Recovery of Symmetrical Peripheral Gangrene of Limbs in a Patient After Performing Hemoadsorption in Septic Shock

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Recovery of Symmetrical Peripheral Gangrene of Limbs In A Patient After Performing Hemoadsorption in Septic Shock

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Abstract

We report a 42-year-old patient who had Hodgkin lymphoma and developed bilateral Symmetrical Peripheral Gangrene (SPG) in the feet and hands, which occurred during septic shock after autologous hematopoietic stem-cell transplantation. SPG is a rare but severe complication of disseminated intravascular coagulation (DIC) and is frequently associated with sepsis. The pathophysiology of SPG includes DIC-mediated intravascular thrombosis and thrombotic occlusion of microcirculation, resulting in low blood flow. Sepsis-induced hypotension has been suspected as one of the other causes of SPG, and it is thought to be aggravated by vasopressor treatments given for hypotension. Our patient first experienced coldness, paleness, and cyanosis in his body's acral parts, and then SPG later developed in both his feet and hands. Septic shock management was performed with hemoadsorption, broad-spectrum antibiotics, and massive fluid replacement rapidly. The patient fully recovered without the need for amputation. Hemoadsorption is an extracorporeal cytokine-adsorption method for removing excess cytokines and may be preferable as a supportive
modality in septic shock management. Prompt management of septic shock and early monitoring of peripheral ischemia are essential to avoid SPG.

**Keywords:** Symmetrical peripheral gangrene, sepsis, septic shock, hemoadsorption, DIC, Extracorporeal blood purification

1 | INTRODUCTION

Symmetrical peripheral gangrene (SPG) is a rare but serious complication that involves bilateral ischemic damage in the distal parts of the limbs in the absence of a major vascular occlusive disease. The risk of mortality is high (up to 40%), and almost half of the survivors need amputation.¹ SPG is observed as a complication of disseminated intravascular coagulation (DIC) in 85% of SPG cases. DIC is commonly associated with septicemia, and DIC-induced intravascular thrombosis causes low blood flow and infarction of the skin and distal extremities.²-⁴

The use of vasopressors leads to spasm of the capillaries and impairment of microcirculation.⁴ Coldness, paleness, and cyanosis are the first signs of the SPG observed in the body's acral parts and rapidly proceed to proximal areas.⁵-⁷ Currently, there is no specific treatment for SPG, and the treatment priorities are usually the underlying condition and DIC.⁸ As sepsis is one of the leading causes of DIC and SPG, there has been increasing interest in the use of extracorporeal devices for the removal of pathogenic components observed during sepsis. Hemoadsorption (HA) is a method of extracorporeal blood purification through a cartridge, where solutes are removed by direct binding to the sorbent material.⁹-¹⁰ This case report presents a patient with Hodgkin Lymphoma (HL) who developed SPG following septic shock. The patient fully recovered without amputation due to early management by HA.
2 | CASE PRESENTATION

A 42-year-old male patient with HL was admitted to the intensive care unit (ICU) for septic shock on the 13th day after autologous hematopoietic stem-cell transplantation (ASCT). He was neutropenic and thrombocytopenic when the first fever occurred. Cefoperazone sulbactam was started. On the second day of febrile neutropenia, the patient progressed to sepsis, after which meropenem, vancomycin, liposomal amphotericin B, and colistin were administered. The patient needed nasal oxygen support because of hypoxia and was admitted to the ICU.

Despite extensive fluid replacement, the patient needed high doses of vasopressors to maintain normotension. Even with infusion of noradrenaline at 3 µg/kg/min, his blood pressure remained consistently low (80/40 mmHg). On the third day of febrile neutropenia, coldness, paleness, and cyanosis started in the acral parts of the body and progressed to SPG in the feet and hands. The patient had a score of 6 on the DIC scale of the International Society of Thrombosis and Hemostasis (ISTH).11

Sepsis HA was started rapidly during the first hours in the ICU. The procedure was performed using a hemoperfusion machine. One disposable hemoperfusion cartridge (HA330 resin, Styrene divinylbenzene copolymers, Jafron Biomedical Co., Ltd., China) was used per day. The blood flow rate was maintained at 200 ml/min. Each procedure continued for 150 minutes, and approximately six total blood volumes were processed. Three absorbers were used over three days. The patient did not have any plasma components.

