Author's response to reviews

Title: Empirical use of antibiotics and adjustment of empirical antibiotic therapies in a university hospital: a prospective observational study

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Answers to the reviewers

We thank the reviewers for their comments and their help in improving the manuscript.

Reviewer 1 (R.A. Seaton):

General:

As requested, more details on the evaluation of application modus of antibiotics (i.v., p.o.) and on the ID consultation service are now provided (cp. below).

Background and Methods:

1. “Role of ID and micro…”: Following sentence was added in the Methods (p. 5), in addition to the explanations on the role of ID and microbiology in the Discussion: “An active infections diseases consultation service is present in the hospital and has a close collaboration with the microbiology laboratory. In addition, weekly infectious diseases rounds are held on all medicine wards, on the bone marrow transplant unit and on the intensive care units.”

2. “What proportion of antibiotic prescriptions/patients with infection is/are ID reviewed?”: There is no formal review of antibiotic prescriptions or patients. Our data show that ID consultants were involved in 16% (84 / 539) of patients started on antibiotics within 24 hours of admission (Tab. 4, p. 25). In addition, patients with infections on the intensive care units, the bone marrow transplant unit and on all medicine wards are discussed once a week during ID rounds.

3. “Which protocols do the ID team (...) use?": The ID team uses the same internal guidelines available to all prescribers at the University Hospital Basel.

4. “How are micro results communicated?”: results with immediate and relevant consequences are communicated by phone and with a written report (e.g. any growth of micro organisms from blood cultures or cerebrospinal fluid). Identification of *M. tuberculosis* or “alert micro organisms” such as MRSA or ESBL producing bacteria is communicated electronically also to the Section of Hospital Epidemiology. All these results are reviewed once daily during the meeting of the ID department. All ID-physicians, at least one microbiologist and one physician of the Section of Hospital Epidemiology participate in this meeting. All microbiological results are communicated also by a written report.

5. “How is an ID consult triggered?": An ID consult can be required by the physician responsible for the patient by phone (an ID consultant is available 24 hours a day) or with a written form. The ID team gives oral advice and offers a formal consult for all patients with positive blood cultures or other relevant results, who are identified at the daily meeting through the records of the microbiology laboratory.
6. We did not formally analyze the compliance with the ID opinion. Our experience shows that the compliance is quite good (probably ≥ 75%).

7. “…guidelines available on the intranet”: More details were provided as follows (Methods, p. 5): “These internal guidelines include recommendations on diagnosis and treatment of pneumonia, sepsis, endocarditis, urinary tract infections, infections of the central nervous system, intravascular catheter-related infections, fever in neutropenic patients, and on empirical therapy in patients with suspected infection. The guidelines focus mainly on the choice and on the dose of the antibiotic. Recommendations on duration of therapy (and on duration of i.v. therapy) are provided for some indications (e.g. endocarditis, meningitis, intravascular catheter-related infections, urinary tract infections). There are no general recommendations for the switch from i.v. to p.o.

8. “…programme used to advertise their existence…?”: each ID-consultation is discussed with the physicians in charge of the patient. During these discussions, as well as during the weekly ID-rounds on the wards mentioned above, the ID-recommendations are supported also by referring to the internal guidelines.

9. “To what extent were the (...) guidelines (...) used and were other sources also used ?”: The internal guidelines and the “Sanford guide” were used when they included recommendations addressing the problem of the case in discussion. Otherwise other sources, such as published recommendations (e.g. IDSA guidelines), articles in the literature or textbooks were used.

10. “Why were alternating weeks studied…?": All patients were screened and followed up, and all information was collected by only one person (JM). This guarantees a consistent collection and evaluation of information, but this work is not feasible for one person, if patients were included each day, since all patients admitted through the emergency department had to be followed up for at least 24 hours, and all patients started on antibiotic had to be followed up until discharge.

