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Understanding the PIRO concept: from theory to clinical practice – Part 1

Entendendo o conceito PIRO: da teoria à prática clínica – Parte 1

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ABSTRACT

Despite recent advances in diagnosis and care of critically ill patients sepsis related mortality rate remains unacceptably high. Therefore, new methods of evaluation are necessary to provide an earlier and more accurate characterization of septic patients. Based on the (oncologic) TNM system, the PIRO concept was introduced as a new staging system for sepsis in order to assess risk and predict prognosis, with potential to assist in inclusion of patients in clinical studies and estimate the probability of response of patients to specific therapeutic interventions.

Keywords: Outcome and process assessment (Health Care); Multiple organ failure; Prognosis; Risk assessment; Sepsis/classification; Sepsis/complications; Sepsis/diagnosis; Intensive care/methods

INTRODUCTION

Despite recent advances in diagnosis and care of critical patients, sepsis, defined as a systemic response to infection, mortality rates remains unacceptably elevated.[1] Certainly, an earlier and more accurate characterization of septic patients is timely. A better understanding of immunological and biochemical characteristics of septic patients may allow the development of new tools for the stratification of sepsis. The PIRO concept was introduced as a staging system for sepsis, based on the oncology TNM system, in order to assess risk and predict prognosis, assist in inclusion of patients in clinical studies and estimate the probability of response of patients to specific therapeutic interventions.[2]

Why do we need new staging systems for sepsis?

The heterogeneity of patients with sepsis makes risk stratification a major challenge. Numerous tools were developed to assess severity of illness, organ failure and prognosis in critically ill patients.[3-5] These scoring systems were generated to assess severity of illness of general intensive care unit (ICU) patients and reflect overall physiologic derangements and organ dysfunctions and not primarily for sepsis patients. A clinically useful and accurate staging system is necessary to stratify patients with sepsis by both baseline risk of an adverse outcome and their potential to respond to therapy.[6] Recently, the Mortality in Emergency Department Sepsis (MEDS) Score was developed to predict 28-day in-hospital mortality in patients who present for emer-

gency care with suspected infection and are admitted to the hospital. It was also validated to predict the 1 - year mortality.[7] Despite the recent advances, the risk factors for worsening sepsis remain unclear. Concerning the limitations of clinical staging systems,[8] biomarkers were proposed as useful tools for the stratification of sepsis.[9-11] Biomarkers are currently used to stratify the risk and guide therapy in a wide spectrum of medical disorders such as breast[12] and lung cancer[13] and acute coronary syndromes.[14] Numerous bioactive molecules have been proposed as severity or outcome biomarkers for patients with sepsis[10,11,15,16] and may help to assess the severity and outcomes especially when a single or a panel of markers is coupled with clinical staging systems.[15,17]

The rationale for the PIRO concept

In 2001, a second consensus conference on sepsis definitions was convened, sponsored by several major medical societies.[2] The participants at this meeting agreed that the SIRS concept was not helpful and should no longer be used per se, but rather that the systemic inflammatory response syndrome (SIRS) criteria should be incorporated into a longer list of signs of sepsis. This list includes biologic signs of inflammation (e.g., increased concentrations of C-reactive protein [CRP] or procalcitonin), haemodynamic parameters (e.g., increased cardiac output, low systemic vascular resistance [SVR], low oxygen extraction ratio), signs of altered tissue perfusion (e.g., altered skin perfusion, reduced urine output), and signs of organ dysfunction (e.g., increased urea and creatinine, low platelet count or other coagulation abnormalities, hyperbilirubinemia). The PIRO system for the grading of sepsis uses clinical and laboratory parameters to aid diagnosis and patient classification, with each element being divided according to degree of involvement (e.g., infection can be classified as localized, extended, or generalized; immune response can be classified as limited, appropriate, or excessive; organ dysfunction can be classified as mild, moderate, severe) (Chart 1).

Severe sepsis occurs as a result of a wide array of community-acquired and nosocomial infections including pneumonia, peritonitis, soft-tissue infection, meningitis and viral diseases septic patients represent a heterogeneous group of severely ill patients. The severity of illness is certainly due a combination of the type and intensity of the initial insult, impacting on a patient with comorbidities and individual genetic backgrounds that imply in different patterns of immune response. The combination of the previously mentioned factors may result in organ dysfunction and death. Sepsis should not be seen as a disease but as a syndrome encompassing a group of diseases. Oncologists had learned this for a long time evaluating cancer patients. Cancer has many etiologies with significantly

Chart 1 - Currently available and future perspectives for a PIRO based approach in sepsis

