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Understanding the PIRO concept: from theory to clinical practice – Part 2

Entendendo o conceito PIRO: da teoria à prática clínica – Parte 2

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ABSTRACT

A sepsis staging system focused on predisposition, insult, host response and organ failure may provide a useful basis for risk stratification. Knowledge on interactions among predisposing factors, insult characteristics and host response might help us to improve our understanding on sepsis pathophysiology and allow more individual therapeutic approach. Recent clinical studies documented the clinical importance of PIRO approach for severity stratification in septic patients in intensive care unit, and also for specific conditions such as community acquired pneumonia and ventilator associated pneumonia , with a good performance for outcome prediction. In this review we describe how this new concept can be used in clinical practice and provide some insights on its usefulness to facilitate the stratification and potential for enrollment in clinical trials of sepsis therapies.

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

INTRODUCTION

Although compliance with guidelines improves survival and medical resources use in septic patients, there are still a significant number of patients for whom antibiotics and supportive care are not enough to improve outcomes. Identifying such patients, whom could benefit from adjunctive therapy is still a challenge. One of the possible reasons for fail on multiple trials is heterogeneity in the groups of patients studied, what might mask any potential benefit in specific subgroups of patients. Improvements on targeting of proposed interventions might be obtained through a better characterization of septic patients.[1] Predisposition, insult, deleterious response and organ failure (PIRO) system, a new conceptual framework to understand sepsis, is a staging system that stratifies patients based on their predisposing conditions, nature and extent of the insult, nature and magnitude of the host response and degree of resultant or concomitant organ dysfunction.

A sepsis severity staging system focused on PIRO and interaction among these different domains might provide a useful basis for severity assessment and has potential on identification of specific subgroups for therapeutic interventions. Despite being conceived initially in the early 2000's, it took

several years since the publication of the consensus conference for the first studies based on the PIRO concept to be published.[2]

Clinical studies: a general sepsis PIRO model

The first clinical investigation on the PIRO concept was published by Moreno et al.[3] using the database of the SAPS3 (Simplified Acute Physiology Score 3) project to predict mortality patients with infection and sepsis who stayed in the intensive care unit for >48h. A total of 2,628 patients were available, approximately 41.9% with severe sepsis or septic shock. Community-acquired pneumonia was the most common type of infection. Through the multivariate analysis, several factors related to predisposition, infection and response were associated with hospital mortality. Factors regarding **P**redisposition were age, location from which the patient was admitted to the intensive care unit (ICU), co-morbidities, length of stay before ICU admission (days) and some reasons for ICU admission, as cardiac arrest. The **I**nfection was characterized by acquisition, extension, site and agent. The last component (**R**esponse and Organ Dysfunction) was compounded by dysfunction of the renal and coagulation system, failure of the cardiovascular, respiratory, renal, coagulation and central nervous systems.[3]

The SAPS3-PIRO score performed well for mortality prediction. It should be noted that in this model, evaluation of response and organ dysfunction were collapsed. It was justified because host response to the insult and the resulting organ dysfunction could not be distinguished from each other based on clinical variables and no specific biomarkers were available to be used on clinical practice.[4]

Recently, Rubolotta et al.[5] evaluated the PIRO concept in a large international severe sepsis database involving patients from the PROWESS (aPC for severe sepsis) and PROGRESS (international clinical cohort).[6,7] The authors analyzed variables from 840 PROWESS placebo-treated patients and then this score were validated in a total of 10,610 patients from the PROGRESS study. The risk assessment by PIRO model used a graduation to classify the severity illness. Each variable contributes to outcome prediction with a 30-50% increase in odds of death. In this study, the authors concluded that the PIRO system was an effective model for staging severe sepsis and could be useful to predict mortality. The area under the curve (AUC) was 0.70 in the PROWESS trial population and the Acute Physiologic Chronic Health Evaluation (APACHE) II AUC was 0.68. When APACHE II is added to PIRO for PROWESS, the AUC increased only to 0.74.

These are two systems developed for severity assessment and sepsis characterization described for general sepsis population. Such approach has advantages (e.g. applicability in larger, more heterogeneous group of patients with sepsis, severe sepsis or septic shock) but also limitations (e.g. missing several relevant and prognostic factors specific for distinct clinical syndromes like pneumonia). Otherwise, recently disease-specific PIRO-based models for severity assessment were proposed for community acquired pneumonia (CAP) and ventilator associated pneumonia (VAP).

