CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207131Orig1s000

MEDICAL REVIEW(S)

Addendum to Clinical Review

NDA	207131
Applicant	Celerity Pharmaceuticals, LLC (Celerity)
Date of Submission	10/16/14
PDUFA Goal Date	8/16/15
Established Name	Cefazolin Injection, USP
Referenced Licensed Drug	2 g Cefazolin for Injection USP and Dextrose Injection USP in Duplex® Container manufactured by B. Braun Medical, Inc. (B. Braun) under NDA 50779
Dosage forms / Strength	2 g/100 mL cefazolin and 4% dextrose in a GALAXY plastic container for injection
Proposed Indication	(b) (4) prophylaxis for contaminated or potentially contaminated surgeries (e.g., vaginal hysterectomy, and cholecystectomy in high-risk patients such as those older than 70 years, with acute cholecystitis, obstructive jaundice, or common duct bile stones). (b) (4)
Medical Officer	Peter Kim, MD, MS
Medical Team Leader	Thomas Smith, MD
Recommendation	Approval

The indication has been changed (b) (4) to preoperative prophylaxis because the product (a 2 gram dose of cefazolin) is only to be administered before surgery. Therefore, the Indications and Usage section will read as follows.

1 INDICATIONS AND USAGE

1.1 Preoperative Prophylaxis

Cefazolin injection is indicated for preoperative prophylaxis. The prophylactic administration of cefazolin preoperatively may reduce the incidence of certain postoperative infections in patients undergoing surgical procedures which are classified as contaminated or potentially contaminated (e.g., vaginal hysterectomy, and cholecystectomy in high-risk patients such as those older than 70 years, with acute cholecystitis, obstructive jaundice, or common duct bile stones).

The preoperative use of cefazolin may also be effective in surgical patients in whom infection at the operative site would present a serious risk.

If there are signs of infection, specimens for cultures should be obtained for the identification of the causative organism so that appropriate therapy may be instituted.

1.2 Limitations of Use

Use an alternative cefazolin product when lengthy surgical procedures require supplemental doses and when postoperative dosing is required.

1.3 Usage

To reduce the development of drug-resistant bacteria and maintain the effectiveness of Cefazolin injection and other antibacterial drugs, Cefazolin injection should be used only to prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

The Dosage and Administration section will read as follows.

2 DOSAGE AND ADMINISTRATION

2.1 Preoperative Prophylactic Use in Adults

- Only use Cefazolin injection in patients who require the entire 2 gram dose and not any fraction of it.
- Administer the entire 2 gram dose intravenously 1/2 hour to 1 hour prior to the start of surgery.
- It is important that the preoperative dose be given just prior (1/2 hour to 1 hour) to the start of surgery so that adequate antibacterial concentrations are present in the serum and tissues at the time of initial surgical incision.

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/s/

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07/17/2015

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07/17/2015

Clinical Review

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Proposed Indication	(b) (4) prophylaxis for contaminated or potentially contaminated surgeries (e.g., vaginal hysterectomy, and cholecystectomy in high-risk patients such as those older than 70 years, with acute cholecystitis, obstructive jaundice, or common duct bile stones). The (b) (4) use of cefazolin may also be effective in surgical patients in whom infection at the operative site would present a serious risk (e.g., during open-heart surgery and prosthetic arthroplasty).
Medical Officer	Peter Kim, MD, MS
Medical Team Leader	Thomas Smith, MD
Recommendation	Approval

Introduction

Using the 505(b)2 pathway, Celerity is seeking approval of a premixed, frozen iso-osmotic solution comprised of 2 g/100 mL cefazolin and 4% dextrose in a GALAXY plastic container for the indication of (b) (4) B. Braun for their 2 g Cefazolin for Injection USP and Dextrose Injection USP in Duplex® Container (NDA 050779) on 1/13/12. Celerity proposes that their drug product is qualitatively and quantitatively similar to the B. Braun drug product (i.e., total drug content per container); however, the Celerity 2 g drug product contains sodium bicarbonate as an additional inactive ingredient. Further, the proposed Celerity drug product is formulated (b) (4) . The Applicant contends that this CMC change does not alter the pharmacokinetics, pharmacodynamics, safety, or efficacy of the drug product and intends to rely on the Agency's findings of efficacy and safety for B. Braun's NDA 050779 to support approval.

