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The PIRO (predisposition, insult, response, organ dysfunction) model

Toward a staging system for acute illness

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Multimodal therapy for diseases like cancer has only become practicable following the development of staging systems like the TNM (tumor, nodes, metastases) system. Staging enables the identification of subgroups of patients with a disease who not only have a differing prognosis, but who are also more likely to benefit from a specific therapeutic modality. Critically ill patients represent a highly heterogeneous population for whom multiple therapeutic options are potentially available, each carrying not only the potential for differential benefit, but also the potential for differential harm. The PIRO system (predisposition, insult, response, organ dysfunction) is a template proposal for a staging system for acute illness that incorporates assessment of pre-morbid baseline susceptibility (predisposition), the specific disorder responsible for acute illness (insult), the response of the host to that insult, and the resulting degree of organ dysfunction. However the creation of a valid, robust, and clinically useful system presents significant challenges arising from the complexity of the disease state, the lack of a clear phenotype, the confounding influence of the effects of therapy and of cultural and socio-economic factors, and the relatively low profile of acute illness with clinicians and the general public. This review summarizes the rationale for such a model of illness stratification and the results of preliminary cohort studies testing the concept. It further proposes two strategies for building a staging system, recognizing that this will be a demanding undertaking that will require decades of work.

As medical knowledge advances, the management of disease becomes more complex. In the 19th century, for example, acute appendicitis was typically an autopsy finding, and when it was diagnosed antemortem, no specific therapy was available other than symptomatic relief with analgesics.[1] With the development and promulgation of the technique of appendectomy in the late 19th century, surgical excision became the accepted mode of treatment, and death from appendicitis became a rarity. In the absence of alternate therapies, the challenge to the surgeon lay in establishing the diagnosis; the therapeutic decision was simple—operate. More recently, however, it has become apparent that some patients can be managed conservatively with antibiotics alone,[2] and so surgeons are confronted with a treatment decision, and information to guide that decision is needed. A means of stratifying patients within an overall population of patients with appendicitis could aid in determining who is better served by conservative and who by operative management.[3]

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When therapeutic options are limited, the need for staging patients with a disease is minimal; at best a staging system can serve to provide an early indication of probable clinical trajectory, and so predict outcome. As the management options increase, however, so does the need for reliable stratification models that will ensure that the best treatment or combination of treatments is directed against the illness experienced by an individual patient. This maxim is most fully developed in the field of oncology, and particularly in the treatment of epithelial malignancies for which multiple treatment options—surgery, radiotherapy, chemotherapy, and emerging therapies targeting specific pathways involved in malignant cell growth—are available, each with its benefits, but also each having its risks. Insights derived from collaborative efforts over the past century to stratify patients with cancer have important implications for the future management of patients with acute life-threatening illnesses.

The Evolution of Cancer Staging

Cancer is not a single disease but a generic descriptor for a group of diseases characterized by the abnormal regulation of cell growth and differentiation. For cancers arising in solid organs, a developmental model has been proposed, suggesting that the tumor arises from a transformed cell that proliferates locally before spreading—initially along lymphatics to regional lymph nodes, and subsequently to remote tissues where ongoing proliferation results in the death of the patient. Cancers differ primarily on the basis of the cell type involved, but also on the basis of distinct patterns of gene expression within that cell, and to the extent to which the disease has spread at the time of its initial diagnosis.

This biologic model of disease progression, and the recognition that the cancer patients who were more likely to die were those with more locally extensive or disseminated disease inspired a

Table 1. The sepsis score[9]

Variable	0	1	2	3
Maximum daily temperature (°C)	<38.0	38.0–38.9	39.0–39.9	40.0+
White blood cell count	<12 000	12–18 000	18–25 000	25 000+
Decrease in Glasgow coma score (from baseline)[a]	0	1	2	3+
Insulin requirements (units per hour)[b]	0	1–2	3	4+
Cardiac output *or* systemic vascular resistance[c]	<7.0	7.0–8.9	9.0–10.9	11.0+
	>800	600–800	400–600	<400

[a]The baseline Glasgow coma score is that obtained 24 to 48 h following SICU admission (after recovery from anesthesia); decreasing levels of consciousness are calculated relative to this score. [b]Units of exogenous insulin required to achieve a serum glucose level of 10 mM/L or lower (200 mg/mL). [c]Cardiac output in liters/minute *or* systemic vascular resistance in dyne.sec/cm^5; the most abnormal value is used. Missing data are recorded as 0; the sepsis score is the sum of the worst scores for each variable on a particular day (maximum 15).

variety of initiatives to create staging systems that could stratify patients into subgroups who were more or less likely to experience progression of their illness, and ultimately to die from it.

