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FORO CLÍNICO

The challenges of long-term sepsis survivors: when surviving is just the beginning

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CASE REPORT

A 72 year old man with uncontrolled diabetes and hypertension arrives at the emergency room due to shortness of breath. He's diagnosed with community acquired lobar pneumonia and admitted for observation and empiric antibiotic therapy. Three days later the patient is found agitated, confused and unable to recognize his son. The shortness of breath worsens later in the morning culminating in intubation and mechanical ventilation. Following admission to the intensive care unit (ICU) he develops normocytic anemia, acute renal failure requiring dialysis, and elevation of liver enzymes. Ten days later his condition starts improving. Finally, 32 days after admission the patient is ready to be discharged. He has survived severe sepsis, and does not require further renal substitution, but is persistently weak, short of breath, and confused. What is new in our understanding of sepsis survival? What is the short- and long-term prognosis? What can the medical team do to reduce mortality and improve quality of life following sepsis?

Defining sepsis, severe sepsis, and septic shock

The term sepsis is attributed to Hippocrates, originally referring to a process of decomposition.[1,2] Sepsis is a syndrome where acute systemic inflammatory response occurs due to local or systemic infection.[3] However, in at least a third of patients with sepsis an infectious organism is never recovered, suggesting that –when released in massive concentrations– endogenous (damage-associated) antigens may also trigger sepsis[3-6] (Table 1). Severe sepsis is sepsis in the presence of organ failure. Septic shock refers to severe sepsis with refractory hypotension despite adequate fluid resuscitation. There is considerable clinical overlap between severe sepsis and septic shock, and clinical distinction can be difficult. Severe sepsis and septic shock have to be addressed promptly as both are acutely lethal. In fact, the grim progression of sepsis to severe sepsis and septic shock can occur quickly and often without warning.[7,8]

Several pillars of modern medicine have postulated theories as to the origins of sepsis (Table 2). The first breakthrough in the understanding of sepsis came with the discovery of microbes. Microbes, however, can be only a part of the problem. In fact, humans rely on symbiotic interactions with many Bacteria, Archaes, Eukarya and their viruses, a group of microorganisms collectively known as the

Table 1. Clinical manifestations of sepsis.

- Body temperature higher than 38 °C or lower than 36 °C.
- Heart rate higher than 90/min.
- Hyperventilation evidenced by respiratory rate greater than 20/min or $PaCO_2$ lower than 32 mmHg.
- White blood cell count greater than 12,000 cells/μL or lower than 4,000/μL.

In the presence of suspected or confirmed infection, or massive tissue damage (e.g., trauma, burns, pancreatitis), the presence of one or more should set off the alarm for a diagnosis of sepsis.

Table 2. Historical perspective of sepsis.

Thinker	Seminal idea	Year
Hippocrates	Coined the term sepsis as a process of decomposition.	400 BC
Galen	Proposed sepsis was needed for wounds to heal.	Before 199 AD
van Leeuwenhoek	Documented microbes he called *animalcules*.	1674
Semmelweiss	First to draw a connection between hand washing and reduction of puerperal sepsis.	1841
Lister	Introduced the concept of antisepsis for wounds.	1867
Pasteur	Found microbes are responsible for infections. Birth of the *Germ Theory of sepsis*.	1878
Pfeiffer	Discovered endotoxin and its ability to induce disease in the absence of infection.	1894
Fleming	Discovered penicillin, hinting at the end of infections and sepsis.	1929
Rich and Lewis	Discovered *transmissible factors* (cytokines) produced by the immune system. Birth of the *Cytokine Theory of Sepsis*.	1932
Dinarello and Wolff	Discovered the role of Interlekin-1 in sepsis.	1978
Tracey, Beutler, Cerami	Discovered the role of TNF as inducer of mortality and severe sepsis in the absence of infection.	1986