Due to thrombocytopenia, we did not administer routine systemic anticoagulation except for priming the adsorption set. 7500 IU of unfractionated heparin was used only for raising the adsorption set to prevent clotting in the extracorporeal circuit. The changes of the patient's blood parameters before and after HA are given in Figure 1. No microorganisms
could be grown in microbial cultures. The patient continued extended-spectrum antibiotics for empirical treatment. By the third day of HA, the vaspressors were discontinued.

The progression of gangrene stopped with the withdrawal of vasopressors. Small blisters were noticed in both feet over the next 10 days (Figures 2 and 3). SPG in both feet and hands started to recover, and the patient was discharged from the hospital 38 days after ASCT. Three months after autologous transplantation, the patient was in complete remission, and his bilateral distal extremities fully recovered. His last follow-up was at 15 months after ASCT, and he was in complete remission. The last view of his extremities is shown in Figure 4.

3 | DISCUSSION

We have reported a case of neutropenic fever with septic shock developing after ASCT. The patient had SPG due to septicemia-associated DIC. We rapidly administered broad-spectrum antibiotics, massive fluid replacement, and vasopressor treatment. When we observed ischemic lesions in his feet and hands, we increased supportive care by sepsis HA. The patient had such a very impressive response the modalities that we stopped the vasopressor treatment afterward. HA may contribute to decreasing cytokines and alleviate the septicemia associated with DIC.

The etiology of SPG is multifactorial, but septic shock and DIC are the leading causes. Sepsis is currently defined as a dysregulated host immune response to infection leading to organ failure. The underlying pathophysiology is complex with both pathogenic and host factors. Pathogen-associated molecular patterns and damage-associated molecular patterns play a significant role in activating the endothelium and as a result inflammatory cytokines. The activated endothelium becomes prothrombotic through increases in the expression of tissue factor in the endothelium and monocytes. DIC
develops in cases of impaired balance of anti- and pro-coagulant factors. Early findings of septicemia-associated DIC include apparent coldness, pallor, and pain. The ischemic lesions are often demarcated sharply and symmetric with initial gray, blue, or purple discoloration that progresses to black as the skin undergoes necrosis.\textsuperscript{12,18}

With more understanding about the pathophysiology of immune system factors in sepsis, interest has been increasing in the use of extracorporeal devices for cytokine adsorption. It has been hypothesized that a cytokine storm may be responsible for the self-destruction in sepsis, so the removal of circulating cytokines is a sensible treatment option. The peak-concentration hypothesis was first introduced with acute kidney injury and was subsequently generalized to sepsis more than 10 years ago.\textsuperscript{20} Since that time, it has been repeatedly hypothesized that there is a therapeutic benefit of extracorporeal blood purification modalities, including forms of dialysis or therapeutic apheresis regarding the cytokine storm.\textsuperscript{19-20}

HA330 (Jafron, Zhuhai City, China) is the one of the widely used adsorption cartridges in China.\textsuperscript{9,10} Huang et al. conducted small randomized controlled trials (RCTs) of adjuvant HA330-HA with 44 septic patients who had acute lung injury (ALI) in the ICU. Significant reductions of IL-8 and IL-6 levels and length of stay was seen in patients when HA was performed compared to standard therapy (defined as full intensive care management, including fluid resuscitation, vasopressors, antimicrobial therapy, and ventilatory support). Nevertheless, length of hospital stays and 28-day mortality did not differ between the two groups at day 3.\textsuperscript{21}

In a later study by Huang et al., HA was compared to standard therapy in 46 patients with ALI induced by extra-pulmonary sepsis. The HA group showed a significant reduction in IL-1 and tumor necrosis factor-\(\alpha\) in the broncho-alveolar lavage and plasma. Therefore, the improvement of patients’ hemodynamics was better, and the rate of mortality in the ICU and
28-day mortality were lower in the HA group. But there is still no proof from a prospective RCT for any extracorporeal treatment modality decreasing mortality in sepsis. Regarding sepsis, only therapeutic plasma exchange appears to be potentially effective, but no recommendations have been made in the latest international guidelines.18,23

