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ESPS PEER-REVIEW REPORT

Name of journal: World Journal of Hepatology
ESPS manuscript NO: 31751
Title: Emerging concepts in alcoholic hepatitis
Reviewer's code: 02530787
Reviewer's country: United Kingdom
Science editor: Fang-Fang Ji
Date sent for review: 2016-12-06 18:44
Date reviewed: 2016-12-13 18:16

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
[ ] Grade A: Excellent	[Y] Grade A: Priority publishing	Google Search:	[ ] Accept
[ ] Grade B: Very good	[ ] Grade B: Minor language polishing	[ ] The same title	[ ] High priority for publication
[ ] Grade C: Good	[ ] Grade C: A great deal of language polishing	[ ] Duplicate publication	[ ] Rejection
[Y] Grade D: Fair	[ ] Grade D: Rejected	[ ] Plagiarism	[ ] Minor revision
[ ] Grade E: Poor		[Y] No	[Y] Major revision
		BPG Search:	
		[ ] The same title	
		[ ] Duplicate publication	
		[ ] Plagiarism	
		[Y] No	

COMMENTS TO AUTHORS

Overall the language is good and it is reasonably well written. It covers nearly all the current and relevant literature on the topic. However, the discussion is often superficial and does not highlight the deficiencies in the literature and what specific issues future studies should address. In addition, much of the introduction and pathophysiology discussion revolves around alcoholic cirrhosis rather than AH specifically and may not be relevant to AH. The following points should be addressed: 1. More detailed discussion and critical evaluation of the literature is required throughout. Please relate your discussion to the title: "Emerging concepts". 2. The introduction needs improvement. Most of it refers to alcohol related liver disease and alcoholic cirrhosis rather than AH which should be clarified. It should also correctly define AH as a clinical syndrome of recent onset jaundice and coagulopathy in a person who has been a heavy drinker usually for more than a decade (see Lucey, NEJM 2009). It is not only the histological change referred to in the introduction which is alcoholic steatohepatitis. The trigger for AH is unknown and not only related to heavy alcohol consumption as described: "AH is induced by average daily alcohol use > 80 grams for more than five years". 3. Remove figure 1: this does not contribute anything in addition to the text. 4. In the pathophysiology section on page 5 TH-1

should be defined. 5. The pathophysiology section should also comment on the immune dysfunction documented in AH including defective monocyte function (Vergis, Gut 2016) and monocyte/T cell signalling (Markwick, Gastroenterol 2015). 6. Risk factors for development of AH. This section provides evidence of risks for development of progression of alcoholic liver disease not AH. This should be clarified. It would be preferable to alter this section to only discuss the risk factors for AH which are less well documented and include obesity, gender and ethnicity as well as quantity of alcohol consumption. 7. Diagnosis section (page 10). 25-30% require biopsy – reference needed to support this. It is not consistent with the UK experience of AH. 8. Abstinence section (page 14). Mention that none of the medications discussed have been trialled in the context of AH and few in patients with advanced chronic liver disease. More detailed discussion of these treatments and the limitations of the published studies would be useful. 9. Nutritional supplementation section (page 15). The recent meta-analysis (Fialla, Liver Int 2015) only included 3 small studies in patients with AH and did not have a separate analysis for this subgroup. The overall data they provide is of low quality. This should be commented upon. 10. Corticosteroids (page 16): "Corticosteroids decrease the inflammatory process by suppressing transcription factors nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB) and activator protein 1 (AP-1)". The mechanism of action of corticosteroids is much more complex than described in this sentence. Corticosteroids have wide ranging immune modulatory functions including suppression of these pro-inflammatory transcription factors. 11. Corticosteroids (page 16). The Rambaldi and Mathurin meta-analyses are out of date. Include the updated ones instead: Singh, Gastroenterol 2015 and Thursz, AASLD abstract 2016). 12. Corticosteroids (page 16). Discuss findings of STOPAH trial in this section. 13. Corticosteroids and pentoxifylline (page 17). Specifically comment on the Mathurin, JAMA 2013 study. 14. Immune modulations (page 20). Correct subtitle to read Immune Modulators 15. ELAD (page 23). Comment on specific disadvantages of ELAD (cost, access, patient selection). 16. Conclusions (page 25). This summary paragraph is weak and generic. It should explain what the authors feel is the future of the management of AH and relate it to the title "Emerging concepts in AH". Are we going to be using novel single target

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ESPS PEER-REVIEW REPORT

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		[ ] Plagiarism	
		[Y] No	

COMMENTS TO AUTHORS

Nice attempt but some limitations and concerns as highlighted below: 1. Introduction: Should highlight more on AH disease burden data rather than alcoholic liver disease 2. Pathophysiology section also should also highlight more on AH and also author may consider to shorten this section as seemingly this is too redundant and long. 3. Risk factors: I think authors again discuss risk factors which predispose to ALD. It should be recognized that the risk factors for development of AH are not well known. There are two recent papers on protection from AH among dinkers with increased coffee consumption and increased risk with PNPLA3 polymorphisms. 4. Diagnosis: Statement that this is a clinical diagnosis seems too strong. Authors may like to give clinical definition of this syndrome and provide data on accuracy of clinical diagnosis. Paper from US on the NIH consortia data earlier this year in Gastroenterology provides the approach to clinical diagnosis of AH and this should be highlighted. 5. One of the most controversial issues in AH management is on liver transplantation and this section seems too short for this review if the focus of the review is AH. Authors are expected to review the literature on this (3 papers in last 12 months in AJT, LT, and Annals of surgery) in addition to two other papers in Hepatology 2012 and NEJM 2011. 6. I like to

section on biomarkers and predictors of AH (metabolomics data). 7. Section on new targets seems appropriate and well covered (table with existing and potential new therapies will be useful for readers)

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COMMENTS TO AUTHORS

The manuscript entitled "Emerging Concepts in Alcoholic Hepatitis." by Phoenix Fung and Nikolaos Pyrsopoulos is an excellently written concise review about the understanding of the pathogenesis, natural course as well as current and future therapeutic options. This review article on this distinct acute manifestation of alcoholic liver disease should be published with high priority. Alcoholic hepatitis is a severe complication of alcohol abuse still having a high mortality rate. For developing adequate therapeutic measures it is crucial to understand the complex pathophysiology of this disease entity. Controversy exists about the best therapeutic strategy in addition to the essential abstinence from alcohol. Recently, several clinical trials with different therapeutic strategies have been conducted to shed light on this controversial subject. Especially the question about the evaluation of these patients for liver transplantation is highly controversial. The submitted manuscript by Phoenix Fung and Nikolaos Pyrsopoulos covers these issues in an excellent manner. There are only minor concerns: 1. For non-Anglo-American readers it would be useful to give the critical amounts of alcohol intake also in International System units e.g. in milliliters for the size of a standard drink. It would also be helpful to add the alcohol content in grams in figure 1 or in the

subsequent paragraph. 2. In the section preceding Figure 3 the complex mechanisms how ethanol induced ER stress leads to the mitochondria related hepatocyte apoptosis should be explained a little more in detail. The term "mitochondrial ER stress" is somewhat misleading. 3. In the section on genetic risk factors for the development of alcoholic hepatitis (after references 51 and 52) Acetaldehyde dehydrogenase gene polymorphisms are meant. 4. In the part on new therapeutic options I would prefer if ELAD is listed after the pharmaceutical options. 5. On the end of this comprehensive review the conclusion could be more detailed including the key concepts of every part of the review.