11. “Clarify primary and tertiary care”: the University Hospital Basel provides primary care (e.g. family medicine in an outpatient department) to tertiary care (e.g. bone marrow and organ transplantation) for the Canton of Basel-Stadt. It is also the tertiary care referral centre for several other Swiss Cantons as well as for some French and German regions at the Swiss-French and Swiss-German border.

12. “It is not clear who collected and analysed the data…”: This is clarified in the Authors’ contributions section as follows: “JM followed up all patients admitted through the Emergency Department, identified all patients qualifying for the study, prospectively collected the information on each patient, reviewed each patients’ chart and drafted the manuscript. JM and SB reviewed together each case report form with the corresponding chart to assess the adequacy of the antibiotic therapy. SB conceived of the study and helped to draft the manuscript. MS and PS performed the statistical analysis. All authors participated in the design of the study, helped to interpret the data and to draft the manuscript. All authors read and approved the final manuscript.” (p. 16). As reported in the list of authors and their affiliations (p. 1) all authors are MD or MD with statistical training (DSc, MS), except M. Simcock, who is a statistician.
13. “How often were charts reviewed...?": daily.

14. “Were prescribers aware of the study...?": Only the heads of department were formally informed about the study. However, some prescriber was aware of the study, and a “study-effect”, as in all studies, is possible. No interventions by the study team occurred beside data collection.

15. “Did prescriber change during the study period?: Only some residents changed during the study. Almost no change occurred among senior residents, registrars and senior staff.

16. “The authors have excluded a substantial proportion of patients who received antibiotic therapy prior to admission. This needs to be explained as often patients are admitted because community therapy is failing (particularly LRTI and soft tissue infection).”: The aim of the study was to investigate empirical therapy (i.e. therapy of infections which are not yet documented) started at the University Hospital Basel and the adjustment of this therapy. We excluded patients who received antibiotics before admission as outpatients mainly because this group is not very relevant to the aim of our study. Indeed, most of these patients are not treated empirically, since they already have an established diagnosis of infection at admission (such as LRTI or soft tissue infections, as pointed out by the reviewer).

17. “The authors have excluded patients who received AB Rx 24 hrs post admission. This needs to be explained as this excludes those in whom infection has been initially missed and those who have acquired infection in hospital.”: It is not possible to easily identify all patients treated with antibiotics at our hospital, because we don’t have electronic prescribing. We had to prospectively follow up all admitted patients by evaluating each patient’s chart on the wards, looking for the prescription of antibiotics (this was done for 2943 patients, cp. Results). Therefore, we had to limit our study group and included only patients started on antibiotics within 24 hours of admission. We believe that this group of patients is representative because most patients admitted because of acute bacterial infection are started on antibiotics within 24 hours of admission. The adequacy of treatment of nosocomial infections was not an aim of the present study.

18. “Inadequate” prescribing must be better defined. Does this mean “inappropriate” i.e. over or under use or does it imply “insufficient” AB Rx...?": Criteria for the evaluation of the quality of prescribing have been developed by several authors. Some authors use the term “inappropriate”, but this term does not mean only “over or under use” (cp. Gyssens IC in “Antibiotic policies, theory and practice”, eds. Gould and van der Meer). We used the term “inadequate” and the definition follows previous studies in the literature. The definition is given in the Methods section (p. 6) as follows: “... we defined an antibiotic therapy as inadequate when one or more of the following points were not in accordance with local written recommendations or published guidelines (e.g. The Sanford Guide to Antimicrobial Therapy): spectrum, dosage, application modus of antibiotics, or the duration of therapy, and/or when pathogenic bacteria that were resistant to the antibiotic used were isolated.”

