 (±2.8)</td>
<td>3.2 (±2.4)</td>
<td>2.6 (±1.6)</td>
<td>NS</td>
</tr>
<tr>
<td>Initial adipose omentum</td>
<td>6.9 (±4.4)</td>
<td>4.0 (±3.3)</td>
<td>3.6 (±2.1)</td>
<td>0.04</td>
</tr>
<tr>
<td>Initial omentum</td>
<td>4.1 (±3.1)</td>
<td>1.9 (±0.8)</td>
<td>2.0 (±0.9)</td>
<td>0.03</td>
</tr>
<tr>
<td>Closure omentum</td>
<td>5.0 (±2.9)</td>
<td>3.5 (±1.5)</td>
<td>2.8 (±1.0)</td>
<td>0.05</td>
</tr>
</tbody>
</table>

*BMI groups: A = 40-49, B = 50-59, C = 60.

$^1$Analysis of variance.
concentrations were found to fall short of appropriate therapeutic levels. Specifically, cefazolin concentrations in the incisional skin approximated therapeutic levels in 29.4%, 18.2%, and 10% of patients in groups A, B, and C, respectively. Overall, in BMI group A, 48.1% of all tissue specimens exhibited therapeutic levels of cefazolin $\leq 8 \mu g/g$, but therapeutic levels were achieved in only 28.6% and 10.2% of Groups B and C, respectively.

**DISCUSSION**

Perioperative antimicrobial prophylaxis has been shown to reduce the probability of postoperative SSIs. The derived effectiveness of antimicrobial prophylaxis must incorporate three basic principles: (a) the agent selected must cover the spectrum of anticipated microbial contamination at the surgical locus, (b) the agent must be given in a timely fashion such that tissue concentration in the wound (tissues) exceeds the MIC of potential microbial pathogens, and (c) a sufficient therapeutic concentration of the antimicrobial agent should persist in the tissues for the duration of the operative procedure; if not, a second dose must be given, corresponding to the tissue pharmacokinetics of the drug. The historical infection rate for patients undergoing gastric operations for morbid obesity has been reported to range from 1.3% to 21%. Risk-adjusted infection rates reported by the National Nosocomial Infection Surveillance system suggest that the pooled mean rate of SSI associated with open gastric surgical procedures ranges from 2.6 (0 risk factors) to 8.8 (risk index 2). This rate, however, is modified downward if the procedure is performed laparoscopically, in which case the SSI rate for a 0-risk-category patient is reduced from 2.6 to 1.01.

Forse and colleagues reported that a 1 g prophylactic dose of cefazolin given to patients undergoing vertical banded gastroplasty for morbid obesity resulted in tissue concentrations that were below the MIC for both gram-positive and gram-negative surgical pathogens. Raising the dosage to 2 g resulted in a 75% to 100% increase in adipose tissue concentrations, sufficient to cover most common microbial contaminants. In addition, the authors reported that use of a 2 g dose of cefazolin resulted in a marked reduction in SSI rate (5.6%) compared with a 1 g preoperative dose (16.5%). Pories demonstrated in 1981 that patients undergoing gastric bypass using a Roux-en-Y

![Fig 2. Mean concentration ($\mu g/g$) of cefazolin in skin, adipose, and omentum of gastric bypass patients, collected postincision and at closure.](image-url)
jejunal loop exhibited a lower rate of postoperative SSI (4%) if given a 1 g dose of cefazolin at induction of anesthesia compared with placebo control (21%). In both studies patients received their second dose of antibiotic in the postoperative period. In a recent study, patients undergoing bariatric surgery were given either 1 or 2 g cefazolin at induction of anesthesia. No significant difference was observed in wound infections or subsequent occurrence of nosocomial infection in either group. During the 12-month interval of this study, 214 (33 open; 181 laparoscopic) Roux-en-Y gastric bypass procedures were performed for morbid obesity, and a total of 12 postoperative SSIs were detected during routine inpatient/outpatient surveillance, for a crude SSI rate of 5.6%. It is interesting to note that a separate review of 3 study subjects who presented with superficial incisional site infections revealed that all 3 patients had tissue (incisional skin and adipose) concentrations of cefazolin that were less than 2.5 µg/g, a level which is subinhibitory for selected strains of gram-positive and gram-negative surgical pathogens.

