

The Editorial Office

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Re: 66242 – Answering reviewers

16 June 2021

66242 – Answering reviewers

We thank the reviewers for their thoughtful comments and offer these explanatory notes and amendments based on their feedback:

Reviewer comment:

The case report presents a multidisciplinary resuscitation of septic shock and ARDS in an adolescent female, who was diagnosed with a Panton-Valentine Leukocidin *S. aureus* and influenza virus H3N2 infection. The patient suffered a dramatic exacerbation and severe complications after admission, and following a rapid multidisciplinary response, the patient

recovered and discharged. The report describes a rare medical record that is educational, however improvements need to be made in the following aspects.

1. PVL-SA is associated with the potential risk factors, including recent history of skin and soft tissue injury, history of antimicrobial use, and weight loss, etc. The patient has no previous history of immunodeficiency, but any other history of risk factors should be described in the past history.

Thank you for this point. The patient reported a febrile viral upper respiratory tract illness in the week preceding her presentation. There was no history of cutaneous injury or lesions. The manuscript has been amended to make this point in the history. Section history of now has the addition of: *There was no history of cutaneous injury or pathology.*

Reviewer comment:

2. PVL-SA causes injury to immune cells such as leukocytes mainly. The report neglected to describe the alteration of leukocyte morphology and number as well as the alteration of inflammation-related indicators such as procalcitonin and C-reactive protein during the patient's disease process.

Thank you for this point. We acknowledge the relevance of these test results and provide the blood tests results inclusion with the manuscript. Blood film examination was not performed. Laboratory examinations now include the addition of: *Of note, the patients' blood work up demonstrated a leukopaenia with neutrophil count 0.8 on initial presentation. This was consistent with the clinical working diagnosis of suspected septic shock. Blood film analysis was not performed. Further blood test results were performed and are summarized in Table 1.*

Reviewer comment:

3. It is mentioned in the report that the patient received approximately 6000mL of crystalloid and albumin fluid resuscitation on admission to the hospital. According to the fluid resuscitation protocol for patients with sepsis, the patient was 53 kg weight, whether this volume of fluid resuscitation was overloaded, which speed of resuscitation was given, what type of assessment was used during resuscitation, how the resuscitation goals were measured, and the initial post-resuscitation protocol and other treatment strategies were not described. The case reports should provide detailed treatment strategies, and new treatment strategies attempted should be analyzed if they do not conform with treatment guidelines, in order to provide experience and reference for clinicians.

The reviewer makes an excellent point which was acknowledged in the text. It could have been further described as the volume of fluid used was far greater than that advised in the managing sepsis guidelines. We acknowledge that more can be written about this aspect of the case in further detail, but we decided to keep this section brief as there are other aspects of care we wished to draw attention to. We make the following points for the benefit of further review:

The text does refer to progressively worsening haemodynamic instability despite aggressive fluid resuscitation. We describe ECHO findings of hyperdynamism and underfilling. We further describe ongoing profound metabolic acidosis, tachycardia and hypotension despite filling and multiagent vasopressors. We have amended the manuscript to make the additional point of using ECHO guided fluid resuscitation and comment upon capillary refill examination. We acknowledge the significant amount of fluid administered. We make the additional of: *The resuscitation process was adjusted from ED to ICU to maintain a life sustaining blood pressure whilst reducing the very high levels of vasopressors and inotropes to reduce risk of iatrogenic arrhythmias whilst maintaining acceptable cardiac output and oxygen delivery. Despite the measures described, adequate life sustaining blood pressures*

were not adequately maintained, and high fluid volumes were required. At all times dynamic assessments of fluid responsiveness were used to guide resuscitation.

Reviewer comment:

4. The patients suffered from ECMO catheter stuck during treatment and catheter breakage when removing the catheter by incision. Whether there was any preoperative failure to perform vascular assessment? The reasons for the rare complications of ECMO, the management option for the complications, and the lessons learned from them should be discussed.

We thank the reviewer for their comment. Full ECMO protocols were adhered to, including pre cannulation vascular assessment. This was made challenging by the poor peripheral perfusion at the time. Size of insertion cannulae are determined by the patient's size and the estimated need for extracorporeal flows- often higher in septic shock, hence the desire to place the largest cannulae for the size of the patient. There were no difficulties in vascular access, or dilatation. So it was only at the insertion of the final cannula which would not advance further or retract, that the problem first came to light. The Lead Cardiothoracic surgeon was involved at this stage, with a group of consultant intensivists and a perfusionist very experienced in ECMO from one of the busiest national ECMO centres. A thorough review of the case and lessons has been undertaken, including a Schwartz rounds reflection. As with the above point, more could be written on this aspect of the patients care, but would detract from the overall picture and learning points we wish to highlight to the readership.

There is an addition to the manuscript which now reads: *Full ECMO cannulation protocols were followed, and vascular pre-assessment was performed.*

Reviewer comment:

5. Only the X-ray chest film of the patient at 8h of admission is provided in the report, whether the chest CT and other relevant examinations were repeated during the treatment. More imaging examinations should be provided to summarize the evolutionary features of pulmonary pathological changes in ARDS caused by PVL-SA.

