Dear Editor,

Thank you for carefully reviewing our manuscript previously titled "***Clostridium perfringens*** bloodstream infection secondary to acute pancreatitis: A case report" for possible publication in the World Journal of Clinical Cases. We are grateful to you and your reviewers for their constructive critique. We have revised the manuscript, highlighting our revisions in red, and have attached point-by-point responses detailing how we have revised the manuscript in response to the reviewers' comments below.

Thank you for your consideration and further review of our manuscript. Please do not hesitate to contact us with any further questions or recommendations.

Yours Sincerely,

Ming Li

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Round-1

Reviewer Comments:

Reviewer #1:

Scientific Quality: Grade D (Fair)

Language Quality: Grade C (A great deal of language polishing)

Conclusion: Major revision

Specific Comments to Authors: 1. The paper by Ming Li*, Ning Li. entitled "Clostridium perfringens bloodstream infection secondary to acute pancreatitis: A case report" is a paper providing notification regarding the danger and fatal behavior of a clostridium perfringens infection. The patient's clinical course is instructive and useful for readers, but I have some questions regarding this case report. 2. I have the following concerns. 1) The authors diagnosed the patient with acute pancreatitis, but there are no comments regarding the cause of pancreatitis. What induced her pancreatitis? Gall stones? Biliary debris? Alcohol? Idiopathic? The authors should mention the cause of the acute pancreatitis along with her biochemical tests, ex liver function, CRP, procarcitonine, and blood culture at the first visit to the hospital. In typical clinical cases, we sometimes experience liver abscess after gallstone cholangitis, so we presume that bacteremia from CP came from acute cholangitis and liver abscess, not from acute pancreatitis. There are some cases with no fever in cholangitis and high-grade sepsis. If the authors insist the bacteremia of CP came from acute pancreatitis, they should mention their reasoning. 2) In the CASE REPORT section The authors describe "A 62-year old Han Chinese on January 8, 2020, and stay 2 days because of epigastric," However, the manuscript also states, "the patient refused hospital stay and she admitted at second visit," so the expression above appears to have a contradiction. 3) In the CASE REPORT section Laboratory data at first visit to the hospital should be included (ex, AMY, T-bil, D-bil, AST, ALT, LDH, ALP, LAP, γGTP, CRP). 4) In the DISCUSSION section The authors stated that acute pancreatitis was a cause of bacteremia of CP and explain the possibility of the causes are bacterial translocation in pancreatitis. This discussion is important and the authors should discuss this using more case reports with CP bacteremia from mild pancreatitis. 5) In the DISCUSSION section. The authors regretted not having

obtained a blood smear and aspiration of liver abscess for diagnosing CP bacteremia. They should tell us how to treat the results. Example: The specimen from the abscess can be immediately used for gram stain. Clostridium perfringens is a gram-positive bacilli and has a distinctive form and we suspect a CP infection. Blood culture. Blood smear is not useful for diagnosis of CP because of the small amount of inclusive bacteria, but anaerobic culturing of blood might be useful even though several days are needed. 6) In the Discussion session The discussion about thyroid dysfunction can be deleted. This is not familiar with the clinical course of this case. 3. 1) The English in the manuscript needs improvement and editing by a native English speaker. I strongly recommend use of an English editing service with higher quality. 2) In the CASE REPORT section The authors describe, “She had a history of hyperthyroidism (she had radiotherapy anti pancreatic treatment.” This is from her past history, and as such it should be described first, rather than in this section.

Response: 2.1) Liver function, CRP, procarcitonine, and blood culture at the first visit to the hospital were not tested. Urobilinogen and urobilirubin were negative. Total cholesterol was 6.84 mmol/L (reference: <5.2). Low density lipoprotein was 4.54 mmol/L (reference: <3.12).Abdominal computed tomography (CT) scan showed pancreas edema and peripancreatic exudation (Figure 1) but no cholecystitis and cholangiectasis. Abdominal ultrasound showed no cholelithiasis, cholecystitis and cholangiectasis. The cause of acute pancreatitis might be hyperlipemia or idiopathic. I have added these contents in CASE REPORT section. 2) I have deleted ”stay 2 days”. 3) T-bil, D-bil, AST, ALT, LDH, ALP, LAP, γGTP, CRP were not tested at first visit to the hospital. Urobilinogen and urobilirubin were negative. 4) No more case reports with CP bacteremia from mild pancreatitis is found in the recent 10 years. So this case report is significant to a certain extent.5）”The specimen from the abscess can be immediately used for gram stain. Clostridium perfringens is a gram-positive bacilli and has a distinctive form and we suspect a CP infection. Blood culture. Blood smear is not useful for diagnosis of CP because of the small amount of inclusive bacteria, but anaerobic culturing of blood might be useful even though several days are needed.” have been added in the Discussion session. 6) The discussion about thyroid dysfunction has been deleted.3. 1）The manuscript has been improved and edited by a native English speaker 2）Medical history is described before physical examination.