It is evident from review of the study data that adequate concentrations of cefazolin were lacking in selected serum and tissue specimens when compared with the minimal inhibitory concentration for current surgical pathogens. Although 90% of serum samples demonstrated therapeutic concentrations sufficient to cover a majority of staphylococcal isolates and selected Enterobacteriaceae, a significant gap in coverage was evident especially for those organisms with MIC > 32 µg/mL (46.2% staphylococcal; 21.4% Enterobacteriaceae). This gap was more pronounced when individual tissue concentrations were analyzed; 29.4% of tissue specimens in group A had cefazolin concentrations ≥ 8 µg/g, but only 10% of tissues from group C patients revealed cefazolin concentrations ≥ 8 µg/g. The mean and standard deviations reported in Table II demonstrate that few tissue samples achieved a concentration of 8 µg/g, but most tissue specimens from groups B and C were less than 4 µg/g. These findings suggest that cefazolin tissue concentrations documented in the present study would have been subinhibitory for approximately 80% of staphylococci recovered from SSIs within the time duration of this study. Alternatively, 39.3% of the gram-negative isolates recovered from surgical patients over the same time interval

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**Fig 3.** Percent susceptibility of selected microbial isolates recovered from postoperative surgical site infection during 2002 and 2003. Cefazolin therapeutic breakpoints for aerobic gram-positive cocci and gram-negative (enteric) rods; ≤8 µg/mL = sensitive, 16.0 = intermediate, ≥32 µg/mL = resistant.
would have found these tissue concentrations to be subinhibitory. This is a potentially problematic issue since \textit{S aureus}, \textit{S epidermidis}, and \textit{E coli} are the first, second, and fourth most frequent isolates from SSIs in the United States.\textsuperscript{15}

It is important to note that serum and tissue concentrations observed in the current study for group A (BMI = 40-49) were numerically similar to those reported in previous studies in which the mean BMI was 47.\textsuperscript{10,11} However, although serum concentrations in all three groups were similar to those reported in earlier studies, tissue concentrations observed in the higher BMI groups (B and C) were less than those reported by both Pories and Forse. It is also important to note that both authors found the 2 g dose of cefazolin to produce tissue levels sufficient to inhibit the growth of selected gram-positive and gram-negative surgical pathogens. Current patterns of antimicrobial resistance suggest that a significant shift in staphylococcal and Enterobacteriaceae susceptibility to first-generation cephalosporins has occurred over the past 15 to 20 years, raising questions about the prophylactic efficacy of this specific compound in selected surgical patients. An inability to achieve adequate tissue levels in surgical patients is indeed problematic not only in bariatric patients but potentially in all surgical patients with BMI > 50.

What options are available for prophylaxis in high-BMI surgical patients? The problem of insufficient tissue levels may be alleviated in part by altering the mode of drug delivery. The cephalosporins as beta-lactam agents are viewed as time-dependent drugs, which suggests that the longer the drug is in the host at concentrations above the minimal inhibitory concentration, the greater the bacterial killing.\textsuperscript{19} Waltrip reported that in patients undergoing coronary artery bypass surgery, a pre-operative bolus dose of 3 g of cefazolin followed by continuous infusion of the drug resulted in higher (3 to 5 times higher) tissue levels compared with patients who received 1 g without continuous infusion.\textsuperscript{20} Therefore, a prophylactic strategy involving continuous antibiotic (cefa zolin) infusion could result in higher tissue levels with an extended duration of inhibitory activity above the MIC for selected surgical pathogens. However, constant infusion of cefazolin may not by itself increase drug distribution, especially in selected tissues such as adipose and omentum. Concentration-dependent drugs (quinolones) may be more effective at penetrating into adipose or omentum of patients with BMI > 50. In addition, pharmacodynamically the quinolones exhibit a relatively long postantibiotic effect, allowing for large dosing but at a less frequent interval.\textsuperscript{19} The quinolones, however, are currently viewed as highly effective therapeutic agents for severe infections, and prophylactic use is strongly discouraged.

