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HELLENIC INSTITUTE FOR THE STUDY OF SEPSIS

Under the auspices

ΕΛΛΗΝΙΚΗ ΕΤΑΙΡΕΙΑ ΧΗΜΕΙΟΘΕΡΑΠΕΙΑΣ
HELLENIC SOCIETY OF CHEMOTHERAPY

European Sepsis Alliance

International Symposium on Immunotherapy of Severe Infections

16-17 May 2024, Kalamata / Greece
Elite Congress Centre

Abstract Book

ImmunoSep, HAP2, HDM-FUN projects have received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 847422 (ImmunoSep), 847782 (HAP2), 847507 (HDM-FUN).

The “International Symposium on Immunotherapy of Severe Infections”, organized in May 2024 in Kalamata, Greece, is shedding light to the rapidly evolving topic of immunotherapy of infections. The topic became very attractive during the pandemic following the approvals of anakinra, dexamethasone and tocilizumab for severe COVID-19 pneumonia. These approvals generated the belief that immunotherapy may also become treatment for severe infections other than COVID-19.

None of the organizers are considering ourselves as experts. However, we consider ourselves as pioneers who, after receiving funding from the European Union, are putting our efforts together trying to change the traditional way of sepsis management. This is why this Conference is carrying the logos of three major consortia who brought novelty in sepsis management:

- **ImmunoSep**, co-ordinated by Prof. Mihai G. Netea, which studied the precision treatment of macrophage activation-like syndrome and sepsis-induced immunoparalysis with anakinra and recombinant human interferon-gamma respectively;
- **HAP2**, co-ordinated by Prof. Antoine Roquilly, which studied the intervention with recombinant human interferon-gamma and dexamethasone in patients with severe hospital-acquired pneumonia; and
- **HDM-FUN-Candidemia**, co-ordinated by Prof. Frank van de Veerdonk, which studied the intervention with recombinant human interferon-gamma in patients with severe candidemia.

This book contains the abstracts of 14 large-scale studies which are presented during the Conference, and which are demonstrating novel pathways of pathogenesis or strategies of precision immunotherapy for severe infections.

May 2024,

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Abstract 01

Blood metabolome longitudinal study reveals patterns linked to respiratory complications and treatment response in non-septic critically ill patients.

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Background Hospital-acquired pneumonia (HAP) and acute respiratory distress syndrome (ARDS) are frequent respiratory complications in critically ill patients, which are associated with unfavourable outcomes, including prolonged mechanical ventilation. Despite the use of adapted antibiotics, the treatment fails for 30% of cases. In accordance with the concept of personalised medicine, it is essential to adapt the treatment to each patients in order to maximise the chance of cure.
Methods Blood metabolome data were generated from a cohort of critically ill patients (called IBIS) at three different timepoints (D0, D4 and D7 of ICU stay). First, linear regression models enabled to identify 19 metabolites with different abundance between HAP and no HAP patients. These metabolites were used to perform the longitudinal consensus clustering of the patients having complete data (n=82 patients).
Results and Conclusions Three different clusters have been identified, each corresponding to a different level of risk of respiratory complication: low, moderate or high risk. These levels of risk have been validated in an external cohort (PREV-HAP) using classification trees. This cohort has been created for the clinical trial of IFN-γ as HAPpreventive treatment. Interestingly, the effect of IFN-γ was different according to the group of risk, showing benefit only for high-risk patients.

This work has been carried out thanks to the support of the LabEx IGO project (n° ANR-11- LABX-0016) funded by the «Investissements d'Avenir» French Government program, managed by the French National Research Agency (ANR).

Abstract 02
Towards personalized medicine: a scoping review of immunotherapy in sepsis

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Background Despite significant progress in our understanding of the pathophysiology of sepsis and extensive clinical research, there are few proven therapies addressing the underlying immune dysregulation of this life-threatening condition. The aim of this scoping review is to describe the literature evaluating immunotherapy in adult sepsis patients, emphasizing on methods providing personalized approaches.
Methods In line with our previously published protocol [1], studies were identified by searching PubMed, Embase, Cochrane CENTRAL and ClinicalTrials.gov, from the first paper available until January 29th, 2024. Inclusion criteria were 1) randomized controlled trials or cohort studies; 2) immunomodulatory therapies, in 3) adults with sepsis. Studies regarding COVID-19 were excluded.
Results The search resulted in 15,853 studies. Title and abstract screening resulted in 1409 studies (9%), assessed for eligibility; 771 studies were included (Figure 1), of which 282 (37%) were observational and 489 (63%) interventional. A personalized approach was incorporated in 70 studies (9%). Trials often showed conflicting results, possibly due to the lack of patient stratification or the potential influence of severity and timing on immunomodulatory therapy results.
Conclusions A significant breakthrough in this field of research has yet to be achieved. When patient enrichment was applied, trends of benefit for several interventions emerged.

