PIRO: The Key to Success?

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Background

Over the years, there has been considerable confusion regarding the definition of sepsis, with terms such as "infection" and "sepsis" often being used interchangeably. While obviously related, these elements are not exact synonyms; sepsis is the host response to an infection by an invading microorganism, be it virus, bacteria, or fungus. In 1992, as the links between inflammation and sepsis were becoming increasingly clear, a consensus conference on sepsis definitions introduced the term SIRS (systemic inflammatory response syndrome) in an attempt to clarify and simplify the definitions of sepsis [1]. A patient was classified as having SIRS if he/she had at least two of four parameters (temperature >38 or <36°C; heart rate >90 beats/min; respiratory rate >20 breaths per minute or PCO_2 < 32 mmHg; white blood cell count >12 or <4 × 10^9/l). Sepsis was defined as SIRS plus infection. However, it soon became apparent that nearly all intensive care unit (ICU) patients meet the SIRS criteria at some point during their ICU stay [2, 3], making this approach too sensitive to be useful in diagnosing sepsis [4].

Almost 10 years later, a second consensus conference on sepsis definitions was convened, sponsored by the Society of Critical Care Medicine (SCCM), the European Society of Intensive Care Medicine (ESICM), the American College of Chest Physicians (ACCP), the American Thoracic Society (ATS), and the Surgical Infection Societies (SIS) [5]. The participants at this meeting agreed that the SIRS concept was not helpful and should no longer be used per se, but that the SIRS criteria be incorporated into a longer list of signs of sepsis that could be employed to support a diagnosis of sepsis. This list includes biologic signs of inflammation (e.g., increased serum concentrations of C-reactive protein [CRP] or procalcitonin), hemodynamic 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,

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hyperbilirubinemia). The participants also suggested that as the definitions did not allow for precise characterization and staging of patients with sepsis, a clinically useful staging system that could stratify patients by both their baseline risk of an adverse outcome and their potential to respond to therapy was needed. Building on a system that had emerged at the Fifth Toronto Sepsis Roundtable held in Toronto, Canada, in 2000 [6], the sepsis definitions conference participants, therefore, proposed the PIRO system [5], which can classify patients on the basis of their *p*redisposing conditions, the nature and extent of the *i*nfection, the nature and magnitude of the host *r*esponse, and the degree of concomitant *o*rgan dysfunction.

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Similarities Between Sepsis and Cancer

Disease stratifications systems are widely used in clinical medicine, but perhaps the most familiar and frequently employed is the TNM system, which was developed by Pierre Denoix in the 1940s [7], and is universally recognized as a standard for classifying patients with cancer. The TNM system classifies malignant tumors based on descriptors of the extent of the primary tumor (T), on the presence, absence, and extent of metastases to regional lymph nodes (N), and on the presence or absence of distant metastases (M) (Table 1). Each patient with a tumor will, therefore, receive a specific classification, e.g., T1, N0, M0, for that tumor. TNM classifications are then grouped into stages, usually from I to IV, which provide valuable prognostic information. Importantly, staging systems in cancer stratify patients not only according to prognosis, but also according to the probability that they will respond to a particular therapy.

Sepsis is in many ways very similar to cancer. Both disease processes are common, with high mortality rates. Both are the result of a complex pathophysiological process involving cellular dysregulation. Both can develop in (almost) any organ, and both frequently require surgical and medical therapies. Treatments for both are expensive and often involve several pharmacological agents. Finally, when treatment is successful, it is associated with slow step-by-step improvement.