19. “The authors refer to “application modus of antibiotics” in the methods. Does this refer to i.v. or oral mode of administration?...”: “Application modus of antibiotics” refers to i.v., i.m. or p.o. mode of administration. As stated in the Methods, the
application modus was one of the criteria used to define adequacy of therapy. If the application modus was considered to be not appropriate, the reason was recorded (Tab 3) as follows: “therapy underdosed” (e.g. if a patient with catheter-related bloodstream infection caused by *S. aureus* was treated with amoxicillin/clavulanate p.o.), or “therapy overdosed” (e.g. if a patient with uncomplicated pneumonia caused by susceptible *S. pneumoniae* was kept on penicillin i.v.). This explanation was added in the Methods (p. 6, last sentence).

We evaluated whether the whole antibiotic treatment (i.v., p.o. or combined) of each patient was adequate for the diagnosed infection. As reported in the Results (p. 9) 83.7% of patients received an antibiotic i.v. and empirical i.v. antibiotics were switched to oral administration a median of 4 days after admission (range: 0 – 43; IQR 3). At the time of the study, at our hospital there were no recommendations or guidelines with criteria for the switch of antibiotics from i.v. to p.o. In the absence of defined and accepted criteria, we didn’t perform a more detailed analysis of antibiotic i.v.-oral switch.

20. “Statistics. There appear to be short comings in this analysis in that risk factors for (defined) inappropriate use were also themselves used to define inappropriate use. Statistical expertise is required…”: We did not use risk factors for inappropriate use to define inappropriate use. Below (point 26) the reviewer states, that “…the lack of an infectious disease diagnosis was found to be associated with a risk for inadequate antibiotic therapy. This was in fact a criteria for defining inadequate AB therapy…”. The characteristics reported in the tables (“risk factors”) include the main infectious disease diagnosis upon admission (cp. Tab. 1), and not at discharge, because the decision to start empirical antibiotic treatment and the choice of antibiotics has to be made at this moment. If the physician in charge of the patient did not record any infectious diseases diagnosis but the patient received antibiotics, the patient was included in the study (and the diagnosis recorded as “no infectious disease”). The prospective follow up showed that in some of these patients the use of antibiotics was appropriate because they actually had an infection. E.g. a patient admitted with fever considered to be caused by arteritis temporalis was nevertheless treated with antibiotics. Urine cultures grew *E. coli* in relevant amount and on repeated questioning the patient reported symptoms of UTI. In this patient, the antibiotic therapy was appropriate, while the initial evaluation, or at least the documentation of initial evaluation, was probably not very accurate.

Results:

21. “Why were patients referred to another hospital within 48 hours ?...”: Reasons for referral of patients to another hospital within 48 hours include transfers to a geriatric hospital or to a psychiatric or psychosomatic clinic, and transfer to peripheral hospitals of patients who don’t need tertiary care and are not living in the Canton Basel-Stadt, or transfer of patients not living in Basel (e.g. tourists) to an hospital near their home. We excluded these patients, since it was not possible to follow up prospectively these patients in other hospitals. We did not collect any data on these 224 patients (out of 3387, 6.6%).

22. “Pathogenic bacteria isolated; Does not seem to have been a differentiation between bacteria isolated in blood (very significant), urine (may be significant), sputum/BAL fluid (potentially dubious significance). Can the authors explain how the
microbiology was interpreted…? (...) I would be more interested to focus on unequivocal microbiology i.e. blood cultures of typical community acquired organisms.”

As the reviewer points out, it is not possible to establish the relevance of an isolated microbiological result without considering the patients' history, clinical findings, results of all laboratory and radiological examinations, course of the disease, response to therapy etc. We considered all these information by collecting the data prospectively and by reviewing the chart of each patient (as reported in the “Methods”, p. 6 second paragraph). On the basis of this information we decided whether a bacterial isolate was to be considered pathogenic and significant or not. This is in our opinion an important strength of our study and allowed us to evaluate all antibiotic therapies. It is easier to establish only the significance of bacteria isolated in blood cultures; however, most antibiotic therapies are performed in patients with no or negative blood cultures.