The best known and most durable of these staging systems was developed by the French oncologist, Pierre Denoix, head of the International Union Against Cancer (UICC).[4] Denoix proposed an anatomic model based on independent consideration of the size and degree of local infiltration of the **tumor**, the presence and extent of regional spread to local lymph **nodes**, and the presence or absence of distant **metastases**. Through a large scale international collaboration, the model has been tested and validated empirically on the basis of the ability of each of these domains to predict recurrence following treatment and ultimately, survival. Patients were initially stratified on the basis of the anatomic site and histologic type of the primary tumor. Prognostic characteristics of the tumor (size, differentiation, degree of invasion), nodes (number, vascularity), and metastases were evaluated to refine the system.[5] As staging has evolved, it has become apparent that even within discrete histologic tumor types there are distinct subgroups identifiable on the basis of both differential prognosis and response to treatment and differential expression of key genes associated with tumor progression.[6-8]

Cancer as a disease lends itself to the development of reliable staging models. It has a pathologic phenotype that enables it to be diagnosed locally and detected systemically, and so that provides an objective basis for the evaluation of staging systems. It develops slowly, it evolves in a relatively predictable anatomic fashion, and its progression can be monitored over time, facilitating studies of natural history. Its therapy is multimodal, including surgery, radiation, cytotoxic chemotherapy, and biologically targeted therapy, so the need for staging is apparent to practitioners. Finally, it is common and resonates in the public perception, so that research funding to enable large-scale studies is more readily available than it is for research in the domain of acute illness.

The challenges of creating an analogous staging system for patients with acute life-threatening illness are substantial; the PIRO model is an initial exercise to address this challenge.

Clinical Staging of Acute Illness: The PIRO Model

The PIRO model arose from an exercise to create a candidate staging model analogous to the TNM system for staging a homogeneous cohort of patients admitted to a surgical intensive care unit in Halifax, Canada.[9] By analogy to the TNM system, patients were stratified on the basis of the initial **insult** (documented infection vs. no infection), the magnitude of the host **response** and the extent of **organ dysfunction**. The diagnosis of infection required the identification of a pathogen invading normally sterile tissues, the magnitude of the host response was quantified using a sepsis score[9] (**Table 1**), and the degree of organ dysfunction quantified using the multiple organ dysfunction (MOD) score.[10]

In a study of 477 patients (APACHE II score 13.4 ± 6.8, hospital mortality 18.7%), we found that outcome was independently impacted by each of these domains. The presence of infection was independently associated with an increased risk of ICU mortality (**Table 2**). Neither the site nor the microbiology of the infection significantly altered the risk of death. However the prognostic impact of infection was dependent upon the concomitant severity of the host response as measured by the sepsis score (**Table 3**). Although a diagnosis of infection increased the risk of death at all levels of severity of the sepsis score, the relative effect was greatest in those patients who had minimal evidence of a systemic inflammatory response.

Whether infection was present or not, the magnitude of the clinical inflammatory response correlated with the probability of ICU mortality and with the degree of organ dysfunction evolving over the ICU stay. These concepts formed the basis for discussions at the 2002 SCCM/ESICM Consensus Conference on definitions of sepsis.[11] At that meeting, a further domain—**predisposition**—was added to the construct, creating the PIRO model.

Although it is not clear how each of these domains is best described and measured, there is ample evidence that each contributes to the clinical phenotype of critical illness, and to the probability of a successful outcome.

Predisposition

The domain of predisposition includes all of those factors that are present *before* the onset of acute illness, and that by their presence, can modify the subsequent clinical course. Predisposing factors may be genetic, or they may be influences acquired after birth; these, in turn, can include socioeconomic factors such as poverty and malnutrition, environmental factors, medical co-morbidities, and even religious and cultural perspectives on illness and death.

