Author’s response to reviews

Title: Myocardial Oedema in an 8-year-old Chinese Boy with Idiopathic Systemic Capillary Leak Syndrome

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Author’s response to reviews:

We thank the reviewers for bringing to our attention this outstanding article, which at the time of our submission, was not yet published. However, we agree that this is an important reference to cite, and supports the notion that this is a worthwhile disorder to include in different journals, especially since our case is the first child who present with myocardial dysfunction. All comments/suggestions by the reviewers have been addressed and changes in the text are highlighted in yellow.

REVIEWER COMMENTS TO AUTHORS:

Reviewer: 1 (Dr Gregorio Milani)

Authors have put efforts to address my comments. I have still some concerns that should be addressed before considering the manuscript acceptable for publication.

We thank the reviewer for acknowledging our efforts.
1) Authors report that 21 cases of pediatric ICLS are described in literature. However, at least 32 cases are described (please refer to "Bozzini et al. European Journal of Pediatrics (2018) 177:1149-1154"). We have reviewed the suggested article and addressed the discrepancy accordingly. (Page 3, line 55 and page 8, line 186)

Idiopathic systemic capillary leak syndrome (ISCLS) is rare, and there has been about 32 cases reported in children worldwide since this disorder was first described in 1960. Approximately 500 adults and 32 paediatric cases of ISCLS have been described [2-19].

2) Furthermore, please consider that hypotension is not always present in pediatric ICLS. Therefore, signs of tissue hypoperfusion can be considered instead of hypotension ("Bozzini et al. European Journal of Pediatrics (2018) 177:1149-1154"): reword the text accordingly.

We have added the comment in the background that signs of tissue hypoperfusion can be considered instead of hypotension. We have now reworded the text accordingly. (Page 4, lines 83-85 and Page 12, lines 280-282)

The original proposed classic triad consisted of severe hypotension, hypoalbuminaemia and haemoconcentration [1, 2]. In children, signs of tissue hypoperfusion may be more evident than hypotension [3]. Though ISCLS is rare in children, this disorder should be suspected when a patient presents with a rapid development of hypotension or signs of tissue hypoperfusion, haemoconcentration and hypoalbuminemia [1-3].

3) The sentence "The family was counselled on a written contingency plan to ensure an immediate visit to a physician upon the first sign of any acute illness in the future." is superfluous and it is just authors' practice.

We have now removed this sentence. (Page 7, lines 176-177)

He has remained asymptomatic so far for more than 12 months at his most recent clinic follow-up.

4) In the acute treatment section, please remove or reduce the parts on adults. Furthermore, I would avoid describing the management of compartment syndrome, since it is only one of the several possible complications of this syndrome.
We have now reduced the parts of on adults and the removed the part on management of compartment syndrome. (Page 10, lines 246-249)

The dose and duration of treatment varied between different reports in children, and the effectiveness of these therapies during the acute phase is controversial [7-9, 13]. We did not start any pharmacological agents for our patient during the acute phase as this child was already improving significantly from supportive treatment alone.

5) Most information/recommendations reported in the current version of the discussion are not evidence-based but just supported by anecdotic reports. Please significantly reduce the therapeutic and prophylactic sections. For instance, remove sentences from "Upper respiratory infection….from only a few isolated cases". This is mainly a list of authors' opinions. Authors should limit their opinions and try to report information supported by data (even if I recognize that ICLS is a very rare condition).

The therapeutic and prophylactic sections has been reduced significantly by more than 70% (from 748 to 510 words). We have now remove all the sentences from ‘Upper respiratory infection... from only a few isolated reported’ as suggested. (Page 9-11, lines 227-277).

Acute treatment

The first episode of ISCLS usually remains undiagnosed as the presentation is similar to many other diseases such as sepsis and angioedema. If ISCLS is suspected, a secure vascular access is essential for preparing rapid and repeated fluid infusion. There has been no data to clearly demonstrate superiority of one specific type of fluid over another. Overly aggressive fluid rehydration can potentially lead to complication such as compartment syndrome during the leak phase and pulmonary oedema in the recovery phase. Diuretic therapy can be useful as the patient enters the recovery phase [29]. Refractory shock due to ISCLS requiring ECMO support is rare.