23. “Duration of i.v. therapy…”: as suggested, we changed the data to median and provided the IQR as follows: “Empirical intravenous antibiotics were switched to oral administration a median of 4 days after admission (range: 0 – 43; Interquartile range: 3).” (p. 9)

24. “Adjusted therapy; is this just referring to i.v. to oral switch…”: Adjusted therapy is not referring to i.v. to oral switch. To clarify this point the definition of adjusted therapy was completed as follows (Methods, p. 6): “The adjusted antibiotic therapy was the antibiotic regimen after the first change of antibiotic substance. The switch of the same antibiotic from i.v. to p.o. was not considered to be an adjustment of therapy.”

The application modus (i.v. or p.o.) was one of the criteria used to define appropriate therapy: cp. point 19 above.

25. “It is valid to state that negative cultures “rule out infection” and therefore render the prescription inadequate ?...”: It is valid if you interpret the negative cultures (in particular urine cultures) together with all available information, as we did (cp. point 22). Obviously, we did not consider an infection to be ruled out only because blood cultures were negative. To interpret the microbiological results we also considered whether each individual patient received antibiotics before microbiological samples were taken (all samples, i.e. blood cultures, CSF, etc., not just urine). This was done by evaluating the chart and the admission protocol of the emergency department, where all diagnostic and therapeutic procedures are recorded. We did not formally analyse the number of patients who received antibiotics before urine culture, but the great majority received the antibiotics after urine cultures were taken.


27. “In the univariate model for antibiotic switch, switch due to bacteriological results was associated with adequate antibiotic treatment. Surely this is obvious as this was one of the criteria for defining “adequate” antibiotic therapy !...”: Switch due to bacteriological results was one of the reasons given by the physicians in charge of the patients to explain why an antibiotic therapy was changed. Whether the therapy was adequate after the switch has still to be determined according to the criteria and the information mentioned above (cp. point 22). The fact that 11% of patients who had a change of therapy because of lab results were treated inadequately confirms that the interpretation of microbiological results may be difficult and may also lead to wrong conclusions.
28. “Does female sex as a risk for inappropriate AB imply "UTI" and hence negative culture ie are the confounding variables here ?”: As stated in the discussion, the reason for the association between female sex and inappropriate therapy is unclear. The diagnosis UTI was not significantly associated with inappropriate therapy. Therefore “negative culture” can not be the confounding variable. In addition, “negative culture” was interpreted as explained above (point 25).

29. “I am not clear (…) what the effect of the ID consult was…”: the tables were modified to clarify that the two characteristics examined were whether ID consultants were involved within 24 hours of admission or whether they were involved at all. This point was clarified by adding following paragraph (Discussion, p. 13): “The impact of infectious diseases consultations was considered by recording whether infectious diseases consultants were involved within 24 hours of admission or whether they were involved at all. In the univariate analysis involvement of infectious diseases consultants was significantly associated with inadequate empirical therapy (Tab. 4). This can be explained by the fact that consultation is usually required for patients with more severe or difficult to manage infections or with unclear clinical presentation, who are usually started on empirical antibiotic therapy before the infectious diseases consultation is obtained, in order to avoid delays. Thus, adjusted therapies may show more reliably what the effect of infectious diseases consultations was. Indeed, involvement of infectious diseases consultants was associated with adequate adjusted therapy (Tab. 5) in univariate analysis.

Tables:

30. “Table 1. Females not required… Age should be expressed as median and range given:” Tab. 1 was modified as suggested.

31. “I would include neurology with medicine and geriatrics…”: Neurology was separated because patients on this ward have a different spectrum of infections compared to patients on medicine and geriatrics (e.g. encephalitis, Lyme neuroborreliosis etc.). ICUs were combined consistently for purposes of analysis (Tables 4 and 5).

32. “Terminology of site of infection; UTI referred to variably include…”: This group of diagnoses is now consistently reported as “urinary tract infections, prostatitis, epididymitis” (Tab. 1, 4-5).

