4th HASC meeting, London 27.11.19
Chairs Jessica Manson and Rachel Tattersall

Attendees

Fred Chen	Adult Haematology	Barts, London
Amit Patel	Adult Haematology	Christie, Manchester
Strachan MacKenzie	Adult Haematology	UCH, London
Matt Collin	Adult Haematology	Newcastle
David Wrench	Adult Haematology	Guys
Arian Lawrence	Adult Haematology	UCH, London
Ben Carpenter	Adolescent Haematology	UCH, London
Kris Bauchmuller	Adult Intensivist	Sheffield
Danny McAuley	Adult Intensivist	Belfast
Jeronimo Cuesta	Adult Intensivist	North Middlesex
Shelley Riphagen	Paediatric Intensivist	Evalina, London
Jennifer Handforth	Paediatric ID and Immunology	Evalina, London
Ethan Sen	Paediatric Rheumatologist	Newcastle
Phil Riley	Paediatric Rheumatologist	Manchester
Kirsty McLellan	Paediatric Rheumatologist	Glasgow
Taryn Youngstein	Adult Rheumatologist	Hammersmith
Puja Mehta	Adult Rheumatologist	London
Eleana Ntatsaki	Adult Rheumatologist	Ipswich
Anne Kinderlerer	Adult Rheumatologist and GIM	Charing Cross
Jessica Manson	Adult Rheumatologist	UCH, London
Rachel Tattersall	Adult/Adol Rheumatologist	Sheffield
John Stack	Adult Rheumatologist	Kings, London
Mike Brown	Adult Infectious diseases	UCH, London
Neil Jenkins	Adult Infectious diseases and GIM	Birmingham
Nina McCann	Adult infectious diseases	London
Mark Kacar	Adult Immunology	Leeds
Catherine O'Sullivan	Paediatric Immunology	London
Emilie Sanchez	Virology	UCH, London
Eithne McMahon	Virology	GSTT, London
Tim Card	Gastroenterology	Nottingham
Heather Burnett	Advanced nurse practitioner	Evalina, London
Kimberley Gilmour	Immunology	GOSH
Maria-Teresa Cutino Moguel	Virology	Barts, London

The meeting opened with an item from Jessica Manson on the very sad news of the death of Johnathan Ainsworth who had been active, early member of HASC and a passionate advocate for HLH recognition and treatment. He will be sadly missed.

Standing agenda items

1. **Conflicts of interest statements** – none received
    1.1. Rachel Tattersall received an offer from SOBI for an unrestricted grant to help run HASC eg fund teleconferences or MDTs. Matt Collin suggested could SOBI give a grant to Histio UK, to avoid any direct links. All to feedback to Jess about the possibility of funding from SOBI to help run the network – accepting the issue that SOBI make both drugs that we might use – emapalumab and anakinra

2. **Education delivered on behalf of HASC/HLH in general**
    2.1. Jessica Manson: ID trainees meeting, general medical training day, Swindon, London hospitals ID departments, general med meeting Portugal, SOA ICU conference Birmningham
    2.2. Rachel Tattersall: Northern ITU training day, UK PIN, Infectious diseases, Elderly medicine, regional rheumatology training days
    2.3. Kimberley Gilmour: Oxford regional day, Freiburg European immunology meeting, Indian national HLH meeting, haem/rheum/paed rheum annual teaching
    2.4. Mike Brown quarterly teleconference (national network) – HLH frequently addressed
    2.5. Some discussion about other potential avenues
        2.5.1. Neil Jenkins mentioned multi-drug resistant TB network – reactive rather than planned MDT but forum to discuss HLH. ? would NHS-E fund this
        2.5.2. Online forums have clinical queries posted – is HLH discussed on this?
        2.5.3. Kimberley Gilmour immunology has an email list ‘travellers list’ to which there are quick responses – another thing to post HLH on?
        2.5.4. Eithne suggested an invitation to speak at national virology meeting
            2.5.4.1. ACTION POINT EITHNE WILL PURSUE THIS
            2.5.4.2. ACTION POINT ALL TO CONTINUE TO DELIVER AND LOG TRAINING
            2.5.4.3. ACTION POINT TO IDENTIFY CLINICAL IMMUNOLOGISTS TO JOIN HASC

