FRIDAY, 14 JUNE 2019

15:30:00 – 17:00:00

Calming the cytokine storm in children and adults__**SP0153 CALMING THE STORM IN ADULT MAS/HLH IN RHEUMATIC DISORDERS**

Jan van Laar. Erasmus MC, University Medical Center Rotterdam, Internal Medicine, Division of Clinical Immunology, Netherlands

Background: Hemophagocytic lymphohistiocytosis (HLH) is a rare and often overlooked clinical manifestation of an aberrant hyper inflammatory immune response leading to a fatal cytokine storm(1). Diagnostic criteria according to The HLH Study Group of the Histiocyte Society include fever, splenomegaly, bicytopenia, hypertriglyceridemia and/or hypofibrinogenemia, hyperferritinemia, low/absent NK activity, increased soluble CD-25 levels and hemophagocytosis(2). Prompt recognition and differentiation from severe sepsis is essential to improve the outcome. HLH reflects a disbalanced immune system in response to infectious, malignancy, or autoinflammatory/autoimmune mediated triggers(1). The latter group of patients are regarded as having Macrophage Activation Syndrome (MAS-HLH)(3). In adults MAS-HLH comprises 12.5% of all HLH causing triggers(4). The most frequent immunological disorders associated with adult HLH-MAS are systemic lupus erythematosus and adult onset Still's disease, but every other immunological disorder can be involved(4, 5).

Treatment: Treatment of adults HLH patients requires swift recognition and an experienced team of specialists that are acquainted with the critical factors influencing the balance between co-morbidity, cytokine storm induced septic-like symptoms and toxicity of chemo-immunotherapy(6). In general, adult patients do not tolerate doses of etoposide that are given in (HLH-94 based) chemo-immunotherapy schedules that have been shown effective in children(7,8). Dose and frequency modifications of etoposide may avoid prolonged neutropenia, infectious complications or hepatic toxicity. The same precautions account for adults patients with MAS-HLH in which treatment differs from the HLH schedules. A step up approach depending on clinical features and severity is warranted(9, 10). High doses of corticosteroids are recognized as first-line treatment(9, 10). In patients with MAS-HLH and SLE steroids, cyclophosphamide or etoposide are given (10). Cyclosporine can be added in patients with insufficient immediate response(9). The cytokine blocking agent anakinra (anti-IL-1 β) given in high doses is emerging as an alternative or additional treatment of adult MAS-HLH(11, 12, 13). Another promising cytokine blocker is anti-IL-6 (tocilizumab). Etoposide at a reduced dose can be initiated in patients with severe non-responsive and active disease or CNS-involvement(10).

Conclusion: Awareness of the clinical emergency MAS-HLH in patients with autoinflammatory/autoimmune mediated disorders is essential for timely recognition and potential life-saving treatment. The management of MAS-HLH in adults requires a team of dedicated specialists with experience in the treatment of critically ill patients with immunological disorders and anticipation on its rapidly changing and deteriorating nature.

REFERENCES:

- [1] Janka GE. Familial and acquired hemophagocytic lymphohistiocytosis. *Annu Rev Med.* 2012;63:233-46
- [2] Henter JL, Horne A, Arico M, et al. HLH-2004: Diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. *Pediatr Blood Cancer.* 2007;48:124-131
- [3] Carter SJ, Tattersall RS, Ramanan AV. Macrophage activation syndrome in adults: recent advances in pathophysiology, diagnosis and treatment. *Rheumatology (Oxford).* 2019;58(1):5-17.
- [4] Ramos-Casals M, Brito-Zerón P, López-Guillermo A, Khamashta MA, Bosch X. Adult haemophagocytic syndrome. *Lancet.* 2014;383:1503-1516
- [5] Fukaya S, Yasuda S, Hashimoto T, et al. Clinical features of haemophagocytic syndrome in patients with systemic autoimmune diseases: analysis of 30 cases. *Rheumatology (Oxford)* 2008;47: 1686–91
- [6] Halyabar O, Chang MH, Schoettler ML, et al. Calm in the midst of cytokine storm: a collaborative approach to the diagnosis and treatment of hemophagocytic lymphohistiocytosis and macrophage activation syndrome. *Pediatr Rheumatol Online J.* 2019;17:7
- [7] La Rosee P. Treatment of hemophagocytic lymphohistiocytosis in adults. *Hematology Am Soc Hematol Educ Program.* 2015;2015:190-196
- [8] Ehl S, Astigarraga I, von Bahr Greenwood T, et al. Recommendations for the Use of Etoposide-Based Therapy and Bone Marrow Transplantation for the Treatment of HLH: Consensus Statements by the HLH Steering Committee of the Histiocyte Society. *J Allergy Clin Immunol Pract.* 2018;6:1508-1517
- [9] Kumar B, Aleem S, Saleh H, Petts J, Ballas ZK. A Personalized Diagnostic and Treatment Approach for Macrophage Activation Syndrome and