An equivalent of HA330 is the extracorporeal whole-blood cytokine adsorber, which is currently approved in the European Union.24 Cartridges are divided into selective and non-selective types.9,25 Cartridge selectivity may have important consequences for treatment. For instance, non-selective cartridges cannot adsorb endotoxin because their cutoff point (~60 kDa) falls below the molecular weight of endotoxin (~100 kDa). HA330 and its equivalent have non-selective cartridges.

According to data from an international registry, whole-blood cytokine adsorber therapy reduced IL-6 levels in 68% of patients with sepsis. No significant decrease in organ failure was observed, but mortality was lower than predicted.26 A recent prospective, randomized, pilot trial investigated the effects of early (<24 h) extracorporeal cytokine removal performed in 20 patients with septic shock. The results indicated a decrease in norepinephrine requirements, an improvement in hemodynamics, and significantly lower levels of procalcitonin and endothelin-1 precursor compared to controls.27 Despite showing a significant reduction in circulating cytokine levels and improvement in clinical situations, there is a lack of evidence, and it is not currently recommended by guidelines. Large prospective randomized trials with carefully selected patient populations are needed to evaluate the efficacy of extracorporeal HA.

The patient in the present case report had septic shock at 13 days after ASCT. In this case, early management of septic shock with massive fluid replacement, antibiotics, and especially the administration of sepsis HA within <24 hours might have prevented amputation from being required. We prefer HA330 cartridges for their easy accessibility and
the affordable cost of the adsorbers. To the best of our knowledge, this is the first case report of successful HA in a patient with SPG.

4 | CONCLUSIONS

In conclusion, early recognition and prompt management of septic shock are necessary to avoid SPG. Vasopressors might exacerbate SPG, so clinicians should be careful, especially in the presence of any sign of hypoperfusion in the extremities. Performing sepsis HA immediately may be a good adjuvant option for the treatment of septic shock while avoiding destructive effects of the cytokine storm and DIC, as in our patient. Nevertheless, RCTs are needed to prove this hypothesized preventive effect.

ACKNOWLEDGMENTS

We would like to thank all staff and the nurses of the intensive care unit, stem cell transplantation unit, and apheresis unit for their devoted work.

DECLARATION OF CONFLICTING INTERESTS

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

FUNDING

The authors received no financial support for the research, authorship, and/or publication of this article.

REFERENCES


Figure 1. Changes of Patient's Blood Parameters Before and After Hemoadsorption

Figure 2. Ischemic changes observed in both feet and hand after septic shock

Figure 3. Ischemic changes and blister formation in feet

Figure 4. The last view of the patient’s extremities 15 months after autologous hematopoietic stem cell transplantation
Recovery of Symmetrical Peripheral Gangrene of Limbs In A Patient After Performing Hemoadsorption in Septic Shock

Abstract

We report a 42-year-old Hodgkin lymphoma patient who had Hodgkin lymphoma and developed bilateral Symmetrical Peripheral Gangrene (SPG) in bilateral-the feet and hands, which occurred during septic shock after autologous hematopoietic stem-cell transplantation. SPG is a rare but severe complication of disseminated intravascular coagulation (DIC), and it is frequently associated with sepsis. DIC-mediated intravascular thrombosis and thrombotic occlusion of microcirculation resulting in low blood flow are among the pathophysiology of SPG includes DIC-mediated intravascular thrombosis and thrombotic occlusion of microcirculation, resulting in low blood flow. Among the other causes of SPG, sepsis-induced hypotension has been suspected as one of the other causes of SPG is accused, and it is thought to be aggravated by vasopressor treatments given for hypotension. In our patient first experienced coldness, paleness, and cyanosis started on in his body's acral parts; later, and then SPG in both his feet and hands was later developed in both his feet and hands. Septic shock management was performed with hemoadsorption, broad-spectrum antibiotics, and massive fluid replacement rapidly. The patient fully recovered without the need for amputation. Hemoadsorption is an extracorporeal cytokine-adsorption method for removing excess cytokines levels and may be preferable as a supportive modality in septic shock management. Prompt management of septic shock and early monitoring of peripheral ischemia are essential to avoid SPG.
**Keywords:** Symmetrical peripheral gangrene, sepsis, septic shock, hemoadsorption, DIC, Extracorporeal blood purification