Table 2. Morbidity and mortality of culture proven infection

	ICU			
Infectious status	***N***	**Stay (days)**	**MOD score**	**Mortality**
No infection	364	4.1 ± 4.0	4.5 ± 3.4	3.3%
Infection at any time	113	12.0 ± 11.1[a]	8.9 ± 5.2[a]	27.4%[a]
Primary	51	7.3 ± 6.8[b]	7.5 ± 4.9[c]	21.6%[c]
ICU-acquired	74	15.7 ± 11.9[d]	10.2 ± 5.1[d]	31.1%[d]

[a]$P < 0.0001$ compared with uninfected patients; [b]P = N.S. compared with patients without primary infection; [c]$P = 0.002$ compared with all patients without primary infection; [d]$P < 0.0001$ compared with all patients without ICU-acquired infection

Table 3. The influence of infection on mortality at increasing increments of sepsis score

Maximal sepsis score	Number of patients	ICU mortality (%)		
		Infected	**Not infected**	***P***
0–3	297	5/33 (15.2)	3/264 (1.1)	<0.0001
4–6	126	10/46 (21.7)	4/80 (5.0)	0.009
7–9	47	12/29 (41.4)	5/18 (27.8)	0.53
10–12	7	3/4 (75)	1/3 (33.3)	0.74

A Danish cohort study underlined the importance of genetic factors in the prognosis for survival following infection.[12] The authors studied a cohort of 960 individuals who had been born between 1924 and 1926 and been adopted as infants. They studied early deaths (before the age of 50) in the patient cohort, and in both the biologic and adoptive parents, classifying these as related to cancer, cardiovascular disease, infection, or other causes, assuming that concordance in the cause of early death between the child and the adoptive parent reflected an environmental influence, while that between the child and the biologic parent reflected genetic factors. Only early death from cancer showed a significant association with environmental factors (odds ratio 5.16, 95% CI 1.20–22.2). In contrast, all causes except cancer showed a genetic link, the strongest being for early death from infection (odds ratio 5.81, 95% CI 2.47–13.7).

This association is readily explicable from an evolutionary perspective. Infectious diseases have been a constant threat to human populations, and a potent driver of evolutionary change; genes encoding elements of the innate response to infection are the most polymorphic genes in the human genome.[13] Polymorphisms in the gene for hemoglobin, for example, occur predominantly in areas where malaria is endemic,[14] and both genome-wide association (GWA) studies and population studies of single nucleotide polymorphisms (SNPs) link heritable factors to susceptibility to a broad spectrum of infectious diseases.[15] Studies of cohorts of patients with infection have revealed that SNPs that alter the expression of innate immune response genes are associated with both altered susceptibility to sepsis,[16,17] and with an altered risk of death if sepsis develops.[18-20] Genetic susceptibility to adverse outcome in acute illness has been most extensively studied in populations of patients with sepsis, but heritable factors have also been linked to clinical outcomes following multiple trauma.[21-23]

Population-based studies demonstrate both sex- and race-based differences in susceptibility to sepsis,[24] and in the risk of mortality once sepsis has developed.[25-28] Whether these reflect genetic variability, socioeconomic factors, or both is poorly understood.

Co-morbidities also modify the course and outcome of acute illness.[29,30] Their incorporation into the APACHE (acute physiology, age, chronic health evaluation) prognostic model reflects the independent impact of age and co-morbidities on the prognosis of acute illness.[31] Co-morbidities and age have a particular impact on longer term outcomes following ICU admission. A population-based study from Denmark disclosed that while 30 d mortality for patients with high rates of co-morbidity was 27%, by three years, 63% of the population had died.[30] Even variables such as marital status have been linked to mortality risk following ICU admission.[32] The impact of co-morbidities and socio-economic and cultural variables on outcome is complex. The competing mortality risk of a co-morbid illness modifies the attributable mortality of the acute illness under study, while cultural, social, and religious factors can modify the therapeutic approach of the treating clinicians or decision-makers;[33] both influences impact assumptions regarding the therapeutic signal associated with an intervention.

