HASC Meeting 27 June 2019 – Minutes

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Agenda

1. Discussion of minutes
2. Actions after last meeting
3. Cases: updates, complex cases, series (e.g. post-BMT)
4. Drug use: how and when to use anakinra/etoposide/others
    a. NHS England document for anakinra
    b. Protocols for drugs
5. Discussion of infection work-up document
6. Other hyperinflammatory states e.g. CAR-T/CRS
7. Genetic testing

Welcome (RT)

- Larger group this year which is welcomed
- Emphasis on the need for commitment to the work of the group

Update from Last Meeting

1) **Teaching & Education**
    - JJM and RT spoke alongside Mike Brown and Helen Lachman at Advanced medicine course at RCP
    - JJM has taught on London ID and at East of England regional day
    - Clinical Immunologist in Leeds has created an HLH session in Immunodeficiency meeting scheduled 6 December 2019 (RT)
    - RT scheduled to speak at 'difficult lung disease' meeting 17 Oct 2019
    - HLH session at national ITU meeting scheduled Dec 2019 (JJM)
    - Kris B first author of a review article for Journal Intensive Care Society
    - JJM/RT also written a review for Rheumatology

2) **Infection minimal dataset –** discussed later

3) **Access to Anakinra**
    - Plan for NHSE clinical commissioning policy application. RT has written document for submission to [post meeting note – submission portal currently closed]
    - Blood guidance promotes etoposide earlier in treatment algorithm, may hinder efforts to acquire access to anakinra. Discussed further later.

4) **Registries**
    - Histiocytosis and autoinflammatory registries to be discussed later
    - Need commitment to recruit through regional MDTs

5) **International Collaborations**
    - JJM via Mervyn Singer (ITU, UCLH) aiming to connect with Histiocytosis group in US building on previous collaboration with RT
    - **<u>Action point:</u> PM has met Jan Van Laar from European group and will make introductions**

6) **National hyperferritinaemia audit – ferritin >10,000 over 3 years**
    - Ethan coordinating data collection
    - Ethan presented and in process of publishing paeds data (12 centres) – 153 children, 33% overall mortality, high proportion in which HLH not considered suggesting potential for missed diagnosis and inadequate treatment.
    - Matching adult data collection in progress
        i. UCH, Royal Free, Leeds, Newcastle, Sheffield completed data collection
        ii. Initial data suggests HLH cases are being missed. Recognition that overall burden of HLH will be under estimated as there is a selection bias – audit does not capture patients in whom ferritin has not been checked.
        iii. Discussion regarding degree of elevation of ferritin: 50% mortality if ferritin >10,000, but caution advised that death still possible with ferritin <3,000.
        iv. Specificity of ferritin >10,000 greater in children, as in adults more potential reasons for ultra-elevated ferritin e.g. paracetamol overdose (requested as part of liver screen) and multiple transfusions. Unclear if level of ferritin elevation correlates with specificity for HLH diagnosis.
        v. Plan is to publish adult and paediatric data separately
    - **<u>Action Point</u>: Centres that haven't finished data collection do so asap and send to ES who is going to collate data**

7) **Use of high ferritin alerts**
    - Discussion regarding the need for a named point of contact if ferritin raised above defined threshold. Workload unclear, as unknown how many alerts likely. Work likely to be beyond remit of specified job plans.
    - Leeds is liaising locally to implement this
    - Local experience from Sheffield group, workload manageable (RT)
    - At UCLH – plan to have ferritin check recommended in anyone presenting with a fever and in ITU (JJM).
    - At Imperial (TY), local alerts have been easy to set up with a named point of contact, but the value is questionable. Caution advised regarding not having an MDT, to avoid one person being overwhelmed. Measuring ferritin in ITU setting useful, but patient may be too sick at that point and perhaps missed opportunity for earlier diagnosis and intervention

8) **Local MDTs**
    - Sheffield – referrals from multiple specialities
    - Southampton
    - UCLH – attended by Rheum, Haem, ID, ITU, Virology, working on potential dial in (JM)
    - GOSH
    - JM: monthly MDT useful forum for learning, reflection and ideas, but there is need for real-time access for urgent clinical advice, when required.
    - Helpful to have national network of MDTs for non-tertiary centres to access expertise in their region.