	P Predisposition	I Infection	R Response	O Organ dysfunction
Available	Age	Pathogen	Clinical Resolution	ARDS
	Comorbidities	Susceptibility	Hypoxemia	Shock
	Chronic conditions	Bacteremia	Hypotension	Acute renal failure
	Baseline severity	Bacterial load	Immune Response	MODS
	Source of admission	Site of infection		SOFA
		Nosocomial or community-acquired infection		
Future	Genetics	Genotyping	Biomarkers	Mithocondrial dysfunction
	Polymorphisms of toll-like receptor, tumor necrosis factor, IL-1 and CD14	Assay of microbial products (LPS), mannan and bacterial DNA	Nonspecific markers of activated inflammation (PCT or IL-6) or impaired host responsiveness (HLA-DR)	Endothelial damage and activation
		Detection of virulence factors		

ARDS - Acute Respiratory Distress Syndrome; MODS - Multiple Organ Dysfunction Syndrome; SOFA - Sequential Organ Failure Assessment; PCT – procalcitonin; IL-1 – interleukin 1, IL-6 – interleukin 6; LPS – lipopolissacaride; DNA – dexoxiribonucleic acid; HLA-DR – D related human leukocyte antigens.

distinct clinical course and therapeutic responses. The TNM model divides the patients with solid tumor in accordance with "T" which refers to the characteristic of the tumor such as size, histology, "N" that identifies the presence of metastasis to regional lymph nodes and "M" means that the presence of distant metastasis. Each area of the system is correlated with probability of survival at 5 years and response to therapy.[18]

Due to these similarities, the PIRO concept was proposed with the aim to improve sepsis staging. In addition, organizing these patients into more homogeneous groups may help to improve the management, to determine prognosis and to aid the inclusion of such patients in clinical studies.[2]

The PIRO is based on:

Predisposition: Premorbid factors such as age, gender, comorbidities, presence and degree of immunosuppression have an impact on prognosis of patients with sepsis influencing both the course of the disease and the management of patients. In addition, the genetic variability has been increasingly important and determining the risk of death of septic patients. For example, a polymorphism of the TNF-alpha gene, the TNF-2 allele, is associated with increased serum levels of TNF and a greater risk of mortality from septic shock.[19] Moreover, single nucleotide polymorphisms, microsatellites, insertion and deletion polymorphisms are all forms of genetic variation that can characterize an individual's risk for sepsis, organ dysfunction, or death.[20] Most genetic traits associated with severe infection are associated with defects in innate immune responses. Recently, polymorphisms in the Toll-like receptor 1 gene were reported to be associated with increased susceptibility to organ dysfunction, death, and Gram-positive infection in sepsis.[21]

Racial differences in susceptibility to and outcomes from sepsis are well described,[22] and older patients are known to be at increased risk of developing sepsis with poorer outcomes.[23] Gender differences are reported in several studies and women are less likely to develop sepsis than men.[24] However, particularly septic older women, may have worse outcomes than men.[25,26] Chronic predisposing conditions such as cirrhosis, diabetes, and chronic obstructive pulmonary disease (COPD) and imunossupression may predispose to sepsis, specific pathogens and worse outcomes. However each factor may have a different impact on the other three PIRO components,[22] affecting the maginitude of response (e.g. immunosupression) or increasing the risk for development of acute organ dysfunction (e.g. chronic renal failure). These are complex relationships with multiple confounding factors and further research is needed to clearly define which factors should be taken into account and to identify how knowledge of increased risks can be translated into improved clinical outcomes. Genomics, and the broader field of proteomics, are likely to be increasingly used in routine patient management in hospitals of the future, and will facilitate the task of assessing predisposition[22] and allow a more individualized approach for each patient.

Infection: in the case of sepsis the insult to the body is the infection and the characteristics of the insult as site, type and its extension, which have great impact on prognosis.[2] Just as the "T" in the TNM system describes the aspect of the surgically treatable cancer, the "I" describes that aspect of the septic process that responds to conventional anti-infective therapy. Four key aspects related to the underlying infection can influence management and prognosis in patients with sepsis: Source, degree, hospital-acquired versus community-acquired, and microorganism.[27] Recently, studies have proposed new strategies to evaluate the infection and, consequently, to increase our ability to accurately stratify severity of the disease. In this context, Rello et al. tested the hypothesis that bacterial load may be associated with outcomes in pneumococcal pneumonia. Patients with $\geq 10^3$ copies/ml of *Streptococcus pneumoniae* DNA in their blood were associated with higher risk for septic shock (OR=8.0), need for mechanical ventilation (OR=10.5) and hospital mortality (OR=5.43).[28] Whereas previous studies have suggested that severe sepsis is related to delay in therapy or an exaggerated host inflammatory response, this study suggests for the first time that insult, the bacterial burden, also plays a key role in development multiple organ dysfunction syndrome (MODS). In addition, there was recent demonstration of the correlation of bacterial load measured by quantitative tracheal aspirate (QTA) with serum CRP as an indicator of inflammatory response in episodes of ventilator-associated pneumonia and association of its variation with antibiotic appropriateness.[29] In addition, data on the virulence of microorganisms may provide valuable clues to the development of strategies directed at pathogen-specific targets.[30] Also, the emergence of a community-acquired meticilin-resistant *Staphylococcus aureus* (MRSA) strain has increased the concerns about the role of exotoxins and other bacterial products in the pathogenesis of severe infections, such as Panton-Valentine leukocidin and hematoxin. In pneumococcal pneumonia, role of toxins such as pneu-

