

Format for ANSWERING REVIEWERS

Mart 25, 2015

Dear Editor,



Please find enclosed the edited manuscript in Word format (file name: 16592-review.doc).

Title: Minimally invasive management of pancreatic pseudocysts

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The manuscript has been improved according to the suggestions of reviewers:

1 Format has been updated

2 Revision has been made according to the suggestions of the reviewers

(1) REVIEWER

This is a review article about the minimally invasive management of pancreatic pseudocyst. The authors mentioned about the diagnosis, indication for the intervention and the intervention procedure. This is well summarized and written. However, there were some points to be clarified.

Major point 1, In EUS-guided pseudocyst drainage, author should mention about the use of self-expandable metallic stent, especially highly dedicated stent, including appropriate references.

We accepted reviewer's recommendation and made the changes in the manuscript accordingly (the new paragraph has been added in the section titled „Endoscopic drainage of pancreatic pseudocysts“).

Minor points 1, In clinical presentation and laboratory findings, references were lacking in the third and forth sentences.

We accepted reviewer's remark and made the changes accordingly (added the requested references).

2, In page 10, references were lacking in the paragraph about pancreatic enzyme replacemet.

This is the paragraph where the references were lacking:

“Clinical experience has shown some benefit in the administration of pancreatic enzyme supplementation. The rationale for using pancreatic enzyme supplementation as a therapy for PPC is that it will decrease pancreatic secretions and aid in pseudocyst resolution. To date, no studies have tested administration of pancreatic enzyme supplementation as a therapy for PPC, and its application is usually based on local expertize and their preferences“.

The text clearly indicates that the administration of pancreatic enzyme supplementation is based on the experience of clinicians (own and other experts) as well as the established theoretical

assumption about the usefulness of their application but that there are no relevant results available in the literature to support this. We thought that this type of conservative treatment should be mentioned in this manuscript. However, since the three (3/5) reviewers gave their comments regarding this paragraph, we have decided to delete it.

3. In page 13, the description of 'The technique involves pancreatic endoscopic sphincterotomy facilitating cannulation, balloon dilatation of the commonly detected PD strictures' is not true. There were no evidence that sphincterotomy could fasciitate cannulation.

We accepted reviewer's remark and made the changes accordingly (we have reformulated the sentence and omitted the disputed statement)

(2) REVIEWER

Pancreatic pseudocyst (PPC) is a common problem to encounter and the authors tried to address issues of minimally invasive treatment for PPC. The manuscript is well written, but the manuscript does not contain most up-to-date information. In addition, many of times they simply enlisted many of points made by others and themselves, and some contents were repeated over again and again. As a result the manuscript is very loose.

1. According to revised Atlanta classification, the term pseudocyst is supposed to be used in limited cases. Some management of psuedocyst overlap with walled off necrosis, but success rate is much lower in walled off necrosis. Therefore, revised classification should be incorporated in the manuscript.

According to revised Atlanta classification in the first sentence of Introduction section we specified; "A pancreatic pseudocyst (PPC) is defined as a fluid collection in the peripancreatic or intra-pancreatic tissues, and is surrounded by a well defined wall and contains essentially no solid material (see our reference 1)." So, we did incorporate criteria from the revised Atlanta classification in the manuscript. It is true that some aspects of the management of PPC overlap with the treatment of "walled off necrosis" although the success rate of the treatment between the diseases is different. However, the content obtained from the PPC is different compared to the content from "walled off necrosis" which allows differentiation between PPC and "walled off necrosis".

Besides, this is precisely the reason, why the basics of diagnostic methods used in the diagnosis and differentiation of PPCs from similar clinical entities should be presented in the review article about minimally invasive management of PPC.

2. Title of the manuscript is 'Minimally invasive management of pancreatic psuedocysts', but the authors talked about almost all the aspects of pseudocyst. As a result the manuscript looks too redundant. For example, is it necessary to talk so much about imaging and differential diagnosis of pancreatic cysts diseases? Diagnosis of cystic diseases itself can be an item of another review article. (The authors did say that the topic of cystic neoplasms was broad and they would focus on the minimally invasive management.) However, 1/3 of the manuscript is about something other than minimally invasive management. If the authors like to talk about various imaging tools, they better show the connection between those studies and minimally invasive studies. Also, I can understand why the authors like to talk about conservative treatments, but most of them do not have strong evidence that they worked. If it is so, they should not be mentioned too much.

