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Comment on the Recent Publication Entitled by Ellis et al. "Association Between Biliary Pathogens, Surgical Site Infection, and Pancreatic Fistula"

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The article of Ellis et al[1] titled "Association Between Biliary Pathogens, Surgical Site Infection, and Pancreatic Fistula"[1] was read with considerable interest. This ancillary observational study included patients in whom an intraoperative bile culture (IOBC) was performed during the multicentric randomized controlled trial showing a reduction in postoperative surgical site infection (SSI) and clinically relevant postoperative pancreatic fistula in patients receiving piperacillin-tazobactam versus cefoxitin as prophylaxis for open pancreatoduodenectomy (PD).[2] Ellis et al. have demonstrated an association between IOBC data and the development of SSI, particularly when organisms resistant to cefoxitin (Enterococcus and Enterobacter species) are present, emphasizing the need to use perioperatively effective broad-spectrum antibiotics for prophylaxis during PD. We would like to compliment the authors on their outstanding work and the significance of their research.

Considering the negative impacts of postoperative infections in terms of hospital stay,[3] delay of adjuvant treatment in the case of pancreatic ductal adenocarcinoma (PDAC) and subsequent reduced overall survival,[4] and risk to see the emergence of broad-spectrum antibiotic resistance, it is crucial to choose an antibiotic effective against the most likely infecting organisms. This prompts the implementation of a systematic IOBC. In addition, there are still unanswered queries regarding the duration of antibiotics, including whether they should be administered only intraoperatively (prophylaxis) or postoperatively (therapy). A survey sent to expert centers in Belgium and France performing more than 60 PD/year revealed substantial heterogeneity in the nature and duration of antibiotic treatment (data not shown). This topic is of particular interest to us. During the design of a randomized trial (clinicaltrials.gov—NCT 05271344), which is currently in the recruiting phase at our center, to investigate the effect of optimized immunonutrition with symbiotics, omega-3 and vitamin D, on the risk of postoperative complications and their potential association with early detected occult bacteremia after PD and gut microbiome patterns, we investigated the effect of bactibilia on the risk of developing SSI after PD using a different approach than that proposed by Ellis et al. A total of 95 patients (2015–2021), in whom an IOBC was performed during PD in our center were classified in 3 groups: sterile bile (N = 40), infected bile with appropriate antibiotic (N = 32) according to speciation and infected bile with inappropriate antibiotic (N = 23) (resistance). All patients, with the exception of those in the sterile bile group (52%), received antibiotics intraoperatively and for at least 48 hours postoperatively until IOBC results. During the study period, 3 antibiotics were given at the discretion of the surgeon/anesthetic: piperacillin-tazobactam (4g intravenously every 6 hours) (39%), cefazoline (2g intravenously every 4 hours) (30%), cefotaxime (2g intravenously every 4 hours) (14%). Demographics (age, body mass index, gender, and American Society of Anesthesiologists score), histological (chronic pancreatitis, PDAC, distal cholangiocarcinoma, premalignant disease, and duodenal tumor), and preoperative data [duration of surgery, blood loss, pancreas texture, Wirsung diameter, pancreatic anastomosis (pancreatico-jejunal versus pancreatico-gastric), and venous resection] were similar among groups.

Of the 44 patients in whom a biliary stent was placed preoperatively, 40 had a positive IOBC ($P < 0.01$). Infected bile with the appropriate antibiotic group had fewer SSI than sterile bile and infected bile with inappropriate antibiotic groups (0% *vs* 25% and 22%, respectively; $P < 0.01$). Interestingly, therapy rather than prophylaxis antibiotics allowed us to avoid SSI. Moreover, patients with sterile bile still develop SSI, suggesting that bactibilia is not the only prerequisite for developing SSI after PD. Finally, in the sterile bile group, the proportion of patients who received antibiotics until IOBC results were obtained (48%) developed a similar rate of SSI to those who received antibiotics intraoperatively only (11% *vs* 36%, $P = 0.08$). This suggests that the duration of antibiotic treatment could be limited to the per-operative period in patients with minimal risk of biliary contamination (absence of preoperative biliary drainage, histology other than peri-ampullary cancer or PDAC).[5]

Clinically relevant postoperative pancreatic fistula and 90-day postoperative complications according to Clavien-Dindo scale >3a rates were not different: 18% and 13% in the infected bile with appropriate antibiotic group, 26% and 26% in the infected bile with inappropriate antibiotic group, 22% and 28% in the sterile bile group ($P = 0.68$ and $P = 0.28$, respectively). Hospital stays, 90-day postoperative re-admission, and mortality rates were similar between groups. Blood loss >1000 cc (adjusted OR, 13.84; 95% CI, 2.07–92.4 [$P < 0.01$]) and Wirsung diameter <3 mm (adjusted OR, 16.43; 95% CI, 1.95–138.3 [$P < 0.01$]) and not bactibilia were the only independent risk factors for the development of Clavien-Dindo >3a complications after PD.

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Among the 18 bacteria species observed in the IOBC, *Klebsiella* species (47%), *Escherichia Coli* (44%), *Enterococcus* (36%), and *Enterobacter* (16%) species were the most frequent. It is noteworthy that, in our population, resistance to Enterobacter species was observed with piperacillin-tazobactam (50%), cefazoline (100%), and cefotaxime (100%). Concerning the Enterococcus species, resistance was observed with cefazoline (100%) and cefotaxime (100%) (piperacillin-tazobactam speciation was not assessed).

Since the national centralization of pancreatic surgery in 2019, piperacillin-tazobactam prophylaxis, in our center has been administered in the absence of preoperative biliary manipulation. In case of biliary manipulation, piperacillin-tazobactam therapy is continued until the results of the IOBC and, if necessary, adjusted so that the patient receives 5 days of effective antibiotic therapy.

In summary, we definitely agree with the authors that large broad-spectrum antibiotics should be the standard of care for patients undergoing open PD to prevent postoperative SSI. Having said that, antibiotic therapy rather than prophylaxis should be considered, especially in patients at high risk of biliary contamination, and second, we must admit that the emergence of piperacillin-tazobactam resistance in our center raises issues about our systematic approach and highlights the relevance of assessing piperacillin-tazobactam speciation in every IOBC.

Again, we would like to congratulate the authors on achieving these excellent results and addressing this exciting topic, while also thanking you for the opportunity to discuss it.

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