Past studies of anti-infective pharmacokinetics in morbidly obese surgical patients have been limited to individuals with a BMI in the mid 40s. The present investigation is a first attempt to study antibiotic distribution in patients with BMI > 50. Although we observed a range of cefazolin tissue concentrations in all study groups, bariatric patients with BMI > 50 achieved therapeutic levels in less than 30% of incisional skin, adipose, and omentum tissues. It is also noteworthy that this investigation represented an ideal scenario for delivery of perioperative prophylaxis. The presence of a study nurse in the operating room assured that the initial prophylactic dose was given at the appropriate time and that the second dose was given precisely 3 hours after initial wound incision. A recent audit conducted in our institution suggests that errors in dosage, timing, and redosing occur on average 10% to 40% of the time, depending on surgical service (unpublished data). Therefore, it is possible that the efforts that were applied in implementing this specific study design lacked a certain sense of reality and that in actual clinical practice, the situation is much worse. Finally, the obvious pharmacokinetic and susceptibility limitations that exist with our current prophylactic regimen suggest that a melding of traditional practices (exquisite surgical technique, improvements in skin antisepsis, and attention to sentinel risk factors) with innovative and thoughtful strategies (alternative dosing schedules or new antiseptic agent/drug delivery technologies) is likely warranted in our ongoing efforts to reduce the risk of SSI in morbidly obese and other high-risk patient populations.

\textbf{REFERENCES}

DISCUSSION

Dr. Mark A. Malangoni (Cleveland, Ohio). The thrust of this study is that the current recommended antibiotic dosing fails to provide tissue concentrations of drugs that are adequate to prevent wound infection.

Dr. Edmiston and his colleagues have designed and executed an exquisite study that demonstrates the vast differences between serum and tissue antibiotic levels in a population of morbidly obese patients undergoing bariatric surgery. Surprisingly, there is little correlation between BMI and tissue or serum levels.

I am tantalized by the implications of these low drug concentrations and the potential for wound infection against the selected organisms that you have stored in your laboratories. But you also provided some information about your infection rate, which in this group of patients was greater than 18%. This is surprisingly high, since most of your operations were done laparoscopically.

Before we accept your premise that these events are truly related, I think we need to entertain other causes for postoperative wound infection such as preoperative antibiotic shower, adequate skin prep, compliance with recommended hair removal, etc. I want to know if you standardized these things in your study. If you did, can you provide us with this information?

Secondly, according to your data, it appears improbable that bactericidal tissue levels will be achieved in the high BMI patients. So do you believe that besides your suggestions, other adjuncts such as intraoperative injection of antibiotics or local instillation in some way should be investigated?

Third, why was your infection rate so high? Can you share some insights on that? Lastly, was there a correlation between the low serum and tissue levels of antibiotics and the occurrence of infection in individual patients? I think this is really the crux of your study. Can you demonstrate that if the level is high, patients don’t get infected, and if the level is low, they do? If that is indeed the case, it really adds tremendous value to what you posited to us today.

Dr. Henry Buchwald (Minneapolis, Minn). A comment and a question. Many years ago, Bob Goodale and I did a very similar experiment. We took fat every 2 hours from the subcutaneous tissue, and we made fat agar and then tested various bacterial preparations to see how the fat agar supported bacterial growth. This was at a time we were using first generation cephalosporins. We came to the conclusion that we should give 2 g of cephalosporins every 2 hours. And that has been our standard at the University of Minnesota now for well over 3,000 bariatric procedures.

Now, my question: although this is not my field, isn’t there a differential binding rate of the cephalosporins to albumin, and therefore, a selection of a certain cephalosporin may be better than another one? What you really want is low binding to serum albumin and seepage of the drug into the peripheral tissue.

Dr. Arthur M. Carlin (Detroit, Mich). I have a comment about the wound infections with the laparoscopic approach. If you review your data, what you will likely find with the end-to-end anastomosis technique is that the port infections are always at the site where the stapler is introduced. Perhaps a local strategy to prevent infections versus systemic antibiotics would be more beneficial in these patients.

Dr. Charles Edmiston (Milwaukee, Wis). Although we continue to focus our efforts on delivering timely and appropriate perioperative antibiotic prophylaxis, we recognize that errors in timing, dosing, and duration
are problematic. A recent audit of selected surgical services at our institution has suggested that errors in timing and dosage do occur with some frequency, and these findings are also reflective of other published studies. Since 2001, we have routinely administered Roux-en-Y gastric bypass patients 2 g of cefazolin preoperatively and a second dose 3 hours into the procedure. We have also standardized our surgical skin prep to a chlorhexidine product, which provides a good to excellent antimicrobial spectrum with excellent residual activity in the area of the incision. We feel that chlorhexidine represents a superior skin prep compared with other agents. Historically, Betadine was used as the surgical skin prep for gastric bypass procedures; however, chlorhexidine is now our agent of choice for this patient population. Hair removal is performed just before the surgical procedure as recommended by the Centers of Disease Control and Surgical Infection Society. I should point out that in this study conditions were ideal; a study nurse was present in the operating room during all procedures to insure that each patient received the 2 g cefazolin initial and subsequent doses on time. In fact, the time differential for the second dose was only plus or minus approximately 6 minutes, which rarely occurs in practice. Even under these optimal conditions, we found that cefazolin tissue concentrations were subinhibitory for 80% of staphylococcal and 39% of gram-negative pathogens.

