ACUTE LIVER FAILURE SPECIALIST INTEREST GROUP MINUTES OF MEETING
Thursday 18th July 2019

Present:	Dr Banwari Agarwal Dr Jennifer Ryan Dr Joanna Moore (Secretary) Dr. Juan Acevedo Dr Kenneth Simpson Dr. Louise China Dr Mansoor Bangash Dr N. Snook Dr Steve Masson Dr Victoria Snowden Professor William Bernal (Chairman) Professor Rajiv Jalan Professor Clare Selden
Apologies:	Dr Mhairi Donnelly

		Actions
Item1	**Welcome and Chairman's introductions** There was a welcome and introduction from the Chair **Minutes of last meeting/matters arising** The last minutes were agreed as accurate, although some SIG members had not received them so they will be recirculated with these minutes.	
Item 2	**Objectives for the meeting** Objectives were presented for the meeting by WB Observations from the Royal Free were then presented by Dr. Faisal Sheikh with oversight from JR. 2008 to 2017 outcomes were presented. The main cause of death was multi-organ failure (20/25 patients). 5/25 patients (20%) died from cerebral oedema. It was found that our traditional prognostic criteria performed well with 80% overall survival in those patients that did not meet the meet the poor prognostic criteria (N=54)	

Item 3	**Reports/Updates to the SIG**	

A. **Activity audit (WB)** - deliberately a limited data set was provided. N = 78 from the centres who submitted data. It was found that outcomes for Paracetamol overdose were inferior to other outcomes which were not in keeping with previous data. Less than 10% of the ALF patients secondary to Paracetamol overdose were transplanted. There was 12% mortality in POD induced acute liver failure who did not meet criteria and 60% in those that did. With annual extrapolation we would expect to see 117 cases of Paracetamol induced acute liver failure nationally, second would be other drug induced liver injury at 33 cases, and other causes at 27 cases. We would expect 15 cases secondary to viral causes.

39 patients with non-POD induced liver failure presented. 94% specificity and 25% sensitivity was found for these patients meeting criteria excluding transplant cases which compares to 86% specificity and 60% sensitivity for those patients with Paracetamol induced acute liver failure.

The aetiologies were as expected amongst the transplant centres. There was some discussion about whether we should look to transplant more of the Paracetamol overdose ALF given their outcomes. There is encouragement to continue collecting data nationally. Professor RJ raised the question of NIHR funding for an on-going registry.

B. **Plasma exchange update (JM and MB**)

It was noted that we now have a national agreed set of variables to collect. Data was submitted from Leeds, Kings, Royal Free and Birmingham. Given the recent submission of this data, a full data analysis has not been present at this current time, but provisional data was presented. N = 100. There was a ratio of 68 v 32 for patients with Paracetamol induced acute liver failure comparatively to non-POD cases. The survival curves were as expected. Questions we would look to answer which are currently not standardised amongst units are which replacement fluid is best, whether low or high volume PEX is sufficient, which aetiologies have better outcomes, the number of plasma exchanges which would be beneficial and we would also want to look at outcomes including the frequency of infection, inflammatory markers change, biochemical change and other patient specific outcomes including whether they spontaneously survived, died or were transplanted, length of stay and ITU stay and organ failure scores including APACHE and SOFA scores. We need to match the data with controlled non-PEX data. Ideally using patients who have met Kings College criteria, similar organ failure scores on admission, similar aetiologies and demographics over a similar time frame. Ideally we would need 100 patients to match the 100 controls. It is not possible at the moment for Edinburgh to submit patient's data with plasma exchange, and therefore this could be a possibility with regards to submitting control data Leeds already

	has some control data which would fulfil these criteria. All centres were encouraged to participate if they wished and can contact the sub-groups. C. **ICP monitoring (MB)** a Again although centres had submitted data, this was only recently and so it was not possible to fully analyse this at the moment. Data was presented from 2008 to 2018. There were 250 patients currently, but Leeds will also have ten year data which they are hoping to submit shortly. 14% of the 250 patients received ICP monitoring. 31% overall were transplanted and 6% had a cerebral mortality. It was noted the rate of Bolt insertion has decreased nationally. It was felt there were three suspected complications associated with Bolt insertion. Dr. KS commented that we need a comparator of cerebral deaths in patients who are not bolted. Professor RJ raised a question whether we could develop surrogates that we could use for raised ICP. Some centres are using reversed jugular catheters but not many. The SIG would aim to provide recommendations including recommendations of the sequence of investigations and also possible triggers.	
Item 4	**Intervention study proposals** <u>Angiotensin 2 (MB)</u> It was noted that vasoplegia is common in patients with Acute Liver Failure and Angiotensin 2 has been shown in the literature to decrease vasopressor requirements. Acute Liver Failure is associated with vasodilatory shock. The proposal is to give Angiotensin 2 v placebo. A non-inferiority trial design could be proposed and outcomes investigated. We would need to prove this does not do any harm in this group of patients. <u>Albumin (MB)</u> The SAFE study and ALBIOS were both referenced. It was also noted that Albumin has affects in an immune modulatory capacity, in addition to the circulatory affects seen in the SAFE study and ALBIOS study. This was the rationale for proposing its use. The aim would be to maintain the serum Albumin greater than 30g per litre, and there were thoughts that this results in a more rapid resolution of shock. It was commented that this would be a difficult to study to power. Surrogate outcomes could be investigated including the SOFA score. We could consider doing this on a multi-centre basis for example in Europe and Asia which would increase the power. <u>Nutrition/Ammonia (WB)</u> It was noted that ammonia correlates with outcomes in acute liver failure. We can look to lower this in the circulation and on a cerebral level by increasing uptake or decrease in metabolism. The ESPEN guideline has proposed deferring protein support for 24 to 48 hours in the context of hyperammonemia.	

