Interdisciplinary symposium on sepsis – Paris, 8 sept. 2022

Session - Diagnostic implications and monitoring of sepsis

Biomarker-guided personalized immunotherapy in sepsis

(Lyon experience feedback on routine clinical practice in rescue therapy)

Guillaume Monneret & Anne-Claire Lukaszewicz

Hôp. E. Herriot - Hospices Civils de Lyon EA 7426 - Pathophysiology of Injury-Induced Immunosuppression - U. Lyon 1



Immuno-inflammatory response to sepsis



nature REVIEWS IMMUNOLOGY

Hotchkiss, Monneret, Payen. 2013

Increased infectious events during sepsis-induced immunosuppression



Severe fungal Infections (Leroy, CCM 2009 ; Hatermink ICM 2003)

Decreased clearance of initial infection (Torgersen 2009)

Viral reactivation : CMV, HSV (Luyt, AJRCCM 2007 ; Limaye, JAMA 2008)

Increased nosocomial infections (Landelle, ICM 2010, Grimaldi ICM 2011)

Aspergillosis ↑ COVID-19

↑ ICU stay

个 Mortality (70-80 % of total mortality)



Next mandatory step = well designed phase III RCT

Patients' heterogeneity



Monneret et al. Cyto A 2019

Biomarkers needed for precision medicine / individualized therapy



one size does not fit all (at all times)



Prognostic and predictive enrichment in sepsis



Stanski & Wong, Nature Rev Nephrol 2020

Awaiting news from RCT, => rescue therapy in the most immunosuppressed patients

Severe ICU patients Weeks in ICU Still worsening Lack of infection control *Check-up* of immune functions



Available tools at immunology lab for routine care

Innate immunity

- immature neutrophils (CD16low) = \uparrow
- Deactivated monocyte (mHLA-DR) = \downarrow

Adaptive immunity

- Lymphocyte count (+ subsets) = \downarrow
- Check point inhibitor (PD-1) = \uparrow



Accredited Laboratory / Fully Certified Laboratory (in France ISO 15189 accreditation) for routine care Interferon gamma as an immune modulating adjunct therapy for invasive mucormycosis after severe burn – A case report

Woman, 61 yo, burn patient, previously immunocompetent, Several septic shock during ICU stay After 2 months => Peri-stomial ulcerations = **diagnosis of mucormycosis**

(IFN-γ) treatment was added after failure of conventional treatment and confirmation of a sustained profound immunodepression. The diagnosis was based on a reduced expression of HLA-DR on monocytes (mHLA-DR), NK lymphopenia and a high proportion of immature neutrophils.

Results: Initiation of IFN- γ was associated with a rapid clinical improvement and a subsequent healing of mucormycosis infection, with no residual fungi at the surgical wound repair.



Tawik et al., 2022 Frontiers in Immunology

Nivolumab and interferon- γ rescue therapy to control mixed mould and bacterial superinfection after necrotizing fasciitis and septic shock





Previously healthy 38-year-old female

streptococcal necrotising fasciitis of the left chest wa + septic shock

At day 9, transferred to our ICU => diagnosis of mucormycosis



В



Lukaszewicz et al., 2022



Immunostimulation with interferon- γ in protracted SARS-CoV-2 pneumonia

JOURNAL OF MEDICAL VIROLOGY



Results: initiation of IFN- was associated with rapid clinical improvement and fall of viral load

Lukaszewicz et al., 2021

A guide to immunotherapy for COVID-19

Frank L. van de Veerdonk¹¹², Evangelos Giamarellos-Bourboulis², Peter Pickkers³, Lennie Derde^{4,9}, Helen Leavis⁵, Reinout van Crevel¹, Job J. Engel¹, W. Joost Wiersinga⁶, Alexander P. J. Vlaar⁷, Manu Shankar-Hari⁸, Tom van der Poll⁶, Marc Bonten⁹, Derek C. Angus¹⁰, Jos W. M. van der Meer¹ and Mihai G. Netea^{9,11}²



Enrichment strategy improvement = combination of markers

A stratification strategy to predict secondary infection in critical illness-induced immune dysfunction: the REALIST score



Enrichment strategy improvement = combination of mRNA markers

Immune Profiling Demonstrates a Common Immune Signature of Delayed Acquired Immunodeficiency in Patients With Various Etiologies of Severe Injury*



Venet F et al. 2021



Enrichment strategy improvement = muti-data / multi-omics approach (signatures / endotypes / trajectories)

Genomic landscape of the individual host response and outcomes in sepsis: a prospective cohort study

Emma E Davenport, Katie L Burnham*, Jayachandran Radhakrishnan*, Peter Humburg, Paula Hutton, Tara C Mills, Anna Rautanen, Anthony C Gordon, Christopher Garrard, Adrian V S Hill, Charles J Hinds, Julian C Knight

BRIGHT FUTURE AHEAD

Transcriptomic Signatures in Sepsis and a Differential Response to Steroids

From the VANISH Randomized Trial

David B. Antcliffe^{1,2*}, Katie L. Burnham^{3*}, Farah Al-Beidh¹, Shalini Santhakumaran⁴, Stephen J. Brett², Charles J. Hinds⁵, Deborah Ashby⁴, Julian C. Knight³, and Anthony C. Gordon^{1,2}

Classification of patients with sepsis according to blood genomic endotype: a prospective cohort study

Brendon P Scicluna, Lonneke A van Vught, Aeilko H Zwinderman, Maryse A Wiewel, Emma E Davenport, Katie L Burnham, Peter Nürnberg, Marcus J Schultz, Janneke Horn, Olaf L Cremer, Marc J Bonten, Charles J Hinds, Hector R Wong, Julian C Knight, Tom van der Poll, on behalf of the MARS consortium* THE AMERICAN JOURNAL OF RESPIRATORY AND CRITICAL CARE MEDICINE

THE LANCET

Respiratory Medicine

THE LANCET Respiratory Medicine Sepsis-induced immunosuppression can be reversed by adjunctive immunotherapy

Biomarkers are available for patients' stratification (precision medicine / enrichment strategy)

Phase III RCT are needed

Approach applicable to first hours (stratification for steroids)

Multi-omics / data-mining / integrative biology (multi-markers) should provide further improvements