Reviewer #2:

Scientific Quality: Grade D (Fair)

Language Quality: Grade B (Minor language polishing)

Conclusion: Rejection

Specific Comments to Authors: In this manuscript, authors reported a case of Clostridium perfringens blood stream infection associated with acute pancreatitis, leading to multiple organ failure. This case is so interesting that the patient had no any underlying immunodeficiency conditions. However, there are some concerns in this report. The reviewer's comments are described as follows. 1. First, the clinical course of this case appears to be typical for Clostridium perfringens bacteremia and toxic shock syndrome. Emphysematous hepatobiliary infection, uterine gas gangrene, and gastrointestinal perforation are well-known complications of Clostridium perfringens toxic shock syndrome. Since Clostridium perfringens is a component of normal intestinal bacterial flora, such infectious disease can occur in healthy people. Therefore, there are no novel and original findings in this case report. 2. Clostridium perfringens infection was diagnosed by the usual bacterial culture, and the treatment for the infection was only empiric antibiotic therapy. Although authors concluded the importance of rapid recognition and aggressive treatment of this infection, they did not provided any specific strategies. Thus, there are also no novel diagnostic or therapeutic significance in this report. 3. Intravascular hemolysis is one of the hallmarks for severe Clostridium perfringens infection with poor prognosis. However, laboratory data in Table 1 and 2 are insufficient because of the lack of LDH and electrolytes. 4. Authors suggested that Clostridium perfringens blood stream infection was ascribed for acute pancreatitis. However, the casualty between the infection and pancreatitis seems to be insufficiently shown. Indeed, there have been a case of severe acute pancreatitis caused by Clostridium perfringens infection (reference #8). Bacterial translocation of Clostridium perfringens associated with acute pancreatitis that authors suggested in Discussion has to be clearly demonstrated.

Response: 1. *Clostridium perfringens* (CP) is an opportunistic pathogen. It can cause infections after birth, after an abortion, and in patients with diabetes, malignancy, liver cirrhosis, or an immunosuppressive state. Here, our patient with no underlying diabetes, malignancy, or liver cirrhosis, acute pancreatitis may be the reason. 2. It is true that we have not provided any specific strategies in this report, but progression of disease is so fast and the patient died only a few hours after the attack.

We could learn some lessons from the patient. 3. In our hospital, LDH is not in the urgent check of liver function, so we have no laboratory data of LDH. I have add data of electrolytes in table 3. 4. Since there are no other sources of CP in blood, translocation of intestinal bacteria according to acute pancreatitis may the only way. During the early stage of acute pancreatitis, massive amounts of cytokines induced by local pancreatic inflammation enter the bloodstream, leading to damage to the intestinal barrier function and an increase of mucous permeability. The intestinal bacteria gain access to the lymphatic or portal system, and finally, reach every part of the body.

Reviewer #3:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

Specific Comments to Authors: The title is informative and relevant. The references are relevant and recent. The cited sources are referenced correctly. Appropriate and key studies are included. The introduction reveals what is already known about this topic. The research question is clearly outlined. The case is well-described, the used methods methods for diagnosing and therapy were valid and reliable. The patient data is presented in an appropriate way. The illustrative materials are relevant and clearly presented. Data is discussed from different angles and placed into context without being overinterpreted. The conclusions are supported by references and own results. Specific comments 1. Introduction does not include any data or mention that there is no data on post-panceratic infection 2. There is no conclusion

Response:1. In **ABSTRACT**, we have clearly mentioned CP infection secondary to acute pancreatitis, with no underlying diabetes, malignancy, or liver cirrhosis.2.I have supplemented conclusion.