microbiota.[9] Our interactions with microbes are crucial for normal mammalian metabolic,[10] immunologic,[11] and intellectual development.[12] At least 1,000 different bacterial species are known to inhabit the human gut, with each subject harboring an average of 160 of these species.[13] Translating this information into genetic currency lends a humbling perspective: the human genome consist of 20,000 genes, while a human carries somewhere between 5 x 10^6 to 8 x 10^6 microbial genes, at least 3 x 10^6 of which reside in the gastrointestinal tract. Therefore, something different within the germs we carry could also impact sepsis. Pfeiffer discovered that lipopolysaccharide, a product released by gram-negative bacteria, is able to cause disease and death, even in the absence of live bacteria.[2,14] This, with critical contributions by Dinarello, Cerami, Tracey, and Beutler launched the Cytokine Theory of Sepsis, focusing on the ability of cytokines and chemokines produced by the immune system to cause sepsis.[15,16]

MAKING SENSE OF THE NUMBERS: THE CONNUNDRUM OF SEPSIS SURVIVAL

Sepsis is one of the top ten causes of death, with an overall acute mortality rate of 20-30%.[5,17] Although complete data from underdeveloped countries remains scarce, the incidence of sepsis seems to be similar to that of developed countries. However, early mortality, including in-hospital as well as 28-day, is higher in lower income regions.[18] A systematic approach leading to the quick identification of sepsis cases followed by early treatment is, however, missing in much of the world. The treatment paradigm consists of empiric antibiotics, fluids, and supportive care. This is relatively simple to attain, even in underprivileged settings, and its early initiation is critical in order to improve outcomes and reduce mortality. While early mortality has decreased, the number of new cases of sepsis has increased, with a calculated annualized increase of 8.7% between 1979 and 2001 in the USA, leading to an ever-expanding population of sepsis survivors.[17] This indicates that surviving sepsis is a more attainable outcome, particularly with better recognition algorithms, and faster initiation of fluid resuscitation and antibiotic therapy. The big current challenge is the poor functional prognosis and high mortality of survivors.

Unfortunately, the challenges of a patient who survives severe sepsis persist long after the acute illness. Five-year mortality rates in adult survivors are alarming, with an overall rate of 75-80%, and this mortality trend continues for at least 15 years after discharge.[19-21] In contrast cancer a much better recognized -and feared- public health problem, has an overall 5-year mortality rate in the US of 33.8%.[22] The best predictors of long-term mortality are advanced age, number of comorbidities, organ dysfunction –the more organs failing before discharge, the higher the long-term mortality–, and being discharged to a continued care facility instead of home.[19,21] Survivors of severe sepsis have impaired quality of life and significant cognitive decline, often requiring continuous support for activities of daily living.[19-21,23,24] Despite the magnitude of the medical problem, as well as its human and financial costs, the pathogenesis and mechanisms underlying the morbidity and mortality of the so called severe sepsis survivor syndrome are largely unknown.

A BRIEF OVERVIEW OF PATHOGENESIS OF LATE SEPSIS

Sepsis is by definition triggered by infection, although there is evidence indicating it can occur in response to sterile injury (e.g., blunt trauma, or severe burns). In the face of infection or damage, the host immune system activates a response against the pathogen –or host-derived–antigens in an attempt to reduce local damage, and to prevent its dissemination. This otherwise normal response can turn deleterious, inducing organ and tissue damage and subsequent acute organ dysfunction. Only a small minority of patients with infections will ever develop sepsis. That underscores two key factors: pathogen load and virulence on one side, and host response on the other. To exemplify pathogen-related factors, in 2009, México and most of North and Central America suffered an outbreak of influenza A(H1N1) that was highly aggressive, highly lethal, and attacked populations usually spared from critical illness: the young and healthy.[25] As an example of host-related factors, single nucleotide polymorphisms of caspase 12 –occurring spontaneously in a subset of subjects of African ancestry– increase the susceptibility to develop sepsis.[26] However, most cases of sepsis develop in circumstances where a clear host factor cannot be identified. Below is a personal view of the current understanding of late sepsis. For a thorough review of the mechanism of acute sepsis, I prompt the reader to the excellent review by Derek Angus and Tom van der Poll.[6]

The host

Host response to infection or tissue damage is heterogeneous, and molded by previous health status and comorbid conditions. Although cytokines have a clear role in acute sepsis, their role in sepsis beyond the first 96 h is not clear, in part because most cytokines are no longer detected in the circulation just hours to a few days after sepsis onset, and because the dynamic mechanism of induction, release, and action of cytokines in sepsis is not well understood.