### INTRODUCTION

Symmetrical peripheral gangrene (SPG) is a rare but serious complication that involves bilateral ischemic damage in the distal parts of the limbs in the absence of a major vascular occlusive disease. The risk of mortality is high (up to 40%), and almost half of the survivors need amputation. SPG is observed as a complication of disseminated intravascular coagulation (DIC) in 85% of SPG cases. DIC is commonly associated with septicemia and DIC-induced intravascular thrombosis causes low blood flow and infarction of the skin and distal extremities.

The use of vasopressors leads to spasm of the capillaries and impairment of microcirculation. Coldness, paleness, and cyanosis are the first signs of the SPG observed in the body's acral parts and proceed to proximal rapidly. Currently, there is no specific treatment for SPG, and the treatment priorities are usually the underlying condition and DIC. As sepsis is one of the leading causes of DIC and SPG, there has been increasing interest in the use of extracorporeal devices for the removal of pathogenic components observed during sepsis. Hemoadsorption (HA) is a method of extracorporeal blood purification through a cartridge where solutes are removed by direct binding to the sorbent material. In this case report, we aim to report a patient with Hodgkin Lymphoma (HL) who developed SPG following septic shock. The patient and fully recovered without amputation by due to early management by HA.

### CASE PRESENTATION
A 42-year-old male patient with HL was admitted to the intensive care unit (ICU) because of septic shock on the 13th day after autologous hematopoietic stem-cell transplantation (ASCT). He was neutropenic and thrombocytopenic while the first fever occurred. Cefoperazone sulbactam was started. On the second day of febrile neutropenia, the patient progressed to sepsis, after which meropenem, vancomycin, liposomal amphotericin B, and colistin were administered. The patient needed nasal oxygen support because of hypoxia and was admitted to the intensive care unit. Despite extensive fluid replacement, the patient needed high doses of vasopressors to maintain normotension. Even with 3 µg/kg/min noradrenaline infusion of noradrenaline at 3 µg/kg/min, the blood pressure remained consistently low (80/40 mmHg). On the third day of febrile neutropenia, coldness, paleness, and cyanosis started on his body’s acral parts and progressed to SPG in his feet and hands. The patient had a score of 6 on the DIC scale of the International Society of Thrombosis and Haemostasis (ISTH). DIC score of the patient was six.

Sepsis HA was started rapidly during the first hours in the ICU. The procedure was performed by using a hemoperfusion machine. One disposable hemoperfusion cartridge (HA330 resin, Styrene divinylbenzene copolymers, Jafron Biomedical Co., Ltd., China) was used per day. The blood flow rate was maintained at 200 ml/min. Each procedure continued for 150 minutes, and approximately six total blood volumes were processed. Three absorbers totally were used in over three days. The patient did not have any plasma components.

Due to thrombocytopenia, we did not administer routine systemic anticoagulation; except for priming the adsorption set. 7500 IU of unfractionated heparin was used only for raising the adsorption set to prevent clotting in the extracorporeal circuit. The changes of the patient's blood parameters before and after HA are given in Figure 1. No microorganisms could be produced in microbial cultures.
He continued extended-spectrum antibiotics for empirical treatment. By the third day of HA, the vasopressors were discontinued.

The progression of gangrene stopped with the withdrawal of vasopressors. Small blisters were noticed in both feet over the next 10 days (Figures 2, and 3). SPG in both feet and hands started to recover, and the patient was discharged from the hospital 38 days after ASCT. Three months after autologous transplantation, the patient was in complete remission, and his bilateral distal extremities recovered fully. In his last follow-up, the patient was on the 15th month of ASCT up was at 15 months after ASCT, and he was in complete remission. The last view of his extremities is shown in Figure 4.

