Author’s response to reviews

Title: Significant predictive factors of the severity and outcomes of the first attack of acute angioedema in children

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Author’s response to reviews:

Dear Editor:

Enclosed is our revised manuscript (RE: BPED-D-19-00477, entitled "Significant predictive factors of the severity and outcomes of the first attack of acute angioedema in children"). We appreciate the constructive comments of the editor/reviewer 1,2,3 and have made major revisions, as noted in our point-by-point responses.

Below are our replies to your comments:
1. In the section "Ethics approval and consent to participate", please include information on the consent to participate.
Answer: We appropriate your comment. This study was performed with the permission of the institutional review board (IRB) of Changhua Christian Hospital in Taiwan. Since this is a retrospective chart review study; therefore, there was no need to obtain informed consent from patients (waiver of documentation of informed consent, IRB permission code: 160612). We have described this information more clearly in the section of Ethics approval and consent to participate.

On Page 22 line 1: This study was performed with the permission of the institutional review board (IRB) of Changhua Christian Hospital in Taiwan. Since this is a retrospective chart review study; therefore, there was no need to obtain informed consent from patients (waiver of documentation of informed consent, IRB permission code: 160612). All review work was performed by ED physicians using a standardized abstraction form (all members were certified their qualifications by IRB). The quality of the review was monitored by regular meetings, and the final output data were de-identified (secondary data).

We hope that you will now find our manuscript sufficient for publication. We look forward to hearing from you.

Best regards,

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Reviewer 1 (Andrew MacGinnnitie):

Enclosed is our revised manuscript (RE: BPED-D-19-00477, entitled "Significant predictive factors of the severity and outcomes of the first attack of acute angioedema in children"). We appreciate the constructive comments of the reviewers and have made major revisions, as noted in our point-by-point responses.

Below are our replies to your comments:
1. The conclusion that admission for short-term observation shortens the clinical course of patients with angioedema is not warranted. (1) First, the duration was much longer for patient admitted to the hospital which. ..... (2) Second, the difference between patients admitted to the observation unit and those sent home (2.1 vs. 2.3 days) ..... (3) Finally, the statistics presented just compare the 3 groups, meaning significance is likely due to the much longer duration in the group the was hospitalized. ....

Answer: We appreciate your very constrictive comments. We agree that a part of conclusion “short-term POU observation and prompt treatment could shorten the clinical course” is not
warranted and might confuse readers. As your three major points mentioned above, the significance of POU short-term treatments (2.1 days) might not be really significant in shortening the clinical course; therefore, this recommendation should be revised. We have revised all these statements in abstract and main text. We have removed the statement of shortening the clinical course and only reported that short-term POU observation and prompt treatment might be benefit for patients who did not require hospital admission. This information has been added in the sections of abstract, conclusion and limitation.

On page 3 line 5: …short-term POU observation and prompt treatment might be benefit for patients who did not require hospital admission.

On page 21 line 4: …short-term POU observation and prompt treatment might be benefit for patients who did not require hospital admission.

On page 19 line 20: In addition, the difference between patients admitted to POU and those sent home might be not clinically significant. It could be influenced by other factors (data on one collected while in observation, the other on follow up, likely days later; different mechanisms of angioedema). Finally, we just compare the duration of angioedema between the three groups, meaning significance could be likely due to the much longer duration in the group of hospital admission.

2. p 7, line 8 would say insect bites and stings

Answer: Yes, we have revised it.

On page 7 line 5: …. insect bites and stings….

On page 13 line 8: …. insect bites and stings….

3. p7 line 15, would say clinician review not peer review

Answer: Yes, we have revised it.

On page 7 line 8: …. determined by clinician review of the….

4. Could combine tables 1 and 2 since they present the same data

Answer: We appropriate your comment. We have combined the two tables as a new table, please see Table 1.

Reviewer 2 (Anette Bygum):

Enclosed is our revised manuscript (RE: BPED-D-19-00477, entitled "Significant predictive factors of the severity and outcomes of the first attack of acute angioedema in children"). We appreciate the constructive comments of the reviewers and have made major revisions, as noted in our point-by-point responses.

Below are our replies to your comments:
1. Due to the retrospective design, the authors should be very careful on their conclusion as a cause-relationship cannot be extrapolated from their data.
We appreciate your comments. A part of conclusion “short-term POU observation and prompt treatment could shorten the clinical course” might be extrapolated from our data. The significance of POU short-term treatments (2.1 days) might not be really significant in shortening the clinical course; therefore, this recommendation should be revised. We have removed the statement of shortening the clinical course and only reported that short-term POU observation and prompt treatment might be benefit for patients who did not require hospital admission. This information has been added in the sections of abstract, conclusion and limitation.

