

## Peer Review File

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### Reviewer Comments

**Comment 1:** The authors say in the abstract “Drug-induced liver injury (DILI) is a common adverse reaction during drug use”. However, for most drugs, idiosyncratic hepatotoxicity is a rare adverse reaction.

**Reply 1:** we have modified our text as advised (see line 26)

Changes in the text: We replaced the sentence.

**Comment 2:** The authors say that “Liver damage and SJS caused by ibuprofen are common clinical adverse reactions”. The authors should include more information speaking of the relevance, such as general incidence rate and/or number of previously reported cases of ibuprofen-induced SJS and acute hepatitis.

**Reply 2:** we have modified our text as advised (see line 31)

Changes in the text: We delete this sentence.

**Comment 3:** The sentence “The liver function indicators...by using the drug again” is confusing and should be rewritten.

**Reply 3:** we have modified our text as advised (see line 31)

Changes in the text: We have rewritten this sentence.

**Comment 4:** The introduction does not contain sufficient background information to give readers some baseline of familiarity with the suspicious drug (ibuprofen) and the conditions described (SJS and DILI).

**Reply 4:** we have modified our text as advised (see line 44-57)

Changes in the text: We read the relevant literature and supplemented the link between ibuprofen and disease.

**Comment 5:** The authors state that (ibuprofen) “is considered to be one of the safest analgesics with minimal side effects”. This sentence should be rewritten.

**Reply 5:** we have modified our text as advised (see line 46-47)

Changes in the text: We have rewritten this sentence.

**Comment 6:** The authors should mention the pertinent past medical history.

**Reply 6:** we have modified our text as advised (see line 68-70)

Changes in the text: We added past history.

**Comment 7:** Please clarify if the authors know when the patient started the medication, dose, frequency, for how long and time since the last ibuprofen intake.

**Reply 7:** we have modified our text as advised (see line 74-75)

Changes in the text: We clarified the use of ibuprofen.

**Comment 8:** The authors should refer the reader to table 1, since the values of bilirubin,  $\gamma$ -GT and bile acids are indicated there.

**Reply 8:** we have modified our text as advised (see line 77-81)

Changes in the text: We added the liver index in the table.

**Comment 9:** The follow up laboratory tests are quite complete and reveal improvement of liver injury after discontinuation of ibuprofen intake. However, knowing the liver profile predrug (baseline) would be interesting.

**Reply 9:** Ibuprofen is a very common treatment option for fever reduction. In the early stage, we cannot predict that it will cause liver damage, so we cannot monitor the early liver condition.

Changes in the text: None

**Comment 10:** The authors did not exclude acute hepatitis E. It should be done if possible, because hepatitis E can masquerade DILI.

**Reply 10:** We did relevant antibody tests and ruled out hepatitis.

Changes in the text: None

**Comment 11:** The authors should discard the presence of hypersensitive factors too. Eosinophil count in the peripheral blood and IgG tests are important to discard autoimmune disease.

**Reply 11:** Eosinophils were checked on admission and there was no high level of eosinophils.

Changes in the text: we have modified our text as advised (see line 111-112)

**Comment 12:** In the text (lines 88-90), the authors state that "Abdominal magnetic resonance imaging (MRI) revealed that: the liver was slightly enlarged, and the gallbladder was enlarged". What was the date of this MRI? Is there an MRI before ibuprofen intake? How the authors know liver insufficiency is related to DILI episode? Please clarify.

**Reply 12:** The MRI test was performed after the child was transferred to our

hospital, July 13th.

Changes in the text: We added the date (see line 100).

**Comment 13:** In the text (line 107), the authors state that "...the patient was discharged after the condition had gradually stabilized.". It is not clear if liver enzyme levels returned to baseline levels spontaneously or due to discontinuation of medication or other treatments. Please clarify.

**Reply 13:** we have modified our text as advised (see line 118-119)

Changes in the text: We clarified the child condition had gradually stabilized in our treatment.

**Comment 14:** The references 3 and 4 are not the most convenient to support the occurrence of SJS after taking nonsteroidal drugs, sulfa drugs, penicillin, allopurinol, and anticonvulsants, since reference 3 talks about SJS and doxycycline and reference 4 talks about SJS and EBV.

**Reply 14:** In reference 3, we elaborated on the possible causes of SJS, trying to find a basis between non-steroidal anti-inflammatory drugs and SJS. Also, I have read the editor's recommended references, but I think we are not trying to explain the relationship between SJS and DILI, but that the child has liver damage and skin disease (SJS) after taking ibuprofen.

Changes in the text: We removed reference 4

**Comment 15:** Line 124-125: The sentence "According to the time...can be excluded" is confusing. Is it referred to ibuprofen or the sentence about SJS?

**Reply 15:** we have modified our text as advised (see line 135-137)

Changes in the text: We have rewritten this sentence.

**Comment 16:** Information in line 131, "Interleukin 2 (IL-2), interleukin 5 (IL-5), and interleukin 13 (IL-13) may also participate in the skin immune inflammatory response of this disease.", should be accompanied with some references.

**Reply 16:** This sentence is not very closely related in this article.

Changes in the text: We deleted this sentence.

**Comment 17:** Lines 140-141. The sentence "There is a clear correlation between HLA-B\*5801 and the severe skin reaction caused by related drugs, and this correlation is race-specific and specific" is confusing and should be rewritten.

**Reply 17:** This sentence is not very certain.

Changes in the text: We deleted this sentence.