Mitochondrial failure

Mitochondrial dysfunction is an appealing candidate for sustained damage in sepsis survivors. Cellular hypoxia during severe sepsis can interfere with ATP production,[27] impaired delivery of pyruvate to the mitochondria, defective electron-transport function, inhibition of the citric acid cycle, and increased mitochondrial membrane permeability.[27,28] Apoptotic cells have a disrupted electron transport system induced by caspase activity upon the mitochondrial electron transport chain.[29] In an environment of increase metabolic demands, mitochondrial dysfunction leads to a decrease in ATP production. Also, redox changes occurring in response to mitochondrial failure can modify the redox environment, which in turn than can magnify sepsis by inducing postranslational modifications of high-mobility group box 1 (HMGB1) that make it either a powerful chemoatractant, or a cytokine-inducer.[30,31]

Cytokines and chemokines

The field of sepsis has been seduced by a reductionist approach to the role of cytokines. Cytokines and chemokines have pleiotropic biological activities that can be beneficial or damaging to the host.[16] One problem of most studies addressing the role of cytokines in the pathogenesis of sepsis is that they base their conclusions on snapshots of individual –or groups of– cytokines going in one direction or the other. Unfortunately, most cytokines are elevated for short periods in a tightly choreographed and poorly understood pattern. For the most part, basic research in sepsis is aimed at understanding acute sepsis, while clinical evidence indicates that sepsis survivors (around two thirds of patients) will have persistent morbidity and highly increased mortality for which we have no explanation, less so a solution. Early during sepsis tumor necrosis (TNF), interleukin (IL-6), HMGB1, and other cytokines activate an *en-masse*, non-specific inflammatory response in an attempt to limit invasion and control damage in response to severe infection or trauma. A role of TNF and HMGB1 in early sepsis is clear. In experimental sepsis *a priori* inhibition of TNF or HMGB1 reduces early mortality.[32,33] At this point, predicting sepsis in clinical settings is next to impossible. Therapeutic strategies targeting early inflammation (e.g., anti-TNF antibodies) have systematically failed clinically, a reflection of a simple fact: in most scenarios, sepsis will be suspected only after the early inflammatory cascade triggering systemic inflammation has already passed. If the mechanism of early sepsis is unclear, even less is known about the pathophysiology of sepsis beyond the first hours. At that point, it is clearly too late to target early mediators, which explains in part why anti-TNF[34] and anti-IL-1[35] strategies have failed to prove clinical benefit. Those human trials make clear that a better understanding of sepsis is need-

ed. The GenIMS study found levels of IL-6, TNF, and IL-10 to be low or undetectable in the majority of patients with sepsis secondary to community acquired pneumonia, and the only reliable predictor of mortality was the concomitant elevation of IL-6 and IL-10.[36,37] Members of group 1 caspases (caspase-1, -5, -11, and -12) are involved in cytokine maturation, rather than apoptosis.[26,38,39] Some of those are indispensable for the activation of the inflammasomes, a group of intracellular sensors of damage, either exogenous (e.g., pathogen-associated), or endogenous (e.g., mediated by tissue damage-).[40-42] Activation of the inflammasomes results in the activation of caspase-1 and, in turn, maturation of members of the IL-1 cytokine family. Inflammasome activation leads also to the release of HMGB1.[43]

The continuum between inflammation and immunosuppression

The concept of a late compensatory anti-inflammatory state in sepsis survivors, originally proposed by Meakins,[44] and later championed by Bone[45] is based on increased susceptibility to secondary infections, as well as limited *in vivo* response to recall antigens and *ex vivo* cell migration and activation assays done with immune cells derived from a subset of patients. Lymphoid apoptosis has been found in patients who die of severe sepsis,[46,47] and although controversial,[3] is a potential explanation for the immunosuppressive state observed in a subset of survivors. On the cytokine arena, the GenIMS study has shown concomitant elevation of pro-inflamatory (IL-6) and anti-inflammatory (IL-10) cytokines, supporting the notion of septic patients facing dysregulated inflammation, rather than moving from a purely inflammatory response to the opposite end.[48] In experimental acute sepsis, the first hours are marked by sharp increases in circulating TNF and IL-6;[49] however, a few days after sepsis onset only chemokine [C-X-C motif] ligand (CXCL) 1, IL-6, and HMGB1 are detectable in circulation,[50] and only HMGB1 is increased after the second week. One possible solution is to find late-occurring cytokines or chemokines that can better explain the sustained inflammation observed in sepsis survivors.

