

20/08/2022

Re: Manuscript Number: ID

Title: **Hepatic involvement in children with acute bronchiolitis**

Good day

Thank you very much for the comprehensive review and the precious time you spent reviewing this study. We accepted all the comments of the expert reviewers. We did the advised changes and answered the queries. All the changes were marked in red for easy tracking by the reviewer. The manuscript looks much better with these changes, and we tried to improve the language we could and checked by a native speaker reviewer and certificate is attached. Thank you again for your precious assistance.

Here we are replying point by point:

Reviewer 1:

	Reviewer Comments	Authors reply
Reviewer #1	Scientific Quality: Grade C (Good) Language Quality: Grade B (Minor language polishing) Conclusion: Minor revision	Thanks
	This is a good retrospective study highlighting the prevalence of liver involvement in children with bronchiolitis, especially with the paucity of data available on this subject.	Thank you for the kind comments.
	I have some questions regarding the study as outlined here. I have attached the file for the authors, and you can see my comments and edits when you open it in preview mode.	All comments were accepted with thanks. Reply to each comment was attached to the note in the manuscript or added directly to the text and highlighted in yellow.
	Was there a difference in kids with single virus versus multiple virus infections in terms of elevated liver enzymes?	In this study, 13 (7.8%) patients tested positive for more than one viral infection. Accordingly, we reanalyzed the data to find the difference between children with single viral infections and those with multiple infections in terms of mean ALT level using the Mann-Whitney U test. We found no significant difference between the two groups as the mean ALT level was 25 ± 30 versus 23 ± 17 U/L, respectively, ($P=0.872$). This point has been added to the method and results in sections. Thank you.
	Why were the CT scans done?	In this study, two patients underwent abdominal CT scans. Both had an associated underlying disease. The first

		<p>patient was a seven-year-old female who had retroperitoneal neuroblastoma and a CT scan was performed as a follow-up for her previous condition. She had chemotherapy that was stopped years before she had acute bronchiolitis. Her medical condition did not cause a sequela in the liver as her ALT level at the time of admission and on follow-up was normal (22U/L, the normal range is ≤ 41U/L). The second patient was a four-year-old male who was diagnosed with polycystic kidney disease and the CT scan was performed as he was planning for a nephrectomy. His CT report did not show any cystic lesions in the liver and the patient was also admitted with normal ALT (22U/L).</p> <p>This point has been added to the result section. Thank you</p>
	<p>Why? Is that standard of care in these hospitals? AAP recommendations are not these.</p>	<p>In this study, all the patients were managed by steam inhalation and bronchodilators. Unfortunately, we found that bronchodilators are still used in cases of acute bronchiolitis in our hospital despite the that most of the studies, guidelines, and recommendations including that of the American Academy of Pediatrics (AAP) showed that using them was ineffective in reducing the hospitalization rate, oxygen requirement, mechanical ventilation, the duration of illness or hospital stay [Fares et al 2011]. This can be explained by the limited therapeutic options that can be delivered to children with acute bronchiolitis making the physician under pressure of giving inhaled bronchodilators even if they were aware of the recommendations.</p> <p>This point has been added to the discussion section.</p> <p>-Fares M, Mourad S, Rajab M, Rifai N. The use of C-reactive protein in predicting bacterial co-infection in children with bronchiolitis. North Am J Med Sci. 2011; 3(3):152-6. doi:10.4297/najms.2011.3152.</p> <p>Thank you</p>
	<p>Why antibiotics for rsv bronchiolitis? Was there a clinical suspicion for bacterial pneumonia (77%) in the majority of these cases?</p>	<p>We agree with the reviewer that considering the low percentage of confirmed bacterial co-infections (14.6%) in this study, antibiotic use in children with acute bronchiolitis is considered high (77%). However, this is comparable to the previously reported percentage in pediatric patients with severe bronchiolitis (79.9%) [Alejandre et al. 2020].</p> <p>Unnecessary antibiotic use in children with acute bronchiolitis is common due to the challenging differentiation between children with isolated viral infections and those with invasive bacterial co-infections [Alejandre et al. 2020].</p> <p>The antibiotic's prescription was found to be associated with high C-reactive protein (CRP) levels despite the that these high levels could not predict the presence of alveolar condensation on chest X-rays [Desmarest et al. 2017].</p> <p>Some radiological findings of acute bronchiolitis and</p>