**Comment 18:** Lines 146-148. The authors state that “There is a correlation between SJS caused by nonsteroidal anti-inflammatory drugs and HLA-A2 and HLA-B12, but studies investigating this correlation are rare”.

**Reply 18:** This sentence is not very certain.

Changes in the text: We deleted this sentence.

**Comment 19:** The paragraph “In this case, the patient...individualized drugs” (lines 148-153) should be rewritten

**Reply 19:** we have modified our text as advised (see line 152-154)

Changes in the text: We have rewritten this sentence.

**Comment 20:** The authors might want add more recent progress on DILI knowledge, related to DILI definition, categories and severity. In line 104, the authors say that “...and cholestatic liver caused by drug damage.”, but there is no information about cholestasis in the report. Moreover, the authors did not say if the patient showed mild, moderate, severe or fatal DILI. The definition of DILI in line 155 is not totally correct.

**Reply 20:** we have modified our text as advised (see line 159-167)

Changes in the text: We have rewritten this paragraph.

**Comment 21:** Information in line 157, “Among liver diseases in China, the incidence of DILI is...”, should be accompanied with some references.

**Reply 21:** The incidence of DILI in our country is a review in Chinese, and the citation is in Chinese. In order to avoid unnecessary trouble, deleting this part of the content has little effect on the full text.

Changes in the text: We delete this part.

**Comment 22:** In lines 163-165, the authors state that “infections such as hepatitis virus, cytomegalovirus, and rubella virus antibody were excluded, as were autoimmune diseases”. However, there are no eosinophil count in the peripheral blood and/or IgG and/or autoantibodies analysis to discard autoimmune disease.

**Reply 22:** We supplemented the data of eosinophils and IgG in the previous article, and excluded autoimmune diseases.

Changes in the text: None

**Comment 23:** In Line 166, the authors say that “According to the adverse

reaction scoring principle of Naranjo's evaluation scale (11), the child's score information was 7 points, which determined the causality as "probable."

**Reply 23:** We cannot tamper with the diagnostic score made by the doctor in our hospital at will. If the editor finds it unreasonable, we delete this score.

Changes in the text: we delete this sentence.

**Comment 24:** Lines 171-174. The authors state that "For example, HLA-B\*5701 alleles are related to liver damage caused by amoxicillin/clavulanic acid, and HLA-DRB1\*1501 alleles are related to drug-induced liver damage caused by flucloxacillin (15,16)". This information is incorrect. Currently, the strongest association observed between an HLA allele and DILI concerns HLA-B\*57:01 and flucloxacillin

**Reply 24:** we have modified our text as advised (see line 175-178)

Changes in the text: We have rewritten this sentence.

**Comment 25:** Reference 17 talks about HLA alleles association with acetaminophen-related SJS, but there is no information about ibuprofen DILI and its associations with HLA alleles. Please rewrite (lines 174-177).

**Reply 25:** I am confused that I am not explain about ibuprofen DILI and its associations with HLA alleles. I mean whether the allergic reactions and liver damage caused by ibuprofen are related to the HLA-B gene still needs further research

Changes in the text: None

**Comment 26:** Lines 177-179. The authors state "After detecting...with HLA-B\*58:01". This sentence should be rewritten. It is still unknown if the allele has associations with DILI and/or SJS.

**Reply 26:** we have modified our text as advised (see line 183-184)

Changes in the text: We have rewritten this sentence.

**Comment 27:** Lines 190-192 should be rewritten. Although HLA-B\*57:01 genotyping prior to abacavir prescription has been mandated by the FDA as well as the EMA due to its high negative predictive value, genetic polymorphisms associated with DILI are not being used as predictive biomarkers, since their positive predictive value is usually low. However, it would be interesting to use them in cases where drugs known to induce DILI are the only available treatment.

**Reply 27:** we have modified our text as advised (see line 192-193)

Changes in the text: We have rewritten this sentence.

**Comment 28:** The reference 18 is incorrect. The correct reference is [Mallal, S.; Phillips, E.; Carosi, G.; Molina, J.M.; Workman, C.; Tomazic, J.; Jagel-Guedes, E.; Rugina, S.; Kozyrev, O.; Cid, J.F., et al. HLA-B\*5701 screening for hypersensitivity to abacavir. N Engl J Med 2008, 358, 568-579, doi:10.1056/NEJMoa0706135]. The reference [Faruki H, Lai-Goldman M. HLA-B\*5701 screening for hypersensitivity to abacavir. Per Med. 2008 May;5(3):297-300. doi: 10.2217/17410541.5.3.297] is an evaluation of the abovementioned article.

**Reply 28:** we have modified our text as advised (see line 268-269)

Changes in the text: We have rewritten this sentence.

**Comment 29:** Table 2. Information of results of HLA-B\*1502 genotyping and the reason for this test should be clarified in the text.

**Reply 29:** We don't want to explore the HLA-B\*1502 genotyping, which is not the focus of this article.

Changes in the text: We delete this result

**Comment 30:** Figure 2. The figure should indicate the dates when patient started and stopped taking the suspected medication (ibuprofen), since this information is not clear in the text and it is really important for SJS and DILI diagnosis.

**Reply 30:** we have modified our text as advised (see line 277-278)

Changes in the text: We have added relevant instructions.

**Comment 31:** The wording of the text is not totally correct. Some abbreviations and their meanings are not indicated in the text.

**Reply 31:** we have modified our text as advised (see Page xx, line 28 - 50)

Changes in the text: We added acronyms and revised the entire article.