[1] Slim MA, et al. BMJ Open. 2022;12(5):e060411.

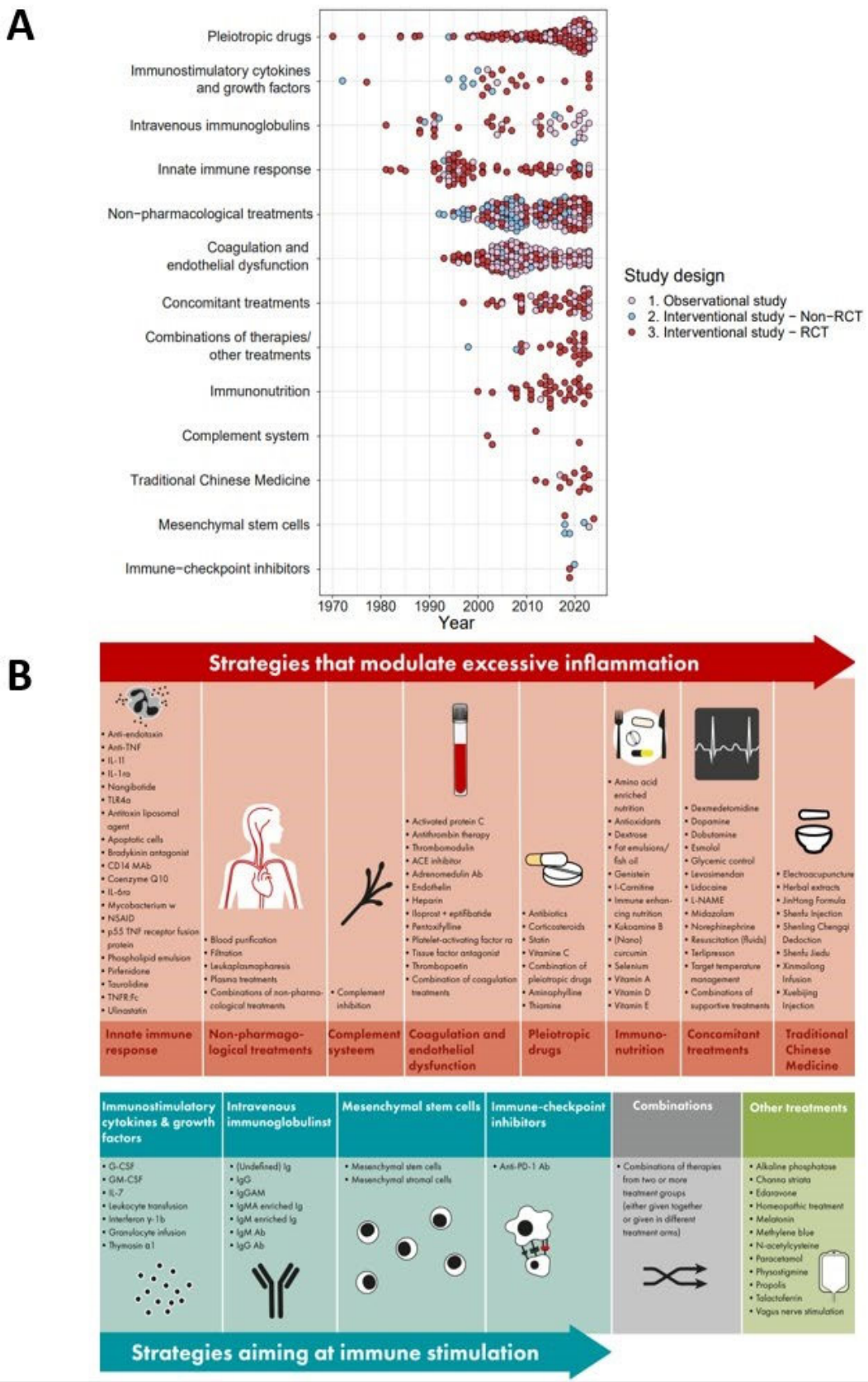

Figure 1. Overview of the included studies and immunomodulatory agents.
(A) Overview of the included studies divided per year, study design and treatment group demonstrated from the earliest to the latest studies overtime and (B) overview of the included studies and immunomodulatory agents per treatment group.