Background

Cefazolin is a semi-synthetic, first generation cephalosporin antibacterial agent with *in vitro* activity against Gram-positive and a limited number of Gram-negative bacteria. It shares the same mechanism

of action as other beta-lactam antibacterials, namely inhibition of cell wall biosynthesis mediated by binding to penicillin-binding proteins. Cefazolin was originally approved for use in the United States in 1973 under NDA 050461 (ANCEF®, GlaxoSmithKline). Celerity referenced publicly available information[1] that noted that B. Braun's NDA 050779 (approved 7/27/2000) made reference to NDA 050461. Although now discontinued, the ANCEF® drug product offered cefazolin for reconstitution in two strengths (1 g single-dose and 10 g pharmacy bulk vials). For intermittent or continuous infusion, the 1 g reconstituted solution was further diluted with 50 to 100 mL of ten (10) potential solutions, including 5% or 10% Dextrose Injection, USP; the resulting concentration of these solutions are approximately 1 g/52.5 mL to 1 g/102.5 mL. Celerity further noted that the currently marketed lyophilized drug product under ANDA 065226 (Cefazolin for Injection, USP; Hospira) contains similar instructions[2] for further dilution after reconstitution.

Celerity intends to maintain the same dosing regimen described in the package insert for B. Braun's 2 g drug product approved under NDA 050779 [the referenced listed drug (RLD) for this application]; namely, the entire 2 g dose will be infused over approximately 30 minutes. The Applicant contends that the administration of the full 2 g dose in 100 mL (Celerity) rather than 50 mL (B. Braun) is not expected to impact drug product performance. Celerity cited the existing precedent for ANCEF® of a 52.5 to 102.5 mL volume for continuous infusion, along with the dilution instructions for the currently marketed lyophilized product Cefazolin for Injection, USP, to support the position that the volume difference between Celerity and B. Braun is not a critical attribute of product performance.

M.O. comment**: Based on the B. Braun package insert for cefazolin, the 2 gram dose is only approved for the indication of* (b) (4) ***The following table was obtained from B. Braun's package insert.

[1] B. Braun's NDA 050779 for Cefazolin and Dextrose; accessed through Drugs@ FDA website (http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label_ApprovalHistory#labelinfo); accessed 10/29/14.
[2] Hospira's Cefazolin for Injection, USP package insert (http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=79afc719-8279-49f9-83b0-e0736c07eb5c); accessed 10/29/14.
[3] B. Braun's Cefazolin Sodium package insert (http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=17f8f038-c204-4dab-80d7-6f7ac41ddbec#nlm34068-7); accessed 10/29/14.

DOSAGE AND ADMINISTRATION

For intravenous use only over approximately 30 minutes. (2)
Use this formulation of cefazolin only in patients who require the entire 1 or 2 gram dose and not any fraction thereof. (2.1)

Recommended Dosing Schedule in Adult Patients with CrCl Greater Than or Equal To 55 mL/min. (2.1)		
Site and Type of Infection	**Dose**	**Frequency**
Moderate to severe infections	500 mg to 1 gram	every 6 to 8 hours
Mild infections caused by susceptible gram-positive cocci	250 mg to 500 mg	every 8 hours
Acute, uncomplicated urinary tract infections	1 gram	every 12 hours
Pneumococcal pneumonia	500 mg	every 12 hours
Severe, life-threatening infections (e.g., endocarditis, septicemia)*	1 gram to 1.5 grams	every 6 hours
Perioperative prophylaxis	1 gram to 2 grams	½ to 1 hour prior to start of surgery
	500 mg to 1 g	during surgery for lengthy procedures
	500 mg to 1 g	every 6 to 8 hours for 24 hours postoperatively

* In rare instances, doses of up to 12 grams of cefazolin per day have been used.

***M.O. comment**: The M.O. also reviewed Dr. Alma Davidson's clinical review for NDA 050779, Supplement 18, which was for use of the 2 gram dose for perioperative prophylaxis. This supplement was approved on 1/13/12.*

CMC

Celerity noted that their proposed drug product is:

> [redacted] (b) (4) to the B. Braun drug product (i.e., total drug content per container); however the Celerity 2 g drug product contains sodium bicarbonate as an additional inactive ingredient. Further, the proposed Celerity drug product [redacted] (b) (4) Cefazolin, USP [redacted] (b) (4) [redacted]

Celerity provided the following table comparing B. Braun's and Celerity's 2 gram cefazolin formulations in the pre-NDA meeting package.