Reviewer #4:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Major revision

Specific Comments to Authors: World Journal of Clinical Cases - Manuscript review of Manuscript NO: 62880 Clostridium perfringens bloodstream infection secondary to acute pancreatitis: A case report Dear Author, First of all, thank you for

submitting your manuscript to the World Journal of Clinical Cases. This is an interesting case report highlighting the importance of appropriate and timely diagnostic and treatment of acute pancreatitis related infections. However, it could be improved with some corrections and supplement. It should also be modified according to the journal requirements. 1 Line 93 –please rewrite case presentation part according to the required structure of the journal. Please check https://www.wjgnet.com/bpg/GerInfo/187. 2 Please add results of CRP and lipase into the table of laboratory results 3 Line 103-105 – please enlist and provide the results of examinations made to rule out other pathologies in the text. 4 Line 107 – clarify the indications for your choice of initial treatment after the patient refused hospitalisation; 5 HgB during the second admission dropped from 132->64? Did you try to find the source of bleeding, performed blood transfusion? 6 Do you have any results from an abdominal ultrasound? Were there any gallbladder or CBD stones? Did you rule out gallstone pancreatitis and cholangitis during the second admission? 7 Some language polishing needed: several articles and commas are missing, some spelling mistakes.

Response: 1. I have rewritten case presentation part according to the required structure of the journal. 2. CRP and lipase were not tested, so I don't have the data. 3. Urobilinogen and urobilirubin were negative. Total cholesterol was 6.84 mmol/L (reference: <5.2). Low density lipoprotein was 4.54 mmol/L (reference: <3.12). Abdominal computed tomography (CT) scan showed pancreas edema and peripancreatic exudation (Figure 1) but no cholecystitis and cholangiectasis. Abdominal ultrasound showed no cholelithiasis, choledocholithiasis, cholecystitis and cholangiectasis. I have added these contents in CASE REPORT section. 4. In **CASE REPORT** section: She refused hospitalization and was given etimicin 300 mg/d IV for empiric antibiotic therapy, lansoprazole 30 mg/d IV for acid suppression, octreotide 0.3g SC injection for inhibiting pancreas secretion, alprostadil 10 mg IV into Murphy's dropper for improving microcirculation of pancreas , dezocine 5 mg IM and ketochrometritol 30 mg/d IV for analgesia, glucose sodium chloride 5%, and potassium chloride 10 ml/d IV for keeping water electrolyte balance.5.CT scan didn't find any intracranial,abdominal and pleural hemorrhage. The patient had no haematemesis and hematochezia. We had planed to perform blood transfusion, but the patient died too fast.6."Urobilinogen and urobilirubin were negative. Abdominal computed tomography (CT) scan showed pancreas edema and peripancreatic

exudation (Figure 1) but no cholecystitis and cholangiectasis. Abdominal ultrasound showed no cholelithiasis, cholecystitis and cholangiectasis." has been added in the **CASE REPORT** section. 7. Thanks very much, I have polished the language and corrected some spelling mistakes

Reviewer #5:

Scientific Quality: Grade C (Good)

Language Quality: Grade A (Priority publishing)

Conclusion: Accept (General priority)

Specific Comments to Authors: I read with great interest the manuscript entitled "Clostridium perfringens bloodstream infection secondary to acute pancreatitis: A case report" and submitted to the World Journal of Clinical Cases. Authors presented a case report of a woman with a deadly progression of acute pancreatitis with Clostridium perfringens bloodstream infection confirmed in blood cultures after the death of the patient. The manuscript is well-written and the quality of English is suitable and it has been proof-read by a professional. In my opinion the manuscript could be accepted for publication in its current fashion. 1 Title. Does the title reflect the main subject/hypothesis of the manuscript? Yes 2 Abstract. Does the abstract summarize and reflect the work described in the manuscript? Yes 3 Key words. Do the key words reflect the focus of the manuscript? Yes 4 Background. Does the manuscript adequately describe the background, present status and significance of the study? Yes 5 Methods. Does the manuscript describe methods (e.g., experiments, data analysis, surveys, and clinical trials, etc.) in adequate detail? Yes 6 Results. Are the research objectives achieved by the experiments used in this study? What are the contributions that the study has made for research progress in this field? N/A. Case report. 7 Discussion. Does the manuscript interpret the findings adequately and appropriately, highlighting the key points concisely, clearly and logically? Are the findings and their applicability/relevance to the literature stated in a clear and definite manner? Is the discussion accurate and does it discuss the paper's scientific significance and/or relevance to clinical practice sufficiently? Yes 8 Illustrations and tables. Are the figures, diagrams and tables sufficient, good quality and appropriately illustrative of the paper contents? Do figures require labeling with arrows, asterisks etc., better legends? Yes 9 Biostatistics. Does the manuscript meet the requirements of biostatistics? Yes, simple descriptive statistics. 10 Units. Does the manuscript meet