Abstract 03

Development and validation of a continuous dysregulated immune profile (cDIP) score in patients with community-acquired pneumonia and/or sepsis

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Background Sepsis is defined as life-threatening organ failure caused by a dysregulated host response to infection. Yet, methods to quantify the extent of host response dysregulation are limited, hampering precision medicine.
Aim To quantify immune dysregulation in community-acquired pneumonia (CAP) and sepsis.
Methods We determined 35 admission plasma biomarkers reflective of key pathophysiological domains in three CAP cohorts: emergency department, ward, and ICU. We ranked patients by their degree of immune dysregulation and developed a machine-learning classifier that was validated in external cohorts.
Results We identified three Dysregulated Immune Profiles (DIP) in 398 CAP patients - minor, moderate, and major dysregulation - and modeled immune dysregulation as a continuum (cDIP:0-1 range). Increasing cDIP was associated with a gradual increase in 30-day mortality and secondary infections ($p<0.001$), independent of disease severity. A simplified 3-biomarker machine-learning framework accurately predicted the 35-biomarker-based degree of dysregulation. The model's prognostic was validated in 4 independent cohorts of varying infections, severity, and care settings (n=766). Furthermore, a rise in cDIP from baseline to day 7 was associated with increased 30-day mortality ($p=0.001$).
Conclusions The 3-biomarker-based cDIP score stratifies patients in degrees of immune dysregulation, with prognostic value for clinical outcomes independent of care settings or severity.

Abstract 04

A robust SARS-CoV-2-specific T and B Cell response is associated with early viral clearance in SARS-CoV-2 Omicron-infected immunocompromised individuals

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Background The immunological determinants of delayed viral clearance and intra-host viral evolution that drive the development of new pathogenic virus strains in immunocompromised individuals are unknown. Therefore, we longitudinally studied SARS-CoV-2-specific immune responses in relation to viral-clearance and evolution in immunocompromised individuals.

Methods Among Omicron-infected immunocompromised individuals, we determined SARS-CoV-2-specific T- and B-cell responses, anti-spike IgG(3) titers, neutralization titers, and monoclonal antibody (mAb)-resistance-associated mutations. The 28-day post-enrollment nasopharyngeal specimen defined early (RT-PCR negative ≤28 days) or late (RT-PCR- positive >28 days) viral-clearance.

Results: Of 30 patients included (median age 61.9 years [IQR 47.4-72.3], 50% females), 20 (66.7%) received mAb-therapy. Thirteen (43.3%) demonstrated early and 17 (56.7%) late viralclearance. Early viral-clearance patients and patients without resistance-associated mutations had significantly higher baseline IFN-γ release and early viral-clearance patients had a higher frequency of SARS-CoV-2-specific B-cells at baseline. In non-mAb-treated patients, day 7 IgG and neutralization titers were significantly higher in those with early versus late viral-clearance.

Conclusion An early robust adaptive immune response is vital for efficient viral-clearance and associated with less emergence of mAb-resistance-associated mutations in Omicron-infected immunocompromised patients. This emphasizes the importance of early SARS-CoV-2-specific T- and B-cell responses and thereby provides a rationale for development of novel therapeutic approaches.

Abstract 05

Compartmentalization of calprotectin in sepsis by the type of underlying infection