	It was proposed that we could do a randomised controlled trial looking at early enteral feed as opposed to delayed enteral feed in hyper acute liver failure. The primary outcome could be to look at the ammonia levels at 48 hours and the secondary outcomes to include, for example, length of stay, sepsis, intracranial events. The hypothesis would be that by lowering the enteral protein load, this is associated with lower ammonia concentrations at the time of maximal hepatic insufficiency. It was presented that this is a real clinical issue, is a relatively straightforward study to do, with minimal risk. The cons are that amongst all the units we would have to ensure standardised feed, and also a common method of measuring ammonia. It was commented that some centres use point of care ammonia e.g.Fujifilm but not all centres do and there has been some discussions as to reliability of point of care measurements. <u>Haemofiltration (WB)</u> The literature was presented on looking at rates of CVVH. It is known that ammonia clearance is linked with filtration rates. The hypothesis is that if you increase the rate of filtration this will be associated with lower ammonia levels and therefore better outcomes. The proposition was if the ammonia is greater than 100 then there would be standard medical therapy plus continued filtration, 25mls per kg per hour v 45mls per kg per hour. The primary outcome would be looking at the change in ammonia at 24 hours and the secondary outcome would be looking at length of stay, sepsis and again intracranial events. The pros are that this is a relatively simple study to undertake. The cons would include standard filtration technology would be needed and again standard ammonia measurements. It was also noted that we have centre differences in that the Royal Free stops CVVH when PEX is given and other centres may not. Kings for example do PEX and CVVH at the same time. Professor RJ proposed that perhaps the two studies could be amalgamated and ammonia could just be checked at for example three different time points, and at that time, the feed and CVVH rate etc could be recorded. Professor RJ also offered to try to source a point of care ammonia testing machines for the transplant centres. <u>Edinburgh Proposal - surviving ALF</u> Dr KS provided a summary of the Surviving Acute Liver Failure data from Edinburgh. The aim would be to develop a protocol and we would expand to centres in England. Costings could then be obtained after	RJ KS

	developing the protocol from NHS Digital. It is felt that we would just need the NHS number and diagnosis for the patient. It was remarked that the only other countries that can currently do this study would be inScandinavia. Dr. KS will send the protocol through to SIG members and interested parties. KS also delivered an update on the Red Cap registry. Data has only been submitted unfortunately by three centres (Edinburgh, Leeds and Kings). He has offered that a Fellow should be joining in Edinburgh and could come to other centres if they wish and collect the data. We can then obtain a snapshot across the UK of one year. KS also mentioned about bio-banking and data collection. We would consider a flagship project eg GWAS perhaps in post-transplant patients with acute liver failure.	
Item 5	**Observational proposals** This was an informal discussion about observational study proposals. BA mentioned that perhaps we would look at the CLIF SOFA score through KS's 12 month snapshot data. VS proposed gauging opinion from referring centres with regards what they find difficult, e.g. fluid balance, antibiotics etc. This could help us with directions for future guidelines. VS will explore this further with a questionnaire. JR raised the proposal of looking at anti-fungal use amongst the transplant centres. We understand this is variable. We could look at rates of fungal sepsis and also look at non-invasive markers such as Beta D glucan. We would look to develop guidelines for sub-acute, acute liver failure etc. JM raised the proposal of looking at the CT volumetric data. This is with a view to validating WB's work looking at predicting outcomes for patients with liver failure based on their CT volumetrics. JM mentioned that she has spoken with the radiologists in Leeds and they have said that they are happy to review all scans from interested centres. They have explained that it should be possible for local centres to anoymise their cases locally before putting them on CD, either as one patient per CD or multiple patients on one CD depending on the local centre's system.	VS
Item 6	**Any Other Business** WB summarised the key discussions from today. We would aim for the activity audit, plasma exchange and ICP monitoring sub-groups to have finished data and be starting to write reports by the time of the next SIG meeting. Control data is required. We will aim to draft a guideline about ICP monitoring. Pitches will be refined for the intervention study proposals and then	

	recirculated. Centres will score their preferred proposals and can declare their interest. We would then look to develop one of these pitches. Similarly interest in the observational study proposals can be expressed to the individuals pitching them. Professor RJ commented that he potentially has extendable ethics to other centres with regards bio-banking.	WB/MB ALL
Item 7	**Date of the next meeting** The date of the next meeting will be planned for December. Hosts expressions of interest can be received. Tentatively it will be in Leeds.	