On page 3 line 5: …short-term POU observation and prompt treatment might be benefit for patients who did not require hospital admission.

On page 21 line 4: …short-term POU observation and prompt treatment might be benefit for patients who did not require hospital admission.

On page 19 line 20: In addition, the difference between patients admitted to POU and those sent home might be not clinically significant. It could be influenced by other factors (data on one collected while in observation, the other on follow up, likely days later; different mechanisms of angioedema). Finally, we just compare the duration of angioedema between the three groups, meaning significance could be likely due to the much longer duration in the group of hospital admission.

2. Figure 1 includes details about medication and food, and this should be further discussed in the text.

Answer: We appreciate your comments. We have discussed the details about medications and foods in the section of discussion. Several previous studies reported that milk, egg, and peanut were the most common foods caused allergic/hypersensitive reactions (urticaria, angioedema or anaphylaxis) in children. (J Allergy Clin Immunol. 2010; 125:1077-1083.; J Allergy Clin Immunol Pract.2017;5:398-409; Pediatr Allergy Immunol. 2019; 30:17-24.) In this study, we found seafood was the most common, followed by milk and fruits. Only 6% of foods related angioedema were caused by peanut. Although NSAID and antibiotics were widely thought to be responsible for most medication related angioedema (also 72% in our study). Int Arch Allergy Immunol. 2002; 128:1-7.; Allergy. 2016; 71:149-61.; however, 13% of them might be associated with vaccination. Since the causes of hypersensitive reactions of vaccination were usually various and difficult to predict, we suspect post-vaccination observation should not be ignored. We have addressed this statement in the section of discussion.

On page 15 line 13: Several previous studies reported that milk, egg, and peanut were the most common foods caused allergic/hypersensitive reactions (urticaria, angioedema or anaphylaxis) in children.[20, 20, 21] In this study, seafood was the most common, followed by milk and fruits. Only 6% of foods related angioedema were caused by peanut. Although NSAID and antibiotics were widely thought to be responsible for most medication related angioedema (also 72% in our study)[22, 23]; however, we still noted that 13% of them might be associated with vaccination. Since the causes of hypersensitive reactions of vaccination were usually various and difficult to predict, we suspect post-vaccination observation should not be ignored.

3. Seemingly atopic dermatitis is included as an allergic history, but atopic is not necessarily allergy.
Answer: As your comment, atopic dermatitis might increase the risk of developing food allergy, allergic rhinitis, and asthma but not necessary allergy. Curr Pediatr Rev. 2018;14:171-179. To not confuse readers, we have excluded the atopic dermatitis from our allergic histories. Please see the section of Methods and Table 1 (data re-calculation, the old Table 1 and 2 were combined together as new Table 1 according to another reviewer’s suggest).

On page 8 line 14: The personal allergic history of the patients, including asthma, allergic rhinitis was obtained from hospital chart records and statements from patients or family members.

4. Please observe if known asthma is a confounder to be hospitalized (POU or hospital admission).

Answer: We appreciate your comments. Among the 406 angioedema children, 71 (17.5%) children have history of asthma, 32 (7.8%) children were co-occurring with asthma attack. If we divided all patients into hospitalization (POU or hospital admission, n=206) or non-hospitalization (ED discharge, n=200) groups. We could find that patients with history of asthma (n= 50, 70.4%) or co-occurring asthma attack (n=30, 14.6%) were both significantly associate with hospitalization (both p&lt;0.001, using Chi-Square test). We have described this information more clearly in the sections of Method, Result and Discussion.

On page 10 line 10: …. the relationships between asthma and hospitalization (POU or hospital admission) were both analyzed by the Chi-Square test…. On page 12 line 16: For all, 71 (17.5%) children have history of asthma, 32 (7.8%) children were co-occurring with asthma attack. Patients with history of asthma (n= 50, 70.4%) or co-occurring asthma attack (n=30, 14.6%) were both significantly associate with hospitalization (POU or hospital admission, both p&lt;0.001, using Chi-Square test).

5. P4, line 8: You mention that allergic angioedema is the most common type - I'm not sure. Please document your statement with original literature.

Answer: We appreciate your comments. Some previous studies reported that allergic angioedema (histamine-mediated) is the most common type (up to 70% of all cases). West J Emerg Med. 2019; 20:587-600; Eur J Intern Med. 2019;59:8-13; Int J Emerg Med. 2017 ;10:15. We have provided references.