Damage-associated molecular patterns (DAMPs) as key actors of sepsis: the role of HMGB1 and CIRP

I will focus on the two DAMPs that have demonstrated to be key mediators of human sepsis: HMGB1 and cold-inducible RNA-binding protein (CIRP).

HMGB1 is an abundant, highly conserved nonhistone protein that is released by innate immune cells in response to bacterial and other pathogenic molecules, as well as in response to tissue injury.[51]

Experimental animal models have shown that HMGB1 has a causative effect in sepsis. During experimental sepsis, HMGB1 is secreted later than TNF, IL-1β or IL-6.[32] HMGB1 is released in response to endogenous and pathogen-derived danger signals and according to the redox state of its conserved cysteine residues, can function as a chemo-attractant in the acute inflammatory phase of sepsis, a cytokine-inducing mediator in the transition to sustained inflammation, or a silent bystander during repair and resolution. Moreover, administration of anti-HMGB1 antibodies have been shown to prevent early mortality,[32] as well as cognitive impairment,[52] and sustained inflammation in experimental sepsis.[50,53] HMGB1 has a unique ability to activate diverse innate immunity receptors, including toll-like receptors (TLR) 2, 4, and 9; C-X-C motif receptor 4 (CXCR4); and the receptor for advanced glycation endproducts (RAGE).[54-57]

In experimental murine sepsis, HMGB1 follows an unusual pattern: An early burst in the immediate hours after surgical sepsis is followed by a drop below detection within 80 h. A second burst of HMGB1 can be detected two weeks after sepsis onset, persisting for at least eight weeks.[50] HMGB1 can undergo posttranscriptional modifications that modulate its extranuclear inflammatory activity. HMGB1 has three cysteines at positions C23, C45, and C106. Redox status of those cysteines critically influences its biological activities.[31,58] We recently found a well orchestrated pattern of redox modifications: An initial elevation of all-thiol HMGB1 –a powerful chemoattractant– occurred two to four weeks after sepsis starts. Then, an increase in the C23-C45 dysulphide form –cytokine-inducing– is observed. Later, between eight to 12 weeks after onset all three cysteines were sulphonated. This latter form is silent from an inflammatory perspective, probably corresponding to resolution of inflammation. The second peak of HMGB1 correlates with leukocytosis, splenomegaly and a peculiar expansion of splenic inflammatory monocytes.[50] It is possible that the increase in activated inflammatory monocytes and elevated HMGB1 are part of a vicious circle of persistent inflammatory feedback.

HMGB1 seems to be directly involved not only in experimental sepsis, but in the pathophysiology of human sepsis as well. HMGB1 is elevated in circulation in patients with sepsis,[59] and a higher circulating concentration correlates with higher mortality.[36] In patients with acute pancreatitis or severe burns, a higher concentration of HMGB1 correlates with disease severity and mortality.[60,61] In burned patients, a bimodal curve with rapid increase on day 1 is followed by a drop by day 3 and a secondary plateau between day 7 and day 21. The first spike in HMGB1 does not predict secondary sepsis, but during the second plateau, patients with sepsis had higher levels than non septic ones.[62] Targeting HMGB1 emerges as a potential tool for treating human sepsis. As mentioned above, HMGB1 is active via a series of different receptors. The early inflammatory effect of HMGB1 is mediated through the interaction of disulphide HMGB1 with TLR4,[50] while the late immuno-modulatory effect is mediated through CXCR4.[53] Potentially, anti-HMGB1 strategies could interfere in two moments in the inflammatory response: within the first hours after sepsis onset it could dampen the early inflammatory response (mediated by TLRs); later, during the first two to four weeks after onset, it could interfere with the persistent inflammatory feedback (mediated by CXCR4). As of today, no specific anti-HMGB1 treatment exists. However, recent evidence indicates that chloroquine inhibits HMGB1 release,[63] while atorvastatin downregulates TLR4 and RAGE, as well as NF-kB, its downstream pathway.[64]