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Background Sepsis following *Clostridioides difficile* infection (CDI) is associated with high mortality probably due to inflammation of the gut mucosa. Calprotectin is a measure of gut inflammation.
Methods A propensity-score matched analysis was designed to compare patients with sepsis due to CDI with septic patients due to other infections. Sepsis was defined according to Sepsis-3 definition and matching was done by Charlson's comorbidity index and SOFA score. Biomarkers and 28-day mortality were measured for both arms.
Results 132 patients with CDI were matched to patients with community-acquired pneumonia, hospital-acquired pneumonia, primary bacteremia and intrabdominal infection other than CDI (128, 74, 98, 117 patients respectively). No difference in mortality was found between CDI and non-CDI infections. Stool calprotectin was measured in 67 CDI patients (median=1008.0 μg/g, Q_1-Q_3=367.0-2783.0 μg/g) and in 149 non-CDI patients (median=120.1 μg/g, Q_1-Q_3=54.5-405.3 μg/g; (p-value<0.0001). Blood calprotectin was measured in 67 patients CDI patients (median=3.34 μg/g, Q_1-Q_3=1.6-6.0 μg/g) and in 196 non-CDI (median=79.6 μg/g, Q_1-Q_3=43.9-233.8 μg/g; p-value<0.0001).
Conclusions Among patients of similar severity and comorbidity burden CDI sepsis displays similar mortality to sepsis from other origin. Stool calprotectin seem to constitute an indicative biomarker of CDI sepsis.

Abstract 06

Emergence of a unique immune evasive SARS-CoV-2 variant during a persistent infection for 613 days in an immunocompromised patient

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Background Persistent SARS-CoV-2 infection in immunocompromised individuals is linked to viral evolution and is stimulated by targeted immune pressure, including monoclonal antibody therapy. Here, we report extensive SARS-CoV-2 evolution in an immunocompromised patient with a persistent infection for nearly 613 days until his death.
Case description We present a 72-year-old male patient with a history of allogeneic stem cell transplantation complicated by development of a posttransplant diffuse large B/cell lymphoma for which he received rituximab. In February 2022, he presented with a SARS-CoV-2 BA.1.17variant infection and was treated with sotrovimab without success. He showed development of known sotrovimab-resistance mutation S:E340K 21 days post-infusion. The following 600 days were characterized by several symptomatic COVID-19 episodes, requiring hospital admission. Longitudinal genome sequencing revealed an additional 50-nucleotide mutations compared to contemporary globally circulating BA.1-variants with multiple amino acid substitutions in the ACE-2 receptor binding site and several deletions in the spike N-terminal domain, indicative of immune-escape. The patient died due to relapse of his underlying illness in October 2023.
Conclusions This case underscores the risk of persistent SARS-CoV-2 infection in immunocompromised individuals as unique SARS-CoV-2 variants may emerge. Therefore, we emphasize the importance of longitudinal genomic surveillance of SARS-CoV-2 evolution in immunocompromised individuals.

Abstract 07

Characterization of host-response heterogeneity in the sepsis transcriptome using two immune axis scores

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Background Host responses during sepsis are highly heterogeneous, complicating the identification of patients at risk of mortality or those potentially benefiting from targeted therapies. Previous studies have identified transcriptomic endotypes to assist with this challenge, to classify patients into categories. Here we introduce a two-dimensional framework for measuring paents' immune system heterogeneity using two continuous "immune-axis" scores.
Methods Whole-blood transcriptome was measured in 479 patients with sepsis at ICU admission using microarray (U219). Genes related to the immune system were selected and principal component analysis (PCA) analysis was performed. The first two PC scores are taken as the immune-axes scores. Gene-set enrichment analysis (GSEA) was performed on the gene loadings to reveal the pathway directionality of the axes, implementing the Reactome database.
Results Positive scores on immune axis 1 (20.6% variance explained) were associated with neutrophil degranulation whereas negative scores with antigen processing. Positive scores on immune axis 2 (11.1% variance explained) were associated with interferon signaling whereas negative scores with interleukin-1 signaling. Immune axes were significantly associated with MARS and SRS endotypes, including the continuous version SRSq ($p < 0.001$). Intriguingly only immune axis 2 was independently associated with mortality ($p = 0.02$), after adjusting for age and APACHE IV score.
Conclusions A 2D immune axis framework reveals relationships between existing endotype classifiers and provides further insights into host-response heterogeneity in sepsis.

