

## Peer Review File

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We thank the reviewers for their thoughtful and pertinent comments. Please find following our response to each point raised by the reviewers.

### **Reviewer A**

*Thank you for sending this manuscript for review at Annals of Translational Medicine. This manuscript was a narrative review of antibiotic prophylaxis in surgical procedures and appropriate antibiotic management in the ICU. The overarching conclusion is that antibiotic stewardship is critical and knowledge of appropriate antibiotic management is imperative given the emergence of multi-drug resistant organisms. I agree with the authors' message and appreciate their synthesis of information on these topics.*

1.1.	The manuscript is quite long and may actually be better served as two separate manuscripts discussing prophylactic antibiotics and appropriate management of antibiotics in the ICU. Given the more “limited” scope if the paper is partitioned into two separate manuscripts, there may be some benefit to following PRISMA guidelines.
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We thank the reviewer for his comments and advices. We totally agree with the reviewer. Two different manuscripts with more limited scopes could indeed be proposed. This manuscript is definitely too long and this is a too broad subject. Unfortunately, we did not choose the title of this manuscript: “Antibiotics in Anesthesia and Critical Care”. It was an editorial request and decision. We then made up with it!	
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1.2.	This may help to uncover some manuscripts that try and address some of the mentioned deficiencies in the literature including our limited understanding of obesity and its effect on antibiotic dosing – see reference below:  Karamian BA, Toci GR, Lambrechts MJ, Siegel N, Sherman M, Canseco JA, Hilibrand AS, Kepler CK, Vaccaro AR, Schroeder GD. Cefazolin prophylaxis in spine surgery: patients are frequently underdosed and at increased risk for infection. Spine J. 2022 Sep;22(9):1442-1450. doi: 10.1016/j.spinee.2022.05.018.
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This article (reference 110) is now included in the obesity chapter.	
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1.3.	Line 324 – “even” is misspelled.
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Changed.	
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1.4.	Please write out all abbreviations the first time they are used (for example CRS).
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Done.	
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1.5.	Line 394 – I believe the word should be “led” instead of “lead”.
Changed.	

## **Reviewer B**

2.1.	The authors extensively report on factors that have influence on the use of antibiotic prophylaxis around surgical procedures and antibiotics at the ICU, which are to very different things. The link between the two topics is not clear to me. Although the review is very extensive, it lacks focus for me.
<p>We thank the reviewer for his comments and advices, and we totally agree with the reviewer. Two different manuscripts with more limited scopes [“Prophylactic antibiotics” and “Appropriate antibiotic management of antibiotics in the ICU”] could indeed be proposed. This manuscript is definitely too long and this is a too broad subject. Unfortunately, we did not choose the title of this manuscript: “Antibiotics in Anesthesia and Critical Care”. It was an editorial request and decision. We then made up with it!</p> <p>That said, as it is stated by the other reviewer, our overarching message is that antibiotic stewardship is critical and knowledge of appropriate antibiotic management is imperative given the emergence of multidrug resistant organisms.</p>	

2.2.	Why discuss microbiota but not disinfection or infection prevention measure?
<p>As already said, this manuscript is too long and this is a too broad subject! Thus, we made choices over others! The gut microbiota is the main reservoir for multi-drug resistant bacteria organisms. Dysbiosis in ICU patients might also have consequences on organ failures and survival. We then introduced to intensive care physicians the gut microbiota basics.</p>	

2.3.	The main message of the manuscript is not clear, and does not help in daily clinical practice to prescribe adequate antibiotic prophylaxis.
<p>Our overarching message is that antibiotic stewardship is critical and knowledge of appropriate antibiotic management is imperative given the emergence of multidrug resistant organisms.</p> <p>SSI prevention guidelines are published by major scientific and professional experts, and are periodically revisited. <u>For daily clinical practice</u>, perioperative antibiotic prophylaxis must follow these recommendations, and each institution should develop their own protocols for the proper surgical prophylaxis to standardize their practices.</p>	

2.4.	I would suggest focusing on the evidence around antimicrobial prophylaxis before surgical procedures and the optimal timing of it based on PK/PD studies, or effective measures in general to prevent the infection of surgical infections (and why this could help e.g. disinfection of the skin to lower the bacterial concentration), and the emerging problem of
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	ESBL/carbapenems and possible solutions for that (which is not taken into account in current guidelines)
These different topics have been largely discussed in the manuscript – e.g. PK/PD and MDR organisms!	

2.5.	Suggested factors in Table 2 other than antimicrobial prophylaxis are not highlighted at all.
<p>Again, we made choices!  Nevertheless, 7 of 9 factors (Selection of perioperative antibiotics according to effectiveness in specific types of surgery; Variability in antibiotic pharmacokinetics within various type of surgical patients/populations; Antibiotic concentrations at the “site of infection”; Antibiotic pharmacokinetic/pharmacodynamic characteristics; Appropriate antibiotic dosing and redosing; Obesity; Multidrug-resistant organisms) were more than highlighted!</p>	

2.6.	English languages needs to be improved: line 28, 40, 45, 49, 55 etc. I would suggest a proof read by a native English speaker.
Done.	