On page 4 line 4: Allergic angioedema (histamine-mediated) is the most common type. [4-6]

6. P4, line 21: You should include original studies related to the subject instead of reference 6


On page 4 line 7: …. such as angiotensin-converting enzyme inhibitors (ACEI).[9-12]

7. P4, line 21-28: You write about the most common anatomical areas involved - it is not clear which kind of angioedema you describe here (idiopathic - drug-induced - ACEI-induced?), please make this clear and be aware of your references.
Answer: Yes, this is allergic (histamine-mediated) angioedema. We have addressed this information and references more appropriately.
On page 4 line 8: Among patients with allergic angioedema, the most common anatomical areas involved are around the eyes, lips, mouth, tongue, extremities, and genitalia. [5, 6, 13]

8. P4, line 28: You use the word hives - every other place in the article you mention urticaria - is this on purpose?

Answer: Yes, urticaria may be more appropriate. We have addressed this in the section of introduction.
On page 4 line 11: An itchy, raised rash called urticaria can occur with angioedema.

9. P4, line 34: You use a reference describing threat of asphyxiation to document swelling of the intestinal tract?
Answer: Yes, this article also reported some abdomen symptoms of angioedema. (Recurrent angioedema and the threat of asphyxiation. Dtsch Arztebl Int 2010, 107:408-414.) To not confuse readers, we would like to add more appropriate references regarding swelling of the intestinal tract. (Intern Med. 2018; 57:319-324.; World J Gastroenterol. 2010; 16: 4913–4921.)
On page 4 line 11: Angioedema may also lead to abdominal pain due to the swelling of the intestinal tract [14-16].

10. P4, line 40: ...........which leads to suffocation, hypotension and even respiratory failure. Please look at this sentence and also the sentence on lines 40-50 which is not totally clear to me.

Answer: We appreciate your comment. These sentences have been re-written.
On page 4 line 13: Sometimes, more severe symptoms occur, including swelling of the airway, which leads to suffocation, hypoxia and even respiratory failure [4, 17, 18]. Although the attack of angioedema might be easily aware (i.e., sudden swelling of eyelid or lip); however, for most parents, the severity of angioedema (life threatening or not) is not easily determined by themselves, especially when their children are suffering their first episodes.

11. P7, line 31: Food or medications were suspected to be the possible etiologies when patients or family members stated that they suffered from skin symptoms after eating a particular food or taking a particular medication. You need to discuss this statement, as the patient/family history is no proof. In relation to food, you can do allergen-specific IgE, SPT and provocation. For some medications, it is also possible to verify such a suspicion.

Answer: We agree with your comment. We have discussed this statement in the section of discussion.
On page 16 line 1: .... Finally, if the allergic history of patient or family is no proof. In relation to food, allergen-specific IgE, skin prick test (SPT) and provocation test might be benefit for patients. For some medications, it is also possible to verify such a suspicion.

12. P13, line 1 (and Table 1): contact materials?
Contact materials were defined as allergens that caused angioedema by skin contact. In this study, only two patients suffered angioedema after skin contact with some materials (one is engine oil and the other one is an old coin). Thus, we classified them into the group of “contact materials”. We have addressed the definition of “contact materials” more clearly in the section of method.

On page 7 line 5: …. insect bites and stings, (6) contact materials (contact allergens, angioedema was induced by skin contact with something), and…. 

13. P15, line 34-37: Angioedema frequently presents with skin lesions, mainly wheals. Please rephrase this sentence.

Answer: We appreciate your comments. We have revised this sentence.

On page 17 line 16: …. Some angioedema patients could present symptoms of urticaria (mainly wheals on the skin)…. 

14. P15, lines 5056: You write that co-occurrence of angioedema with urticaria indicates a more severe clinical presentation - please document this also with references. For me it seems to be the opposite, as bradykinin-mediated angioedema (hereditary angioedema, ACEi angioedema and other drug-induced angiodema) is the most severe and usually does not present with urticaria. It may be different in children, please discuss and document with your data.

Answer: As your comment, for all kinds of angioedema, bradykinin-mediated angioedema is the most severe and does not usually present with urticaria. Since this study has excluded hereditary angioedema (n=3) and only 2 (0.5%) patients were confirmed as ACEI angioedema (ACEI is not the first choice for pediatric hypertension control in Taiwan); therefore, we suspect our population were almost allergic (histamine-mediated) angioedema. Unfortunately, after a careful searching from MEDLINE® and PubMed®, we found that studies focused on discussing the association between allergic/histamine urticaria and angioedema in children were very limited, especially the information regarding the prediction of severity had not been well addressed. In this study, we found that patients who suffered both urticaria and angioedema, were more likely to require hospital admission. There were two possible reasons. First, it might reflect a stronger immune reaction (mast cell/basophil activation was strong enough to trigger both reactions of urticaria and angioedema). Clin Rev Allergy Immunol. 2013; 45:47-62. Second, just more uncomfortable feeling of patients. We have addressed this statement more clearly in the section of discussion.

