

Dear Madam, Dear Sir,

Thank you very much for the revision of the submitted manuscript. According to the recommendations, we revised the manuscript completely. We added the requested data, performed a re-calculation where necessary and adopted it to the text.

Substantial re-calculation was necessary because of the integration of the information on intermediate sensitivity. This did not change the key message but the calculations. Therefore, table 5 and 6 as well as figure 1 was renewed. The former table 3 was omitted and integrated in a new merged table.

We were also asked to add information on the rate of bacteriobilia in different clinical situations. These data are now included. Data from table 1 have been re-calculated and table is completely new now.

In detail and according exactly to reviewers' comments, we changed as shown in detail:

Reviewer 1

The descriptions on the fact of "preoperative cholestasis" of our previous manuscript were not sufficiently precise. Therefore, we have clarified that aspect.

From our surgical point of view, we see the indication for bile duct drainage (PBD) in patients with cholangitis or a relevant cholestasis which means a preoperative bilirubin of more than 8 mg/dl. However, most of our included patients were initially treated in the department of gastroenterology. Indication for PBD and management of these patients is often organized prior to interdisciplinary decision on the definition of the treatment plan. Today, the cooperation has been developed to a closer and standardized work flow.

In the study, "preoperative cholestasis" refers to the last blood value prior to surgery. So, these patients had a cholestasis when the disease was diagnosed and the treatment was started. In many patients, this has resolved completely (PC-) until the date of surgery. However, some patients have a persistent cholestasis at the moment of surgery (PC+). Nevertheless, both groups are PBD+.

Question2: Did the BB rate vary according to patients with malignancy or chronic pancreatitis?

This question led us to an interesting point. The data are added in the completely revised table 1.

The BB rate was (almost significantly) higher in patients with malignancy. As this information may be misinterpreted, we also performed an additional multivariate analysis. This confirmed our clinical expected thesis, that PBD is the only risk factor for bacteriobilia.

Reviewer 2 (Prof. Masayuki Ueno)

1. Question:

The authors are proposing piperacillin/tazobactam for postoperative infection in their conclusion. However, in the sections of "background" in the abstract and "introduction" in the manuscript, they

mention rather adjustment of preoperative antibiotic prophylaxis. We thank you very much for this point. As defined in the title of our manuscript, we are focusing on the subject of prophylaxis. The abstract and the following text have been adapted to this theme.

2. Question:

If their conclusion is about treatment for postoperative infection, they need to describe the rate of postoperative infection related to biliary bacterial colonization. Otherwise, if they try to show the superiority of piperacillin/tazobactam to ampicillin/sulbactam for prophylaxis, they should think about the result that pathogens sensitive to ampicillin/sulbactam were detected even after administration of prophylactic ampicillin/sulbactam; perhaps the dose, timing or duration may be the matter.

The standard PEP has been given 30 minutes prior to surgery. The smear has been taken on average 90 minutes after skin incision. So, an effective concentration of antibiotics might have an influence on the microbiological findings. It might lead to an underestimation of bacteria which are sensitive to ampicillin/Sulbactam. There is a risk of a bias in the evaluation of ampicillin/Sulbactam. According to the actual valid guidelines about PAP, we have to accept this bias. Otherwise to guarantee, that there is no effect of the PAP on the microbiological findings of the smears, we had to abandon this option of a PAP. For a retrospective study this is no option, so we had to accept this bias.

3. Question

The authors excluded the intermediate sensitivity from their analysis. However, this data are important in clinical practice; in usual cases, only sensitive antibiotics are recommended for confirmed infection, and intermediate sensitivity has similar meaning to resistance.

According to these substantial implications, we have recalculated all data referring to antibiotic efficiency.

In the submitted manuscript, the results based on 3252 items of sensitivity and 1252 items of resistance in 342 bacteria. Now, 100 items of intermediate were added to resistance, which equals an influence of 7,9%. Referring to resistance level of the most important antibiotics as pointed out at the end of the results chapter, the resistance rate changed by 0-3%.

All graphs and tables have been recalculated.

4. Question

The authors described the conditions in which preoperative biliary drainage: relevantly elevated bilirubin and if the timing of operation. However, not a few patients underwent preoperative biliary drainage even without cholestasis. They need to explain the reasons for biliary drainage in these patients.

This remark has already been made by the first reviewer. (see above). We have clarified that point.

5. Question

The conclusion of the manuscript appears verbose. They had better summarize their conclusion concisely.

The conclusion is shorter and more precisely focused on the subject of prophylaxis.