2.7.	Line 45: Please clarify what the Surgical Care Improvement Project and Prevention SCIP performance is. Apparently, is it a gold standard or does it entail in clinical practice used measurements, so other important factors (mentioned in Table 2) are currently not taken into account in clinical practice (if this is the reasoning I am not sure if this is correct?) Or why is the project used to compare other potential effective measures with?
<p>Pay for Performance in healthcare (P4P), also known as value-based payment, comprises payment models that attach financial incentives/disincentives to provider performance in the United States. P4P is part of the overall national (US) strategy to transition healthcare to value-based medicine. (What Is Pay for Performance in Healthcare ? NEJM Catalyst March 1, 2018.)</p>	

2.8.	With regard to chapter 1.2. PK/PD characteristics also vary with the antibiotics used as prophylaxis (time of above MIC? Cmax?) The authors mainly focus on the PK component, however, to determine the optimal timing of prophylaxis administration the PD component of the specific antibiotic chosen matters as well!
<p>PK/PD characteristics clearly vary with the classes of antibiotics used as prophylaxis : B-lactams versus aminoglycosides versus glycopeptides. In the manuscript, we focus on PK/PD characteristics, not on only PK characteristics. Nevertheless, there is a paucity of PD data in perioperative antibiotic prophylaxis ! As it is discussed in the manuscript, the concentration-dependent antibiotics may pose a serious problem ! The optimal PD targets for concentration-dependent antibiotics in prophylaxis is uncertain when considering variables such as inoculum size and the potential timing of bacterial contamination.(52,51) Unless the antibiotic has unusually high penetration and long persistence in tissues, achieving a high Cmax/MIC ratio prior to surgical incision should have no benefit if a high-inoculum bacterial contamination occurs near the end of a prolonged surgical procedure.</p>	

2.9.	It would suggest to start the review with section described from lines 135 and further in which the purpose/goals of antimicrobial prophylaxis is explained.
We modified the layout of the chapters.	

2.10.	In chapter 1.4 the info about PD is described. Chapter 1.2 - 1.3 - 1.4 all involve PK/PD issues. It would suggest to use subheadings for these chapter, instead of making them 3 different chapters.
Done.	

2.11.	And an introduction of why the information is included would be nice. As stated in remark 4: I would suggest starting with chapter 1.3, then 1.4. and last 1.2. As chapter 1.2. is about intraindividual variant which is not the most important PK PD related factor.
Done.	

2.12.	Lines 217-223: isn't this related to differences in PK instead of PD? I do not understand the information written in this section.
Removed.	

2.13.	Lines 365 and further: please also see DOI: 10.1093/cid/ciy768. And evidence for rectal culture-based prophylaxis in transrectal PB.
To our knowledge, it was already referenced (113).	

2.14.	What about the duration of prophylaxis for procedures as Transanal endoscopic microsurgery and the contaminated area (and wound) remains for few days after surgery.
Again, for daily clinical practice, perioperative antibiotic prophylaxis must follow the international recommendations, and <u>each institution should develop their own protocols</u> for the proper surgical prophylaxis to standardize their practices. The duration of PAP should be anyway <24 hours!	

2.15.	Line 429: why? Because based on the above the evidence is poor and guidelines are not concise.
It has been modified.	

2.16.	Lines 441-446: Needs more explanation as the message the authors give can be dangerous. Missing a case of sepsis, and not administering antibiotics in time can even more harmful. Patients receiving urgent therapy probably are more ill, so perhaps have a worse prognosis at
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	baseline, this might not have to do anything with the prescribed prophylaxis and could be a bias.
It has been modified.	

2.17.	Table 2 more inventions to prevent infections are mentioned, but the focus of the manuscript is on antimicrobial therapy.
We did not modified/suppressed this table. With this table, we potentially suggest further researches on PAP.	

2.18.	The abstract and conclusion are not in line with the content of the manuscript. What is the main message/purpose of the authors with the manuscript?
<p>As already underlined, two different manuscripts with more limited scopes [“Prophylactic antibiotics” and “Appropriate antibiotic management of antibiotics in the ICU”] could be proposed. This manuscript is definitely too long and this is a too broad subject. We made choices over others! Unfortunately, the reviewer do not agree with these choices! And again, we did not choose the title of this manuscript: “Antibiotics in Anesthesia and Critical Care”. It was an editorial request and decision. We then made up with it!</p> <p>That said, as it is stated by the other reviewer, our overarching message is that antibiotic stewardship is critical and knowledge of appropriate antibiotic management is imperative given the emergence of multidrug resistant organisms.</p>	