Abstract 08

Unraveling sepsis epidemiology in a low- and middle-income ICU setting reveals the alarming burden of tropical infections and antimicrobial resistance: a prospective observational study (MARS-India)

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Background Our study addresses the sepsis research gap in lower middle-income countries, notably India. Here, we investigate community-acquired sepsis comprehensively and explore the impact of tropical microbiology on aetiology and outcomes.
Methods MARS-India was a prospective observational study from Dec-2018 to Sep-2022 in a tertiary-care hospital in South India. Adult patients within 24hrs of ICU admission meeting the Sepsis 3.0 definition were enrolled, with 6-months follow-up (ClinicalTrials.gov number NCT03727243).
Results Over 4000 patients were screened on ICU admission, with 1000 patients meeting the inclusion criteria. Median age was 55 years (IQR: 44-65) with a male preponderance (66%). Almost half the cohort resided in villages and 74·6% worked in the primary sector. Mortality in-hospital was 24·1%. Overall, ~54% had confirmed microbiological diagnosis. Over 18% had a viral cause of sepsis. Surprisingly, we identified leptospirosis (10·6%), scrub typhus (4·1%), dengue (3·7%) and Kyasanur forest disease (1·6%) as notables causes of sepsis. All these infections showed seasonal variation around the monsoon.
Conclusions In India, sepsis disproportionally affects a younger and lower socio-economic demographic, yielding high mortality. Tropical and viral sepsis carry a significant burden. Analyzing local data, we pinpoint priorities for public health and resources, offering valuable insights for global sepsis research.

Abstract 09

Attributable mortality of intensive care unit-acquired acute kidney injury: a prospective cohort study

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Background Acute kidney injury (AKI) acquired in the intensive care unit (ICU) more than 48 hours after admission (ICU-acquired AKI) is commonly caused by sepsis. This study aimed to determine the attributable mortality of ICU-acquired AKI and analyzed plasma biomarker trajectories from ICU admission to AKI diagnosis.
Methods We prospectively studied adults in two Dutch ICUs from 2011 to 2019, who stayed at least 48 hours without initial AKI. Using RIFLE criteria, we identified new onset ICU-acquired AKI and adjusted for disease progression and nephrotoxic medications via marginal structural modeling. We also measured 21 sequential plasma proteins in a subset of patients, indicating activation in (anti)inflammatory, endothelial, and coagulation pathways.
Results Out of 4,228 patients with a length of stay >48h without AKI, 441 (10.4%) developed ICU-acquired AKI. The population attributable mortality fraction of ICU-acquired AKI was 10.2% (95% confidence interval [CI] 6.3-15.2) by day 10 and 16.3% (95%CI 12.1-24.9) by day 20. Compared to those without AKI, patients with ICU-acquired AKI exhibited increasingly higher levels of biomarkers over time reflecting inflammatory and endothelial activation.
Conclusions Our findings indicate that ICU-acquired AKI substantially contributes to mortality and is linked to marked changes in inflammatory and endothelial biomarkers, highlighting the need for targeted preventive strategies.

Abstract 10
A new endotype of sepsis driven by interferon-gamma

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Background Macrophage activation-like syndrome (MALS) and immunoparalysis are the best characterized sepsis endotypes, so far. Interferon-gamma (IFNγ) action on tissue macrophages stimulates the release of the cytotoxic chemokine CXCL9. It was investigated if this may be an independent sepsis endotype (IDS).
Methods A total of 14 patient cohorts from Greece, Germany and Italy were studied. They were 2:1 randomly split into discovery and validation sets. Concentrations of IFNγ, CXCL9, IP10, and ferritin were measured.
Results A total of 5503 patients were studied; 3670 in the discovery and 1833 in the validation sets. IDS was defined as detectable IFNγ and CXCL9 more than 2200 pg/ml. The frequency of IDS in the discovery set was 8.6% and in the validation set 9.1%. IDS patients did not have traits of immunoparalysis contrary to patients with non-detectable IFNγ in the blood. The mortality by IDS was 39.2% in the discovery set and 41.0% in the validation set. IDS was an independent risk factor for death under the presence of other endotypes, severity scores and organ dysfunctions (hazard ratio 1.84 in the discovery set and 2.37 in the validation set) and also in each subgroup (see Figure).

Conclusions IDS is a new sepsis endotype independently associated with unfavorable outcome.