- **<u>Action point (all):</u> Encourage set-up of regional MDTs, and advertise availability of e.g. via grand rounds; have a chair who can co-ordinate with other groups nationally**

Case Discussions

Jonathan Ainsworth (North Middx)- Patient presented pt with Castleman's on background of HIV. Initial presentation with delirium. Imaging and EBUS not diagnostic. Deteriorated with cytokine storm (ferritin 2K→ 16K). Given RTX and TOC via UCLH.

- Within 2 days ferritin 16K to 8K, delerium improved. Later had 4 doses of RTX.
- Discussion re: TOC and risk of infection and difficulty in detecting infection (as TOC normalises CRP as mechanistic effect). In this case TOC useful for HLH and Castleman's, despite concerns re infection. Avoided use of IVMP.

Ruth Pepper (Royal Free) – Two cases of nephrotic syndrome and HLH with FSGS on renal biopsy.

- Case (1) AOSD poorly compliant. Renal bx collapsing GN (severe FSGS). Anakinra at induction, but then patient refused further anakinra, but agreed to high dose steroids
- Case (2) NK cell lymphoma.
- Literature – French series of 11 patients with nephrotic syndrome and HLH. 7/11 died. Most had FSGS. 6 associated with lymphoma, but some cause of FSGS not identified. Learning point – have a low threshold for kidney biopsy. FSGS patients often have AKI. Suggest urine PCR if low albumin.

Jason Yong/Amit Patel (Liverpool) - Case series of 5 patients, all were secondary to infection, 2 post allo-SCT, 1 post induction chemo for ALL, 2 no underlying haem disorder.

- All fulfilled H score 2004. Treatment response monitored by ferritin improvement.
- Discussion re: avoiding etoposide as may damage the graft post allo-SCT. Anakinra and dexamethasone preferred. Once response achieved, taper dex first, followed by anakinra. Gene panel sent to GOS, only 1 result (no mutations) received in 12 months
    - Case 1: 30 yo male. Constitutional upset, rash, fever, ferritin >100K. Treated as AOSD. Given tocilizumab, steroids and anakinra. Referred to teaching hospital. Pancreatic mass grew VRE. Necrosectomy improved clinically. Cont Toc, stopped anakinira.
    - Case 2: post-chemo for ALL. Fever and unwell, ferritin 60K. ITU for resp suport. Dex, anakinra 1mg/kg OD SC. Discharged home within 2/52.
    - Case 3 and 4: Post allo SCT, 30/7 post transplant. Fever, sepsis. Ferritin 60K. One had stat TOC whilst awaiting anakinra and dex; improved in 2/7. Other patient improved only with GCs. Both better within 2/52 and discharged home.
    - Case 4: PUO and disseminated TB, ferritin >100K. Unwell for one month prior. Anakinra 1 dose, but RIP

Simona Deplano (Imperial) - 37F. Unwell, respiratory arrest in ED, intubated and diagnosed with pneumococcal LRTI. Transferred to Royal Brompton for ECMO Low platelets. Ferritin only 2300,

but BM striking haemophagocytosis. Given Dex, Anakinra 200mg BD. Despite MOF requiring ECMO and CVVHDF, patient now much improved clinically (but will need amputation for necrotic legs).

- **Learning point – ferritin may not be strikingly high, despite significant HLH.**
- TY: ECMO and HLH – risks of neurological involvement and risk of intracerebral bleeds. Need registry of these patients.
- JJM: also need raise awareness of impact of cardiac function from HLH (also had a UCLH patient with HLH that needed ECMO).
- AR: in young patients (20-30y), where malignancy not found, consider genetic screen in case of late-onset/at risk genetic HLH.

Brian Davidson (Southampton) - Patient with HLH 18/12 after treated for MS with alemtuzumab (campath). Given Anakinra 200mg SC.

- Question from Neurologist if Campath could be used again? AP: MS patients needing allo-SCT can have profound immunosuppression (B and T cells), despite campath used years prior. T cell suppression may contribute to HLH. Unclear if could restart campath.

RT - MS, thymoma, thymectomy then lymphoma. Then EBV driven PTLD then HLH.