Empiric trials of pharmacological agents for the acute management of ISCLS had included intravenous immunoglobulin (IVIG), corticosteroids, theophylline, terbutaline and TNF- antagonists (e.g., infliximab) [8]. IVIG had seemingly been the most effective in adults with ISCLS [30]. The rationale for the use of IVIG is based on its anti-inflammatory and immunomodulatory properties, anti-idiotypic effect against autoantibodies, and inhibition of complement-mediated damage, all of which should result in less vascular permeability [31, 32]. Both theophylline and terbutaline increase cyclic adenosine monophosphate levels within endothelial cells, which should reduce the capillary leak [8, 33].
The dose and duration of treatment varied between different reports in children, and the effectiveness of these therapies during the acute phase is controversial [7-9, 13]. We did not start any pharmacological agents for our patient during the acute phase as this child was already improving significantly from supportive treatment alone.

Prophylactic treatment

Prophylactic treatment previously reported in children included IVIG, terbutaline, theophylline, montelukast and gingko biloba. The doses varied and there were no established optimal duration of treatment in the literature.

Druey and Greipp recommended oral terbutaline and theophylline as the first-line prophylactic therapy for adults [31, 34]. However, theophylline has a high adverse-effect profile and narrow therapeutic window in children. For these reasons, we avoided the use of theophylline for our patient.

IVIG appears to be the most promising prophylactic treatment in children. It had been well tolerated with minimal side effects. The doses used varied from 1-2 g/kg, infused once a month. Subcutaneous immunoglobulin can be considered for patients who experience significant adverse effects or prefer the convenience of home infusion [4, 35].

Montelukast, a leukotriene receptor antagonist, can theoretically inhibit leukotriene-induced capillary leakage [36]. The majority of reported adverse effects were mild (e.g., headache, ear infection, nausea and abdominal pain) [37]; thus, it may be a better alternative for children. The use of montelukast had been reported in two children in the literature. One patient experienced reduced frequency and severity of attacks [17] while the other suffered one episode of life-threatening relapse of ISCLS [4]. Since montelukast is well tolerated in children and there is anecdotal evidence suggestive of potential benefits, it may be considered as a prophylactic option.

Our patient is the first known case who has been started on IVIG and montelukast. We decided on this combination due to the observed effectiveness and minimal side effect profile as aforementioned. So far, he has been symptom free for 12 months.

6) Recommendations on vaccination are not evidence based. Please, remove them.

Recommendations on vaccination is now removed. (Page 11, 275-277)

Our patient is the first known case who has been started on IVIG and montelukast. We decided on this combination due to the observed effectiveness and minimal side effect profile as aforementioned. So far, he has been symptom free for 12 months.
7) Similarly, please avoid recommending montelukast (in the conclusion). Authors gave IVIG and I am not sure that the success of their treatment was due to the use of Montelukast plus IVIG or only of IVIG. Overall, for therapeutic and prophylactic recommendations in the discussion refer mainly to "Hsu P et al. Pediatrics 2015, 135(3):e730-735" that is the only available, rather large, pediatric case series addressing this issue.

We have now removed the recommendation for therapeutic and prophylactic treatment in our conclusion. (Page 12, lines 280-286)

Though ISCLS is rare in children, this disorder should be suspected when a patient presents with a rapid development of hypotension or signs of tissue hypoperfusion, haemoconcentration and hypoalbuminemia [1-3]. Myocardial oedema and ventricular dysfunction in ISCLS may represent a more fulminant course and could be potentially life-threatening. We suggest early performance of echocardiogram on patients with ISCLS to identify myocardial involvement and immediate transfer to a specialised centre with ECMO support if available when there is evidence of myocardial oedema.

Reviewer: 2 (Dr Steve Leung)

1) Authors addressed all my concerns related to previous review.

We thank the reviewer for acknowledging our efforts.

2) Authors included a comment that there have been approximately 271 cases reported (approximately 250 adult, 21 pediatrics). There was a recent review (Bozzini M et al, European Journal of Pediatrics 2018;177:1149-54) that mentioned approximately 500 patients have been reported. Would recommend review of the article, and address discrepancy.

We have reviewed the suggested article and addressed the discrepancy accordingly. (Page 3, line 55 and page 8, line 186)

Idiopathic systemic capillary leak syndrome (ISCLS) is rare, and there has been about 32 cases reported in children worldwide since this disorder was first described in 1960.

Approximately 500 adults and 32 paediatric cases of ISCLS have been described [2-19].
We thank the reviewers for the above suggestions which significantly improved this manuscript after it has been revised accordingly.