3. **MDT updates**
    3.1. UCLH (+ other London feed in) – multi-speciality, email and monthly meeting
        3.1.1. JJM has 1 PA/month in job plan to run her MDT/co-ordinate MDT care – a useful precedent
    3.2. GOSH – multi speciality
    3.3. Sheffield – multi speciality – email and 2-3 monthly meeting
    3.4. Newcastle – in set up
    3.5. Leeds – a lot of resistance to formal MDT – case-by case discussion on regional basis
    3.6. Birmingham – diagnostics through haematology but no formal MDT and rheumatology less involved. Most through haem/ID
        3.6.1. ACTION POINT JESSICA MANSON to connect Neil Jenkins and the adult rheum team in Birmingham who wanted to come today but couldn’t to explore MDT set up
    3.7. East of England have fortnightly meeting rare diseases at which HLH is often discussed and their complex MDT also discussed HLH but no formal MDT for live management of cases
    3.8. Southampton also have MDT – Brian Davidson (Rheum) and Andrew Duncan (Haem)

4. Ethan Sen has put abstract about HASC into QI stream at RCPCH having had a similar abstract about HASC accepted for BSPAR – thanks to him for this

5. Puja Mehta has constructed an HLH survey monkey in conjunction with European and US colleagues–will go out Jan 2020. Sets a baseline for knowledge of and clinical approach to HLH- thanks to her for this

Investigation guideline (Strachan Mackenzie) for discussion and signoff

1. Strachan introduced the proposed guideline – aims to be a holistic/cross speciality approach to HLH. Huge thanks for all his hard work on this.
2. Audience is for any clinician with a patient with ?HLH
3. Hope is to facilitate MDT working
4. Plan to host on Histio UK website longer term, with annual review to ensure remains up-to-date and relevant
5. Guideline presented as a staged process
   5.1. basic work = stage 1
   5.2. sequential work up with more specialised tests plus consideration of pHLH
6. Kimberley Gilmour commented that all tests at GOSH now UCAS accredited. In 2020 HLH diagnosis will be nationally funded if several criteria are met with significant gatekeeping at the 2 centres doing it [Manchester and GOSH] (otherwise cost is £750). Still long lead time. Will have similar request form to current. South of England to GOSH, North of England to Manchester. Note in acutely unwell child with ? genetic cause – those cases go to Exeter Genetics centre via genetics MDT access.
7. Mike Brown asked about Ix those with relapse or no cause found – KG feels that should be a point for genetic referral.
8. Ben Carpenter wanted clarification about the place of work up wrt CNS involvement. If asymptomatic what is threshold for MRI+LP? Some centres do neuro work up in all but in UK probably need to document manifest symptoms before work up. So only if CNS symptoms, proceed to Ix
9. Jessica Manson pointed out that echo is not currently on guideline. All agreed we should add echo, troponin and BNP and specify why it is being done ie to stratify need for more intensive support
10. Phil Riley commented that for paediatric population Kawasaki is a trigger for HLH and echo is diagnostic so esp important for paediatric
11. All discussed that a pragmatic, scaled down version would be helpful ie what to do in the DGH? We need a volunteer to do that scaled down version…….and write guideline explicitly for this scenario: if you need stage 2 work up you need to refer centrally….
12. Jenny offered to help make guideline applicable to paeds in this context and Strachan will consider this in the second version.
13. All agreed the need have a rider at the front of the guideline to state the contested nature of the HLH and the suspicion of hyperinflammation should prompt Rx. Use common sense approach eg 'Unwell patient with fever check ferritin trigs and fibrinogen and serial blood counts'
14. All agreed procalcitonin which is well recognised to rise in HLH so is not infection specific in this cohort should not be part of a proposed work up
15. Although this guideline is for diagnosis only it could usefully be paired with some exemplar treatment guidelines to be posted alongside on Histio UK website. Amit Patel

was happy to provide his Christie treatment guideline which could be a useful addendum to give an example of treatment approach

16. Ideally, we would also host on the website a list of local experts or MDTs – for the next meeting
    16.1. ACTION POINT: Strachan to circulate one further time with a deadline of end of January to agree final version before posting on UK HIstio website but agreement that in principle from meeting this is good, representative and where possible evidence based document with no major concerns
    16.2. TO INCLUDE A DGH INITIAL WORK-UP: Eleana agreed to help with this

Anakinra

Protocol – Jessica Manson

JJM gave an overview of anakinra as a high cost drug but often with a time limited need for acute use in HLH. Cost £40 per 100mg. She has local CCG agreement for use and as part of this agreement has written a protocol for the use of it. She had 2 questions for discussion.