- Refractory to RTX 4x 375mg/M2.
- Given selective T cells (against EBV) but still died within 2 weeks. Post T cell therapy EBV count >5Million.
- Discussion: delay in treating HLH as haematologist could not give selective T cells in the presence of immune suppression and they felt steroids and anakinra were immunosuppressive. Rheumatology (RST) felt HLH was treated too late therefore, Anakinra eventually given but late. Also discussed the use of GCSF and whether it might trigger HLH – general agreement this is not usually the case and GCSF can be used
- Ben Carpenter – generally treat HLH first then given conventional lymphoma Rx.

RT – Case series accepted in Bone Marrow Transplantation:6 x post allo-SCT HLH.

- 5/6 had severe GVHD. 4 triggered by EBV. No HLH in auto SCT cohort.
- In one patient neuro function worsened when anakinra dose reduced and improved when increased. Now remains on anakinra 3x/week (reduced dose as renal impairment).
- Other patients died HLH is a complication of allo-SCT in 3%. Important to recognise HLH in acute GVHD.
- AP –infection with GVHD (rather than GVHD itself) may be driving HLH. Etoposide contraindicated as may damage graft and low efficacy (does not penetrate blood brain barrier). If neurological Sx use dex and anakinra, or intrathecal MTX.
- Maria Leandro: mild case of HLH with acute GVHD at UCLH, treated with steroids only.

Drugs

ANAKINRA:

- Claire Booth (GOSH): does not use much Anakinra. Uses HLH 1994 rather than 2004. Also moving towards alemtuzumab and emapalumab (anti-IFNg) also being used in paed HLH.
- Anupama Rao (GOSH): not clear across paeds haem/ immunologists re use of anakinra in other paeds/ neonatal centres – this is needed.
- **Action point**: paediatric survey needed regarding sHLH and use of anakinra (Rao)
- TY: Whilst anakinra can be lifesaving should not send out message that anakinra is definitive treatment for many patients with HLH, other than in some rheumatological disease. Will need treatment for underlying driver.

Is anakinra safe in sepsis?

- Kris Bauchmuller (Sheffield): post-hoc analysis of initial Phase 3 RCT, suggested efficacy in hyperinflammatory MALS. Statistical interpretation of safety is questionable.
- PROVIDE trial of anakinra in MALS will help inform.
- John Stack: Need to collect database of anakinra monotherapy. Will also help the case for NHSE clinical commissioning.
- RT: Not clear if anakinra is truly safe in sepsis in long term use but increasing confidence in this situation

IV anakinra:

- Puja Mehta: presented difficulties regarding selection for the route of administration (IV bolus, continuous iv infusion, SC, with/out loading dose IV) and literature search for IV anakinra in HLH.
- General discussion about dosing: doses of up to 8mg/kg used
- **Summary:** IV preferred if SC difficult e.g. low platelets, oedema, or pain if pt awake and needing large doses (multiple SC injections), neurological manifestation as better BBB (some evidence), but infection concerns as shorter half-life.
- But, if given IV boluses there may be troughs, it is unlicensed, higher doses needed with IV route (therefore cost), safety – generally safe but limited data

Action points

1. Send summary of literature search to all with minutes (Puja)
2. JJM to draft protocol on how to use anakinra
3. Need to publish clinical experience in order to collate evidence base in order to try to stratify patients to determine which patients likely to benefit from anakinra (All)
4. Survey monkey to determine use of anakinra (Puja, Fang En, JJM)

ETOPOSIDE:

- SD: Dosing for HLH at Imperial is 100mg/m2 twice/week, which is relatively low dose. Experience is that refractory sHLH pts have responded. Etoposide has anti-macrophage effect. Perhaps not used as 1st line but should be considered and not be feared (Echoed by Lydia Eccersley and AP for lymphoma cohort, as dual efficacy).
- In context of infection, etoposide not being used as chemo but to suppress macrophage activity (different MOA) so should see count improvement but not count suppression.
- Many people report seeing significant impact on counts post-etoposide, but maybe this is a dosing issue
- JJM: Rheum need haem support to use it as lack of experience, and prescribing and administering rights.
- AP: avoid etoposide for post- transplant patients especially in first 30 days