Table 1 Basic TNM classification of cancers

Primary tumor (T)	
Tx	Primary tumor not evaluated
T0	No primary tumor
T1, 2, 3, 4	Size and/or extent of the primary tumor
Regional lymph nodes (N)	
Nx	Regional lymph nodes not evaluated
N0	No regional lymph node involvement
N1, 2, 3	Number and extent of regional lymph node involvement
Distant metastases (M)	
Mx	Distant metastases not evaluated
M0	No distant metastases
M1	Distant metastases

These similarities between sepsis and cancer led to the suggestion that a disease stratification system, similar to the TNM system for cancer, could be developed for sepsis [5]. 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 the degree of involvement (e.g., infection can be classified as localized, extended, or generalized; immune response can be classified as limited, extensive, or excessive; organ dysfunction can be classified as mild, moderate, severe). As with the TNM system, it has been proposed that points could be allocated such that a patient with sepsis could, for example, be staged as $P_1I_2R_1O_0$ [6], depending on the features present for each of the four PIRO components.

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PIRO Components

All aspects of the four components of the PIRO system impact on outcome and can influence therapeutic choices. As the TNM system is divided into clinical (cTcNcM) and pathological (pTpNpM) classifications, so each component of PIRO can be considered to have potentially relevant clinical and laboratory variables (Table 2).

3.1
Predisposition

Predisposition can include multiple factors such as age, sex, presence of certain premorbid diseases, prolonged immunosuppressant or antimicrobial medication, even cultural and religious beliefs [8]. All these factors individually and collectively can impact on outcome,

Table 2 Some suggested variables for the four components of the PIRO grading system

	Clinical	Laboratory
P: Predisposing factors	Age, coexisting diseases (alcoholism, diabetes, cirrhosis etc.), sex, steroid or immunosuppressive therapy	Genetic factors
I: Infection	Site (pneumonia, peritonitis, catheter), hospital acquired versus community-acquired	Bacteriology (infecting organism, virulence, sensitivity)
R: Response	Temperature, heart rate, blood pressure, cardiac output, etc	White blood cell count, prothrombin time, APTT, arterial blood gases, lactate levels, C-reactive protein, procalcitonin, other biomarkers
O: Organ dysfunction	Blood pressure, urine output, Glasgow Coma Scale	PaO_2/FiO_2, serum creatinine, serum bilirubin, platelet count

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modifying both the disease process and the approach to therapy. Recent advances in genetic techniques have enabled several factors associated with an increased risk of infection and of mortality from sepsis to be identified. 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 [9]. Most genetic traits associated with severe infection are associated with defects in innate immune responses. For example, a polymorphism of the tumor necrosis factor (TNF)-α gene, the TNF-2 allele, is associated with increased serum levels of TNF and a greater risk of mortality from septic shock [10]. A polymorphism within intron 2 of the interleukin-1 receptor antagonist (IL-1ra) gene (IL-1RN*2) has been associated with reduced IL-1ra production and increased mortality rates [11]. 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 [12].

Sex differences are another area of interest with several studies reporting that women are less likely to develop sepsis than men [13, 14]. However, women who do develop sepsis, particularly older women, may have worse outcomes than men [15, 16]. Studies have also suggested racial differences in susceptibility to and outcomes from sepsis [17], and older patients are known to be at an increased risk of developing sepsis and succumbing to it [18]. Certain chronic diseases, such as cirrhosis, diabetes, and chronic obstructive pulmonary disease (COPD), as well as chronic use of immunosuppressant medication may also predispose to sepsis and a worse outcome. Moreover, each factor may have a different impact on the other three PIRO components [5]. For example, chronic immunosuppression may increase a person's risk of infection, but may decrease the magnitude of that person's inflammatory response. Undoubtedly these are complex relationships with multiple confounding factors and further research is needed to clearly define which factors should be taken into account when considering the impact of predisposition on prognosis, to determine which carry most weight, and to identify how knowledge of increased risks can be translated into improved clinical outcomes. Advances in genetics technology now enable investigators to create glass slides (chips) with minute quantities of short, gene-specific nucleotides. These gene-specific probe nucleotides, ideally one for each gene in the genome, are arrayed onto the chip surface to produce a DNA microarray. These can be used to generate an expression profile, the transcriptome, for the cell or tissue of interest. Genomics, and the broader field of proteomics, is likely to be increasingly used in routine patient management in hospitals of the future and will facilitate the task of assessing predisposition.