molysin in pathophysiology and new therapeutic possibilities targeting these toxins should also be further assessed.

The timing of onset of infection may also influence outcomes. One study showed that patients who developed septic shock within 24 hours of ICU admission were more severely ill, but had better outcomes, than patients who became hypotensive later during their ICU stay.[31]

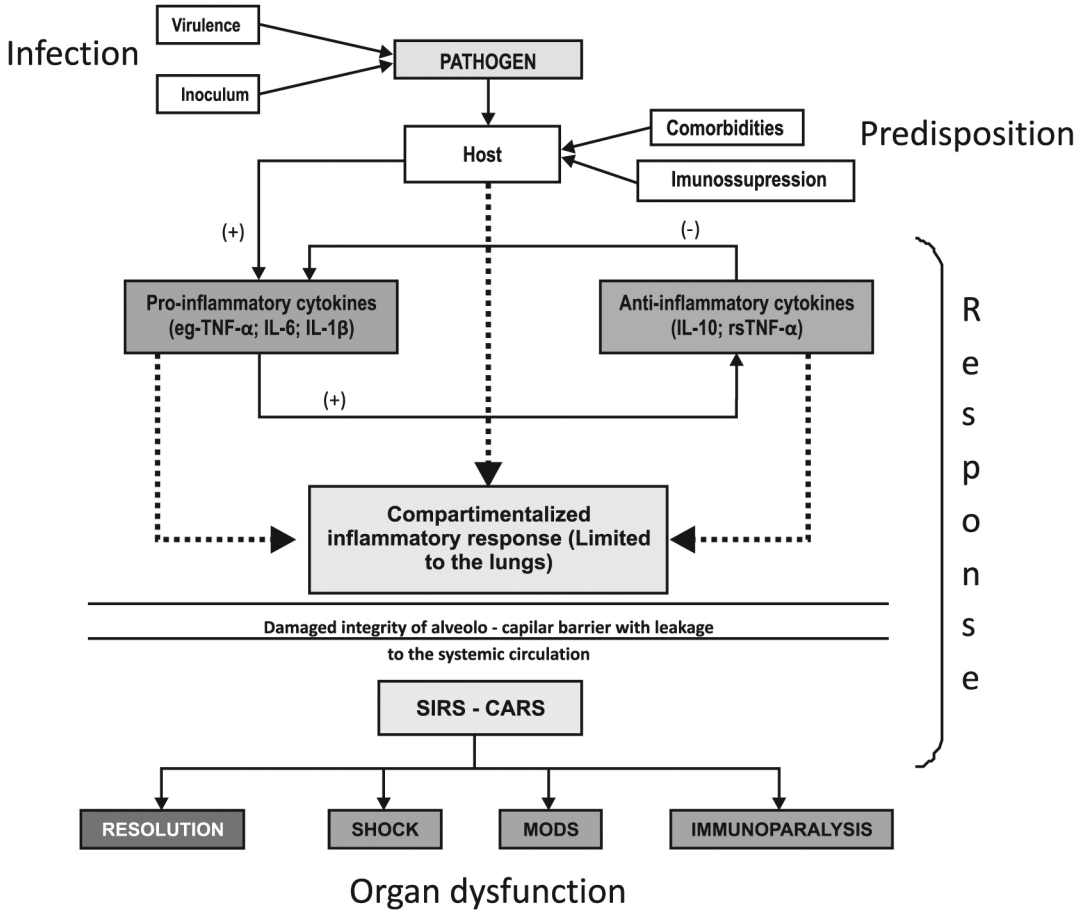
Response: represents the host response to infection and it is the component of sepsis responsible for most adverse events. Modulation of the host response to infection has been proposed for decades with limited efficacy.[32] It is proposed that selection of specific biological markers have to be tailored to the treatment strategy being employed. As the hormone receptor status is used to stratify patients with breast carcinoma, an indicator of dysregulation of the coagulation system might be valuable for making a decision about whether to institute therapy with drotrecogin alfa activated[22] and the adrenal function may predict the response to corticosteroids.[33,34] However, due to controversial results, tailored-therapy strategies based on biomarkers are yet to be validated in severe sepsis.[10]

