Gastroenterology Unit
Hospital of Imola
University of Bologna

January 15th, 2022

Dear Prof. Gerhard Litscher,

please find enclosed the revised version of our manuscript entitled "Single-use duodenoscopes for the prevention of ERCP-related cross-infection – from bench studies to clinical evidence." for consideration for publication on the *World Journal of Methodology*.

We sincerely thank for positive evaluation and for the possibility of resubmit the manuscript.

Please find enclose a point-by-point response to Reviewers' comment in order to increase the overall quality of our manuscript.

Thank you for your time in considering this paper for publication.

Yours sincerely,

Andrea Lisotti on behalf of all co-authors

Reviewer #1:

Scientific Quality: Grade C (Good) - Language Quality: Grade B (Minor language polishing) - Conclusion: Minor revision

Specific Comments to Authors: The paper by Lisotti A et al. presents a review of all available clinical evidence on the use of SUD for ERCP. The review summarizes available clinical evidence on the use of single-use duodenoscopes for ERCP. Authors quantified those outcomes and reviewed all ongoing studies in the field in order to identify which data will become available in the next future. On these bases, this article will represent a basic point for all future research in the field. Thank you for the opportunity to review the manuscript. The paper was well written. Few comments:

Reviewer #1: "In two cases (3.3%), cross-over to a reusable duodenoscope was required due to ERCP technical failure. " What's the technical failure?

Re: The study of Muthusamy et al. [27] reported a 3.3% of technical failure. In one case failure was due to intrahepatic biliary stricture (one case) and neoplastic infiltration of the papilla (one case). We specified this issue in the text.

"In one case (tight intrahepatic stricture dilation in a patient with sclerosing cholangitis) the use of a reusable duodenoscope allowed a successful ERCP completion; in one case, papilla showed neoplastic infiltration."

Reviewer #1: "No difference was observed in term of adverse event (AE) and mortality, when ERCPs performed with the SUD were compared to those performed with a reusable duodenoscope." In this research, there seems no advantage of SUD for ERCP.

Re: We sincerely thank Reviewer #1 for the opportunity of clarifying this issue. All the published studies have been designed to compare SUD to standard reusable duodenoscopes with a non-inferiority purpose, in terms of technical and clinical success rate. Since the estimated rate of duodenoscope-related cross-infection was <8% published studies are underpowered to detect any clinical difference. We added a paragraph in the discussion.

"The lack of a reliable quantification of the impact of duodenoscope contamination-related infections does not allow to correctly evaluate the benefit of the systematic use of a SUD on a cost/effective point of view.

Indeed, All the published studies have been designed to compare SUD to standard reusable duodenoscopes with a non-inferiority purpose, in terms of technical and clinical success rate. Since the estimated rate of duodenoscope-related cross-infection was <8% published studies are underpowered to detect any clinical difference."

Reviewer #1: What is the approximate economic cost of SUD for ERCP? Limitations are not fully described.

Re: We thank the Reviewer for the opportunity to clarify this issue. A recently published (six days ago!) study assessed the cost-effectiveness of the use of SUD, compared to other approaches (partially-disposable duodenoscopes, intensified reprocessing, etc.). We added a paragraph underlying these issues, referring to the recently published manuscript.

“Cost-effectiveness.

A recently published study, based on a “Montecarlo model” assessed the cost-effectiveness of different approaches adopted for the reduction of duodenoscope-related cross-infections [28]. The cost for each ERCP procedure, based on United States data, performed with SUD has been estimated in $2,991. The analysis, based on an estimated <1% risk of duodenoscope-related cross-infections did not identified routinely SUD use as a cost-effective strategy. The Authors acknowledged that these results should be contextualized based on duodenoscope-related cross-infection rate, local ERCP volume, quality adjusted life years, post-ERCP lifespan and environmental costs [28,29].”

Reviewer #2:

Scientific Quality: Grade B (Very good) - Language Quality: Grade A (Priority publishing) - Conclusion: Accept (General priority)

Specific Comments to Authors: Authors reviewed the recent identification of several cluster of exogenous multidrug-resistant bacterial infection caused by duodenoscope cross-contamination necessitated the implementation of various strategies for at least prevention or abolition of that life-threatening risk.

However:

Reviewer #2: The lack of a reliable quantification of the impact of duodenoscope contamination-related infections does not allow to correctly evaluate the benefit of the systematic use of a SUD on a cost/effective point of view.

Re: We thank the Reviewer for the opportunity to clarify this issue. A recently published (six days ago!) study assessed the cost-effectiveness of the use of SUD, compared to other approaches (partially-disposable duodenoscopes, intensified reprocessing, etc.). We added a paragraph underlying these issues, referring to the recently published manuscript.

“Cost-effectiveness.

A recently published study, based on a “Montecarlo model” assessed the cost-effectiveness of different approaches adopted for the reduction of duodenoscope-related cross-infections [28]. The cost for each ERCP procedure, based on United States data, performed with SUD has been estimated in $2,991. The analysis, based on an estimated <1% risk of duodenoscope-related cross-infections did not identified routinely SUD use as a cost-effective strategy. The Authors acknowledged that these results should be contextualized based on duodenoscope-related cross-infection rate, local ERCP volume, quality adjusted life years, post-ERCP lifespan and environmental costs [28,29].”