Applicant	B. Braun (Listed Drug)	Celerity (Proposed Drug)
Product	Cefazolin for Injection USP and Dextrose Injection USP in Duplex® Container	Cefazolin Injection, USP in GALAXY plastic container
Active Ingredient	Cefazolin Sodium, USP	Cefazolin, USP[a]
Total Drug Content	2.0 g	2.0 g
Diluent	3% Dextrose, USP	4% Dextrose, USP[b]
Other Inactive Ingredients	none listed	Sodium Bicarbonate, USP
Volume	50 mL in Duplex® Container	100 mL in GALAXY plastic container
Strength	2.0 g (2 g base/vial)	2.0 g (2 g base/100 mL)
Concentration	40 mg/mL (2 g/50 mL)	20 mg/mL (2 g/100 mL)
Osmolality	Iso-osmotic (approx. 290 mOsmol/kg)[c]	Iso-osmotic (approx. 288-301 mOsmol/kg)[d]
Dosage Form	Injectable; sterile lyophilized dry powder packaged with dextrose solution (ready to mix)	Injectable; frozen, pre-mixed iso-osmotic, sterile solution
Container Closure	Duplex® dual-chamber, single-use container for sterile reconstitution of dry powder and diluent for injection	Single-use GALAXY plastic container for frozen, premixed, iso-osmotic, sterile solution
Route of Administration	Injection: IV infusion	Injection: IV infusion
Dosing Regimen	2 g dose infusion over approximately 30 minutes	2 g dose infusion over approximately 30 minutes
		(b) (4)

[c] B. Braun Package Insert, Cefazolin for Injection USP And Dextrose Injection USP In Duplex® Container, for intravenous use http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=17f8f038-c204-4dab-80d7-6f7ac41ddbec, retrieved 3/21/2014

[d] Data for proposed Celerity drug product (to be included in NDA submission)

Nonclinical Pharmacology/Toxicology

No new nonclinical studies were conducted for this application. The Applicant provided a nonclinical overview in the NDA that contained an updated literature review since 7/27/00 (the last NDA approval date for a cefazolin parenteral drug product). The original nonclinical studies conducted in support of the approval of cefazolin were detailed in the original NDA 050461 [ANCEF®, GlaxoSmithKline (GSK)],

approved in 1973. Of note, B. Braun referenced GSK's studies in support of their NDA 050779 (approved 7/27/2000).[4]

Clinical Pharmacology

No new pharmacology information was included in the current application. The studies conducted in support of the original approval of cefazolin were detailed in the original NDA 050461 [ANCEF®, GlaxoSmithKline (GSK)], approved in 1973. Of note, B. Braun referenced GSK's studies in support of their NDA 050779 (approved 7/27/2000).

Clinical Microbiology

No new clinical microbiology information was included in the current application. The studies conducted in support of the original approval of cefazolin were detailed in the original NDA 050461 [ANCEF®, GlaxoSmithKline (GSK)], approved in 1973. Of note, B. Braun referenced GSK's studies in support of their NDA 050779 (approved 7/27/2000).

Clinical/Statistical Efficacy

No clinical studies were conducted in support of this application. The clinical studies conducted in support of the efficacy of cefazolin for the approved indications are detailed in the original NDA 050461 [ANCEF®, GlaxoSmithKline (GSK)], approved in 1973. B. Braun referenced GSK's clinical studies in support of their NDA 050779 (approved 7/27/2000). In support of the 2 gram dose, B. Braun conducted a pharmacokinetic/pharmacokinetic study that demonstrated that the 2 g formulation delivered acceptable plasma concentrations of cefazolin which exceeded minimum inhibitory concentrations.

***M.O. comment*: The M.O. refers the reader to Dr. Alma Davidson's clinical review of B. Braun's 2 gram formulation of cefazolin for NDA 050779, supplement 018.**

Safety

Review of B. Braun's Cefazolin Label

The B. Braun label for cefazolin notes the following two serious adverse reactions: hypersensitivity reactions and *Clostridium difficile*-associated diarrhea.

The following was noted in section "6.1 Clinical Trials Experience".

[4] Original clinical review for NDA 050779, Cefazolin for injection and dextrose injection in the Duplex container. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2000/50779_Cefazolin_medr.pdf; accessed 10/29/14.