1. Maximum dose: Agreed 1-8mg
2. Off license use for IV – when to use IV cf SC in context of low platelets? Levels of 20? Or 50? Specific paediatric consideration of multiple injections? Or haemorrhagic?
    2.1. Danny McAuley observed that critical illness itself mandates IV Rx as not s/c absorbed
    2.2. Ben Carpenter suggested no absolute platelet cut off. General discussion seemed to lead to suggestion that area of concern was platelets of 20-50 plus other considerations as above

NHS-E application – Rachel Tattersall

The preliminary policy proposal for anakinra use in HLH excluding that associated with SJIA/AOSD for which a PP already exists has passed the first hurdle and PHE have asked RST to help convene a working group. The membership of this needs careful consideration and needs to be representative. Already agreed:

Mike Brown (ID) Jessica Manson, Rachel Tattersall, Stuart Carter (Adult rheum) Ethan Sen (Paediatric rheum) Matt Collin, Amit Patel (Adult Haem) Kris Bauchmuller (ITU). Also need paed haem – Matt to approach Geoff Shenton in Newcastle, immunology

ACTION POINT – EXPRESSIONS OF INTEREST TO RACHEL TATTERSALL PLEASE

Current use of anakinra

Publishing case series? – could we do a HASC publication? Prospectively collect our experience of anakinra. Some people are publishing local experience. Encouraged to get papers out ASAP.

ACTION POINT DISCUSSS NEXT MEETING

Clinical cases

None brought!

Link with Histio UK

Website

Histio UK have agreed to have a HASC page on their website to be a repository of guidelines, exemplar treatment protocols and maybe a list of regional contacts for advice. Lynn Jackson asked what content would HASC want on the UK histio website?

All agreed should be open access not password protected or log-in required

1. HASC meeting minutes
2. Would experts be happy to have their contact details on the website
    2.1. ACTION POINT: TO DISCUSS NEXT MEETING?
3. Diagnostic work up guideline, exemplar treatment protocols (all pdfs to be dated with one year expiry)
4. Education events to flag up
5. Patient stories
6. Can we link a HLH hashtag to website to keep it up-to-date

The HLH bit of HIstio UK webpage is outdated and we need volunteers to help update website

ACTION POINT VOLUNTEERS TO DO WORK ON HISTIO UK WEBSITE PLEASE?

Support for regular meetings (face-to-face and TC)

FIRSTLY A BIG THANKS TO LYNN JACKSON FOR HOSTING THE LAST 2 HASC MEETINGS

Current issue is that GOSH have Histio UK funding for TC. Due to go live in 2020.

ACTION POINT: TO DISCUSS NEXT MEETING RE POSSIBLE WIDER ACCESS TO THAT TC eg non-paediatric teams being able to dial in and discuss cases

Highly elevated ferritin Audit

Ethan Sen has done a huge amount of work on an audit of highly elevated ferritin (HEF) between 2014-2017 in 10 paediatric and 7 adult centres. Paediatric results attached in the form of a poster presented at the BSPAR 2019 meeting (Adult Data still being analysed).

Take home messages are that HEF associates with high rate of mortality and that it looks as if HLH is not always/often considered and is evidence this condition is being routinely missed in clinical practice

Kimberley Gilmour pointed out that neonatal HSV mimics HLH/is complicated by HLH. These babies get steroids but not the whole HLH 2004 pending HSV results and this probably expklains the high numbers of HEF in under 1 year olds in the audit

Further possible work from this?