		<p>elevated CRP levels might mislead physicians. They might force them to use antibiotics unnecessarily in a viral-induced disease. Therefore, the decision of using antibiotics in children with acute bronchiolitis should be taken based on more rigorous evidence such as positive tracheal aspirate, blood, urine, or cerebrospinal fluid cultures [Isa et al. 2022].</p> <p>These points have been added to the discussion section.</p> <p>Thank you.</p> <ul style="list-style-type: none"> - Alejandre C, Balaguer M, Guitart C, Torrús I, Felipe A, Launes C, et al. Procalcitonin-guided protocol decreased the antibiotic use in paediatric patients with severe bronchiolitis. <i>Acta Paediatr.</i> 2020;109(6):1190-1195. doi: 10.1111/apa.15148. - Desmarest M, Aupiais C, Le Gal J, Tourteau L, Le Coz J, de Paepe E, et al. Value of procalcitonin for infants with bronchiolitis in an emergency department. <i>Arch Pediatr.</i> 2017;24(11):1060-1066. doi: 10.1016/j.arcped.2017.08.023. - Isa HM, Mohroofi AD, Alkhan FN, Hasan AZ, Alkubisi MM, Alhewaizem SS, Khalifa SI, Alromaihi NG. C-Reactive Protein Levels in Children with Acute Bronchiolitis. <i>Int J Pediatr.</i> 2022;2022:1311936. doi: 10.1155/2022/1311936.
	<p>I feel like that could be a major confounder for increasing liver enzymes and these cases cannot be counted purely as bronchiolitis cases.</p>	<p>We totally agree with the reviewer that antibiotic use or the presence of bacterial co-infections might form a confounder for increasing liver enzymes. Yet, most of the patients received antibiotics after they have been tested for liver functions. In addition, upon the comparison between group 1 (high ALT level) and group 2 (average ALT level) in this study, patients with high ALT levels showed no significant difference between the two groups in terms of white blood cell count, platelets count, positive blood and CSF cultures, antibiotic use, complications, PICU admission, mortality. Positive urine culture was the only significant factor that was more frequent in group 1 (P=0.030).</p> <p>Moreover, in this study, children were diagnosed with acute bronchiolitis if they fulfilled the American Academy of Pediatrics criteria. The criteria indicate that the diagnosis is based on signs and symptoms suggesting bronchiolitis including rhinorrhea, cough, tachypnea, wheezing, rales, and increased respiratory effort manifested as grunting, nasal flaring, and intercostal and/or subcostal retractions. Radiographic or laboratory investigations were not routinely used to confirm acute bronchiolitis diagnosis.</p> <ul style="list-style-type: none"> - Silver AH, Nazif JM. Bronchiolitis. <i>Pediatr Rev.</i> 2019;40(11):568-74. doi:10.1542/pir.2018-0260. <p>This part was included in the methods and discussion sections and was considered a limitation of this study.</p> <p>Thank you.</p>

	<p>How were the high and average values defined? What level of ALT is considered average and what was high for the purpose of the study?</p>	<p>High and average values were defined based on the alanine aminotransferase (ALT) level being the best enzyme that reflects liver injury. An elevated ALT level of more than 41U/L was considered high while ALT less than or equal to 41U/L was considered average. This point was added in the method section (statistical analysis) and clarified in Table 3. Thank you.</p>
	<p>10 months is a long period to have a complete recovery from the viral illness. If patients had high or higher ALT levels during follow-up, an alternative cause for this elevation was looked for. Was any new illness ruled out? Kids get viral infections frequently; did you rule out other new infections if Alt was elevated? It could be unrelated to the original infection and contribute as a major confounder</p>	<p>We agreed with the reviewer that a median follow-up of an a10-month-duration (IQR, 2.4-23.3) is long enough for complete recovery from a viral illness like acute bronchiolitis. Looking for alternative causes for ALT elevation is important as a new illness with other viral infection, which is common in children, that is unrelated to the original infection might be the cause. Accordingly, we reviewed our data again and found that the 11 patients who had an elevated ALT on follow-up time were further investigated to exclude other causes of ALT elevation. Of the 11 patients, eight were diagnosed at the time of follow-up with other underlying diseases which could be related to their elevated ALT. Dandy walker syndrome, skeletal dystrophy, and ventricular septal defect in the first patient; tracheomalacia, severe combined immune deficiency (SCID), and hypothyroidism in the second patient; polycystic kidney disease on hemodialysis in the third patient; isolated SCID in the fourth patient; cystic fibrosis in the fifth patient; progressive familial intrahepatic cholestasis in the sixth patient; biliary atresia with cirrhosis and ascites in the seventh patient; and intestinal volvulus with gangrene in the eighth patient. One patient died of unclear cause while two patients had no clear medical cause for raised ALT. This point was added to the result section and was also considered a limitation of this study. Thank you.</p>
<p>Reviewer #2</p>	<p>Scientific Quality: Grade B (Very good) Language Quality: Grade C (A great deal of language polishing) Conclusion: Major revision</p> <p>To start with lots of grammar and language mistakes are there and the manuscript must be revised by a native English-speaking expert.</p> <p>In the abstract, we cannot mention during the era of COVID that RSV is the most common viral cause of lower respiratory tract infections without referring to SARS Cov2</p>	<p>Thanks</p> <p>All the grammar and language mistakes were corrected, and the manuscript has been revised by a native English-speaking expert., through an Editing Company Thank you</p> <p>We totally agreed with the reviewer on the significant impact of the COVID pandemic on the viral causes of lower respiratory tract infections in children. However, this study was conducted between September 1st, 2019, and February 29th, 2020, while the first case of SARS Cov2 infection was reported in Bahrain on the 24th of February 2020 which was at the end of this study. This makes the effect of the COVID pandemic on the results of this study limited. Thank you</p>