Reviewer #2: Critical discussion will be the ecological impact of production and wasting of a single-use endoscope.

Reviewer #2: SUDs are made from recycled plastic and are claimed to be recyclable through third party companies, even if material from these duodenoscopes will not be used for production of medical devices.

Re: We thank Reviewer #2 for the opportunity of clarifying this issue. We added a paragraph dedicated on environmental sustainability.

Environmental sustainability

Another point of critical discussion will be the ecological impact of production and wasting of a single-use endoscope.

A recent international named “Green Endoscopy” (Twitter account @GreenEndoscopy) wrote an inspiring editorial on this issue. The Authors estimated a mean 1.5 Kg of waste for each single endoscopic procedure, with very-low amount of recyclable materials.

The disposal SUD is equivalent up to 400 g of household waste and this weight should be added to this waste. The Authors considered “unthinkable” that each ERCP could be performed with SUD based both on cost and environmental burdens.

A comparative study on two different approaches adopted with bronchoscopes [http://ambu.co.uk/pulmonology/environmental-impact] has reported that single-use endoscopy does not much differ since the cost of disposing plastic endoscopes should be balanced with sterilization process, disinfecting equipment and consumable costs.

On the other hand, SUDs are made from recycled plastic and are claimed to be recyclable through third party companies, even if material from these duodenoscopes will not be used for production of medical devices [29].

Reviewer #3:

Scientific Quality: Grade B (Very good) - Language Quality: Grade A (Priority publishing) - Conclusion: Minor revision

Specific Comments to Authors: Single-use duodenoscopes for the prevention of ERCP-related cross-infection – from bench studies to clinical evidence The article is well written, having solid research objectives which need to be quantified, however I found some minor limitations which should be clarify before accepting of the manuscript Minor comments:

Reviewer #3: The bacterial name should be written an italic

Re: We checked throughout the text and corrected.

Reviewer #3: Which guidelines you follow for performing meta-analysis?

Reviewer #3: Please mention the inclusion and exclusion criteria

Re: We thank Reviewer #3 for the opportunity to clarify the “Material and methods” section.

We added two distinct paragraphs accordingly.

Study selection

A systematic literature research was performed through MEDLINE using Pubmed, Google Scholar, and Embase interfaces at the end of November 2021. The search queries were ("duodenoscope"[all fields] OR

"single-use"[all fields] OR "disposable"[all fields]) AND "ERCP"[all fields]). Institutional Review Board evaluation for this purpose was not required. Relevant studies were independently analyzed by two authors (AL, RMZ).

Inclusion criteria were: 1) Population: all adult individuals who underwent ERCP; 2) Interventions: SUD use for ERCP; 3) Objectives: technical success (amount of successfully-completed procedures with SUD among all procedures); 4) Safety: incidence of ERCP-related complications.

Statistical analysis

Technical success rate and other aims were pooled through a random-effects model based on DerSimonian and Laird test. Heterogeneity was estimated using I2 tests: I2 less than 30% was considered low, while I2 >30% but <60% was considered weak. Funnel plots inspection was used to assess possible publication bias.

Main objective was the technical success, (completed ERCP using SUD among the entire amount conducted). Secondary objectives were adverse events (AEs).

Statistical analysis was performed with MedCalc package v20 (MedCalc Software Ltd, Ostend, Belgium; https://www.medcalc.org; 2021).

Reviewer #3: Please mention the data analysis procedure

Re: As requested by the Scientific Editor and Company Editor in Chief, we included a flow diagram according to PRISMA guidelines that clarified the data analysis procedure.

Reviewer #3: Please mention the type of contamination you found from systematic analysis

Reviewer #3: The types of multi drug resistant bacteria you found need to be mention as your study is based on clinically cross-infection, to identify their type, prevalent ratio and risk factors.

Re: Since this systematic review was focused only on disposable SUD, we limited our analysis on these endoscopes. No study reported any cross-contamination. Moreover, no data on specific SUD contamination after ERCP has been provided in the included studies. We specified this issue in the text.

Science Editor:

This manuscript summarizes the existing clinical evidence for the use of disposable duodenoscopy in the treatment of ERCP. It is recommended to supplement the reliable quantification of the impact of duodenoscopy pollution related infection, evaluate the benefits of using SUD in the system from a cost-effective / effective point of view. Language Quality: Grade B (Minor language polishing). Scientific Quality: Grade B (Very good)

Re: We sincerely thank Science Editor for the positive evaluation of the manuscript.

Company Editor-in-Chief:

I have reviewed the Peer-Review Report, full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Methodology, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision by Authors. Authors are required to provide standard three-line tables, that is, only the top line, bottom line, and column line are displayed, while other table lines are hidden.

The contents of each cell in the table should conform to the editing specifications, and the lines of each row or column of the table should be aligned. Do not use carriage returns or spaces to replace lines or vertical lines and do not segment cell content.

Re: We sincerely thank Science Editor for the positive evaluation of the manuscript. We changed the Tables according to WJM standards.

Please add a figure of PRISMA flow diagram. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor.

Re: We added a flow-diagram according to PRISMA guidelines.