We have checked the full text of the manuscript in accordance with the reviewer's remarks regarding

text redundancy. Accordingly, we deleted the first paragraph of the chapter entitled "Diagnosis of pancreatic pseudocysts" because there is a similar paragraph in Introduction section. The rest of the text of the manuscript refers to a brief introduction (265 words), followed by the description of the main diagnostic methods (886 of 4686 words which is less than 20% of the text). The reason for this has been explained within the answer to question 1 to this reviewer. Therefore, we consider that this part of the text should be left in its current form. The rest of the text refers to the description of minimally invasive methods of management of PPCs and concludes with a short evaluation of the described treatments.

The reviewer considers that conservative treatments of PPC do not deserve such a detailed description since most of them do not have strong evidence contributing to successful treatment of PPC. We could agree with the reviewer that there is no strong evidence in the literature about the role of conservative treatment in the management of PPC. However, despite that, conservative treatment is an integral part of almost every treatment of PPC either as the sole type of treatment (including the PPC monitoring) or as an additional treatment in the interventional or surgical treatments of PPC. So, we think that all conservative treatments, which are mentioned in the literature as modalities of the treatment of PPC, should be mentioned. Besides, it is very difficult to design and implement relevant study to test the effectiveness of conservative treatment. Maybe that is the reason (and not because it is not efficient) that the conservative treatment is often applied on the basis of the experience of experts and not on the basis of data from relevant clinical trials which provide evidence in order to support the methods' applicability.

3. Instead of just saying how treatment is made, showing figures will be helpful to understand. (At least, some images of pseudocyst should be shown)

See composite at the end of the manuscript

4. Some statements made by the authors do not have references. For example, the authors said use of pancreatic enzyme have shown some benefit, but there is no reference for it. It appears that this statement is based on the authors' experience. I wonder whether it is appropriate to even mention treatment which does not have supportive data in review article.

See our reply to Reviewer 1, question 2.

5. Each treatment has its own indications, advantage and disadvantage. I do not think the authors addressed them adequately. They are probably key points in deciding which treatment to choose.

We partly agree with the reviewer that "each treatment has its own indications, advantage and disadvantage". However, we disagree with the reviewer that "they are probably key points in deciding which treatment to choose".

We consider that applicability of different techniques is highly dependent on the availability of specialized expertise and multidisciplinary teams dedicated to the management of pancreatic diseases. Proof of this is that there are very few studies which compare different minimally invasive techniques used in the treatment of PPC. Therefore, we have presented all minimally invasive techniques pointing to their advantage and disadvantage. In conclusion, we have provided a summary of about each technique implicitly, expressing our attitude regarding when and which of the techniques should be applied.

6. Some messages are not very clear because the authors stated self-contradicting statements in the same paragraph. For example, the authors said 'Somatostatin (octreotide) has an inhibitory effect on

pancreatic exocrine secretion and it can be used to decrease of pancreatic secretion, leading to the resolution of PPC. Octreotide has also been used in conjunction with PCD of PPCs, resulting in a shorter drainage time.' in the beginning. It sounded as somatostatin can be used for the treatment of pseudocyst. Then they said 'The role of somatostatin in the management of PPCs is not clear because this treatment has not been adequately tested and only a handful of case series have been published.' After reading them all, I do not know whether the authors are recommending this treatment or not.

The reviewer has interpreted this paragraph exactly the way we intended to explain the role of somatostatin. So, it is not disputed that somatostatin (octreotide) has an inhibitory effect on pancreatic exocrine secretion and that it can be used to decrease pancreatic secretion, leading to the resolution of PPC. Octreotide has also been used in conjunction with PCD of PPCs, resulting in a shorter drainage time. These facts lead to conclusion that somatostatin can be used for the treatment of PPC. However, the role of somatostatin in the management of PPCs is not fully explained, because this treatment has not been adequately tested and only a few series have been published (see references). So, after reading the paragraph, it is clear that we consider that somatostatin could be useful in the treatment of PPC but that there is not much evidence in the literature to back up this statement.

7. For transmural endoscopic drainage, there have to be more prerequisites. For example, distance between the cyst and the stomach or duodenum has to be measured. Also, the wall maturation has to be confirmed. There are also some other conditions to consider. However, the only indication I see in the manuscript is the compression of the cyst against digestive tract, which is not even considered as must-follow-indication in EUS age. What is your opinion on performing ERCP before transmural drainage? In addition, many of recommendations made by endoscopic society were not mentioned. There is no mentioning about use of antibiotics before endoscopic drainage or use of EUS before endoscopic treatment. Recently, several reports about using metal stent for drainage have.