G-CSF:

- PM: unclear if GCSF can trigger or worsen HLH. 4 case reports in literature suggest temporal worsening of HLH with GCSF use, 1 as potential trigger
- SD: has occasionally used G-CSF, no worsening of clinical picture seen but generally ineffective, therefore less likely to use. 1 case of no response to 300 mcg but responded after 480mcg but unclear if GCSF or improved HLH generally?
- AP: used when post-transplant or infection-associated where unlikely to affect underlying cause e.g. leukaemia. Often doesn't work significantly but no observed worsening
- **Action Point**: collating cases where GCSF used without adverse event (worsening of HLH) for publication as letter, to ask the question. Potential contributors to contact Puja

Infection Data Set

- Mike Brown: Discussed minimum infection data set circulated.
- The term 'comprehensive' is preferred to minimum
- Geographical panel with one sample to reference lab is cheaper than asking for single tests separately
- Tests on bone marrow – needs specific requests and sometimes fresh sample so liaison with laboratory specifically required.
- Kimberley Gilmore: babies under 6m all have maternal Ig (placental passage) so needs careful interpretation
- HSV driven cases seen with striking phenotype.
- Difficulty in interpreting Abs in patients post SCT/chemo – may not seroconvert, HLH itself is also immunosuppressive
- IVIG may cause false positive serologies
- Emilie Sanchez: Low threshold for doing PCR
- **Action point:** MB/JJM to circulate updated version

Genetic testing

- KG: if driver eg lymphoma/post SCT etc found, patient responding to treatment and no FHx – genetics may not be necessary
- Send genetics if FHx of unexpected deaths e.g. leukaemia or lymphoma, relapse (irrespective of age).
- Patients with EBV or serious infection driven HLH under 30 – should be investigated.
- Implication is that they may be eligible for SCT (curative), without which there is a high mortality.
- If going to do HLH genetics, do it all or do none
- Screen protein functional tests first 10mls EDTA from pt + 10mls from non-related healthy person, sent in within 24 hours and processed within 48 hours. Prefer Mon-Thurs (but will accept samples any day)
- Next generation sequencing will be available via NHS soon, after functional tests
- GOSH and Newcastle are only UKAS accredited lab
- Soluble CD25 separately can be useful as marker of response (serum sample)
- TY: Are we detecting somatic mosaicism or polygenic disease through whole blood sequencing? KG – depends on panel, but some likely to be missed. May be useful research project.
- NB: Cytokine analysis not indicated, unless trying to obtain anti-IFNg.
- NB Emphasise the importance of obtaining a bone marrow and repeated BM (may be useful to document, to aid with any resistance)

Consensus: We also need a document re: all other specialty tests inc haem/ ID/ Rheum/ Genetics/ Renal with stratification including – basic initial test (based on paed protocol in paper Ethan will circulate), next steps if no improvement, and contact list for local MDT / HLH specialists.

- **Action Point** – Strachan/JJM will coordinate creation of above document.

Registries

- Need registry data to characterize disease population, and to inform trial selection.
- Two new registries appropriate for patient recruitment

Newcastle Histiocytosis Registry:

Ethan Sen: Prof Matt Collin based in Newcastle with interest in Histiocytosis (Erdheim Chester).
Redcap online portal encompassing wide range of histiocyte disorder including HLH.
Website up and running with patient consent form.

- Need to adapt existing dataset to include data for HLH subgroup.
- Suggested 3 forms:
    - Baseline data
    - Treatment
    - Follow up (post-treatment)
- Once updated can go live together in near future
- Will need local R+D approval but does have IRAS approval.
- Can only be accessed via NHS computers with plan for VPN access for outside use
- Consent also covers collection of biological samples (which are collected at time of clinical testing/ treatment, not extra sample collection) including consent from relatives for pts who died, digital images.
- JJM: detailed level of data collection will be impractical in smaller centres
    - Perhaps two levels – e.g. minimal for epidemiology (but will need enough information to confirm diagnosis of HLH) and for those centres able to – more detailed entry
    - Confirmed HLH +/- probable and suspected – KG/ JJM: important to include these patients
- KG – batch testing, reduces prices. Can probably store samples in liquid nitrogen to use samples later if needed – for research or for clinical tests with responsible clinician's authorisation
- **URGENT Action point** –Subteam to define inclusion criteria to be able to use Erdheim Chester registry consent. Subteam members: JJM, Ethan, Amit, Simona, Ruth pepper. Need to coordinate with Claire Booth. 1 month deadline ie 01/08/2019.

