Responses to the reviewers.

Dr. Lim and colleagues report an example of the difficulties in adjudication when more than 1 drug is potentially causal. In this case, a 12-year-old boy is treated with multiple courses of different antibiotics over a period of a few weeks. He is hospitalized and several days after having received amoxicillin, ceftriaxone, vancomycin, ampicillin/sulbactam, and steroids along with a course of clindamycin following discharge, he develops fever, fatigue, headache, and dark urine 5 days after discharge. There is evidence of hepatic injury with elevations in ALT to more than 10 times normal, AST about 3 times normal, and alkaline phosphatase just above normal with a total bilirubin of 3 times normal, mostly direct. A search for various viruses and other infectious causes are negative and over the course of the next several days, liver enzymes show a continued rise in bilirubin and alkaline phosphatase with peripheral eosinophilia. Total bilirubin reaches a peak of nearly 12 mg. No coagulopathy or encephalopathy are present. An MRCP is normal. Forty-eight days after the illness begins, a liver biopsy is performed, which showed changes of cholestasis and mild chronic inflammation and portal fibrosis. Over the course of the next 5 months, jaundice and pruritus improve more than 50%.
The authors state that clindamycin, being the last antibiotic given, may have been responsible for this event. They subjected clindamycin and the other antibiotics to the various causality assessment scales including RUCAM, MV, and the Japanese DDW-J scale. They report that all of the antibiotics involved were either possibly or probably related except for amoxicillin, which showed a low score in the MV clinical diagnostic scale. As a result, they are unsure as to which drug may have been the offending agent, which raises important questions as to how to treat this child in the future for an infection using any of these antibiotics.
I have a number of questions and comments regarding the manuscript.

(1)It would be useful if the authors would provide a detailed strategy that they would employ to reintroduce any of these suspect antibiotics should this (or another child) require antimicrobial therapy. Since this child was exposed to a number of very common antibiotics, what would they specifically suggest in the future to avoid a rechallenge situation where an allergic type reaction could be precipitated?

Response from authors:
We advise this patient against using Clindamycin unless there is no available substitute of this antibiotic for the particular future infection the patient may have.

(2)The authors note that in the DDW-J scale in Japan, a drug lymphocyte stimulation test is utilized. However, an LST is neither sanctioned by the FDA nor available in the United States. Was, in fact, this test performed in their patient? If so, what were the results? A much more complete discussion of the pros and cons of the LST should be provided, especially given the fact that the reproducibility and accuracy of the test outside of Japan has been called into question.

Response from authors:

The test was not performed in this patient.
Pros: The pros of LST is that we will have a clue which drugs would be the prime candidate causing the reaction and the information could be used as a guide for an avoidance of the suspected drug.

Cons In theory LST is the ideal and objective way to understand the immunologic response to the offending drug; however many reactions are idiosyncratic, so the same drug(s) may not cause the same reaction in the future.

(3)The authors provide a rather brief discussion of DILI related to the various antibiotics used in this patient. There literature review would best be limited to the pediatric age group if such reports can be found. They include case reports of amoxicillin, ceftriaxone, vancomycin, and ampicillin sulbactam, but only 2 instances of clindamycin (References 20 and 21) are both in adults. Are they able to describe any pediatric cases that would support their contention?. Did they search the LiverTox database of the National Library of Medicine or the FDA AERS database for additional informationon these agents in the pediatric age group? Isolated case reports in older adult patients with underlying systemic diseases may not be as useful as cases in the pediatric population, such as those reported from the DILIN network by Molleston, et al, which they have mentioned.

Response from authors:

It is true from the work of Molleston et al about isolated cases in the adult cases may not reflect on the clinical aspect in children. Although the reports in pediatric cases were limited, there was a recent pediatric report comparing several antibiotic use with a focus on hepatic injury. Maraqa et al reported reported a 13 year old child with clindamycin related DILI. The time to onset was 17 days and time to resolution was 10 days. As for LiverTox database it only speaks of case reports in adults for hepatic toxicity from clindamycin. The rest of journal articles only relate hepatotoxicity to clindamycin in adult patients which are added in the manuscript nonetheless.

Serranti D, Montagnani C, Indolfi G, Chiappini E, Galli L, de Martino M. Antibiotic induced liver injury: what about children? J Chemother. 2013;25:255-72.

Maraqa NF, Gomez MM, Rathore MH, Alvarez AM. Higher occurrence of hepatotoxicity and rash in patients treated with oxacillin, compared with those treated with nafcillin and other commonly used antimicrobials. Clin Infect Dis. 2002;34:50–4.

(4)Has this patient required further antibiotics? If so, which one was chosen and what was the result?

Response from authors:

Fortunately the patient did not require further antibiotic use or the need to be on clindamycin again.

(5)Do the authors recommend allergy testing in this situation with or without desensitization procedures so that this child or those in a similar situation may be able to be retreated without risk of injury in the future?

Response from authors:

We did obtain allergy consultation on this case. Currently we do recommend to hold off the use of clindamycin unless indicated. Unfortunately, even for IgE mediated drug allergy testing is very limited, and for this kind of situation there is not any testing that would be helpful given most likely idiosyncratic mechanism in nature. When we look at cases like this, all that can be done to consider which drugs are more likely to have this type of side effect, and then proceed cautiously. However for an idiosyncratic reaction, it is unpredictable as the same drug(s) may not do the same thing in the future.

(6)The authors touch on the fact that there is no pathognomonic diagnostic test for DILI from any specific agent causing idiosyncratic injury. Whether or not pharmacogenetics, biomarkers, et cetera will allow for an accurate diagnosis in the future remains to be seen.

Response from authors:

We agree with this. This matter will be frustrating to a clinician caring for any child with DILI from multiple drug administration.

(7)The main thrust of their paper is that the existing causality assessment scales are not able to differentiate between multiple potential causes of DILI, especially when they are given back to back and even repetitively. The old adage that the last drug before an event is the one that may be responsible may be more of a coincidence than anything else. The authors state that they felt clindamycin was the most likely cause in the patient. It would be useful to know if their pediatric hepatologist agreed with this assessment and what additional reports exist with clindamycin in a pediatric population as noted above.

Response from the Authors:

We have to agree that the conclusion on the offending drug in this report is still inconclusive. By looking at the rest of drugs he used the proportion of report and the frequency of drug use in clinical setting make clindamycin more highly suspected than others.

Yes Dr. Wikrom Karnsakul is the senior author and pediatric hepatologist of this manuscript. The case was also discussed with senior hepatopathologists at our institution and consulted to

some DILIN experts. As Pharmacia / Upjohn Package Insert reported jaundice and elevated hepatic enzymes from systematic use of clindamycin.

(8)In the case report, 2nd paragraph beginning with “Over 5 days after the hospital discharge”, line 12, the sentence beginning 3 days later is confusing. Does this mean after 2 weeks have already elapsed or is this 3 days after admission? The authors need to clarify this so that the time line is more easily understood.

Response from the Authors:

We meant by this sentence was 3 days after his admission into Emergency Department where he was brought five days after discharge. The sentence has been mended to be more representative of what we meant in the new draft.

(9)The longer term outcome of this case needs to be provided since we are only told that improvement was 50%. It is well known that cholestatic injury generally takes longer to recover than does hepatocellular injury and a number of antibiotics are associated with the vanishing bile duct syndrome, which was not present in this case at 48 days after the illness began when the liver biopsy was performed, but the final outcome should be recorded.

Response from authors:

A follow up at 4 years after the presentation the patient resolved from jaundice and hepatocellular injury.