Author's response to reviews

Title: Ampicillin / Sulbactam versus Cefuroxime as Antimicrobial Prophylaxis for Cesarean Delivery: a Randomized Study

Authors:

Eleftherios Ziogos (elziogos@yahoo.gr)
Sotirios Tsiodras (tsiodras@med.uoa.gr)
Ioannis Matalliotakis (matakgr@yahoo.com)
Helen Giamarellou (hgiam@ath.fortnet.gr)
Kyriaki Kanellakopoulou (kyrkanel@yahoo.gr)

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Author's response to reviews:

Ms Roxane Rajabi
The BioMed Central Editorial Team
Tel: +44 (0) 20 3192 2013
e-mail: editorial@biomedcentral.com
Web: http://www.biomedcentral.com

Athens September 15th, 2010

Dear editor of the journal BMC Infectious Diseases

I would like to ask you to review for the original research section of the Journal BMC Infectious Diseases the attached revised manuscript entitled: “Ampicillin / Sulbactam versus Cefuroxime as Antimicrobial Prophylaxis for Cesarean Section: a Randomized Study” by Ziogos et al.

The authors would like to thank the editorial staff and the reviewers for the instructive criticism and believe that with the incorporated changes the manuscript has significantly improved. Please find below a detailed item by item response to all the comments raised by the editorial staff and the reviewers.

All authors have contributed significantly to this work and have seen and approved this manuscript. This manuscript has not been previously published and is not being considered for publication elsewhere. There are no potential conflicts of interest for the participating authors. The study was registered in the NIH clinical trials registry (Clinicaltrials.gov identifier: NCT01138852).

Please do not hesitate to contact me should you have any further questions
regarding this manuscript

Sincerely,

Sotirios Tsiodras, MD, MSc, PhD
Assistant Professor in Medicine
4th Dept of Internal Medicine
Athens University Medical School
Email: tsiodras@med.uoa.gr

Detailed response to the reviewers

EDITORIAL REQUESTS

Editorial request 1

“…Experimental research that is reported in the manuscript must have been performed with the approval of an appropriate ethics committee. Research carried out on humans must be in compliance with the Helsinki Declaration (http://www.wma.net/e/policy/b3.htm), and any experimental research on animals must follow internationally recognized guidelines. A statement to this effect must appear in the Methods section of the manuscript, including the name of the body which gave approval, with a reference number where appropriate…”

Authors’ response

A statement to this effect is already present in the originally submitted manuscript

Editorial request 2

“…Please can you include your trial registration number in your abstract. The last section of the abstract should be Trial Registration: listing the trial registry and the unique identifying number, e.g. Trial registration: Current Controlled Trials ISRCTN73824458. Please note that there should be no space between the letters and numbers of the trial registration number….”

Authors’ response

This was done as suggested.

Editorial request 3

“…We recommend that you copyedit the paper to improve the style of written English….”

Authors’ response

This was performed and the paper was copyedited by a native English speaking
person. The authors would appreciate any editorial assistance in this regard.

Editorial request 4

“…Please can you include all of the author’s email addresses in the title page…”

Authors’ response

This was incorporated as suggested.

Editorial request 5

“…Manuscripts submitted to BMC Infectious Diseases must include an ‘Acknowledgement’ section…..”

Authors’ response

The authors have no acknowledgments to declare.

Editorial request 6

“…Please list the source(s) of funding for the study, for each author, and for the manuscript preparation in the acknowledgements section. Authors must describe the role of the funding body, if any, in study design; in the collection, analysis, and interpretation of data; in the writing of the manuscript; and in the decision to submit the manuscript for publication…..”

Authors’ response

There was no funding for this study.

Editorial request 7

“…Please highlight (with ‘tracked changes’ / coloured / underlines / highlighted text) all changes made when revising the manuscript to make it easier for the Editors to give you a prompt decision on your manuscript. Please also ensure that your revised manuscript conforms to the journal style (http://www.biomedcentral.com/info/ifora/medicine_journals ). It is important that your files are correctly formatted…..”

Authors’ response

This was done as suggested using the track changes feature of word.

REVIEWERS’ COMMENTS

REVIEWER 1

Comment 1

“…I recommend to insert in the Discussion a brief consideration about usefulness of this alternative schedule in term of antibiotic stewardship….”
The authors would like to thank the reviewer for the encouraging comments and the acceptance of the manuscript. A brief statement to this extent was added in the discussion section of the revised manuscript together with a statement about the cost of the two regimens (see detailed response to 2nd reviewer).