	<p>In the methods section, please clarify that PCR was done on what samples???</p>	<p>In this study, PCR was performed on nasopharyngeal swab samples. This point was clarified in the method section. Thank you</p>
	<p>In the results, there was no mention of respiratory distress as a very common presentation of acute bronchiolitis although shown in Figure 2.</p>	<p>We agree with the reviewer that respiratory distress is a very common presentation of acute bronchiolitis. In this study, most of the patients presented with cough (n=124, 74.7%) and other signs of severe respiratory distress such as shortness of breath (n=31, 18.7%), cyanosis (n=8, 4.8%), and tachypnea (n=2, 1.2%). This point was added to the result section. Thank you</p>
	<p>The fever has to be detailed as low-grade fever or high-grade fever</p>	<p>In this study, fever was defined as a rectal temperature $\geq 38^{\circ}\text{C}$ (100.4°F) or axillary temperature $\geq 37.5^{\circ}\text{C}$ (99.5°F). Fever can be calcified into low-, moderate-, high-grade fever, and hyperpyrexia. Low-grade fever ranges between $38.1\text{-}39^{\circ}\text{C}$ ($100.5\text{-}102.2^{\circ}\text{F}$) while high-grade fever is between $40.1\text{-}41.1^{\circ}\text{C}$ ($104.1\text{-}106^{\circ}\text{F}$) rectally. In our hospital patient's temperature was measured rectally if the patient's age was below one year or axillary in those older than one year of age after adding 0.5°C to the measured temperature. In this research, we looked at the presence or absence of fever as a clinical presentation, but we did not specify the degree of fever as this was not the aim of this study. This point was added in the methods and the study limitation sections. - Ogoina D. Fever, fever patterns and diseases called 'fever'--a review. J Infect Public Health. 2011;4(3),108-124. https://doi.org/10.1016/j.jiph.2011.05.002 Thank you</p>
	<p>A panel test including IgG and IgM for Legionella and Mycoplasma and Coxiella cannot be designated viral serology profile.</p>	<p>We agreed with the reviewer that Legionella, Mycoplasma, and Coxiella cannot be included as viruses since they are considered as bacterial microorganisms. So, the panel test's name was modified to become a 'microbial serology profile' to include all the microorganisms. This point was changed in the Methods, Results, and Discussions sections. Thank you</p>
	<p>What antibiotics and antipyretics are given to these patients?</p>	<p>In this study, most patients received antibiotics (128/166, 77.1%). The antibiotics were cefotaxime (n=61, 46.9%), ampicillin (n=47, 36.1%), gentamycin (n=20, 15.3%), ceftriaxone and clindamycin (n=9, 6.9% each), amoxicillin/clavulanic acid (n=8, 6.1%), vancomycin (n=7, 5.3%), clarithromycin (n=5, 3.8%), metronidazole, meropenem and ceftazidime (n=4, 3.1% each), piperacillin/tazobactam (n=3, 2.3%), and ciprofloxacin, rifampicin and sulfamethoxazole/trimethoprim (n=1, 0.7% each). Some patients received a combination of antibiotics.</p>

		<p>Paracetamol was the antipyretic used in these patients as syrup, suppositories, or intravenous, and rarely ibuprofen was used.</p> <p>This point was added in the result section.</p> <p>Thank you.</p>
	<p>Could they be a cause for impaired liver function?</p>	<p>Although some antibiotics and antipyretics can cause impaired liver functions. However, all the patients in this study were tested for liver functions at presentation even before any medications were given to them.</p> <p>This point was added in the discussion section.</p> <p>Thank you.</p>