3.2
Infection

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 [19]. In terms of source, for example, infections of the urinary tract are usually less severe than intra-abdominal or pulmonary infections. In the Protein C Worldwide Evaluation in Severe Sepsis (PROWESS) trial [20], patients with urinary tract

infections as a source of severe sepsis had a 28-day all-cause mortality of 21% compared with patients with a pulmonary source of sepsis who had a mortality rate of 34% ($p < .01$). The size of the inoculum, virulence, and sensitivity of the infecting organisms are also important in determining outcomes. In the Sepsis Occurrence in Acutely Ill Patients (SOAP) study, infection with *Pseudomonas spp*. was independently associated with increased ICU mortality (OR: 1.62 [95% CI 1.09–2.42], $p = 0.017$) [16]. In a multicenter study from China, Gram-positive bacterial infection and invasive fungal infections were risk factors for hospital mortality [21]. However, classifying the relative importance of infections on outcome can be difficult. Cohen et al. [22] recently generated specific risk codes for the six most common infections: bacteremia, meningitis, pneumonia, skin and soft tissue infections, peritonitis, and urinary tract infections. For each infection site and organism, a two-digit code was generated according to the mortality rate associated with that infection (from 1: ≤5% to 4: >30%), and the level of evidence available to support the mortality risk (level A representing evidence from more than five studies with greater than 100 patients, through to level E where there was insufficient evidence from case reports). This Grading System for Site and Severity of Infection (GSSSI) needs to be validated, but could be a useful means of characterizing the risks associated with infections caused by various organisms in different sites.

The timing of the onset of infection may also influence outcomes. One study showed that patients who developed septic shock within 24 h of ICU admission were more severely ill, but had better outcomes, than patients who became hypotensive later during their ICU stay [23].

3.3
Immune Response

Sepsis is defined as the host response to infection, yet that host response has proved difficult to characterize [24]. Various approaches have been proposed, including the presence of characteristic signs and symptoms or the degree of elevation of biological markers, such as procalcitonin or C-reactive protein, but as yet, none of the suggested markers is specific for sepsis. 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 proinflammatory cytokines has been replaced by the realization that the inflammatory response is a normal and necessary response to infection, and interrupting that response at any point may do more harm than good. Indeed, the early hyperinflammatory phase of sepsis is soon replaced by a hypoinflammatory state. The host response to infection thus varies between patients and with time in the same patient [25]. This differentiation is important for therapeutic decisions, as antiinflammatory therapies may be harmful if given to a patient who is already in the hypoinflammatory phase; such a patient may benefit rather from a proinflammatory therapy to boost their immune system. As with genomics, technological advances now enable multiple markers to be assessed simultaneously from small blood samples. This approach could provide clinicians with an immune profile for individual patients. Again, considerable research is needed to indentify which markers should be included on such microarrays. Furthermore, the optimal set of biologic markers for

any patient may depend on the therapy being proposed [5]. For example, an indicator of dysregulation of the coagulation system might be more valuable when deciding whether or not to give drotrecogin alfa (activated), whereas a marker of adrenal dysfunction might be more useful for determining whether to give hydrocortisone.

3.4
Organ Dysfunction

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 [26]. The degree of organ involvement can be assessed with various scoring systems, such as the Sequential Organ Failure Assessment (SOFA) [27]. This system uses parameters that are routinely available in all ICUs to assess the degree of dysfunction for six organ systems: respiratory, cardiovascular, renal, coagulation, neurologic, and hepatic, with a scale of 0 (no dysfunction) to 4 for each organ. Importantly, organ dysfunction can be recorded for each organ separately or a composite score can be calculated. 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 h in the ICU predicting a mortality rate of at least 50% [28]. Levy et al. reported that early improvement in cardiovascular, renal, or respiratory function from baseline to day 1 was significantly related to survival [29]. 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.

In the future, organ dysfunction scores may be replaced by or combined with more direct assessment of cellular stress and injury, for example, measures of mitochondrial dysfunction, apoptosis, or cytopathic hypoxia.