The following adverse reactions were reported from clinical trials:

Gastrointestinal: Diarrhea, oral candidiasis (oral thrush), mouth ulcers, vomiting, nausea, stomach cramps, epigastric pain, heartburn, flatus, anorexia and pseudomembranous colitis. Onset of pseudomembranous colitis symptoms may occur during or after antibacterial treatment [see *Warnings and Precautions (5.3)*].

Allergic: Anaphylaxis, eosinophilia, urticaria, itching, drug fever, skin rash, Stevens-Johnson syndrome.

Hematologic: Neutropenia, leukopenia, thrombocytopenia, thrombocythemia.

Hepatic: Transient rise in SGOT, SGPT, and alkaline phosphatase levels has been observed. As with other cephalosporins, reports of hepatitis have been received.

Renal: As with other cephalosporins, reports of increased BUN and creatinine levels, as well as renal failure, have been received.

Local Reactions: Instances of phlebitis have been reported at site of injection. Some induration has occurred.

Other Reactions: Pruritus (including genital, vulvar and anal pruritus, genital moniliasis, and vaginitis). Dizziness, fainting, lightheadedness, confusion, weakness, tiredness, hypotension, somnolence and headache.

The following was noted under section "6.2 Cephalosporin-class Adverse Reactions".

In addition to the adverse reactions listed above that have been observed in patients treated with cefazolin, the following adverse reactions and altered laboratory tests have been reported for cephalosporin-class antibacterials: Stevens-Johnson syndrome, erythema multiforme, toxic epidermal necrolysis, renal impairment, toxic nephropathy, aplastic anemia, hemolytic anemia, hemorrhage, hepatic impairment including cholestasis, and pancytopenia.

M.O. comment*: *The adverse reactions listed in section 6 of B. Braun's cefazolin label are common to many cephalosporins.

Literature Review

In 2011, Dr. Alma Davidson reviewed the literature related to the use of the 2 gram dose of cefazolin in perioperative surgical prophylaxis while reviewing B. Braun's NDA 050779, supplement 018 for Cefazolin for Injection, USP and Dextrose Injection, USP in the Duplex Container. Please refer to Dr. Davidson's clinical review for the literature review from the 1980's to 2011.

On 10/29/14, the current M.O. reviewed PubMed for additional safety data related to the use of the 2 gram dose of cefazolin in perioperative surgical prophylaxis from 2011 to 2014. The search string used was "cefazolin 2 gram". This search yielded 46 references published between 2011 and 10/29/14. Further limiting the search by adding "clinical trial" to the search string yielded one publication during the time frame.

Pevzner L, Swank M, Krepel C, Wing DA, Chan K, Edmiston CE Jr. Effects of maternal obesity on tissue concentrations of prophylactic cefazolin during cesarean delivery. Obstet Gynecol. 2011 Apr;117(4):877-82.

ABSTRACT

OBJECTIVE: To estimate the adequacy of antimicrobial activity of preoperative antibiotics at the time of cesarean delivery as a function of maternal obesity. METHODS: Twenty-nine patients scheduled for cesarean delivery were stratified according to body mass index (BMI) category, with 10 study participants classified as lean (BMI less than 30), 10 as obese (BMI 30-39.9), and nine as extremely obese (BMI 40 or higher). All patients were given a dose of 2 g cefazolin 30-60 minutes before skin incision. Antibiotic concentrations from adipose samples, collected after skin incision and before skin closure, along with myometrial and serum samples, were analyzed with microbiological agar diffusion assay. RESULTS: Cefazolin concentrations within adipose tissue obtained at skin incision were inversely proportional to maternal BMI (r=-0.67, P<.001). The mean adipose concentration was 9.4 plus or minus 2.7 micrograms/g in the lean group of women compared with 6.4 plus or minus 2.3 micrograms/g in the obese group (P=.009) and 4.4 plus or minus 1.2 micrograms/g in the extremely obese group (P<.001). Although all specimens demonstrated therapeutic cefazolin levels for gram-positive cocci (greater than 1 microgram/g), a considerable portion of obese and extremely obese did not achieve minimal inhibitory concentrations of greater than 4 micrograms/g for Gram-negative rods in adipose samples at skin incision (20% and 33.3%, respectively) or closure (20.0% and 44.4%, respectively). No significant difference in cefazolin concentration was observed in mean closure adipose, myometrial, or serum specimens across the BMI categories. CONCLUSION: Pharmacokinetic analysis suggests that present antibiotic prophylaxis dosing may fail to provide adequate antimicrobial coverage in obese patients during cesarean delivery.