Insult

The nature of the inciting insult impacts the host response, and so the ultimate clinical outcome. Infection is the most common insult resulting in a deleterious endogenous host response (termed sepsis, when infection is the cause); however there is considerable heterogeneity in the response, dependent upon the infecting organism—a feature that enables characteristic clinical descriptions of specific infections. Although both are caused by gram-positive bacteria and can produce life-threatening illness, necrotizing soft tissue infections caused by group A streptococci produce a clinical phenotype that differs from that of pneumococcal pneumonia, and life-threatening viral illnesses differ strikingly in their clinical manifestations. On the other hand, rarely does a pathogen produce a clinical syndrome that is

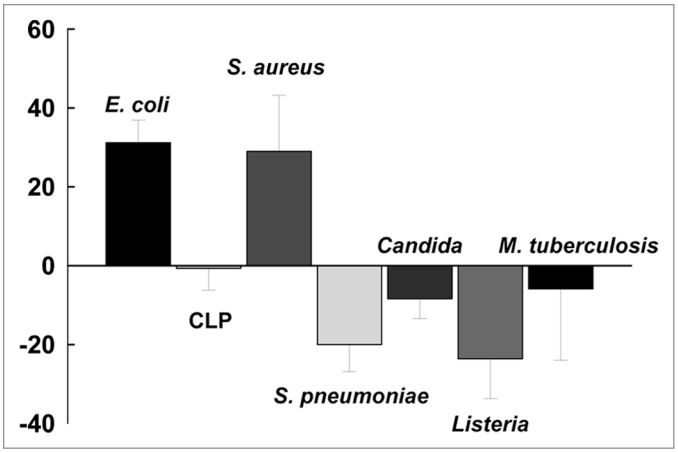

Figure 1. Studies of the neutralization of tumor necrosis factor in a variety of pre-clinical models reveal that the consequences are model-dependent. Survival is improved in models of systemic challenge with endotoxin, *E. coli*, or *S. aureus*, unaffected in cecal ligation and puncture (CLP) models, and reduced when the challenge organism is *S. pneumoniae*, *Candida*, *Listeria*, or *M. tuberculosis*. Adapted from reference 37.

sufficiently distinct that it can be diagnosed on clinical grounds alone.

Non-infectious insults can evoke the same inflammatory mediator response that results from infection, for the mechanisms underlying the recognition of danger are similar, or even identical. Toll-like receptor 4—the cellular receptor that plays a central role in the host response to endotoxin—can also be activated by non-infectious ligands such as heat shock proteins, oxidized phospholipids, and the alarmin, HMGB1.[34] Gene array studies of the transcriptional response to differing harmful stimuli disclose that these stimuli can evoke overlapping patterns of response.[35,36] Conversely, and even more importantly, it is apparent from animal studies that the consequences of modifying the host response vary with the nature of the specific insult. In animal studies of the consequences of neutralizing tumor necrosis factor (TNF), a strong beneficial effect is seen in those models in which the insult is systemic challenge with endotoxin, gram-negative bacteria, and certain gram-positive species, particularly *S. aureus*.[37] However TNF neutralization is harmful in models of challenge with *S. pneumoniae*, as well as in models where the infecting organism is a fungus or an intracellular pathogen such as *M. tuberculosis*, and without clear benefit or harm in a complex polymicrobial infection such as that resulting from cecal ligation and puncture (**Fig. 1**). Data from human studies are limited, although studies of endotoxin neutralization in sepsis show that neutralization increases mortality in those patients whose infections are caused by gram-positive organisms.[38,39]

Response

The response of the host to an acute insult can be quantified by physiologic variables such as temperature and blood pressure, or by the levels of circulating cells or molecules whose levels change in response to that insult.

Independent of whether infection triggered the response, we found, in a cohort of 212 critically ill surgical patients, that the magnitude of the host inflammatory response, measured using a sepsis score, was strongly and independently associated with the risk of death.[9] Indeed, when patients were stratified by maximal sepsis scores, the influence of infection on mortality risk was no longer evident. The impact of the physiologic response also varies dependent upon the nature of the insult that evokes it. Fever has been shown to be an independent risk factor for mortality in patients without infection, but a beneficial adaptive response whose correction worsens outcome when fever is present.[40] Moreover, hypothermia is an independent risk factor for mortality in patients with septic shock.[41]

The risk of adverse outcome in sepsis has been associated with increasingly abnormal levels of multiple different host-derived molecules that plausibly play a pathogenic role in disease progression.[42,43] How each of these reflects discrete components of a complex process, and whether the information each provides is distinct and non-redundant, is largely unknown. Moreover, while abnormal expression of each may correlate with the ultimate risk of mortality, their ultimate value lies not in forecasting death or mirroring disease severity but in identifying discrete aspects of a biologic process that are amenable to intervention, and in monitoring the subsequent response to intervention. It follows that the optimal marker or markers will be dependent upon the intervention planned. Levels of TNF as measured by ELISA in a study of the efficacy of an anti-TNF monoclonal antibody in sepsis showed enormous variability, ranging from 7 to 56 000 pg/ml (unpublished). It would seem intuitively apparent (and is supported by observations from another study of an anti-TNF antibody) that therapy would be most efficacious in those patients with the highest levels of TNF.