We thank the reviewer for their comment. The images included in the manuscript are from the initial hospital presentation which is the focus of the case presentation. Further imaging does exist, but is from the subsequent transfer to the SARF (ECMO) centre. We are happy to provide this further imaging if the journal requests. CT chest imaging performed in the tertiary centre showed an expected diffuse consolidation with minimal aerated lung, as is customary in our extensive experience of severe cases of viral plus bacterial pneumonia related ARDS requiring ECMO support.

With the permission of the journal, we provide panel images to present the dynamic changes as in the case of this patient in Figure 1:A-C in the image file from the initial hospital presentation.

Reviewer comment:

6. What is the treatment strategy in case of multi-organ failure such as diffuse intravascular coagulation and renal failure during ECMO treatment? How to deal with the high bleeding risk during the later adjustment from VA-ECMO mode to VV-ECMO, and how to assess the time to switch the ECMO mode? In conclusion, the process of treatment reported in the case should be presented in a continuous chronological order, and the whole history of the disease can be clearly reflected by drawing a test-exam-treatment-time diagram to show good educational significance. In the discussion section, the non-standard protocols or innovative treatment measures used in the case should be discussed to reflect the key role of multidisciplinary treatment. The diagnosis, treatment, and prognosis aspects of the case

history should be clearly elaborated hierarchically in order to present a complete vision of the treatment of the disease.

We thank the reviewer for their comments. We provide the key points of the case report as advised by the journal. Whilst a different order of presentation may be preferable to the reviewer, we would need to be advised of this by the editorial team before amending as the current flow of the case, highlighting important points, may be affected detrimentally by changing the current structure.

The non-standard components of her care are referred to in the discussion. There is a further comment on line 366 to 369, page 13 reading: *Further, the rapid intervention of an experienced cardiothoracic surgeon to prevent potential massive blood loss following ECMO complications highlights the importance of having the right people in the right place, at the right time.*

Because of the concern regarding compromised blood flow to the left leg, and acceptable Biventricular function on repeat TTE, together with concerns of not being able to anticoagulate a V-A ECMO circuit, a decision was made to convert her from VA to VV ECMO that night. This has been the original intention but had required a change of approach in the emergency situation when the patient had a cardiac arrest and extracorporeal Cardiopulmonary resuscitation (eCPR) became the only lifesaving strategy approach. The discussions between ECMO intensive care, Cardiothoracic surgery, Vascular Surgery and Haematology consultants determined the course and timings of actions taken, with due consideration to physiological and haematological data, evaluation of benefits and risks to life and limb. These were ongoing daily. The left lower limb had poor perfusion for several days. Further discussions about percutaneous or surgical revascularisation procedures were considered but discounted due to high risk of bleeding complications. The experienced expertise was undoubtedly a major factor in her survival and subsequently in preservation of

her limb. She required a prolonged course of rehabilitation, physiotherapy at home and in the gym, orthotic shoes, leg splints and a skin graft to the leg after debridement of a poor healing skin ulcer. She continued in regular joint care between her Rehabilitation and Paediatric physicians and the ECMO follow up service. She is due to return to her School studies in Dubai this week, 2 years after that extraordinary event.

Science editor comments and response

We thank the science editor for their comments.

Issues raised:

1. The title is too long and it should be no more than 18 words.

The title is 17 words long in its current format. If the issue is regarding hyphenated words, the initial title of “Against the odds” could be removed. However, this subtitle highlights the near fatality of the case and nature of eventual survival and good outcome which we feel is relevant to the case.

2. The authors did not provide original pictures. Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor

The images will be prepared and presented as a PPT file as requested.

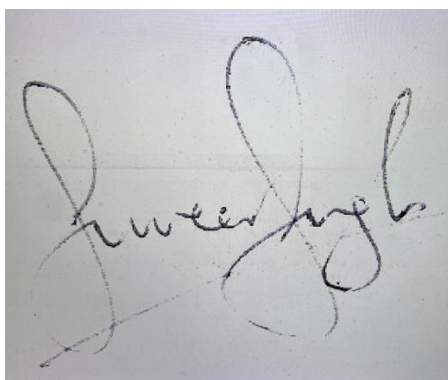
3. The “Case Presentation” section was not written according to the Guidelines for Manuscript Preparation. Please re-write the “Case Presentation” section, and add the “FINAL DIAGNOSIS”, “TREATMENT”, and “OUTCOME AND FOLLOW-UP” sections to the main text, according to the Guidelines and Requirements for Manuscript Revision.

The manuscript is now written more clearly in this format. We have moved the antimicrobial therapy section into “treatment” which we think addresses this issue.

The manuscript has been reviewed and passed through a grammatical checker (Grammarly) since the changes described above. There are a number of grammatical and spelling changes that have been made since the previous submission. None of which change the content beyond that described above.

Yours sincerely

Dr Josh Cuddihy and Dr Suveer Singh on behalf of all authors.

A handwritten signature in black ink, appearing to read 'Suveer Singh', written in a cursive style on a light-colored background.A handwritten signature in black ink, appearing to read 'Josh Cuddihy', written in a cursive style with a long horizontal stroke extending to the right.