CIRP is a member of the cold shock response proteins.[65] CIRP is constitutively expressed at low levels and is upregulated during mild hypothermia, hypoxia, and UV light exposure. Its role in human hemorrhagic shock and sepsis has been recently demonstrated, and its mechanism has been experimentally shown to be mediated through TLR4-MD2 interaction.[66] Further, as in the case of HMGB1, recombinant CIRP has been shown to induce murine sepsis, and neutralizing CIRP in sepsis attenuates disease and reduces mortality.[66] This early evidence deserves further investigation, as a role in human sepsis has not yet been demonstrated. However, if CIRP is found to be involved in sepsis, it could open novel therapeutic avenue.

TREATMENT

The recent history of failed trials for sepsis underscores the importance of better understanding of sepsis at all stages. For instance, an overview of several trials targeting molecules or pathways that had shown promise in preclinical studies starting with anti-IL-1 or anti-TNF,[35,67-70] and culminating with the recent withdrawal from the market of Drotrecogin alfa[71] is a good reminder of the great need to better understand the disease and develop translatable animal models. However, the lack of specific treatment does not mean lack of treatment options. On the contrary, I want to emphasize that the key aspect of sepsis management resides in its early recognition, leading to immediate directed treatment. This includes early fluid resuscitation; the use of empiric antibiotics targeted to the common local pathogens; and directed care as soon as sepsis is suspected.

The Surviving Sepsis Campaign has recently updated the evidence-based recommendation for management of acute sepsis and septic shock.[72] For practical reasons, the Surviving Sepsis Campaign intervention is divided in two parts.[72,73] The first is the resuscitation bundle, referring to the urgent measures that have to be initiated within the first 3 h after sepsis is suspected. The second bundle includes those interventions to be achieved within 6 h (Table 3) that will further guide individual management of sepsis.

Evidence clearly supports intervening as early as possible. The early goal-directed therapy (EGDT) trial evaluated a series of interventions focused on early identification of patients at high risk of cardiovascular collapse, with the ultimate goal of maintaining a close balance between oxygen delivery and consumption. The results, although derived from a single institution, indicate that EGDT significantly reduces mortality and outcome of patients with severe sepsis and septic shock.[74] EGDT focuses on early resuscitation with fluids to maintain central venous pressure in the 8-12 mmHg range, on maintaining a mean arterial pressure between ≥ 65 and ≤ 90 mmHg. Is it necessary to undergo invasive and expensive procedures in order to improve outcome? The ProCESS trial evaluated whether all elements of the EGDT are needed in order to increase survival. This trial showed that mortality and outcome were similar whether the assessment of adequate perfusion was clinical, or if central hemodynamic and oxygen saturation measurements were used.[75] Although the ProCESS trial failed to find differences in invasive *vs.* non-invasive management of early sepsis, the main message is that it encourages early recognition, early administration of antibiotics, and early volume resuscitation, over invasive hemodynamic measurements, as key elements

Table 3. A summary of the surviving sepsis campaign bundles.

To be completed within 3 h:

- Measure lactate level, and use it as an indicator of hypoperfussion.
  a) Central venous pressure 8-12 mm Hg; mean arterial pressure ≥ 65 mmHg.
  b) Urine output ≥ 0.5 mL/kg/h.
  c) Adequate central oxygen saturation (superior vena cava > 70%; mixed venous oxygen > 65%).
- Obtain blood cultures prior to administration of antibiotics.
- Administer broad spectrum antibiotics, even if blood cultures were not obtained.
- Administer 30 mL/kg crystalloid for hypotension or lactate 4 mmol/L.