In that same trial, patients were stratified on the basis of the serum level of IL-6 at baseline, on the hypothesis that patients with higher levels of IL-6 would show a greater response to neutralization of TNF. A cutoff level of IL-6 of 1000 pg/ml was selected; although the mortality difference for treated patients with IL-6 levels above and below this value did not differ, an analysis of treatment effect by IL-6 level suggested greater efficacy in patients whose IL-6 levels were more than 8000 pg/ml (**Fig. 2**).[42,44] In contrast, an analysis of the effects of the adequacy of source control intervention on ultimate outcome showed that patients whose IL-6 levels were less than 1000 pg/ml had significantly improved survival (76.9 vs 60.3%, $P < 0.001$) if they had received adequate source control intervention; this benefit was no longer apparent for patients whose IL-6 levels were greater than 1000 pg/ml (unpublished).

These observations are admittedly selective and post hoc analyses, a reflection of how few data are available on the ability of a biomarker to reflect treatment responsiveness, rather than overall mortality risk. This principle is well-established in oncology. In breast cancer, for example, expression of estrogen receptors or the Her2/Neu receptor on the surface of the cancer cell identifies a subpopulation of patients who will benefit from treatment with anti-estrogen compounds[45] or trastuzumab respectively.[46] In patients with colorectal cancer, microsatellite instability identifies a subpopulation that is more likely to benefit from adjuvant chemotherapy.[7]

Organ dysfunction

Organ dysfunction is the consequence of the activation of an inflammatory response, and despite being potentially reversible, the proximate event preceding death. In the contemporary intensive care unit, death despite maximal resuscitative and supportive measures is distinctly uncommon, and when it does occur, usually reflects profound cardiopulmonary instability secondary to myocardial infarction, pulmonary embolism, or uncontrollable hemorrhage. Most deaths in the ICU result from a conscious decision to withdraw continuing supportive care in the face of a combination of non-resolving dependence on exogenous life support technologies and an underlying pre-morbid health state that makes a return to an independent life improbable. Thus organ dysfunction—its evolution and its persistence—represents a critical nexus in the decision-making process regarding ongoing support.

In a trivial sense, the development of organ dysfunction stratifies patients on the basis of the need for exogenous support of the organ whose function is failing. Refractory hypoxemia is treated with intubation and positive pressure ventilation, whereas declining renal function resulting in azotemia and volume overload is managed by dialysis. However the severity of organ dysfunction can also identify populations of patients who may differentially benefit from other interventions. For example, although the merits of early and appropriate antibiotic therapy in sepsis are well-established, these benefits accrue largely to those patients who do not have significant organ dysfunction at the time the treatment decision is made; the administration of appropriate antibiotic therapy to patients with more advanced organ dysfunction is without obvious benefit.[47,48] In contrast, activated protein C appeared to be most effective in those patients with significant degrees of organ dysfunction.[49]

Modeling PIRO: What Has Been Done?

There have been a number of studies that have tested the underlying hypothesis of the PIRO model—that outcome following acute illness is independently impacted by abnormalities in each of the four PIRO domains. Their focus—of necessity—has been prognostication of survival, rather than of response to treatment.

Moreno and coworkers evaluated a cohort of 2628 septic patients who remained in the ICU for at least 48 h. PIRO variables were drawn from the data collected for SAPS 3 scores, and the domains of response and organ dysfunction were combined.[50] They showed that mortality risk was increased in patients with septic shock, and identified variable reflecting each of the three domains that contributed to a prognostic model. Lisboa and colleagues studied 441 Spanish patients with ventilator-associated pneumonia.[51] They reported that a four-variable PIRO score calculated at the time of VAP onset and reflecting tertiles of risk correlated well with both mortality risk and need for resource use. They further showed that such a prognostic model could also be applied for patients with community-acquired pneumonia, and the prognostic capacity of the model exceeded that of the APACHE II score and dedicated prognostic criteria for pneumonia.[52]