To achieve appropriate tissue concentrations in this patient population, we may need to think outside the box and adopt an innovative approach to the way we deliver antimicrobial prophylaxis. In 1990, Joe DiPiro published a paper demonstrating that high (cefazolin) tissue concentrations could be achieved in surgical patients by the use of a continuous infusion technique. I would suggest that an initial loading dose of 3 g cefazolin combined with continuous infusion of 15 to 20 mg per minute for the duration of the surgical procedure might optimize tissue-drug concentrations, reducing the period of sub-inhibitory coverage. In addition to augmenting traditional prophylactic practices, innovative technologies involving antiseptic impregnated biomedical devices, such as sutures, may be beneficial as an adjunctive strategy for reducing the risk of superficial incisional site infections in selected patient populations.

In terms of our infection rate in this patient population, the historical (published) rate has ranged from 1% to 21%. In addition to wearing the hat of a faculty member in the Department of Surgery, I am also the hospital epidemiologist and therefore track our SSI rate. Last year 214 Roux-en-Y gastric bypass procedures were performed in our institution, the majority (82%) of which were done laparoscopically. In all, 12 infections were identified during the 12-month study period for a crude (non-risk-adjusted) rate of 5.6%. Unfortunately, seven of those patients happened to enroll in our study, giving a false appearance of a higher infection rate for this selected procedure.

To correlate these findings with the occurrence of SSI, I should first point out that this was designed as a pharmacokinetic study that would look specifically at serum and tissue concentration, not wound infection rates. Second, dissecting out the factors associated with postoperative SSIs is a rather complex if not mystifying endeavor. To conduct such a study would require a large multicenter effort that addresses the complex, often multifactorial processes contributing to SSIs. I do believe, however, that when one looks at postoperative infection and studies it as a discipline, one realizes immediately that SSIs most often involve a "systems problem," such as errors in prophylaxis, inadequate skin prep, or a myriad of other recognized (and possibly unrecognized) intrinsic or extrinsic risk factors. Finally, one cannot overlook the role of hyperglycemia as a significant risk factor, especially in the morbidly obese patient population, in which a significant percentage of our patients present with type II diabetes. However, the delivery of IV insulin within the perioperative window of opportunity is problematic for some health care institutions. This is a very complex process, and it is evident that we must attack this problem aggressively if we are to improve patient outcomes in this area.

Yes, you are absolutely correct with that statement, if the drug is bound to tissue protein, it is not available for the contaminating microbial populations sequestered within the tissues. If you look at protein binding for a drug like ceftriaxone, it is relatively high (90%), whereas a cephalosporin such as cefazolin is between 70% and 80%. Newer agents such as cefepime have very low protein binding (20%), but this is viewed as an important therapeutic agent, and therefore it is unlikely that we will see this agent in our prophylactic arsenal anytime soon. The half-life for cefazolin is approximately 90 minutes, so providing that we can achieve intraoperative therapeutic levels in the tissues, cefazolin would appear to be a prudent choice. What is not clear, however, is what impact staphylococcal resistance has on eroding the value of the first-generation cephalosporins as prophylactic agents in surgery. Our findings would suggest that because of increased staphylococcal and gram-negative resistance, the time may come when it will be difficult (if not impossible) to achieve intraoperative antimicrobial levels which are inhibitory to those organisms traditionally associated with wound contamination.

I must commend your practice of redosing cefazolin every 2 hours, and in this manner you are likely achieving higher inhibitory tissue levels. I might also add that we are in the process of evaluating a continuous infusion strategy for our Roux-en-Y gastric bypass and selected vascular patients in an attempt to reduce the probability of subinhibitory tissue levels during the intraoperative period. Because cardiac output through adipose and omentum is less than 5%, we may need to be more imaginative in our efforts to optimize antimicrobial prophylaxis in patients with high BMIs. It is extremely important that we recognize that beta-lactam...
antimicrobials are mechanistically time-dependent drugs—the longer the tissue-drug concentration is above the MIC of the anticipated surgical pathogen (contaminant), the greater the prophylactic efficacy.

That is an excellent observation. We know that any biomaterial, even a surgical staple, can be a nidus for contamination and subsequent infection, providing that appropriate risk factors are present.