3 | DISCUSSION

We have reported a case of neutropenic fever with developing septic shock developing after ASCT. The patient had SPG due to septicemia-associated DIC. We rapidly administered broad-spectrum antibiotics, and massive fluid replacement, and vasopressor treatment rapidly. When we observed ischemic lesions in his feet and hands, we increased supportive care by sepsis hemoadsorption. The patient had such a very impressive response the modalities that we stopped the vasopressor treatment afterward. Hemoadsorption may contribute to decreasing cytokines and turning back alleviate the septicemia associated with DIC.

The etiology of SPG is multifactorial, but septic shock and DIC are the most leading causes of SPG. Sepsis is currently defined as a dysregulated host immune response to infection leading to organ failure. The underlying pathophysiology is complex with both pathogenic and host factors. Pathogen-associated molecular patterns and damage-associated molecular patterns playing a significant role in activating the endothelium and as a result inflammatory cytokines. The activated endothelium becomes prothrombotic...
through increases in the expression of tissue factor increases on the endothelium and monocyte\textsuperscript{12,18}. DIC develops in cases of impairedment of anti- and pro-coagulant factors' balance of anti- and pro-coagulant factors. Early findings of Septicemia-associated DIC include apparent coldness, pallor, and pain. The ischemic lesions are often demarcated sharply and symmetric, with initial gray, blue or purple discoloration that progresses to black as the skin undergoes necrosis\textsuperscript{12,18}. 

With the more understanding about the pathophysiology of immune system factors in sepsis, the more interest has been increasing in the use of extracorporeal devices for cytokine adsorption. Because of the it has been hypothesized that a cytokine storm may be responsible for the self-destruction in sepsis, so the removal of circulating cytokines is a sensible treatment option. The peak-concentration hypothesis was first introduced with acute kidney injury and was subsequently generalized to sepsis more than 10 years ago\textsuperscript{20}. Since that time, it has been repeatedly hypothesized of that there is a therapeutic benefit of extracorporeal blood purification modalities, including forms of dialysis or therapeutic apheresis regarding the so-called "cytokine storm," have been repeatedly discussed in the literature\textsuperscript{19-20}.

HA330 (Jafron, Zhuhai City, China) is the one of the widely used adsorption cartridges in China\textsuperscript{9,10}. Huang et al. conducted small randomized controlled trials of adjuvant HA330-HA in with 44 septic patients with who had ALI in the ICU. Significant reductions of IL-8 and IL-6 levels and length of stay was seen in patients when it \textsuperscript{5} performing-ha was performed compared to standard therapy (defined as, full intensive care management, including fluid resuscitation, vasopressors, antimicrobial therapy, and ventilatory support). Nevertheless, length of hospital stays, or and 28-day mortality did not differ between the two groups at day 3\textsuperscript{21}. 
In a latter study by Huang et al., HA was compared to standard therapy in 46 patients with ALI induced by extra-pulmonary sepsis. The HA group showed a significant reduction in IL-1 and tumor necrosis factor-α in the broncho-alveolar lavage and plasma was seen in the HA group. Therefore, the improvement of patients’ hemodynamics was better, and the rate of mortality in the ICU and 28-day mortality was lower in the HA group. But still there is not yet any proof by from a prospective RCT for any extracorporeal treatment modality to decrease mortality in sepsis. Regarding sepsis, only therapeutic plasma exchange appears to be potentially effective, but no recommendations have been made in the latest international guidelines.

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recommended by guidelines. Large prospective randomized trials with in-carefully selected patient populations are needed to evaluate the efficacy of extracorporeal HA.

The patient that we reported in this in the present case report had septic shock at 13 days after ASCT. In this case, early management of septic shock with massive fluid replacement, antibiotics, and especially the administration of sepsis HA within <24 hours might have prevented the patient from amputation from being required. We prefer the HA-330 cCartridges for their easy accessibility and the affordable cost of the adsorbers. To the best of our knowledge, this is the first case report of successful HA in a patient with SPG.