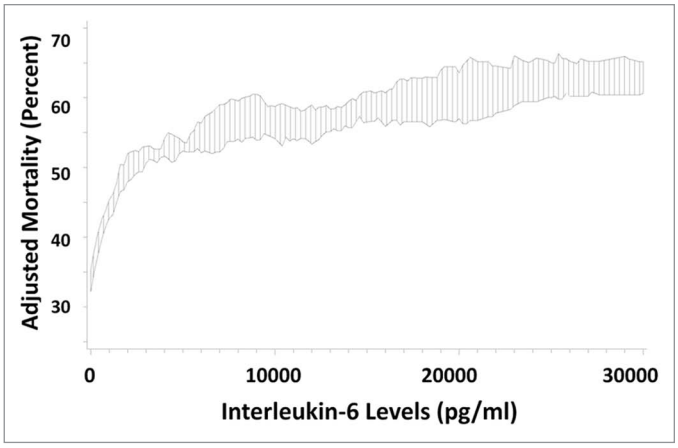

Figure 2. The impact of baseline interleukin-6 levels on survival following neutralization of tumor necrosis factor in a randomized controlled trial of 2634 patients with sepsis; survival curves were modestly separated at the cutoff level of 1000 pg/ml used in the trial, but diverged further at higher levels of IL-6.[44]

Using two databases from studies of activated protein C in sepsis, Rubulotta found an independent mortality contribution associated with variables reflecting each of the four PIRO domains, and reported that an aggregate model based on these was highly predictive of hospital mortality.[53] Granja incorporated evaluation of response and organ dysfunction variables over time into a model that also showed good prognostic capacity when used in a cohort of Portuguese patients admitted to an ICU with sepsis.[54]

Toward a Staging System for Acute Illness

Each of these studies, however, is relatively small, recruited patients with an a priori diagnosis of illness, and focused on the prediction of clinical outcome, rather than on the prediction of response to therapy.

The utility of the TNM system arises not so much from its ability to predict mortality or cancer recurrence, although it is patently able to do both, but rather from its ability to identify subgroups of patients within the larger population of individuals with a disease who might benefit from specific modes of treatment. A patient with a colon cancer that is confined to the site of the primary tumor, with no evidence of spread to regional nodes or distant organs has only a 10% to 25% risk of recurrence over 5 y following resection, depending on the size and local extension of the tumor, and so surgery alone may be adequate therapy. On the other hand, evidence of nodal spread increase the risk of recurrence to 45% to 50%, and it is this group of patients who are optimally managed with both surgery and systemic chemotherapy.[55] When there is evidence of spread beyond the regional nodes at the time of initial presentation, local measures will not result in cure, and more aggressive approaches are warranted, recognizing that their primary objective is not

cure but palliation. Successful multimodal therapy in oncology has only become a reality with the development of an effective disease stratification system.

Can a similar approach better inform multimodal therapy for patients with sepsis or other acute inflammatory disorders? There are a number of important differences between the two disease groupings that make the prospect a challenge. First, cancer is a disease that, by and large, begins locally and spreads over time, making the distinction between the need for local or systemic therapy much more evident. This process, moreover, evolves gradually, and so enables the oncologist to devote the needed time to accurate pathologic diagnosis and staging before finalizing a therapeutic plan. Sepsis, on the other hand, characteristically presents as a systemic process with life-threatening physiologic consequences, and treatment decisions must be made expeditiously. Cancer has a visible pathologic phenotype—the transformed cells that represent the malignant process. It can be detected locally or systemically; its absence can also be confirmed with a reasonable degree of accuracy. Sepsis, on the other hand, has no distinct pathologic features. It is associated with the abnormal expression of hundreds of putative biomarkers; however the role each of these might play beyond simply reflecting disease severity and mortality risk is largely unknown. Finally, and perhaps most importantly, successful staging in oncology has evolved over a long period of time because of the large scale collaborative efforts of oncologists around the world through global organizations such as the International Union Against Cancer; similar collaborations do not exist in acute care, and so initial attempts to develop models have been built on small existing data sets, guided by the particular perspectives of a small group of investigators, and constrained by the data available for analysis.

These challenges notwithstanding, however, there are at least two initiatives that could be undertaken to advance the objective of developing a validated and clinically useful staging system for acute illness.

PIRO as a Template for the Design of Clinical Trials

At this early stage in its conceptualization as a tool that can ultimately inform clinical decisions, PIRO is probably best seen as a checklist of domains that should be considered during the design of a clinical research program. Explicit consideration of each of the 4 PIRO domains may improve the articulation of entry and exclusion criteria for clinical trials.

