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Correspondence

Prevalence and risk factors for multi-drug resistant bacterial infections in patients undergoing endoscopic retrograde cholangiopancreatography

Dear Editor,

Multi-drug resistant (MDR) bacterial infections represent one of the most challenging public health issues. Some studies highlighted a growing risk of transmission of carbapenem-resistant *Enterobacteriaceae* and other MDR infections in patients undergoing endoscopic retrograde cholangiopancreatography (ERCP) [1–3]. Recent evidence reports that a thorough protocol of endoscope reprocessing and screening of patients for MDR might reduce the risk of biofilm accumulation and colonization [4,5]. However, the risk factors for developing an infection in this setting are poorly characterized. Particularly, patient stratification according to age, comorbidities, type of surgery, and use of prophylactic antibiotic is still uncertain. Starting from these premises, in this single-centre study we aimed to evaluate the effectiveness of infection control measures in preventing MDR bacterial infections in patients undergoing ERCP. We estimated the prevalence of periprocedural infections occurring after the implementation of an infection surveillance protocol. As a secondary aim, we analyzed the impact of potential risk factors and we evaluated the adherence of the hospital physicians in implementing the infectious control procedures.

This prospective study included all adult patients referred to the Digestive Endoscopy Unit where the ERCP, regardless of the indication, was performed in June 2019-June 2021. The two duodenoscopes used were Olympus TJF-Q180V (fixed-end cap).

In 2018 the Infectious Committee released a protocol with additional measures for controlling periprocedural ERCP infections, involving both the patient and the endoscopes. Regarding patients, one week before endoscopy, rectal swabs had to be obtained to detect MDR bacteria (i.e., carbapenemase- and extended spectrum beta-lactamase- producing enterobacterales, vancomycin-resistant enterococci) through phenotypic and molecular characterization. The swab was not routinary repeated thereafter, and patients were followed as per clinical practice. MDR-positive samples had to be stocked and analysed with whole genome sequencing. As for the correct management of the endoscope, in addition to the already planned manual washing of the endoscopes with disposable toothbrushes dedicated to the distal part of the tool and to the diagnostic and operational channels, the endoscopic swabs and the washing liquid of the instrumental canal were also sent to the microbiology laboratory, at least every 40 ERCP examinations or, in any case, once a month regardless of the actual number of ERCP performed. Following the manual washing for the decontamination of the instrument, a high disinfection process with double long washing cycle in the washer was provided. In addition, microbiological tests were planned on endoscope washers' water every six months. A checklist was finally filled to assess the adherence of the medical and nursing staff with the new infection control protocol.

After the implementation of this protocol, we collected data of a series of 112 patients who underwent ERCP. As a primary endpoint, we reported the rate of positive rectal swab and of sepsis before or after (periprocedural) the ERCP. As a secondary endpoint, we looked at potential demographic or clinical variables associated with the risk of having a positive rectal swab.

Continuous variables were expressed with mean and standard deviation or median and interquartile range (IQR), while categorical variables were expressed as number and percentage. A multivariable analysis for potential factors affecting the risk of having a positive rectal swab was fitted. The statistical analysis was performed with the software STATA 16. The study was approved by the local Ethics Committee in 2019 (protocol number P-35354/2019).

The initial study population consisted of 112 patients undergoing ERCP. Among them, 95 patients (mean age 75±14 years, F:M ratio 1:1.1) underwent screening rectal swab, according to our new infection control policy, and hence were considered in the analyses. Supplementary Table 1 reports the general demographic and clinical characteristics of the cohort, while Table 1 reports the results of the rectal swabs, the isolated pathogens, and the antibiotic therapy. Most were non-smokers, and roughly one fifth had diabetes mellitus. The most common causes of admission were cholangitis or gallstones (56.9%), while 14.7% pancreatic neoplasms, 6.3% pancreatitis, and 3.2% other lesions of the Vater papilla. In most cases, surgery was not necessary during hospitalization, 21.1% of patients underwent cholecystectomy, while duodenocephalopancreasectomy was performed only in 4.2%; the remaining 6.3% of patients performed heterogeneous surgeries other than those mentioned above.

With regard to the prevalence of colonizations and infections diagnosed through rectal swab (primary endpoint), 15 (15.8%) rectal swabs turned out to be positive for MDR germs, of which 11 (73.4%) of them for *Vancomycin resistant Enterococcus faecium* (VRE), 2 (13.3%) for *Escherichia coli* ESBL+ (i.e., Enterobacteria producing beta lactamase with resistance to antibiogram at amoxicillin, ampicillin, cefotaxime, trimethoprim-sulfamethoxazole), and 2 (13.3%) for *Klebsiella pneumoniae* resistant to penicillin and cephalosporins. Of these 15 patients, 13 had an overt infection requiring treatment. No carbapenem-resistant enterobacteriaceae were found.

One *VRE*-positive patient was given cephalosporins, and other two were given carbapenems. One of these patients had cholangiocarcinoma and was hospitalized for multimicrobial cholangitis with isolation of *E. Faecium, E. Faecalis, E. Cloacae, K. Oxytoca*; piperacillin+tazobactam and then vancomycin+meropenem were given. Piperacillin+tazobactam was administered to other seven patients colonized by *VRE*. A therapy based on amoxicillin,

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Table 1
Results of the rectal swabs, isolated pathogens, and antibiotics used in the cohort under study.