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Figure 1. Changes of Patient's Blood Parameters Before and After Hemoadsorption

HA: Hemoadsorption, CRP: C reactive protein, PT: prothrombin time, LDH: lactate dehydrogenase
Figure 2. Ischemic changes observed in both feet and hand after septic shock
Figure 3. Ischemic changes and blister formation in feet
Figure 4. The last view of the patient’s extremities 15 months after autologous hematopoietic stem cell transplantation
Re: Resubmission of manuscript, Recovery of Symmetrical Peripheral Gangrene of Limbs In A Patient After Performing Hemoadsorption in Septic Shock, JCA-20-152

Address to the Editor  25/02/2021
Prof. Reinhard Klingel
Review Editor, Journal of Clinical Apheresis
klingel@apheresis-research.org

Dear Editor,

We would like to thank you for the letter dated 22-Jan-2021, and the opportunity to resubmit a revised copy of this manuscript. We would also like to take this opportunity to express our thanks to the reviewers for the detailed feedback and helpful comments for correction and revision. The manuscript has been revised to address the reviewer comments, which are appended alongside our responses to this letter.

We edited our manuscript, if you give approval , we would like to change the title as ‘ Recovery of Symmetrical Peripheral Gangrene of Limbs After Performing Immunoadsorption in Septic Shock’

We very much hope the revised manuscript is accepted for publication in the Journal.

Sincerely yours,
on behalf of the authors.

Dr Bahar Uncu Ulu

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Reviewer 1

1- ‘The following statement of the first review remains without change “It is only a speculation that HA330-hemoadsorption treatment was the most important component of the polypragmatic therapy.” The statement of the abstract in lines 30-32 must be changed. The term “hemoadsorption” must be specified with mention of the target, e.g., a cytokine adsorber.’

- We changed (‘Hemoadsorption may be an option for the management of septic shock, especially in the presence of any sign of hypoperfusion in the extremity.’) the sentence as below.
  ‘Hemoadsorption (HA) is an extracorporeal cytokine adsorption method for removing excess cytokine levels and may be preferable as a supportive modality in the management of septic shock.’

2-Page 15, lines 12 ff: The treatment regime is still not clear. How many days, treatment volume per adsorber, how many adsorbers, hours per treatment?

- We rewrite the paragraph as below;
  ‘Sepsis HA was started rapidly during the first hours in the ICU. The procedure was performed using a hemoperfusion machine. One disposable hemoperfusion cartridge (HA330 resin, Styrene divinylbenzene copolymers, Jafron Biomedical Co., Ltd., China) was used per day. The blood flow rate was maintained at 200 ml/min. Each procedure continued for 150 minutes, and approximately six total blood volumes were processed. Three absorbers were used over three days. The patient did not have any plasma components.’

3-Page 15, line 16-18: Thrombocytopenia is mentioned as contraindication for anticoagulation. Figures of PLT counts should be added to table 1. The English must be rephrased, as eg, “the patient did not use…..” makes no sense.
• We rewrite the paragraph as below:

‘Due to thrombocytopenia, we did not administer routine systemic anticoagulation except for priming the adsorption set. 7500 IU of unfractionated heparin was used only for raising the adsorption set to prevent clotting in the extracorporeal circuit.’

• We added the PLT counts to the Figure 1

4-Page 15, line 18: Unfractionated heparin was used only for rinsing or as an iv bolus, which would mean the patient received anticoagulation to prevent clotting in the extracorporeal circuit?

• We corrected the sentence as written above.

5-Page 16 ff, discussion section: There is still much redundancy of explanations related to SPG or sepsis given in the introduction and discussion sections. The discussion section should be shortened by app. 50%. There is no need to repeat all the hypothetical considerations of “treating the cytokine storm” etc. again, especially as this case does not add robust proof for any of them. Referencing the recent review on the cytokine storm by Fajgenbaum and June (NEJM 2020;383:2255-73) could replace much of the text. This case report should focus on describing the unique findings related to this case, and why the apheresis treatment might have contributed to the clinical outcome.

We shortened the the introduction and discussion sections. We added the Fajgenbaum’s article in to the reference 19. We added a new paragraph into discussion to focus on the case.