Discussed looking at non-ferritin variables

Anne Kinderlerer + Jessica Manson happy to look at trends of variables in data to which they have access along similar lines to HEF audit. Anne has data set for sepsis and uses sepsis CQUIN money to hire statistician. Danny McAuley keen to work in combination with Anne/Jess on this

ACTION POINT DM/AK/JJM to look at working up this project

Registries/ongoing collation of HLH cases

HLH Epidemiology project - PI Joe West (Nottingham) and Tim Card working with Mary Bythell (PHE) Histio UK funded

Tim Card discussed epidemiological study. There are 3 codes for HLH

1. D76.1 HLH
2. D76.2 HLH second to infection (primary and secondary potentially)
3. D76.3 HLH secondary to cancer – seems not to relate to HLH

D76.1/76.2 perform better for HLH and using these, the SMR for HLH has risen rapidly over 10 years, so this reflects better recognition ie reflects better completion of death certificates rather than clinical improvement! PHE have collected the patients coded HLH under the rare disease strategy. Mary Bythell heads NCARDRS which started 2015 part of national rare disease strategy. Under section 251 in the rare diseases there is approval to requisition patient data per specific codes of which HLH is one so facilitating audit etc. There is a clear imperative for HASC to be involved as the team need to validate that what is collected under HLH coding is what we recognise as HLH and we need a capture-recapture check on coding too – are all the cases we manage coded correctly. There is scope to combine the HASC clinical network and the epidemiology approach together to get a better idea of true HLH incidence. PHE would have an HLH registry and this is the basis for ongoing research to drive evidence based care. Next step agreed that Tim would provide a paragraph to go out with the minutes as a call for HASC members to help with the validation exercise and this project remains a standing agenda item.

ACTION POINT: TIM TO SUMMARIZE PROJECT AND WHAT IS REQUIRED BY HASC MEMBERS

IRAS approved Research Tissue Bank (funded by UK Histio) – Matt Collin

This is a redcap software based national registry for histiocytosis including HLH. Ethan Sen has worked hard to define the data fields (many thanks for this) for the HLH section. There are national ethics for registered sites to upload anonymised data about their HLH patients (current or previous) keeping their own key to that anonymisation in their secure NHS domain. Can collect blood under ethics for this – keep locally if possible and can access archive pathology. A data access committee then approve study on the patients entered in the database eg access to any blood backed to look for biomarker etc. There was discussion about how local sites might flag this project and the suggestion is to approach local R&D depts. For maximum case pick up we need HASC volunteers to register as a site. DM suggested we get an opinion from individual site or two R&D dept about opening sites in trusts to set a precedent and JJM RST will try to get their sites open. At next HASC meeting we can then discuss wider roll out

ACTION POINT: JJM/RST will try to get their sites open. At next HASC meeting we can then discuss wider roll out

NIHR bioresource – the rare diseases

This is another registry project – discuss next time and prioritise the 2 studies above in terms of HASC members time and enthusiasm!

ACTION POINT: discuss next meeting

On-call rota/National access to expert advice

Currently no coordinated expert rota for opinions re HLH and local services are reliant on single people. Jessica Manson asked whether there is an appetite for a local or regional 'on-call' rota? Rachel Tattersall sounded a note of caution re governance and giving advice at arms-length and concerns were echoed. This is an ongoing issue

ACTION POINT: On agenda for next time but we ought to explore auditing the current practice of HLH MDTs – how they are set up, barriers and enablers RST and JJM to explore

AOB

Next meeting 8th June 2020 1-5pm

Action point: We need a TOR/decision about chair elections etc on agenda for next meeting as HASC grows.

Post meeting notes:

ACTION POINT: TIM TO SUMMARIZE PROJECT AND WHAT IS REQUIRED BY HASC MEMBERS

“Dear all

Following our recent meeting of the HLH across specialty collaboration we are hoping to help validate cases of HLH identified by Public Health England via their Rare Disease Registration service. To do that we would really appreciate people to volunteer to complete a data collection form (an excel spreadsheet) of all the cases of HLH that PHE can identify within NHS Trusts that occurred between 2013 and 2018. This data would be incredibly useful for the purpose of understanding the contemporary occurrence, burden and mortality of HLH. It will also underpin the prospective register of HLH that we are hoping to roll out soon.

If you are willing and able to help please email Veronika Siskova Veronika.Siskova@phe.gov.uk in the Rare Diseases Registration team at Public Health England who will liaise with you about sending the lists of patients with HLH in your trust for 2013-2018. We expect that in reasonably big NHS Trusts that cover an area the size of Nottingham or Sheffield there will be about 40 cases to validate. In smaller trusts there will be far fewer.”