Considering that there are several different variations of this method, we believe that we have managed to explain it adequately for the purposes of a review article.

However, we have made some corrections in this section of the manuscript in accordance with reviewers' comments. We thank the reviewers on their useful recommendations which have now improved the manuscript.

In the conclusion section we gave our statement about the use of ERCP before transmural drainage.

We consider that the use of antibiotics as prophylaxis before endoscopic drainage is inappropriate because it is very difficult to predict the possible infection type.

A new paragraph and references about the role of metal stents in the treatment of PPC have been added in the section titled „Endoscopic drainage of pancreatic pseudocysts“.

(3) REVIEWER

Pancreatic pseudocyst is one of the most common problems associated with pancreatitis and pancreatic surgery. Therefore, the idea of presenting a structured review of modern approaches to minimally invasive treatments is well justified. The authors presented a comprehensive analysis of most therapeutic options, but the manuscript requires some major revision to improve its readability.

1. While the aim of the manuscript is to review minimally invasive treatments, the authors discuss to a considerable extent issues related to aetiology, diagnosis, and conservative treatment. This is somehow

irrelevant and distracts the reader from the actual scope of the article.

See replies to Reviewer 2.

2. The manuscript is a narrative description of nearly all therapeutic options for pseudocysts and it is very difficult to draw any clear conclusions or recommendations to be applied in clinical practice. Some statements are not supported by relevant citations (i.e. supplementation of pancreatic enzymes) or even are contradictory to previous sections. Therefore, results from randomized clinical trials comparing different therapies should be more emphasised and preferably summarised in tables with success rates and complications.

We have described only minimally invasive approaches in the treatment of PPC (conservative, percutaneous, endoscopic and laparoscopic approach). There are very few results from randomized clinical trials and other studies comparing different minimally invasive PPC therapies in the available literature, which we have cited.

We have addressed the questions regarding the administration of pancreatic enzymes within our replies to Reviewers 1 and 2.

3. The authors referred to the most recent revision of the Atlanta classification, but did not comment on the fact that most previous studies on minimally invasive treatment of pancreatic pseudocysts used evidently different definition of a pseudocyst. Therefore, previous observations may have little applicability to the current clinical practice.

See our reply to Reviewer 2, question 1.

4. Some language correction is required.

Corrected

(4) REVIEWER

In this article, the latest management of pancreatic pseudocysts is reviewed. I have only minor comments.

Many similar abbreviations, such as PPC, PD, PCD, make this article hard to read. For surgeons, PD usually means pancreatoduodenectomy.

Regarding abbreviations, we are guided according to usual journals instructions. If Editor considers that it should be changed we will change it

ESGE is an abrupt abbreviation in the section of tranmural endoscopic drainage.

ESGE is very frequently used abbreviation for European Society of Gastrointestinal Endoscopy, usually not needing further explanations. However, we have made the correction according to the reviewer's remark.

Maybe singular form "method" seems correct in the following sentence. Image-guided percutaneous drainage of PPCs is a well-established and relatively inexpensive drainage methods which involves

either

Corrected

Conclusion section may be unnecessary.

We consider that it is important to explain the relation between various minimally invasive techniques which are used in the treatment of PPC (See our reply to Reviewer 2, question 2).

(5) REVIEWER

This is an excellent review of pancreatic pseudocysts. It covers a number of areas but importantly reviews the treatment modalities. It is a little long winded and could do with some reduction in length, it also has a small number of grammatical errors that need addressing. There are some data that are proposed without good evidence to support their inclusion, these include the use of a low fat diet, pancreatic enzyme supplements and somatostatin analogues in the resolution of pancreatic pseudocysts. This should be made very clear in the text as I suspect that they are based on the authors clinical preference. The role of percutaneous drainage of pancreatic pseudocysts has fallen into disrepute in larger centres because of the risk of leaving a long term fistula and infection of the cyst contents in favour of either endoscopic guided or radiological guided insertion of stents into the cysts via (usually) the gastric lumen. Again I would suspect that the authors are rather keen on this approach and while it needs mentioning it should be made clear that in 2015 this is not a favoured approach. Overall the manuscript is well written and worthy of publication.

**All of the above
well as within t**

**ie previous replies to reviewers' comments as
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3 References and

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