the requirements of use of SI units? Yes 11 References. Does the manuscript cite appropriately the latest, important and authoritative references in the introduction and discussion sections? Does the author self-cite, omit, incorrectly cite and/or over-cite references? Yes 12 Quality of manuscript organization and presentation. Is the manuscript well, concisely and coherently organized and presented? Is the style, language and grammar accurate and appropriate? Yes 13 Research methods and reporting. Authors should have prepared their manuscripts according to manuscript type and the appropriate categories, as follows: (1) CARE Checklist (2013) - Case report; (2) CONSORT 2010 Statement - Clinical Trials study, Prospective study, Randomized Controlled trial, Randomized Clinical trial; (3) PRISMA 2009 Checklist - Evidence-Based Medicine, Systematic review, Meta-Analysis; (4) STROBE Statement - Case Control study, Observational study, Retrospective Cohort study; and (5) The ARRIVE Guidelines - Basic study. Did the author prepare the manuscript according to the appropriate research methods and reporting? Yes, CARE checklist attached 14 Ethics statements. For all manuscripts involving human studies and/or animal experiments, author(s) must submit the related formal ethics documents that were reviewed and approved by their local ethical review committee. Did the manuscript meet the requirements of ethics? Yes

Response: Thanks very much for the positive comments

Reviewer #6:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

Specific Comments to Authors: The authors reported a severe case with Clostridium perfringens (CP) sepsis. Her sepsis progressed rapidly, and the patient died a half day after her hospitalization. In the discussion, representative clinical course of CP infection and appropriate treatments were shown from the literature review. A few cases of CP infection in pancreatitis have been already reported, determined by a database search. A reviewer has some queries for the authors. Main point 1. Laboratory data is not described enough. Please show liver functional test at the first admission in Table 2. The evaluation of pancreatitis is not completely performed. 2. Microbiological result was obtained ten hours after her death (page 6). In clinical course the result of the blood culture was confirmed two days after her death (Table 3).

There is a discrepancy. Culture from other specimens, for example sputum or urine, was not shown. 3. Autopsy should be informative in this rare case. 4. Please indicate appropriate examination for rapid and accurate diagnosis for this patient. What should we do to cure such patients? Minor point Serotypes of CP were discussed in the literature. How was serotypes in this case? COVID-19 was negative in the patient?

Response: 1.Liver function was not tested at first visit to the hospital, but urobilinogen and urobilirubin were negative. 2."Ten hours" has been corrected to" About two days". Sputum and urine were not cultured.3.The relatives of the patient refused autopsy. 4. I think there is no rapid means of diagnosis for CP infection, the experience is very important. Rapid recognition, drainage for the liver abscess, "appropriate" antibiotics are not a single one can be omitted. We don't know the serotypes of CP in this case.COVID-19 was not tested, but there was no local cases in China at that time.

Reviewer #7:

Scientific Quality: Grade D (Fair)

Language Quality: Grade C (A great deal of language polishing)

Conclusion: Major revision

Specific Comments to Authors: In this clinical case the authors report the incidence with a fatal exitus of a rare C perfringens infection in a patient with acute pancreatitis. This is a rare condition certainly but probably due to the antibiotic treatment of the initial disease of the patient. We do not find particularl interest in this case but given its rarity it could be useful to signal it I the scientific community. I do not recognize macroscopic clinical errors in the text, may be it could be interesting to stress how this infection could be related to antibiotic patient profilatic and its general incidence in acute pancreatitis.

Response:I think this possibility is extremely unlikely.If CP infection is due to the antibiotic treatment, then it will have a high incidence among patients with bacterial infections, actually CP infection is very rare.

Reviewer #8:

Scientific Quality: Grade E (Do not publish)

Language Quality: Grade B (Minor language polishing)

Conclusion: Rejection

Specific Comments to Authors: Dear Authors, I have read with great interest the

enclosed case report. Unfortunately, I found that this study does not add any relevant information to scientific knowledge. The soy sauce color-like urine could be due to cholangitis. The patient probably had gallstone pancreatitis complicated by cholangitis. In this case, endoscopic retrograde cholangio-pancreatography should be performed as soon as possible. The systemic infection due to CP, that is usually found in gut microbiota, was due to cholangitis. I found that important steps are quite unclear (i.e. case of pancreatitis).