***M.O. comment*: The authors noted that the study was not powered to demonstrate a difference in the rates of surgical site infections (SSI); however a 6-week follow-up chart review was able to be performed on 25/29 of the patients. Two of the patients in the BMI 40 or greater group developed SSI. Both patients had adipose cefazolin concentrations below the MIC of 4 at both incision and closure. No other safety information was provided in the paper.**

As with many other drugs, including but not limited to antibacterial agents, extremely obese patients may require higher doses than those studied or noted in the product label based on the predicted pharmacokinetics.

Additionally, the M.O. reviewed the following eight papers for adverse event information. They were identified using the search string “cefazolin 2 gram”; however, they were not clinical trials.

Rodriguez L, Jung HS, Goulet JA, Cicalo A, Machado-Aranda DA, Napolitano LM. Evidence-based protocol for prophylactic antibiotics in open fractures: Improved antibiotic stewardship with no increase in infection rates. J Trauma Acute Care Surg. 2014 Sep;77(3):400-8.

Himebauch AS, Nicolson SC, Sisko M, Moorthy G, Fuller S, Gaynor JW, Zuppa AF, Fox E, Kilbaugh TJ. Skeletal muscle and plasma concentrations of cefazolin during cardiac surgery in infants. J Thorac Cardiovasc Surg. 2014 Jul 22. pii: S0022-5223(14)00888-5.

Blumenthal KG, Youngster I, Shenoy ES, Banerji A, Nelson SB. Tolerability of cefazolin after immune-mediated hypersensitivity reactions to nafcillin in the outpatient setting. Antimicrob Agents Chemother. 2014 Jun;58(6):3137-43.

Abdul-Jabbar A, Berven SH, Hu SS, Chou D, Mummaneni PV, Takemoto S, Ames C, Deviren V, Tay B, Weinstein P, Burch S, Liu C. Surgical site infections in spine surgery: identification of microbiologic and surgical characteristics in 239 cases. Spine (Phila Pa 1976). 2013 Oct 15;38(22):E1425-31.

Wu CK, Wang JH, Lee CH, Wu KL, Tai WC, Lu SN, Hu TH, Chuah SK. The outcome of prophylactic intravenous cefazolin and ceftriaxone in cirrhotic patients at different clinical stages of disease after endoscopic interventions for acute variceal hemorrhage. PLoS One. 2013 Apr 22;8(4):e61666

McLeod LM, Keren R, Gerber J, French B, Song L, Sampson NR, Flynn J, Dormans JP. Perioperative antibiotic use for spinal surgery procedures in US children's hospitals. Spine (Phila Pa 1976). 2013 Apr 1;38(7):609-16.

Oliveira LG, Luengo J, Caramori JC, Montelli AC, Cunha Mde L, Barretti P. Peritonitis in recent years: clinical findings and predictors of treatment response of 170 episodes at a single Brazilian center. Int Urol Nephrol. 2012 Oct;44(5):1529-37.

Ho VP, Barie PS, Stein SL, Trencheva K, Milsom JW, Lee SW, Sonoda T. Antibiotic regimen and the timing of prophylaxis are important for reducing surgical site infection after elective abdominal colorectal surgery. Surg Infect (Larchmt). 2011 Aug;12(4):255-60.

***M.O. comment:** None of these papers provided useful adverse event information related to the cefazolin 2 gram dose. Using the search string "cefazolin prophylaxis 2 gram", 16 papers were identified that were published between 2011 and 2014. None of these papers provided additional information that would inform the safety of this dosing regimen.*

Review of FAERS data

The M.O. consulted OSE Safety Evaluator, Dr. Ronald Wassel, to search FAERS for adverse event reports associated with cefazolin for the time period from 1/1/11 to 9/22/14, including a breakdown of reports among patients prescribed the 2 gram dose.

***M.O. comment:** The reported adverse events are consistent with the adverse reactions listed in the current B. Braun cefazolin label.*

Pediatrics

(b) (4)

Labeling

(b) (4)

(b) (4)

(b) (4)

Recommendations/Risk Benefit Assessment

The recommendation is to approve this preparation of cefazolin for the indication of (b) (4). Celerity's 2 gram cefazolin preparation is not approved for (b) (4) indications in the B. Braun package insert because they are approved for doses lower than 2 grams.