33. “Does gastrointestinal infections include gastroenteritis and diverticulitis, peritonitis etc. …?”: “Gastrointestinal infections” includes gastroenteritis, diverticulitis, peritonitis, enterocolitis, appendicitis, abdominal abscess, acute abdomen. This information was added (Tab. 1).

34. “What is the difference between “sepsis” and “suspected systemic infections without identified focus”…?”: “Sepsis” was defined according to the accepted definition in the literature as “clinical evidence of infection plus SIRS”. Patients with “suspected systemic infections without identified focus” did not meet the sepsis criteria. These definitions were added (Tab. 1).
35. “In how many were no data recorded on the site of infection ?”: As reported in Tab. 1, in 25 patients a systemic infection was suspected, but the site of infection was not identified.

36. “ENT infections seemed to have been included but ENT wards were excluded; please explain.”: many patients with ENT infections are not hospitalized on the ENT ward but on other wards (e.g. patients with sinusitis on the medicine or neurosurgery ward, or on the ICU).

37. “Table 2. Looks fine except crucially I cannot tell how many of each received i.v. or oral…”: This table presents data on the use of antibiotic substances. As reported in the Results (p. 8), 83.7% of patients received at least one antibiotic i.v. The modus of administration was evaluated for each patient as discussed above (point 19).

38. “Table 3. Major omission is inappropriate route of administration as previously discussed…”: The route of administration was evaluated as discussed above (point 19). In 9 patients the empirical antibiotic therapy was inadequate because of > 1 reason.

39. “How was appropriate duration determined? Does this refer to i.v. or oral therapy being too short or too long…”: We evaluated whether the whole antibiotic treatment (i.v., p.o. or combined) of each patient was adequate for the diagnosed infection. Appropriate duration was determined, as the other criteria, according to local written recommendations or published guidelines (Methods, p. 6).

40. “What do the authors mean by overdosed ?”: administration of a too high dose of antibiotic.

41. “Table 4. A comparison of median age…”: the mean age was replaced by the median, as suggested.

42. “Do the data suggest ID consults were associated with less appropriate Rx…?”: cp. point 29.

43. “Not sure what the other sub analysis is referring within this block of results…”: “renal failure reported”, “hepatic failure reported” etc. have nothing to do with ID consults. The table was modified to avoid this misunderstanding.

44. “Terminology…”: The terminology of ID diagnosis was modified to match that in the earlier table.

45. “Table 5 adds nothing…”: That is not true. Tab. 4 reports the data for patients with empirical antibiotic treatment. Tab. 5 the data for patients with adjusted antibiotic treatment. Both data sets are necessary to evaluate the empirical use of antibiotics and adjustment of therapy, which was the aim of the study.

Discussion:

46. “Inadequacy” continues to confuse here.”: The terms “inadequate” and “inadequacy” continue to be used consistently also in the Discussion, in agreement with the definition given (cp. point 18).
47. “The section on the ID consultation…”: more information on ID activities was added in the methods section (cp. point 1).

48. “Persistent fever…”: This was one of the most common reasons recorded in the charts of patients unnecessarily switched to broad spectrum antibiotics.

**Reviewer 2 (Curtis Donskey):**

Minor essential revision.

1. We agree with this comment. The conclusion was modified as follows (Conclusions, last 2 sentences): “Thus, interventions aiming at improving antibiotic prescribing should focus on both initial empirical therapy and streamlining and adjustment of therapy. Furthermore, the impact of microbiological results on the clinical management of patients should be improved.”

Discretionary revisions.

2. Examples were provided e.g. for the evaluation of application modus (p. 7).

3. Methods: the information on guidelines used was completed as follows: “Finally, we defined an antibiotic therapy as inadequate when one or more of the following points were not in accordance with local written recommendations or published guidelines (e.g. The Sanford Guide to Antimicrobial Therapy, practice guidelines of the Infectious Diseases Society of America)…” (p. 6).