On page 18 line 1: …. Since this study excluded hereditary angioedema and only 2 (0.5%) patients were confirmed as ACEI angioedema; therefore, we suspect our population were almost allergic (histamine-mediated) angioedema. We noted that patients who suffered both urticaria and angioedema, were more likely to require hospital admission. It might be associated with a stronger immune reaction (mast cell/basophil activation was strong enough to trigger both reactions of urticaria and angioedema) or just more uncomfortable of patients.[37]

15. Figure 2: How do you define Inhalants? (inhalation allergens?) and Contact materials.

Answer: We appreciate your comments. The inhalants were defined as inhalation allergens (including animal dander, cockroach, dust mites, and pollen). Contact materials were defined as
allergens that caused angioedema by skin contact (please see the answer of Question 12). We have described the definitions of inhalants and contact materials more clearly in the section of method.

On page 7 line 4: …. (4) inhalants (inhalation allergens, including animal dander, cockroach, dust mites, pollen), (5) insect bites and stings, (6) contact materials (contact allergens, angioedema was induced by skin contact with something….

Reviewer 3 (Inmaculada Martinez-Saguer):

Enclosed is our revised manuscript (RE: BPED-D-19-00477, entitled "Significant predictive factors of the severity and outcomes of the first attack of acute angioedema in children"). We appreciate the constructive comments of the reviewers and have made major revisions, as noted in our point-by-point responses.

Below are our replies to your comments:

1. Is there data on the course of the patients. Correlates the first angioedema with a severe course and correlates the age at the first angioedema with a severe course. Please discuss.

Answer: We appreciate your comments. Among the children suffered first angioedema, we found 50.7% of children required hospital stay (hospital admission, n=109; 26.8%; POU observation, n=97; 23.9%). Some characteristics of patients would associate more severe course, including co-occurrence of pyrexia or urticaria, etiologies related to medications or infections, presence of respiratory symptoms, and a history of allergies (asthma, allergic rhinitis).

Furthermore, we also noted that pre-school age (2-6 years) children were more associated with severe course (56.9% required hospital admission, n=62). Some previous studies reported that bradykinin-mediated angioedema (hereditary and ACEI related) was rare but more common in young children. Eur J Pediatr. 2012;171:1339-48.; Pediatrics. 2016; 138 pii: e20160575. However, in this study, we excluded hereditary angioedema and only 2 (0.5%) patients were confirmed as ACEI angioedema. Therefore, we suspect our population were almost allergic (histamine-mediated) angioedema. Although the allergens tolerance would be developed in most children before school age; however, we suggest that allergens exposure should be avoided for pre-school age or younger children. Allergol Immunopathol (Madr). 2019 30. pii: S0301-0546(19)30094-1.; Korean J Pediatr. 2017;60:99-105.; Ann Allergy Asthma Immunol. 2018; 121:313-319. Finally, if the allergic history of patient or family is no proof. In relation to food, allergen-specific IgE, skin prick test (SPT) and provocation test might be benefit for patients. For some medications, it is also possible to verify such a suspicion. We have addressed this information in the section of discussion.

On page 15 line 3: Among the children suffered first attack of angioedema, we found 50.7% of children required hospital stay. Some characteristics of patients would associate more severe course, including co-occurrence of pyrexia or urticaria, etiologies related to medications or infections, presence of respiratory symptoms, and a history of allergies (asthma, allergic rhinitis).
On page 16 line 16: Furthermore, pre-school age children were more associated with severe course (56.9% required hospital admission, n=62). Some previous studies reported that bradykinin-mediated angioedema (hereditary and ACEI related) was rare but more common in young children.[26, 27] However, our population were almost allergic (histamine-mediated) angioedema. Although the allergens tolerance would be developed in most children before school age; we still suggest that allergens exposure should be avoided for pre-school age or younger children. [28-30]

On page 16 line 1: …. Finally, if the allergic history of patient or family is no proof. In relation to food, allergen-specific IgE, skin prick test (SPT) and provocation test might be benefit for patients. For some medications, it is also possible to verify such a suspicion.

2. According to the results of this retrospective study, a recommendation for treatment should be made at the end.

Answer: We appreciate your comments. Finally, we recommend that short-term stays and treatment in the POU might be benefit for patients who did not require hospital admission. The injectable forms of medications (antihistamine and steroid), supplemental fluids and monitoring of vital signs (including the O2 saturation level, allowing the administration of oxygen when needed) could be benefit for angioedema children. We have added this recommendation at the end of manuscript. Please see the section of discussion.

On page 19 line 5: Finally, we recommend that short-term stays and treatment in the POU might be benefit for patients who did not require hospital admission. The injectable forms of medications (antihistamine and steroid), supplemental fluids and monitoring of vital signs (including the O2 saturation level, allowing the administration of oxygen when needed) could be benefit for angioedema children.