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PIRO in Practice

The PIRO concept at its simplest provides a means of putting some order to the various aspects of sepsis. Further work is needed to determine exactly which factors should be included in each of the four components and whether or how they should be measured and weighted to achieve a quantitative measure by which heterogeneous groups of septic patients could be characterized and categorized. Once validated, it is possible that patients could receive a PIRO grade or stage, e.g., $P_3I_2R_1O_2$, which would help direct treatment and indicate prognosis. In addition to characterizing individual patients, such grades would facilitate comparison of patient populations for clinical trial purposes and help focus clinical research.

Several groups have already attempted to apply the PIRO system clinically and the results of these studies will be discussed in more detail in later chapters. Moreno et al. used the SAPS III database to assess whether the PIRO system could be useful for predicting

mortality in patients with sepsis [30]. For each of the four PIRO components, multivariate analysis was used to select variables significantly associated with hospital mortality, which were then weighted and allocated points. The authors felt it was not possible to separate host response from the resulting organ dysfunction, so they combined these two components. For predisposition, the final variables were age, location of patient prior to ICU admission, length of stay before ICU admission, certain comorbidities (cancer, cirrhosis, acquired immunodeficiency syndrome [AIDS]), and cardiac arrest as the reason for ICU admission; for infection, the variables were nosocomial infection, respiratory infection, and infections by *Candida* species or other fungi; for response/organ dysfunction, the variables were renal or coagulation dysfunction, and failure of the cardiovascular, renal, respiratory, coagulation, or central nervous systems. The authors suggested that, although further prospective validation is needed, the proposed SAPS III PIRO system could be used to stratify patients at or shortly after ICU admission to enable better selection of management according to the risk of death [30].

In a prospective, observational study, Lisboa et al. [31] applied the PIRO concept to patients with ventilator-associated pneumonia (VAP), again using multivariate logistic regression to identify variables independently associated with ICU mortality for inclusion in the PIRO model. In this study in VAP patients, the variables for predisposition were comorbidities (COPD, immunocompromise, heart failure, cirrhosis, chronic renal failure); for infection, the variable was bacteremia; for response, the variable was systolic blood pressure <90 mmHg; and for organ dysfunction, the variable was acute respiratory distress syndrome (ARDS). A four-point score was thus developed, with one point for each component. Mortality increased with increasing score: A score of 0 was associated with a mortality rate of 9.8%, increasing to 93.3% for patients with a score of 4. These authors suggested that the VAP-PIRO score could thus be a useful practical tool to predict disease severity in patients with VAP.

The two studies discussed briefly above are just two clinical examples of how the PIRO system could be adopted for use clinically.

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Conclusion: Could PIRO Be the Key to Success?

Mortality remains high in patients with severe sepsis (around 40%) and septic shock (around 60%) and is closely associated with the degree of multiple organ failure. Results from studies of proposed new interventions in severe sepsis have largely been disappointing with few demonstrating any positive effect on outcomes. One of the possible reasons for the multiple "failed" trials is that the groups of patients studied have been too heterogeneous and that global results have masked any potential benefit in specific subgroups of patients [32]. Better targeting of proposed interventions by better characterization of septic patients with the PIRO system may lead to better outcomes. 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, just as the TNM system is adjusted to specific cancers [33], so the PIRO system will need to be adapted to fit specific patient

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groups, local practice, purpose (e.g., clinical trial inclusion, prognostication, 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 hemodialysis, the presence and degree of renal failure are likely to be most pertinent [24].

However, despite general acceptance of the PIRO concept and belief that it may contribute to improving outcomes in patients with sepsis, many questions remain unanswered. For example, in patients with cancer, correct staging is critical because treatment is directly related to disease stage. Thus, incorrect staging can lead to improper treatment and to reduced patient outcomes. Whether the same would hold true for patients with sepsis is unknown. Clearly, considerable work remains to be done in testing and validating the PIRO system, but it represents an important step toward more successful management of the patient with severe sepsis.

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