Secondary Hemophagocytic Lymphohistiocytosis in Adults. *J Clin Immunol.* 2017;37:638-643

- [10] Gavand PE, Serio I, Arnaud L, et al. Clinical spectrum and therapeutic management of systemic lupus erythematosus-associated macrophage activation syndrome: A study of 103 episodes in 89 adult patients. *Autoimmun Rev.* 2017;16:743-749
- [11] Wohlfarth P, Agis H, Gualdoni GA, et al. Interleukin 1 Receptor Antagonist Anakinra, Intravenous Immunoglobulin, and Corticosteroids in the Management of Critically Ill Adult Patients With Hemophagocytic Lymphohistiocytosis. *J Intensive Care Med.* 2017;885066617711386
- [12] Schuler G, Minoia F, Bohnsack J, et al. Effect of Biologic Therapy on Clinical and Laboratory Features of Macrophage Activation Syndrome Associated With Systemic Juvenile Idiopathic Arthritis. *Arthritis Care Res (Hoboken).* 2018;70:409-419
- [13] Zhou S, Qiao J, Bai J, Wu Y, Fang H. Biological therapy of traditional therapy-resistant adult-onset Still's disease: an evidence-based review. *Ther Clin Risk Manag.* 2018;14:167-171

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15:30:00 – 17:00:00

Know your methods! Interactive discussion_____**SP0154 REASONS FOR QUALITATIVE RESEARCH FOR HPR**

Romualdo Ramos. University Medical Center Utrecht, Netherlands

Qualitative research plays a pivotal role in clinical practice by providing insights from the patient's perspective. This becomes all the more relevant, as we move into the era of patient-centered care. In this presentation, we shed light on the different approaches to qualitative data collection and analysis, as well as systematic literature reviews of qualitative research. We will also elaborate on how qualitative research methods are used to better understand which outcomes are relevant to patients, self-management of symptoms, non-adherence to medication and non-pharmacological methods, the doctor-patient relationship, and to evaluate policy and interventions within the realm of RMDs. Finally, in an open panel, we will discuss how qualitative and quantitative methods triangulate, contributing to mixed methods approaches.

Disclosure of Interests: None declared

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SP0155 REASONS FOR QUANTITATIVE RESEARCH FOR HPR

Mwidi Ndosi. University of the West of England, Nursing and Midwifery, Bristol, United Kingdom

Health professionals in rheumatology are expected to provide care that is evidence-based. Evidence-based practice is the careful integration of best research evidence with clinical expertise, patient values and needs in the delivery of high-quality, cost-effective health care.¹ A sound understanding of quantitative methods is essential for correct evaluation of research and appropriate implementation into clinical practice.

Quantitative methods are used in a wide range of topics, from validating patient-reported outcome measures, sample size estimation, assessing associations between variables or predicting risk factors and evaluating the effectiveness of interventions. Furthermore, quantitative methods can be used to pool the results of several studies into a meta-analysis and thus provide better estimates of effectiveness than what can be achieved in individual studies.

This presentation will debate the case for quantitative research using examples of research conducted by health professionals in rheumatology. It is hoped that delegates will gain more confidence in using quantitative methods in their own research or evaluating evidence for clinical practice.

REFERENCE:

- [1] Sackett, D.L.; Straus, S.E.; Richardson, W.S.; Rosenberg, W.; Haynes, R. B. (2000). *Evidence-based medicine: How to practice and teach EBM.* 2. London: Churchill Livingstone.

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15:30:00 – 17:00:00

Missing data in clinical research: to impute or not to impute, that is the question

SP0156 MISSING DATA: IS IT ALL THE SAME?

Stian Lydersen. Norwegian University of Science and Technology, Department of mental health, Trondheim, Norway

Introduction: In most studies, there are “holes” in the data set, such that data are missing partly or completely for some of the subjects. This results in reduced statistical power. More seriously, missing data may cause biased results, since data are usually not missing completely at random.

Missing data mechanisms: In which way, and to what extent, does the probability that data are missing, depend on observed and/or unobserved data values? This is called the missing data mechanism, and is important for an appropriate choice of analysis method. Three types of missing data mechanisms have been defined, see for example (Sterne et al. 2009).

MCAR: *Missing completely at random.* There are no systematic differences between the missing values and the observed values. The probability that values are missing does not depend on any of the data, observed or unobserved.

MAR: *Missing at random.* The probability that values are missing may depend on observed data values, but not on unobserved data values. For example, some variables are missing more frequently for patients with higher age. Data are missing at random *conditionally* on observed data.