To be completed within 6 h:

- Apply vasopressors for hypotension that does not respond to initial fluid resuscitation to maintain a mean arterial pressure ≥ 65 mmHg.
- In the event of persistent arterial hypotension or lactate ≥ 4 mmol/L (36 mg/dL).*
  a) Measure central venous pressure (CVP).
  b) Measure central venous oxygen saturation (CVO_2).
- Measure lactate again if initial lactate was elevated.*

* A note on points 6 and 7 from the 6 h bundle: Data obtained should be analyzed immediately as CVP, CVO_2, and lactate are critical for individualizing care.

to improve survival.[75,76] Recently published studies indicate that administration of albumin is not superior to crystalloids alone (ALBIOS study),[77] and that increasing the target mean arterial pressure to > 80 mmHg will not improve patient outcome (SEPSISPAM trial).[78] The source of infection has to be investigated and controlled early. For that purpose, a carful clinical examination, blood cultures, microbiology assessment of possible sites of infections, as well as imaging tests have to be put in place in parallel to the early resuscitation. As soon as a source of infection is found or a microorganism isolated, targeted therapy has to be initiated.

Although the broad applicability, as well as the therapeutic value of EGDT have been questioned, it is clear that early initiation of volume resuscitation and empiric antibiotics as soon as a patient with potential sepsis arrives to the emergency unit significantly reduce mortality.[72,74,75]

Altogether, the results of the recent trials summed to the Surviving Sepsis Campaign recommendations indicate that early resuscitation, initiation of antibiotics, and maintaining adequate perfusion with clinical measurements (mean arterial pressure, lactate level, urine output, sensorium, skin turgor and mottling) and can be incorporated into the treatment algorithm of sepsis even in hospitals lacking advanced diagnostic capabilities (e.g., absence of microbiological laboratory, invasive hemodynamic capabilities, or advanced imaging systems).

Last, an effort to educate medical and nursing staff in the early recognition and management of sepsis and severe sepsis can have remarkable results.[79] A multicenter educational program in Spain demonstrated that staff education around sepsis resulted in a significant reduction in ICU, in-hospital, and 28-day mortality.[80] According to the Spanish experience, simple nationwide educational efforts would translate into hundreds of lives saved each year. Nationwide efforts are, however, more difficult to attain than changes at a single institution. A single-institution educational program at a tertiary care hospital in Brazil demonstrated that the beneficial effects of education were not immediate, and compliance with the early treatment bundles took time to establish into the standard of care, but mortality decreased with increased program compliance.[81] A cost-effective measure is to enforce as much as possible immunization campaigns against the two most common causes of community acquired pneumonia: *Streptococcus pneumoniae* and influenza virus.[82] Unfortunately, rampant misunderstanding about the potential risks of immunization based on (at best) anecdotal data (e.g, the already disproved –but still believed by many– connection between immunizations and autism) is an accident waiting to happen with potential devastating effects for the community at large, as well as for the health system.

DISCUSSION

Sepsis is one of the most common causes of death in the world, a devastating problem for patients that leaves long-standing physical and intellectual wounds in survivors and their families.[5,6,17] Under adequate early treatment, around two thirds of patients with severe sepsis are expected to survive. Surviving sepsis is, however, not enough: sepsis survivors have a five-year mortality rate close to 80%, poor quality of life, and limited chances of a complete functional recovery.[83,84] Most survivors develop permanent physical and intellectual deficits of sufficient relevance as to interfere with their activities of daily living and hamper their ability to regain independence.[20,23] At particular risk are those at the ends of the age spectrum,