Response: Urobilinogen and urobilirubin were negative. Total cholesterol was 6.84 mmol/L (reference: <5.2). Low density lipoprotein was 4.54 mmol/L (reference: <3.12).Abdominal computed tomography (CT) scan showed pancreas edema and peripancreatic exudation (Figure 1) but no cholecystitis and cholangiectasis. Abdominal ultrasound showed no cholelithiasis, cholecystitis and cholangiectasis. Cholangitis can be excluded.

Reviewer #9:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

Specific Comments to Authors: This is an interesting case report. What is the cause of acute pancreatitis in this patient? (Alcoholic or gallstone?). The early stages of acute pancreatitis are generally aseptic. However, gallstone pancreatitis with cholangitis can lead to sepsis even in the early stages of pancreatitis. Consider these possibilities in the text.

Response: Urobilinogen and urobilirubin were negative. Total cholesterol was 6.84 mmol/L (reference: <5.2). Low density lipoprotein was 4.54 mmol/L (reference: <3.12).Abdominal computed tomography (CT) scan showed pancreas edema and peripancreatic exudation (Figure 1) but no cholecystitis and cholangiectasis. Abdominal ultrasound showed no cholelithiasis, cholecystitis and cholangiectasis. The cause of acute pancreatitis might be hyperlipemia or idiopathic.

Round-2

Dear Editor,

Thank you for carefully reviewing our manuscript previously titled "***Clostridium perfringens*** bloodstream infection secondary to acute pancreatitis: A case report" for possible publication in the World Journal of Clinical Cases. We are grateful to you and your reviewers for their constructive critique. We have revised the manuscript, highlighting our revisions in red. and have attached point-by-point responses detailing how we have revised the manuscript in response to the reviewers' comments below.

Thank you for your consideration and further review of our manuscript. Please do not hesitate to contact us with any further questions or recommendations.

Yours Sincerely,

Ming Li
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Reviewer Comments:

Reviewer #1:

It is unlikely that the disease will develop from mild acute pancreatitis. In addition, the cause of acute pancreatitis is suspected to be gallstone. MRCP and EUS are good modalities for diagnosing biliary pancreatitis

Response: I agree that MRCP and EUS are good modalities for diagnosing biliary pancreatitis. But this patient died so quickly,there was no time to do the examinations of MRCP and EUS. There was no biliary dilation and jaundice, urobilinogen and urobilirubin were negative. I think there was no indication for MRCP and EUS according to the initial clinical data.

Reviewer #2:

Dear authors, Thank you for carefully revising your manuscript (Manuscript NO.: 62880) regarding the provided suggestions and raised questions. The manuscript was revised according to comments in the Peer-Review Report. All raised issues were resolved and needed corrections were made. The authors have provided a point-by-point response to raised questions. As this case report raised a lot of questions and different opinions between peer reviewers, I think this manuscript should be published, so that the discussion could be continued. I have several suggestions and questions, though: -

Personal and family history: after the word „alcohol" - the word „consumption" is missing - the correct term is „hyperlipidemia", not „hyperlipemia" - „CT scan and abdominal ultrasound had excluded the possible diagnoses of acute pancreatitis, acute cholecystitis, acute gastritis, acute appendicitis, and gastrointestinal perforation, examinations were performed to rule out diagnoses, and acute pancreatitis was finally confirmed, the severity of which was graded as mild." I suggest to rewrite this paragraph

in several sentences. One sentence sounds a bit confusing and hard to follow.

- „She refused hospitalization and was given etimicin 300 mg/d IV" Why did you prescribe IV antibiotics if the patient was not hospitalised and you ruled out infections? Antibiotics are not a standart practise if there are no signs of infection and high CRP levels. Was it planned to give it one time, or did you prescribe oral form as well? Why exactly this antibiotic?

Response:I had corrected the words and rewritten the paragraph. Etimicin was given in the ER which was different department of the hospital by other doctors. I just recorded the medical advice faithfully. In our hospital, patients with acute pancreatitis are usually given antibiotics, but there is no evidence that the patients will benefit from this.

Reviewer #3:

Dear Authors, I have read with great interest also the revision version of your manuscript. My personal concerns remain unchanged. However, I recognize that you answered to most of the issues raised by other reviewers. I leave to the editor te final decision.

Response:I don't know this respectable professor was which reviewer in the first-round review.So I don't know if I can answer the concerns further. I can not offer more data. My answers may remain the same. Thanks very much.

Reviewer #4:

The authors addressed all the issues risen from the all nine reviewers. The paper has been improved significantly according to the referees` notes. I am impressed by author` rigorous defense of the presented details.

Response:Thanks very much.