6- Page 17, lines 9-12: Use of the term hemoadsorption with this list of diseases or morbid conditions makes no sense. In particular referring to chronic uremic symptoms is not understandable. Hemodialysis treating end stage renal disease is no hemoadsorption process. Hemoadsorption is just a methodological description, e.g. there are two different full blood adsorbers for lipoprotein apheresis on the European market. Authors are again recommended to check the general sections of the current ASFA-guidelines (Padmanabhan A, Connelly-Smith, Aqui N, et al. Guidelines on the use of therapeutic apheresis in clinical

We deleted the sentences that mentioned about the list of diseases.

7-Page 17, line 13/14: As mentioned in the first review. Such a statement is not justified by existing data. Which adequately powered RCT can be referenced? Ref 9 is an editorial ending with the final sentence “Only through well-conducted randomized controlled studies with appropriate patient selection criteria and endpoints of physiological relevance will we know whether haemoadsorption techniques are a future therapy for sepsis.”. Which study on the HA330 adsorber summarized in ref 10 provided such quality of data? Ref 21 is a porcine model. Therefore the following concerns of the first review have to be repeated here: “The peak concentration hypothesis was first introduced with acute kidney injury and was subsequently generalized to sepsis more than 10 years ago (Ronco et al. CJASN 2008;3:531-544). Since that time hypotheses of a therapeutic benefit of extracorporeal blood purification modalities including forms of dialysis or therapeutic apheresis regarding the so called “cytokine storm” have been repeatedly discussed in the literature. There is not yet any proof by a prospective RCT for any extracorporeal treatment modality to decrease mortality in sepsis.

We deleted the references 21. We added the sentences that you emphasised.

8. Page 18, lines 1-7: Cytosorb is a trade mark name and must be limited to methods sections of articles presenting research data on that device. E.g. “whole blood cytokine adsorber” would be an appropriate wording.

What are the data showing that Cytosorb is non-selective and HA330 is selective? What stands selective for in this context? This must be explained.

We deleted the trade mark and explained that the selectivity with a new paragraph.

‘Cartridges are divided into selective and non-selective types. Cartridge selectivity may have important consequences for treatment. For instance, non-selective cartridges cannot adsorb endotoxin because their cutoff point (~60 kDa) falls below the molecular weight of endotoxin (~100 kDa). HA330 and its equivalent have non-selective cartridges.’
9-Page 18, lines 24/25: This statement is not justified by results of this case report. Future conduct of adequate RCT must prove this hypothesized preventive effect.

We changed the last sentences as below;

‘Performing sepsis HA immediately may be a good adjuvant option for the treatment of septic shock while avoiding destructive effects of the cytokine storm and DIC, as in our patient. Nevertheless, RCTs are needed to prove this hypothesized preventive effect.’

**Reviewer 2**

Detailed review comments

1-Page 13, abstract, lines 25-28: English language must be improved.

We edited all the text.

2-Page 14, line 8: Typo with “%40” must be corrected.

We corrected the typo.

3-Page 14, line 13: “Aggravation of microcirculation” is not understandable. Shall this refer to impairment of microcirculation?

- We corrected the word.

4-Page 14, line 14: English language must be improved.

- We corrected the sentences and the text was edited by native speaker.

5-Page 15, lines 3-6: This very long sentence is hard to understand. The English language must be improved.

- We rewrite the paragraph as below;
He was neutropenic and thrombocytopenic when the first fever occurred. Cefoperazone sulbactam was started. On the second day of febrile neutropenia, the patient progressed to sepsis, after which meropenem, vancomycin, liposomal amphotericin B, and colistin were administered. The patient needed nasal oxygen support because of hypoxia and was admitted to the ICU.

6-Page 15, lines 10/11: “in both his hands” is no correct English language.
   • We corrected the sentences.

7-Page 15, lines 13-16: Rephrase to correct English.
   • We corrected the sentences.

8-Page 15, line 19/20: “No microorganisms ……empirical treatment.” Both sentences must be rephrased using correct English.
   • We corrected the sentences.

9-Page 17, lines 12-25: Link of statements and references is unclear for the reader.
   • We corrected the references and this discussion section.
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