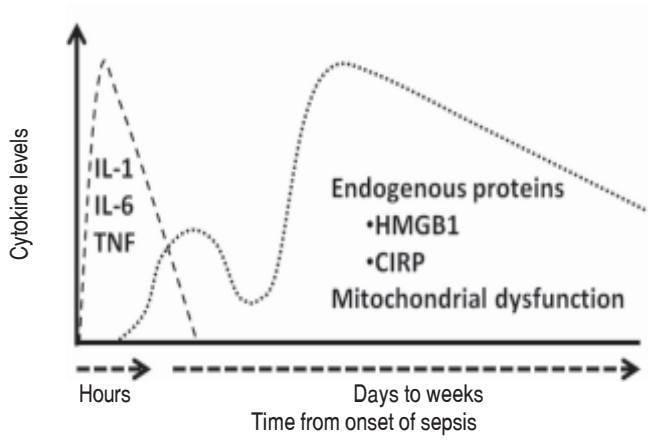

Figure 1. *Late inflammatory mediators are also potential therapeutic targets for established sepsis. While targeting early-occurring cytokines has proven unsuccessful due to the very tight window of therapeutic opportunity, focus on later mediators of sepsis, like HMGB1, is gaining interest. Those targets open the therapeutic window for days or weeks after sepsis starts, potentially making sepsis-specific treatment an attainable goal.*

those with multiple organ failure or required ventilator support, and those with cognitive decline.[85] As Iwashyna has pointed out, sepsis survivorship is the defining challenge of critical care in the 21st century.[84]

In order to find new therapeutic options for survivors, reducing long-term mortality, and improving their quality of life we first need a far better understanding of the adaptive immunological mechanisms at work during the transition to sepsis survival. At present, our understanding of both the acute stage and the persistent pathophysiologic changes of sepsis survivors is very limited. Current experimental models addressing severe sepsis try to extrapolate findings from tightly controlled animal models to a highly heterogeneous clinical syndrome. What is taking place on a daily basis in our ICUs oftentimes has only a vague resemblance to what happens in the controlled experimental setting of a laboratory. The relevance of analyzing survival in order to understand the adaptive pathophysiology of sepsis survivorship cannot be overemphasized. Understanding the sequence of responses to inflammation and tissue damage, as well as adaptive (and maladaptive) responses is necessary to define novel therapeutic targets that can be translated into better patient care of acute sepsis and a reduction in the burden of morbidity of survivors of severe sepsis. Although inflammation and cytokines have been historically tied to the pathogenesis of acute sepsis, the chain of events in survivors to acute sepsis is poorly understood. Identifying late mediators of sepsis is therefore crucial, molecules that can potentially be therapeutically targeted once sepsis has started (Figure 1). HMGB1 and CIRP are critical novel mediators of sepsis that have been recognized in animal models, as well as in patients with sepsis as inducers of immune dysregulation and, in the case of HMGB1, cognitive and physical dysfunction in sepsis survivors. A clearer picture of their role in sepsis is just emerging. A better long-term outcome for patients surviving sepsis will require a better understanding of late-occurring events, inflammatory or otherwise, and how to modulate them.

CONCLUSION

Sepsis survival is a clinical problem that, after decades of neglect, is finally gaining attention. A brief answer to the questions posed on the opening clinical vignette is not very encouraging. Although great progress has been made in setting standards of detection and early treatment, the vast majority of patients surviving severe sepsis will be dead within five years. It is clear that while waiting for new, more effective treatments able to improve long-term outcome, simple steps (early detection, early fluids and antibiotics) can go a long way into preventing later consequences. A current challenge in sepsis research resides in increasing survival, as well as understanding the mechanisms that lead to high mortality and low quality of life in survivors. The discovery of endogenous molecules able to modulate sepsis should generate optimism. For instance, late-occurring targets –like HMGB1 and CIRP– have the added benefit of a potentially longer therapeutic window. Sepsis survival remains a syndrome without specific treatment. Finally, at the present time the ideal pathway of management of this emerging healthcare catastrophe stands on prevention, which itself rests on a good understanding of sepsis pathophysiology.

QUESTIONS AND ANSWERS

1. Dra. Norma A. Bobadilla. Investigadora, Unidad de Fisiología Molecular, Instituto de Investigaciones Biomédicas, Universidad Nacional Autónoma de México e Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán (INCMNSZ). The evidence from both, experimental and human sepsis, shows cytokine levels measured in circulation, rather than in the infected tissues -the source of the inflammatory response. What is the role of cytokines in plasma

and in the target tissue? Do plasmatic levels reflect tissue levels?