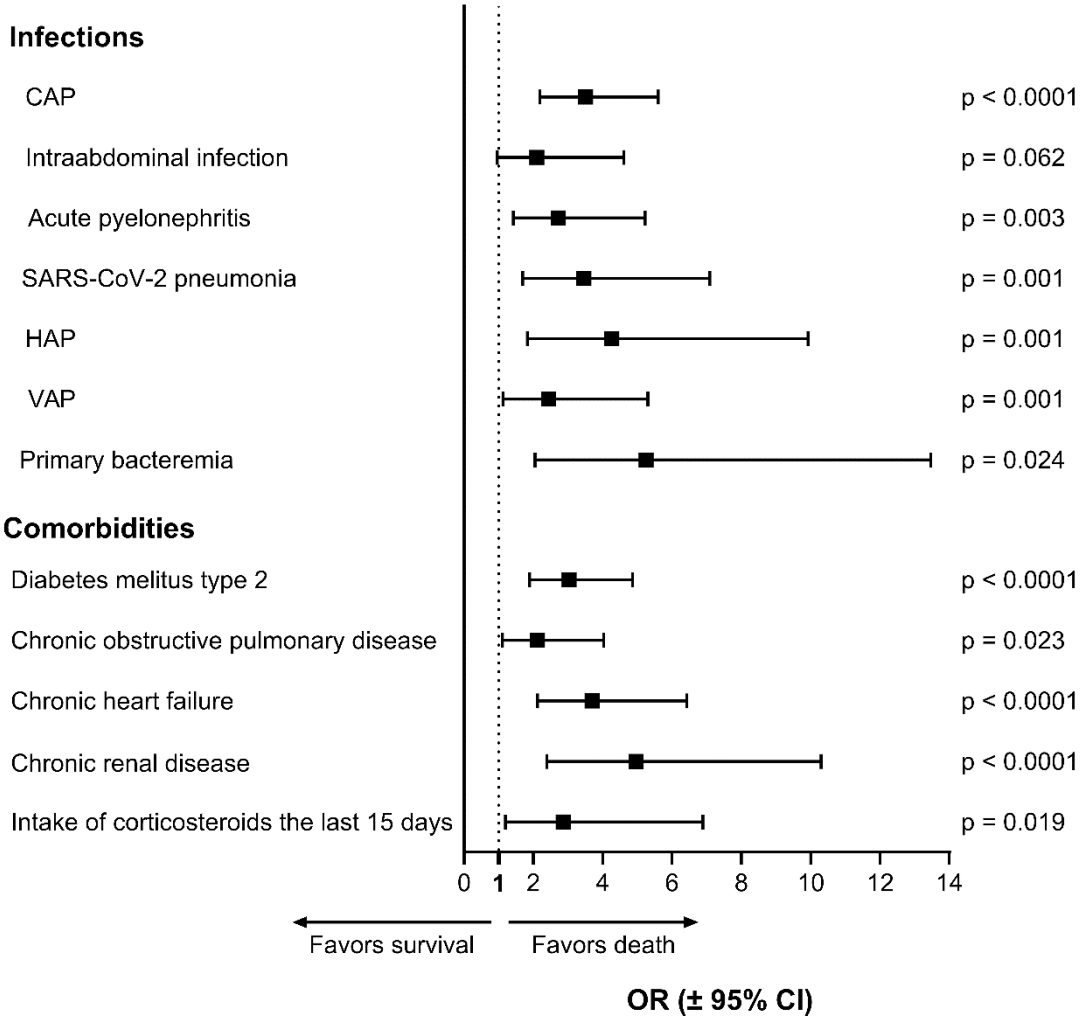

Figure The odds ratio (OR) for death in each subgroup by the IDS endotype
CI: confidence interval

Abstract 11
Precision bezlotoxumab treatment for *Clostridioides difficile* infection

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Background *Clostridioides difficile* infection (CDI) may lead to organ dysfunction and death. Early risk stratification guided immunotherapy is warranted.
Methods BEYOND study was conducted into two stages. The first stage involved the development of a risk score for adverse outcome. The second stage was a randomized, double-blind controlled trial; patients with a positive score were assigned to standard-of-care treatment plus either Bezlotoxumab (monoclonal antibody against *C. difficile* toxin B) or placebo. The primary outcome was the incidence of adverse outcome: progression into organ dysfunction, CDI relapse and/or death.
Results The first stage involved 153 CDI patients and 150 comparators. The newly defined BEYOND score integrated decreases of hemoglobin, increases of blood urea and interleukin-8 concentrations, carrying G allele of rs2091172, and the presence of *Terrisporobacter glycolycus*, *Enterococcus avium* and *Anaerovorax odorimutans* in the stool. The score has 84.6% sensitivity and 95.8% specificity for the early prediction of adverse outcome. At the second stage, forty-four patients were enrolled. The primary endpoint was met in 72.7% (51.9 to 86.9%) in the placebo arm and 31.8% (16.4 to 52.3%) in the Bezlotoxumab arm (absolute difference, 40.9%; 11.4% to 61.9%; p=0.015). No drug-related adverse events were reported.
Conclusions BEYOND score can accurately predict adverse outcome in CDI patients and guide efficient Bezlotoxumab treatment.