No new data from clinical or nonclinical studies were included in this submission. A waiver of bioequivalence studies was granted. This formulation of cefazolin was assessed as bioequivalent to B. Braun's 2 g Cefazolin for Injection USP and Dextrose Injection USP in Duplex® Container, NDA 50779. No new safety information was presented or identified in the literature or available FAERS data that would alter the favorable risk/benefit assessment of cefazolin in the treatment of the labeled indication of (b) (4).

No postmarketing risk evaluation and management strategies or postmarketing requirements or commitments are recommended.

References

1. Abdul-Jabbar A, Berven SH, Hu SS, Chou D, Mummaneni PV, Takemoto S, Ames C, Deviren V, Tay B, Weinstein P, Burch S, Liu C. Surgical site infections in spine surgery: identification of microbiologic and surgical characteristics in 239 cases. Spine (Phila Pa 1976). 2013 Oct 15;38(22):E1425-31.

2. B. Braun's Cefazolin Sodium package insert (http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=17f8f038-c204-4dab-80d7-6f7ac41ddbec#nlm34068-7); accessed 10/29/14.

3. B. Braun's NDA 050779 for Cefazolin and Dextrose; accessed through Drugs@ FDA website (http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label_ApprovalHistory#labelinfo); accessed 10/29/14.

4. Blumenthal KG, Youngster I, Shenoy ES, Banerji A, Nelson SB. Tolerability of cefazolin after immune-mediated hypersensitivity reactions to nafcillin in the outpatient setting. Antimicrob Agents Chemother. 2014 Jun;58(6):3137-43.

5. Himebauch AS, Nicolson SC, Sisko M, Moorthy G, Fuller S, Gaynor JW, Zuppa AF, Fox E, Kilbaugh TJ. Skeletal muscle and plasma concentrations of cefazolin during cardiac surgery in infants. J Thorac Cardiovasc Surg. 2014 Jul 22. pii: S0022-5223(14)00888-5.

6. Ho VP, Barie PS, Stein SL, Trencheva K, Milsom JW, Lee SW, Sonoda T. Antibiotic regimen and the timing of prophylaxis are important for reducing surgical site infection after elective abdominal colorectal surgery. Surg Infect (Larchmt). 2011 Aug;12(4):255-60.

7. Hospira's Cefazolin for Injection, USP package insert (http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=79afc719-8279-49f9-83b0-e0736c07eb5c); accessed 10/29/14.

8. McLeod LM, Keren R, Gerber J, French B, Song L, Sampson NR, Flynn J, Dormans JP. Perioperative antibiotic use for spinal surgery procedures in US children's hospitals. Spine (Phila Pa 1976). 2013 Apr 1;38(7):609-16.

9. Oliveira LG, Luengo J, Caramori JC, Montelli AC, Cunha Mde L, Barretti P. Peritonitis in recent years: clinical findings and predictors of treatment response of 170 episodes at a single Brazilian center. Int Urol Nephrol. 2012 Oct;44(5):1529-37.

10. Original clinical review for NDA 050779, Cefazolin for injection and dextrose injection in the Duplex container. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2000/50779_Cefazolin_medr.pdf; accessed 10/29/14.

11. Pevzner L, Swank M, Krepel C, Wing DA, Chan K, Edmiston CE Jr. Effects of maternal obesity on tissue concentrations of prophylactic cefazolin during cesarean delivery. Obstet Gynecol. 2011 Apr;117(4):877-82.

12. Rodriguez L, Jung HS, Goulet JA, Cicalo A, Machado-Aranda DA, Napolitano LM. Evidence-based protocol for prophylactic antibiotics in open fractures: Improved antibiotic stewardship with no increase in infection rates. J Trauma Acute Care Surg. 2014 Sep;77(3):400-8.

13. Wu CK, Wang JH, Lee CH, Wu KL, Tai WC, Lu SN, Hu TH, Chuah SK. The outcome of prophylactic intravenous cefazolin and ceftriaxone in cirrhotic patients at different clinical stages of disease after endoscopic interventions for acute variceal hemorrhage. PLoS One. 2013 Apr 22;8(4):e61666.

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