- Dr. Sergio Iván Valdés-Ferrer. The role of circulating cytokines is clear. Evidence of in situ activity indicates a local inflammatory effect is driven by tissue cytokines. For instance, calcitonin precursors are upregulated in several tissues in response ot sepsis. In necrotizing enterocolitis, increased expression of human nitric oxide synthase (NOS-2), and interferon-γ mRNA lead to enterocyte apoptosis, altering gut permeability. At this point, however, the full impact of tissue cytokines during sepsis in incompletely understood.

2. Dr. Eduardo Carrillo-Maravilla. Médico adscrito a la Dirección de Medicina, INCMNSZ. Are the three cysteines (C)-23, C-45, C-106) the determinants of HMGB1 function? Are the posttranslational forms occurring in response to proteases or only to redox changes?

- Dr. Sergio Iván Valdés-Ferrer. The activity of HMGB1 changes in response to posttranslational modifications. The best understood of those are the mutually exclusive changes in response to redox state. When all three cysteines are in thiol state, HMGB1 is a potent chemo-attractant to other cells of the innate immunity, including monocytes and granulocytes. If C-23 and C-45 form a disulfide bond, HMGB1 becomes a powerful inducer of TNF and IL-6. For the second part of the question, HMGB1 can also undergo other posttranslational changes (e.g., acetylation or methylation), although the net functional effect is less clear.

3. Dr. Carlos Rodríguez-Osorio. Médico adscrito a la Unidad de Terapia Intensiva, INCMNSZ. Has the concentration of HMGB1 -and its different forms- measured *in situ?*

- Dr. Sergio Iván Valdés-Ferrer. Not yet.

4. Dr. Carlos Rodríguez Osorio. INCMNSZ. It is interesting to point out the role of infections, due to their impact on organ failure and associated mortality. HMGB1 is elevated in late stages during severe infections. If HMGB1 is elevated late in sepsis (similar case to IL-6), what is its role inducing mortality, and what is the mechanism for the higher mortality?

- Dr. Sergio Iván Valdés-Ferrer. I may have not made it clear during my presentation, but HMGB1 release has two peaks, one occurring between 12 and 80 h, and the second between two and eight weeks after sepsis onset. The early elevation is associated with higher mortality, probably by priming –therefore magnifying– the tissue response to other early cytokines (TNF and IL-6). The second elevation makes a plateau, rather than a clear spike. In this case, the persistent elevation primes splenocytes, monocytes, B-cells and, probably other antigen-presenting cells, upregulating other inflammatory cytokines *in situ*. We and others have demonstrated that this effect of HMGB1 persist for long enough as to be an amenable therapeutic target.

5. Dr. Carlos Rodríguez Osorio. INCMNSZ. It has been previously observed in phase I and II trials that the use of immunoactive drugs (interferons, corticosteroids) improves the immune response and prognosis of sepsis due to modulating and regulatory effects upon the inflammatory response of septic patients. Is this also valid for HMGB1?

- Dr. Sergio Iván Valdés-Ferrer. Immuno-moduloatory drugs have proven to be a double-edge sword, and have unfortunately failed in clinical trials. In specific settings, like infectious meningitis, steroids may be invaluable tools to reduce morbidity and mortality. Their routine use in sepsis, however, is not justified. If what we have observed in experimental animal models is replicated in humans stricken by severe sepsis, then blocking HMGB1 (rather than potentiating its effect) may be a great therapeutic tool. Until evidence derived from clinical trials, emergency this prediction is purely speculative.

6. Dr. Eduardo Carrillo-Maravilla. INCMNSZ. The activation of inflammasomes after maturation of procaspase-1 leads to production and release of inflammatory cytokines. In the case of sepsis, is this related to an auto-inflammatory state?

- Dr. Sergio Iván Valdés-Ferrer.Among the inflammatory events occurring during sepsis, procaspase-1 is cleaved, NLRP3 inflammasome (and probably others in response to specific pathogens) becomes active leading to the release of IL-1β, IL-18, and HMGB1. It is possible that those cytokines, acting through TLRs and other innate immunity receptors, perpetuate the inflammation and lead to an something similar to an auto-inflammatory state, although to my knowledge there is not sufficient evidence to support or reject this idea.

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