MNAR: *Missing not at random.*

Even after the observed data are taken into account, systematic differences remain between the missing values and the observed values: The probability that values are missing depends on unobserved data values as well.

It is possible to distinguish between MCAR and MAR by inspecting the data at hand. But it is never possible to determine whether data are MNAR from your data.

Methods for handling missing data

Some commonly used methods, from the less to the more complex ones, are listed below, with an indication of when they give unbiased estimates:

- Complete case analysis (disregarding cases with partially missing data) (MCAR)
- Single imputation methods (sometimes under MAR but underestimates uncertainty)
- Multiple imputation (MAR)
- Full information maximum likelihood (MAR)
- Linear mixed models in longitudinal studies (MAR)

In longitudinal studies, Last observation carried forward (LOCF) is a simple method for imputing missing values. But it is not unbiased under any sensible assumptions, and should not be used (Lydersen 2019).

Reporting: In general, report the amount of missing data in the different variables, and how this was handled in the analysis. This is recommended in the Consort Guidelines (Moher et al. 2010) as well as the STROBE Statement (STROBE 2014), see also (Lydersen 2015)

REFERENCES:

- [1] Lydersen, S. 2015. Statistical review: frequently given comments. *Ann. Rheum. Dis.*, 74, (2) 323-325. Lydersen, S. 2019. Last observation carried forward - simple but not recommended. In press, *Tidsskrift for Den norske lægeforening*
- [2] Moher, D., Hopewell, S., Schulz, K.F., Montori, V., Gotzsche, P.C., Devereaux, P.J., Elbourne, D., Egger, M., & Altman, D.G. 2010. CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials. *BMJ*, 340, c869
- [3] Sterne, J.A., White, I.R., Carlin, J.B., Spratt, M., Royston, P., Kenward, M. G., Wood, A.M., & Carpenter, J.R. 2009. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. *BMJ*, 338, b2393
- [4] STROBE Statement 2014. Strengthening the reporting of observational studies in epidemiology.

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SP0157

PRO SESSION: IMPUTATION IS A POWERFUL ANALYTICAL TOOL, WHEN APPROPRIATELY USED

Loreto Carmona. Instituto de Salud Musculoesquelética, Research, Madrid, Spain

Analysing a study with missing data very likely will yield biased results. Of course, the first principle is to avoid missing data by designing the study and the data collection very thoughtfully. If the study is already done and data collected, then one needs to study how important, and what type of missingness is affecting our data. Simple *ad hoc* methods, such as LOCF, or imputing the mean or other value are generally invalid. Multiple imputations need additional work and expertise, but generally yield better results, closer to reality.

Many statistical programmes have macros available for imputing missing values and analysing imputed data. We will review how these work. Understanding what multiple imputations do will make the decision clearer.

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SP0158

CON SESSION: PREPARE YOUR DATA COLLECTION WELL: IMPUTATION DOES NOT REPLACE ‘REAL DATA’

DOUGADOS Maxime.

The recently proposed sophisticated statistical methods to impute missing data are very attractive.

For the clinical researchers in charge of data collection, it might be tempting to “neglect” the quality of data collection in favor of the time spent by one database manager/statistician to impute missing data.

This presentation will be a plea in favor to make all the possible efforts to collect appropriately the data in clinical research studies/trials. In particular, emphasis will be placed on the importance of writing a specific section in any research protocol describing the techniques used to avoid these missing data and also the a priori decided technic that will be used to manage the missing data. One point of importance in this section: to specify in advance the maximum percentage of missing data over which no imputation can be made.

Two different situations:

- Cross-sectional studies. Any item (for example HLA B27, MRI SIJ inflammation positivity) should be considered as mandatory or not before running the study.

- Longitudinal studies: any longitudinal protocol should include a section detailing the technic to appropriately follow the patients in order to avoid the “lost of follow-up patients”. This is particularly important in longitudinal follow-up of patients suffering from a recent onset disease (e.g. early synovitis cohorts, early inflammatory back pain cohorts) since it is well known that the “lost of follow-up” have specific baseline characteristics suggesting a less severe disease. It is also important to decrease at a minimum level the “lost of follow-up” patients participating at a therapeutic trial/registry since the reason of “lost of follow-up” might be related to a specific drug effect.

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Don't panic – round table discussion on risk perception

SP0159

WHAT DO WE KNOW – WHAT SHALL WE DO – WHAT DO WE TELL

Timothy R. Radstake. University Medical Center Utrecht, Netherlands

There is an increasing need for patients to be involved in research as well as matters that can influence their own clinical journey. One aspect of science that links optimal clinical care is the increased use of biomarkers for so-called personalized medicine approaches.