	N.	%
Sample size	95	100
Outcome of the rectal swabs		
Negative	80	84.2
Positive	15	15.8
Pathogens isolated in positive rectal swabs		
Vancomycin Resistant Enterococcus faecium	11	73.4
Klebsiella Pneumoniae	2	13.3
E. Coli ESBL+	2	13.3
Colonized patients not undergoing antibiotics	2	13.3
Patients undergoing antibiotics due to overt infection	13	86.7
Antibiotic prophylaxis		
Yes	29	30.5
No	66	69.5
Class of antibiotics administered to patients with positive rectal swab		
Penicillin or beta lactamase inhibitors (Amoxicillin, Piperacillin+Tazobactam)	9	60
Cephalosporins	3	20
Carbapenems (Meropenem)	2	13.3
Glycopeptides (Vancomycin)	1	6.7
Quinolones (Levofloxacin, Ciprofloxacin)	2	13.3
Azole, antifungals (Metronidazole, Fluconazole)	1	6.7

Table 2
Multivariable analysis for factors associated with the risk of having a positive rectal swab.

Odds Ratio		95% CI	p-value
Sex	0.65	0.43-5.28	0.52
Age (continuous variable)	1.05	0.99-1.12	0.058
Diabetes mellitus	10.48	3.02-36.31	<0.0001
Use of prophylactic antibiotic	0.51	0.14-1.90	0.322
Having a biliary-pancreatic high-risk condition	0.63	0.16-2.36	0.494
Surgery during hospitalization	0.44	0.09-2.14	0.310

metronidazole, and fluconazole was given to a patient who developed iatrogenic intestinal perforation during ERCP. Regarding the two patients colonized by *K. pneumoniae*, hospitalized for biliary tract sepsis, they were successfully treated with ceftriaxone and piperacillin+tazobactam, respectively. As for *E. Coli ESBL+*, one of the two cases was given ceftriaxone. None of the patients developed post-ERCP sepsis due to the pathogens found in the rectal swab.

Among patients with negative rectal swabs, three of them developed infections after ERCP procedure. One patient developed necro-haemorrhagic pancreatitis with positive intra-operative swab for *Enterobacter cloacae ESBL* and *E. coli*, another one abdominal drainage infection (inserted for fluid collection after cholecystectomy), and the last patient developed post-procedure sepsis recovered after empirical antibiotic treatment.

There was a 100% adherence to the preventing measures of infection spreading through the endoscopes. Microbiological checks were carried out on the instruments and on the endoluminal washing liquid and microbiological controls were performed on the washing waters as provided in the new Protocol issued by the Hospital Infectious Committee. In all cases, the endoscopes turned out not to be colonised by any sort of bacteria.

Table 2 reports the results of the multivariable analysis for potential factors associated with a positive rectal swab. The analysis showed that only diabetes mellitus strongly correlated with this outcome (OR 10.48; $p<0.0001$). Instead, sex, age, the use of antibiotics, having a biliary-pancreatic high-risk condition, and surgery were not found to have a significant correlation.

Our study showed that 15.8% of patients admitted to the Digestive Endoscopy Unit of our hospital undergoing ERCP had a positive screening rectal swab. More in detail, 73.4% of these patients tested positive for VRE, 13.3% for *Escherichia Coli* ESBL+, and 13.3% for *Klebsiella pneumoniae* resistant to penicillin and cephalosporins. Further, in our cohort the percentage of post-ERCP infections sustained by the same pathogen isolated from the rectal swab prior to the procedure was 0%.

The available literature reports various figures regarding the prevalence of periprocedural ERCP infections. A recent systematic review that included 117 articles showed that the frequency of infections following ERCP is on average 0.8% with *Pseudomonas aeruginosa, Enterobacteriaceae* and Gram-positive cocci being the most common pathogens [6]. Other studies estimated that the prevalence of other infectious complications following ERCP (e.g., cholangitis and sepsis) would be roughly 0.5% to 3% [7].

In our cohort the highest percentage of positive rectal swabs was found in the group of patients with diabetes mellitus, both in oral hypoglycaemic therapy and insulin therapy; at multivariate analysis diabetes mellitus was the major risk factor associated with rectal swab positivity to multidrug-resistant bacteria (OR 10.48; $p<0.0001$). Although this result may not be surprising, as it is known that diabetes is associated to a higher risk of developing systemic infections [8], this datum in the context of ERCP is novel and should warrant further *ad hoc* research. Instead, there were no strong statistically significant associations between the cause of admission, surgery during hospitalization, the type of intervention, having a biliary and pancreatic infectious risk condition, and the risk of developing ERCP-related infections. Likewise, sex, age and use of prophylactic antibiotic appeared not to affect the risk of periprocedural infections.

In the light of our results, as for the adherence to the implementation of the infectious control procedures, we conclude that it was 100% effective, as no contaminations of the endoscopes were noticed. Indeed, considering the limits of the study, particularly the small sample size and the low number of infections, which prevented a larger multivariable analysis including other potential risk factors that were not considered, larger prospective studies are needed to corroborate what emerged from our analysis. Unfortunately, the outbreak of the Covid-19 pandemic resulted in a dramatically lower number of ERCP performed during the study period, and this may have biased our results.

To conclude, specific measures and tools for reducing the risk of ERCP-related infections, as postulated in previous papers [9,10], are warranted.

Conflict of interest

None to disclose for all authors.

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Author contributions

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.dld.2023.06.018.

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