NIHR rare disease bioresource have 2 potential ways that HLH patietns can be enrolled in the bioresource

Newcastle Histiocytosis registry

Matt Collin has included HLH in the bioresource proposal for all histiocytoses

Leeds autoinflammatory/adult onset Still's disease:

Sinisa Savic who has interest in AOSD of whom a percentage present with HLH has enabled the HLH cohort to be recruited to this bioresource proposal

- **See addendum**

AOB

Tuberculosis

- SD: If no trigger found for HLH – would one empirically start anti-TB Rx given it is a common trigger? Anecdote of good response with empirical anti-TB Rx
- Mike Brown: Unable to justify blanket treatment in all cases, but in certain groups perhaps
- KG: reminder to send genetic sample pre anti-TB Rx
- **Action point:** To be discussed at next meeting – with illustration case presentations

Post-SCT and CAR-T cell therapy associated cytokine release syndrome / HLH

- AP: Smaller subgroup to look at post-transplant and CAR-T cell therapy associated HLH
- KG: Cytokine profiles will be helpful in cytokine release syndrome

Epidemiology capture of HLH

- ES: British Paeds society previously sent survey to all paeds rheumatologists asking if they have seen pts with HLH. Can this be done in adults with bursary for funding?

Next meeting 27th November + network meeting

Action point	Who is responsible?	Update as of September 2019
Connect up with European HLH groups (via Jan Van Laar)	PM/JM	Initial email sent; JJM to follow-up
Highly elevated ferritin study – all participants to send data to Ethan Sen asap	All/ES	JS has sent data
Encourage set up of regional MDTs which can interlink via HASC	All	Need an update
Paediatric survey of anakinra use	AR	Need an update
Publish experience of use of anakinra	All	Need an update
Survey monkey for anakinra use	PM/FS/JM	Drafted by FS/PM
Produce protocol for use of anakinra	JJM	Drafted and going through local committees
GCSF affect on HLH	PM to co-ordinate	Drafted by PM
Infection comprehensive data set – small ammednments to be made eg maternal Ig/HSV	MB	Will include
General guideline	SM/KG/JM	Drafted and being sent round
Registry data collection	ES to co-ordniate with in-put from JM/RP/AP	Done

Addendum

Summary of telephone conference between Rachel Tattersall, Sinisa Savic, Ethan Sen and Matthew Collin

There are 13 NHS Bioresources in the UK – Leeds and Newcastle among them – website here https://bioresource.nihr.ac.uk/

Essentially people are recruited on the basis of their genotype/phenotype to the bioresource. Currently all recruits have EDTA tube for DNA and serum sample saved but there is not a provision for cell saving currently
All recruits get specific SniP RNA arrays done and there is the potential to do genome sequencing if proposals for those specific pieces of research are lodged with the bioresource and approved although this part of the process is not well characterised as yet

Each bioresource site has a CD and the CDs will collectively drive the bioresource

Matt Collin and Sinisa Savic have both successfully applied to the bioresource to collect samples on patients for the following indications

- Sinia Savic – systemic Autoinflammatory disease (SAID) including Adult Onset Stills Disease (AOSD)
- Matt Collin – All Histiocytoses including HLH

In addition, and supported by UK Histio, Matt has a Histiocytosis registry in progress. This could potentially capture all patients in UK with HLH and then we could assign them to the limited bioresource recruitment so that AOSD/SAID associated goes through Sinisa's pathway and selected others through Matt's

The main push therefore should be to helping Matt set up the HLH registry to enable HLH bioresource recruitment – where HLH is caused by AOSD shold go into the Leeds arm, other causes to the Matt Collin proposal but we need to be potentially a bit selective to ensure that we don't overwhelm recruitment and risk therefore not getting a spread of heterogenous cases . Ethan Sen is kindly completing the suggested data fields for the HLH part of the registry and Matt will let us know when the registry is live