Clinical studies: a disease-specific PIRO-based model

The complexity of pneumonia might be better understood after assessment of these aspects of the disease. Predisposition factors such as the genetic profile of an individual are likely to be a major determinant of the lifetime predisposition to sepsis and progress continues to be made in identifying relevant candidate genes. But presence of co-morbid conditions and age are also important predisposing factors that affect outcomes in pneumonia. The site of infection and the nature and spread of the pathogen within the body are also important features, including the presence of bacteremia and radiological spread pattern. Although some elements of the variables that affect the host response to infection are easy to identify (age, nutritional status, sex, co-morbid conditions), others are more complex and arise from interactions between inflammation, coagulation, and sepsis. Development of shock and hypoxemia are important factors related with host response to infection. Use of biomarkers might identify response patterns helping to assess severity. Finally, development of organ dysfunction is a clear sign of poor evolution.

A new PIRO-based score was tested in more homogeneous subgroups of patients with severe infections. Recently, Rello et al evaluated a PIRO based model in patients with severe community-acquired pneumonia (CAP) in a historical cohort with 529 patients from the CAPUCI study[8,9] to compare the performance of the PIRO score with the APACHE II score and 2007 ATS/IDSA (American Thoracic Society/Infectious Disease Society of America)[10] criteria as a prognostic index. Variables identified in the final model as prognostic factors in severe CAP patients admitted in the ICU were included in PIRO-based model and a score was built. Variables used for severity assessment in CAP pa-

Chart 1 – Prognostic factors included in PIRO severity assessment tool for community acquired pneumonia and ventilator associated pneumonia

	P – Predisposition	I – Insult	R - Response	O – Organ dysfunction
Severe CAP	Age>70y	Bacteremia	Hypoxemia	ARDS
	COPD	Multilobar opacities	Shock	Acute renal failure
	Imunosupression			
VAP	Comorbidities:	Bacteremia	Shock	ARDS
	COPD, CHF, CRF and imunosupression			

CAP - community acquired pneumonia; VAP - ventilator associated pneumonia; COPD – chronic obstructive pulmonary disease; ARDS - acute respiratory distress syndrome; CHF - congestive heart failure; CRF - chronic renal failure.

tients are shown in chart 1. When PIRO was compared with these scores, it performed better than the others to identify patients with higher risk of death, predicting adequately 28-day mortality. Furthermore, PIRO score also is associated with increased healthcare resource utilization in CAP patients admitted in the ICU.

Severe CAP is a progressive disease and, in the event of evolution from a local to a systemic infection, the following spectrum of sepsis-related complications may develop: sepsis, severe sepsis, septic shock, and multiple organ dysfunction. Progression of severe CAP is associated with hypercoagulability, hypotension, alteration of the microcirculation and ultimately multiple organ dysfunction. Nearly all patients who die as a consequence of severe CAP develop severe sepsis, septic shock or organ dysfunction during disease evolution.

Lisboa et al.[11] used the PIRO concept to assess the severity of critical ill patients with nosocomial ventilator-associated pneumonia. These patients were stratified into different groups according to the risk of mortality. A total of 441 ICU mechanical ventilated patients were enrolled. Through the multivariate analysis, four variables were identified as components of the PIRO model, P: comorbidities, I: bacteremia, R: systolic blood pressure (SBP) <90mmHg and O: acute respiratory distress syndrome (ARDS), that compounded the VAP PIRO score. The authors concluded that it could be used to assess severity and health-care resources utilization and to improve prediction of ICU mortality in VAP patients. Disease-specific approaches may yield better results not only by enrolling more homogeneous populations but also by considering variables that are specific and highly relevant to the type of infection under evaluation.

These systems have the advantage over SAPS3-PIRO and PROWESS-PROGRESS PIRO model of being easier to compute, more specific to the specific risk factors of the analysed infections (CAP and VAP) but at the price of losing their applicability in large groups, more heterogeneous of patients with severe infection, sepsis and septic shock.[4]

Future directions

In a perfect world, the critical care specialist would approach the patient in the emergency room and as severe sepsis was diagnosed, a panel of biomarkers that were sensitive and specific surrogates for predisposition (genetics, immune response), infection (real time polymerase chain reaction (PCR)), response (cytokines, chemokines, hormones and coagulation) and organ dysfunction (endothelial and mithocondrial function) would be available in minutes for optimal decision making. However, this is far from happening not only for technological but also for practical (eg.costs) reasons.