Importantly, the initial theory that sepsis was simply an uncontrolled inflammatory response and could be treated by blocking or removing any or several of the pro-inflammatory cytokines, has been replaced by the realization that the inflammatory response is a necessary host response to infection, and interrupting that response at any point may do more harm than good. The host response to infection thus varies between patients and with time in the same patient.[22] This differentiation is important for therapeutic decisions, as anti-inflammatory therapies may be harmful if given to a patient who is already in the hypoinflammatory phase or immunoparalysis; such a patient may benefit rather from a pro- inflammatory therapy to boost their immune system.[35] Response modulation, with the use of macrolides for example, has been associated with improved survival in patients with severe community-acquired pneumonia. This effect is independent of their antimicrobial activity and seems to be associated with the immunomodulatory effects on the cytokine response to macrolides.[36] This effect is the likely explanation for the improved survival found with macrolide combination therapy of bacteremic pneumococcal pneumonia. Biomarkers such as cytokines, CRP, procalcitonin, and cortisol identified as markers of host-response to sepsis might improve traditional scoring factors in predicting outcomes and guiding response to therapy,[37] but this approach has yet to be validated.

Organ dysfunction: By analogy with the TNM system, the presence of organ dysfunction in sepsis is similar to the presence of metastatic disease in cancer and its is an important determinant of prognosis.[38] In a PIRO-based approach to a patient with severe sepsis, the presence, number and severity of organ dysfunctions may be useful not only to predict prognosis, but also to predict response to adjunctive therapies.[39] Organ dysfunction in severe sepsis is not a simple 'present' or 'absent' variable, but presents a continuous spectrum of varying severity in different organs over time.[40] The degree of organ involvement can be assessed with various scoring systems, such as the sequential organ failure assessment[5] (SOFA). Thus with repeated scores, a dynamic picture of the effects of sepsis on individual or global organ dysfunction can be developed. Sequential assessment of the SOFA score during the first few days of ICU admission has been shown to be a good indicator of prognosis, with an increase in SOFA score during the first 48 hours in the ICU predicting a mortality rate of at least 50%.[41] Levy et al. reported that early improvement in cardiovascular, renal, or respiratory function from baseline to day 1 was significantly related to survival.[42] Continued improvement in cardiovascular function before the start of day 2 and start of day 3 was associated with further improvement in survival for patients who improved compared with those who worsened. Recent literature shows that severity of illness and the number of organ failures are important predictors of response to activated protein C[39] and the presence of refractory septic shock,[34] acidemia and coagulopathy[43] may predict response to steroids.

COMMENTS

Recently, numerous tools had been developed to assess severity of illness, organ failure and prognosis of general ICU patients. However, these scores underscore the importance of significant prognostic factors specific for septic patients .The PIRO concept aims to describe the sepsis considering the relationship among premorbid factors, infection insult and host response, and how it impacts on development of organ dysfunction and prognosis of septic patients. It might help us to understand why the same infection with the same bacteria can produce different levels of host response and organ dysfunction in different patients. Further studies



SIRS - Systemic Inflammation Response Syndrome; CARS - compensatory anti-inflammatory response syndrome; MODS - Multiple Organ Dysfunction Syndrome.

Figure 1 - A PIRO-based look at the pathophysiology of severe infections: the case of pneumonia.

should assess the impact of a PIRO-based approach in the management of critically ill septic patients.

RESUMO

Apesar dos avanços recentes no diagnóstico e manejo de pacientes criticamente enfermos, a taxa de mortalidade relacionada à sepse continua inaceitavelmente alta. Assim, são necessários novos métodos de avaliação para proporcionar uma caracterização mais precoce e precisa de pacientes sépticos. Com base no sistema TNM (oncológico), o conceito PIRO foi apresentado como um novo sistema de estadiamento para sepse com a finalidade de avaliar o risco e predizer o prognóstico, com potencial de auxiliar na inclusão de pacientes em estudos clínicos e estimar a probabilidade de resposta a intervenções terapêuticas específicas.

Descritores: Avaliação de processos e resultados (Cuidados de Saúde); Insuficiência de múltiplos órgãos; Prognóstico; Medição de risco; Sepse/classificação; Sepse/complicações; Sepse/diagnóstico; Cuidados intensivos/métodos

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