Abstract 12
Effects of delayed consent on patient`s characteristics in sepsis

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Background The ethical adequacy of enrolling patients unable to give informed consent is not undisputed as it may violate the patient's right to participate in a clinical trial free of will. As a consequence, state authorities and ethical boards may insist of restricting research to patients capable of giving informed consent.
Objective To describe characteristics and outcome depending on the informed consent process at enrolment in patients with sepsis. We hypothesize that patients incapable of giving informed consent form a unique phenotype of sepsis.
Methods We conducted a post-hoc analysis of the randomized multicenter trials MAXSEP [1], SISPCT [2], and CandiSep [3]. Patients were stratified according to their ability to give informed consent at enrolment. Patients unable to give informed consent were either enrolled by obtaining informed consent from a previously appointed legal representative or by a deferred consent process.
Results 1981 patients included into this analysis (Table). Patients unable to give informed consent were more severely ill reflected by higher APACHEII and SOFA-scores, and higher 28-day mortality (Table). Pneumonia was less frequent in patients able to give informed consent (25.8% vs. 43.2%; p<0.001).

Table: Baseline Characteristics

Patient status to give informed consent at enrollment	**Able (n=407)**	**Unable (n=1574)**	**p-value**
Age (years)	66.0 [54.0-75.0]	69.0 [58.0-76.0]	0.012
Male sex	250 (61.4%)	1017 (64.6%)	0.247
SOFA at baseline	8 [6-10]	10 [8-13]	< 0.001
APACHE II	19 [16-23]	23 [19-29]	<0.001
Lactate (mmol/l)	2.4 [1.6-4.1]	2.8 [1.7-4.8]	0.007
Procalcitonin (ng/ml)	8.2 [2.6-34.1]	6.8 [1.5-23.0]	0.007
Septic shock (SEPSIS-3)	168/400 (42.0%)	912/1560 (58.5%)	<0.001
Vasopressors /inotropes	287 (70.5%)	1451 (92.2%)	<0.001
Mechanical ventilation			<0.001
None	276 (68.0%)	172 (11.0%)	
Non-invasive	87 (21.4%)	275 (17.7%)	
invasive	43 (10.6%)	1110 (71.3%)	
28-day mortality	67/399 (16.8%)	456/1561 (29.2%)	<0.001

Continuous data: median and interquartile range (p-value: Mann-Whitney-U-Test); Categorical data: frequency and percentage (p-value: Chi-squared test or Fisher's Exact Test as appropriate).

Conclusions The pooled data from three large German multicenter trials show marked differences in disease severity, sepsis characteristics and outcomes depending on the ability to give informed consent.

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Abstract 13

Syndecan-1 as a marker of glycocalyx injury: association with host response biomarker changes across five pathophysiological domains in patients with community-acquired pneumonia

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Background Endothelial glycocalyx degradation plays a pivotal role in pneumonia, for which syndecan-1 is an established biomarker. Previous studies linked syndecan-1 to clinical outcomes without fully exploring its role in pneumonia's pathophysiology.
Methods We studied admission samples of three community-acquired pneumonia (CAP) cohorts: emergency department, general ward, and ICU. We determined the association between syndecan-1 tertiles and 34 biomarkers reflective of five pathophysiological CAP domains: endothelial cell activation, coagulation activation, systemic inflammation, cytokines, and neutrophil degranulation.
Results Increased glycocalyx degradation, as reflected by syndecan-1 tertiles, was associated with higher 30-day mortality ($p<0.001$) and an increased proportion of immunosuppression, chronic kidney disease and diabetes. Each domain showed a positive association with syndecan-1. Increased syndecan-1 was particularly associated with heighted coagulation activation followed by systemic inflammation and endothelial cell activation. On a single biomarker level, D-dimer and sTREM-1 showed the strongest increase with increasing syndecan-1 (both $p<0.001$). Conversely, ADAMTS13 decreased with an increase in syndecan-1 ($p<0.001$).
Conclusions The degradation of the glycocalyx, marked by syndecan-1, is highly associated with the coagulation activation and systemic inflammation. The strong positive association with coagulation activation and D-dimer and the negative association with ADAMTS13 might hint that glycocalyx degradation in CAP leads to a prothrombotic state.