REVIEWER 2

Comment 1

“…The paper of Ziogos et al. evaluates the efficacy and safety of a single dose of ampicillin/sulbactam compared to a single dose of cefuroxime at cord clamp for prevention of postcesarean infectious morbidity. However, there are some major points that required clarification.

1. The major problem is that the authors used two broad spectrum regimens not generally recommended for surgical prophylaxis, while narrow spectrum antimicrobials are usually recommended. No discussion on antimicrobial resistance has been included…”

Author’s response

The authors would like to thank the reviewer for the instructive criticism. The authors agree with the reviewer that ampicillin sulbactam has a broader spectrum coverage than cefuroxime or other simple cephalosporin regimens often used in prophylaxis such as cefazolin. On the other had cefazolin as well as other cephalosporins, such as cefuroxime, have been widely used for prophylaxis in abdominal and gynecological surgery (J Hosp Infect 1995; 29: 245–255). Despite the wide use of cephalosporins as prophylaxis in elective abdominal surgery, they lack activity against Enterococcus species. (AMADrug Evaluations. Chicago, Ill: American Medical Association; 1995:1413-1480; Dancer SJ. The problem with cephalosporins. J Antimicrob Chemother. 2001;48:463-478). The alternative regimen of ampicillin-sulbactam (presented in this report) has been extensively used for perioperative prophylaxis in past studies. In an obstetrical study it even fared better than ampicillin alone in preventing post-cesarean infection in women that had ruptured membranes (Am J Perinatol 1995;12:322-4). Additionally in our study it was associated with essentially negligible drug related toxicity and it may be associated with reduced selection of pathogens resistant to cephalosporins such as enterococci. The one enterococcal SSI was noted in the cefuroxime treated patient. It is important to note that we had no occurrence of infection due to a resistant pathogen in our ampicillin-sulbactam treated group. More research is necessary as newer reports suggest that the use of extended-spectrum regimens (involving azithromycin or metronidazole) after cord clamp may reduce post-cesarean maternal infection by up to 50% (Obstet Gynecol 2009;113:675-82). However, these two strategies have not been compared with each other. In addition, their effect on neonatal infection or infection with resistant organisms warrants further study. Nevertheless the authors agree that simple
narrow spectrum antimicrobials should continue to be used for peri-operative prophylaxis (especially in low-risk patients) and should be integrated in an appropriate antimicrobial stewardship program (see response to first reviewer).

Statements to this effect were added in the revised discussion section of the submitted manuscript together with a statement about the cost of the two regimens.

Comment 2

“… Why did the authors compare 3 g of ampicillin/sulbactam to 1.5 g cefuroxime? The two drugs are similar and 1.5 g of ampicillin / sulbactam is almost equivalent to 1.5 g cefuroxime...”

Author’s response

The authors thank the reviewer for the comment. The study by design had picked these dosing regimens that have been previously used in the literature in perioperative prophylaxis in numerous studies (Gynecol Obstet Invest 1997;44:21-5; J Matern Fetal Med. 2000 Nov-Dec;9(6):348-50, Arch Surg. 2006; 141: 1162-1167).

Comment 3

“…The first dose of antimicrobial prophylaxis is recommended before surgical incision and not thereafter...”

Author’s response

The authors thank the reviewer for this insightful comment. For cesarean section the standard practice was until very recently ( August 2010) to administer the prophylaxis regimen intravenously after the time the umbilical cord is clamped which was done accordingly in our study. Since our study was performed much earlier than this guidance was issued we administered the antimicrobial regimen according to the previous guidelines. The reviewer is correct that this guideline was changed recently and a position statement towards this effect was published by The American College of Obstetricians and Gynecologists entitled: “ Committee Opinion No 465: Antimicrobial Prophylaxis for Cesarean Delivery: Timing of Administration, Obstetr Gynecol Sep 2010”. According to this very recent guideline the prophylaxis should be given 1 hour prior to the operation. A statement to this effect was added in the revised manuscript.

Comment 4

“…Some data sound uncommon. The authors’ infection rate was quite high in both groups. Moreover, duration of surgery seems too long for elective conditions as well as the number of patients that performed general anesthesia or had significant blood loss...”

Author's response
The authors would like to thank the reviewer for this comment. As specifically stated in the original manuscript in the limitations section we had a significant number of emergency procedures due to the nature of our institution which is a tertiary care center with several referrals from suburban and regional hospitals. This may have created a selection bias for patients at a higher risk for infection. In fact over 30% of the population studied had a high ASA score.

Comment 5

“…References have to be updated. Other Cochrane reviews and other studies have been published in the last years on this topic…”

Author’s response

The 2 new important papers are included in the revised manuscript. The authors would appreciate any further comments about other papers that need to be included.