Improved classification of septic patients using the PIRO system may, thus, facilitate the development and evaluation of clinical trials of sepsis therapies and will also encourage further study into the pathophysiology and epidemiology of sepsis. Importantly, as the TNM system is adjusted to specific cancers, so the PIRO system will need to be adapted to fit specific patient groups, local practice, purpose (e.g., clinical trial inclusion, prognosis, patient management), or proposed therapies. For example, if the planned intervention is an anticoagulant then evidence of coagulopathy is likely to be more relevant than presence of respiratory failure, while if considering haemodialysis, the presence and degree of renal failure are more likely to be pertinent.

Another interesting and unexplored utility for the PIRO approach is the structured patient evaluation based on this concept at the bedside. In chart 2, an example of this alternative for patient discussion is presented. This PIRO-based approach could allow a more individual evaluation, taking into account patient-specific characteristics and should be further evaluated on clinical practice in ICU.

Chart 2 - Severe sepsis: a clinical scenario using a PIRO based approach

80 yo, man, COPD, CRI, admitted with fever, tachycardia, dyspnea, purulent secretion BP = 80/50, need of vasopressors Pneumococcal vaccination X-Ray with bilateral infiltrates Lab: Leukocytosis, hypoxemia P/F = 120, Lactate 4.1, CRP = 180 mg/L Sputum Gram stain: Gram-positive *cocci* rtPCR for *S.* pneumoniae: 10.000 copies in blood High flow hemofiltration	**P:** Age, COPD, pneumococcal vaccination. **I:** S. pneumoniae, bacteremic episode, multilobar opacities **R:** Elevated CRP, lactate; SIRS; hypoxemia **O:** ARDS, shock/vasopressors, AKI

Yo - years-old; COPD - chronic obstructive pulmonary disease; CRI – chronic renal insufficiency; CRP= C-reactive protein; rtPCR - reverse transcriptase polymerase chain reaction; SIRS - systemic inflammation response syndrome; ARDS - acute respiratory distress syndrome; AKI – acute kiney injury.

In addition, however, there is an interesting lesson to be learned from studies that applied good stratification strategies in infectious diseases to guide therapeutic interventions. In the 1980's, patients with *P. jirovecci* pneumonia and acquired immunodeficiency syndrome (AIDS) were stratified to receive steroids according to a PIRO-based approach, although it was only coined 20 years later. Then, patients with a T-cell type immunodeficiency (**P**redisposition), with *P. jirovecci*, the same infectious microorganism (**I**nfection*)*, presenting with hypoxemia (**R**esponse) and respiratoty failure (**O**rgan dysfunction) were considered eligible to receive adjunctive corticosteroids. This approach was successful and remains so even decades after its initial proposal.[12]

Optimization of therapy based on this novel approach is a strategy that should be evaluated, as higher risk patients might benefit from more aggressive strategies or adjunctive therapy. As PIRO allows a more appropriate stratification of patients into different severity groups, clinical trials designed to evaluate therapeutic strategies for severe sepsis patients should use this tool in analysis of outcomes. It is probably more specific and accurate than the APACHE II. Therefore it may replace this general score in the definition of subgroups who could benefit more from specific adjunctive therapies. Such approach should be further evaluated.

Future studies in severe sepsis should follow this design enrolling more homogeneous populations and avoiding the flaws of recent trials.[13] An impressive amount of data on pathophysiology, epidemiology and risk-assessment was generated in the past 20 years. Now it is time to gather relevant data and look for innovative approaches in future trial design.

RESUMO

Um sistema de estadiamento da sepse com foco na predisposição, no insulto, na resposta do hospedeiro e na falência orgânica pode fornecer uma base útil para a estratificação do risco. O conhecimento das interações entre os fatores predisponentes, características do insulto e resposta do hospedeiro pode nos ajudar a melhorar a compreensão sobre a fisiopatologia da sepse e permitir uma abordagem terapêutica mais individualizada. Estudos clínicos recentes documentaram a relevância da abordagem PIRO na estratificação da gravidade de pacientes sépticos na unidade de terapia intensiva, e também para condições específicas como pneumonia adquirida na comunidade e pneumonia associada a ventilação mecânica, com bom desempenho para previsão do desfecho. Nesta revisão, descrevemos como este novo conceito pode ser utilizado na prática clínica e fornecemos algumas compreensões sobre a sua utilidade para facilitar a estratificação e potencial para inclusão em estudos clínicos de tratamentos da sepse.

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

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