Present and Future Considerations for Sepsis Management

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IN A HIGHLY interesting session on sepsis management during the 33rd annual European Congress of Clinical Microbiology and Infectious Diseases (ECCMID) congress, held in Copenhagen, Denmark, between 15th–18th April, speakers discussed the definition of sepsis, as well as the present and future considerations for sepsis management. The session was co-chaired by Thierry Calandra, Lausanne University Hospital, Switzerland, and Willem Joost Wiersinga, Division of Infectious Diseases of the Amsterdam University Medical Centers (UMC), University of Amsterdam, the Netherlands.

Calandra introduced the International Sepsis Forum (ISF), a not-for-profit organisation, with a mission to reduce the global burden of sepsis and improve the care of patients with sepsis. Calandra presented the joint ISF-ECCMID Sepsis Award to Claire Dahyot-Fizelier, University of Poitiers, France, who went on to present their session on the use of ceftriaxone to prevent early ventilator-acquired pneumonia (VAP) in patients with brain injuries and are comatose.

PREVENTING EARLY VENTILATOR-ACQUIRED PNEUMONIA

Patients with brain injuries in intensive care units (ICU) are particularly vulnerable to VAP, yet very little research has been completed. Prior to 2013, only one trial reported the beneficial effect of antibiotic-prophylaxis after tracheal intubation.

A randomised double blind, placebo-controlled clinical study conducted by Dahyot-Fizelier and colleagues aimed to assess the efficacy of a single dose of ceftriaxone (2 g) in preventing early VAP. The trial included patients from eight centres in the 'AtlanRea' research network. The secondary goals were to measure the incidence of all-VAP and type of bacteria, antibiotic exposition, mechanical ventilation exposition, ICU and hospital stay, neurological prognosis, and mortality.

A total of 345 patients were randomised into two groups to receive ceftriaxone or placebo 12 hours after tracheal intubation, where the primary outcome was the proportion of patients developing an early-VAP, with a cut-off period of 7 days.

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Patients who received ceftriaxone displayed a decreased risk of developing early-VAP, from 33% to 14%. The same trend was observed for the secondary outcomes. At Day 15, the median ICU free-days and median hospital-free days were higher in the ceftriaxone group, and no safety complications or difference in resistance acquisition were observed within these groups. Dahyot-Fizelier concluded by stating that a single dose of ceftriaxone protects patients with brain injuries from early-VAP, antibiotic and mechanical ventilation exposition, and mortality (at Day 28), as well as ICU and hospital exposition (at Day 60).

PROGNOSTIC AND PREDICTIVE ENRICHMENT IN SEPSIS

Tom van der Poll, Department of Medicine, Amsterdam UMC, University of Amsterdam, the Netherlands, emphasised that precision medicine for sepsis is only in its infancy. They discussed the introduction of prognostic and predictive enrichment in sepsis, where prognostic enrichment refers to the selection and classification of patients with high or low risk of mortality. Van der Poll recommended that patients with a good prognosis (i.e., a low mortality risk) should be treated with standard of care, whereas predictive enrichment should be applied to predict which patients may benefit from certain interventions.

Van der Poll discussed the SCARLET trial, which evaluated the effect of soluble thrombomodulin, an anticoagulant protein, in patients with sepsis. The researchers attempted to enrich the population in a prognostic and a predictive manner. For prognostic enrichment, they selected patients based on cardiovascular and/or respiratory failure; however, for predictive enrichment, they solely selected patients with coagulopathy. Van der Poll discussed various clinical trials that have utilised proteomic analysis to aid informed treatment decisions. The speaker reviewed the need to identify patients who may benefit from soluble thrombomodulin treatment and emphasised the need for the integration of real-time spatial-dynamic information on the host response linked to clinical decision-making tools.

Van der Poll concluded by acknowledging that sepsis is highly complex, non-linear, and spatially dynamic system. The complexity of sepsis cannot be fully understood by single-timepoint and reductionist studies, hence the focus should be on longitudinal and continuous biological data collection. They stated that the complexity of sepsis will require a huge multidisciplinary effort, wherein computational approaches derived from complex systems science must be integrated with biological data.

IMPROVING SEPSIS DIAGNOSIS

Brigitte Lamy, Nice University Hospital, France, highlighted that patients with sepsis are a highly heterogenous population, thereby increasing the demand for personalised medicine. A higher rate of mortality was observed when the time to receive the appropriate antimicrobial treatment was more than 12 hours; hence, fast diagnosis is necessary to avoid these complications.

Lamy listed the various characteristics of an ideal diagnostic test, such as an accurate, rapid, inexpensive test that can be performed directly on (blood) samples and available at a point of care (<30 minutes). The ideal test would also remain unaffected by antimicrobial therapy, be able to differentiate contaminants from pathogens, and would permit informed decision making regarding antibiotic choices. Lamy offered recommendations to tackle the issue of high heterogeneity in patients by using biomarkers, artificial intelligence, and microbiological findings, as well as the prospect of using a single biomarker to accurately identify patients with sepsis. They acknowledged that new biomarkers are currently being investigated, such as circulating microRNA, as well as endothelial-related biomarkers aimed at indicating severity and predicting sepsis incidence.

Lamy concluded by stating that the cost-effectiveness of these rapid methods is still unclear; emerging and promising technologies are rapidly becoming available, but it is too early to have firm evidence on whether they can help with sepsis diagnosis. Hence, there is a need for better diagnostics permitting for the rapid identification of pathogens and characterisation of the host response, well-designed clinical trials with enrichment strategies to better manage patient heterogeneity, and biomarker tests for sepsis.

CONCLUDING REMARKS

The session went on to discuss sepsis management in low- and middle-income countries, as well as implementing biomarker-driven immunotherapy. Flavia Machado, Federal University of São Paulo, Brazil, highlighted the importance of understanding challenges, increasing awareness, prevention, and survivorship, as well as improving recognition, treatment, and research capacity.

Evangelos Giamarellos-Bourboulis, National and Kapodistrian University of Athens, Greece, underscored the main challenge of patient heterogeneity and emphasised the need for biomarker-guided therapeutics. Giamarellos-Bourboulis discussed the need for biomarkers that are informative to a degree, whereby certain pathways that, for example, impact mortality can be directly targeted using therapies, thereby advocating for the treatment based on biomarkers, irrespective of physical and clinical signs.

A common theme throughout this session revolved around personalised medicine in sepsis management being a rapidly emerging and promising field, with substantial potential to improve patient outcomes. However, further randomised controlled trials are requisite to investigate the feasibility of utilising biomarkers for sepsis management. ●

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