Abstract 14

Anakinra efficacy in COVID-19 pneumonia guided by soluble urokinase plasminogen activator receptor: association with the inflammatory burden of the host

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Background Anakinra was approved by the European Medicines Agency and received Emergency Use Authorization by the Food and Drug Administration of the United States for patients with COVID-19 pneumonia at risk for severe respiratory failure (SRF) with blood levels of the biomarker suPAR (soluble urokinase plasminogen activator receptor) ≥ 6 ng/ml. We report the final results of the phase II open-label single-arm trial SAVE trial in a larger population (NCT04357366).
Methods Patients with COVID-19 pneumonia and suPAR levels ≥6 ng/ml received subcutaneously anakinra 100mg once daily for 10 days. The primary outcome of the the incidence of SRF by day 14 was associated with the inflammatory burden of the host as expressed by the median levels of biomarkers.
Results From March 2020 to March 2022, 992 patients were enrolled. The incidence of SRF was 18.8% being similar to the results of the phase III pivotal trial SAVE-MORE. Using comparators of the pivotal phase III trial, it was found that prevention of the incidence of SRF using anakinra was similar among patients subgrouped by the levels of inflammatory mediators and D-dimers.
Conclusions We conclude that suPAR-guided anakinra treatment in COVID-19 pneumonia resulted in similar clinical outcomes irrespective the level of inflammation.

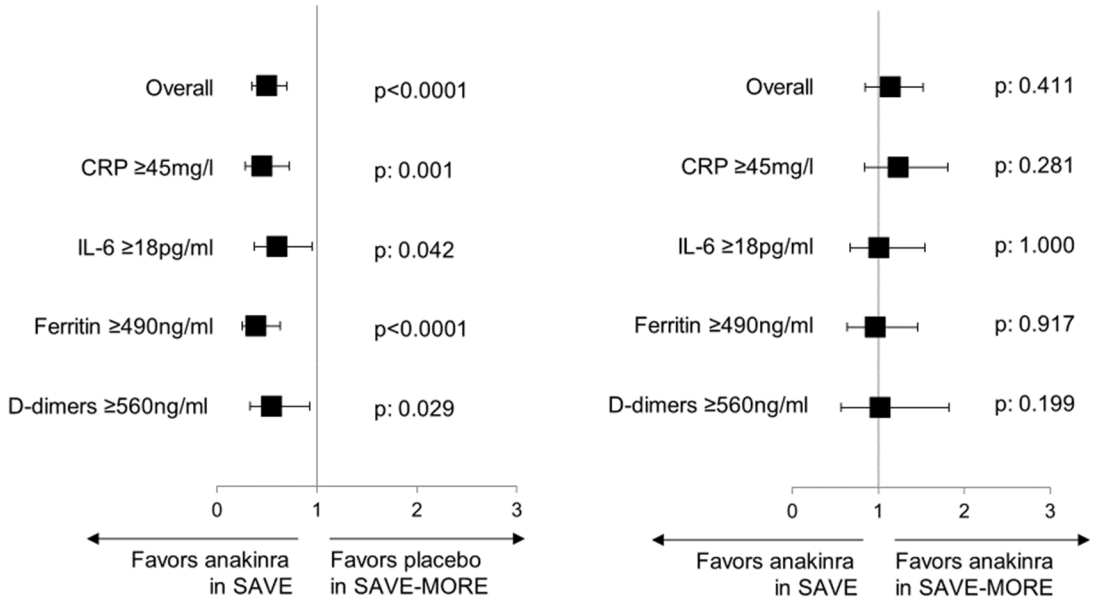

Figure: Exploratory analysis of the progression into SRF in relation to the degree of inflammation and coagulation between participants of the SAVE and SAVE-MORE trials

The organizers of the International Symposium on Immunotherapy of Severe Infections wish to express their gratitude to our supporters

ELPEN

Hellenic Institute for the Study of Sepsis

Menarini Hellas

ImmunoSep (Horizon 2020 grant 847422)

Radboud UMC

Sobi AB (publ)

Uni-Pharma, Kleon-Tsetis