As an example, suppose we are contemplating a trial to evaluate the optimal duration of antibiotic therapy for patients with ventilator-associated pneumonia, and that our planned primary endpoint was the proportion of patients randomized to one of two treatment durations who were discharged from hospital by day 90. In considering predisposition, we would want to exclude patients with co-morbidities associated with a significant independent risk of mortality over 90 d, as well as patients who, for other reasons, were likely to remain in hospital for an extended period of time. Recruitment would be restricted to those patients having ventilator-associated pneumonia (insult), and we might further restrict entry to patients with a particular response (fever, hypoxia, or laboratory findings such as leukocytosis or elevation of procalcitonin or TREM-1 levels) that resulted in a sicker group of patients who were both more likely to actually have pneumonia, and more likely to experience an adverse outcome from that disease. Finally, we might exclude patients with significant organ dysfunction based on the probability that they would both be more likely to experience a prolonged hospitalization and to have a less favorable response to antibiotics.

Alternatively, we might be contemplating a clinical trial of early albumin resuscitation for patients with septic shock. There are no obvious predisposing factors that would identify a group of patients who might experience either differential benefit or harm from the intervention. On closer consideration of the insult, we find no biologic reason why patients with infection as the cause of a systemic inflammatory response might experience greater benefit, and so elect to enroll all patients with distributive shock and evidence of systemic inflammation (response). Since there is evidence that albumin is harmful in patients with closed head injury,[56] we would exclude these patients. Finally, since we have no evidence that organ dysfunction modifies the response to albumin treatment, we would not consider the degree of organ dysfunction as an entry or exclusion criterion, but may choose it as a stratification variable to evaluate differential treatment efficacy.

We might take a very different approach if the intervention was a strategy to neutralize tumor necrosis factor in critically ill patients. On the basis of epidemiologic work and studies in patients receiving anti-TNF therapies for rheumatic diseases, it appears that genetic polymorphisms alter levels of TNF expression and **predispose** to adverse outcomes in sepsis;[18] moreover there is emerging evidence that genetic factors may alter the response to anti-TNF therapy in rheumatoid arthritis.[57] We may choose to focus our intervention on those patients who are predicted to gain the greatest benefit. In reviewing the impact of **insult**, we find no reason to limit the study population to patients with infection, since patients with acute non-infectious disorders such as burns[58] and ruptured abdominal aortic aneurysms[59] are known to have elevated TNF levels, and anti-TNF therapies have found their greatest efficacy in such non-infectious disorders as arthritis[60] and inflammatory bowel disease.[61] Since TNF is involved in the adaptive response to infection, we might choose to exclude patients with infection for whom there is evidence that neutralizing TNF increases infectious susceptibility,[62] or worsens outcome.[37] Finally, as discussed earlier, we might limit our study population to patients who do not have significant organ dysfunction at the time of study entry.

The explicit consideration of a PIRO classification results in the elaboration of very different study populations for each of these three interventions. It should also be recognized that the classic entry criteria for sepsis trials embody an implicit PIRO model: Predisposition is incorporated by the exclusion of patients at risk of early death from factors that can't be modified by the intervention, insult is defined variously as suspected or proven invasive infection, response by the presence of SIRS criteria, and organ dysfunction by the presence of one or more organ

dysfunctions. The problem, however, is that this generic model does not optimize the entry criteria for any specific intervention, be it antibiotics, fluids, or a particular inflammatory mediator.

Development of large databases understand the epidemiology of critical illness

Beyond efforts to incorporate the PIRO concept into the design of future trials, there is a need for large cohort studies—to better understand the factors that drive the course of critical illness and how these modify the response to clinical interventions. This is a substantial undertaking both in concept and size. For example, in considering the impact of medical co-morbidities, it will be important to understand not only how co-morbid conditions such as cirrhosis or congestive heart failure alter prognosis for patients admitted to an intensive care unit, but also how this prognosis differs from that experienced by patients with the same co-morbidities who are not critically ill, how combinations of co-morbidities interact, how they change the philosophy of care at baseline and in response to subsequent clinical course, and how they are impacted by cultural and socio-economic factors. In evaluating putative biomarkers it will be important to know not only how they predict outcome, but how they add independent predictive capacity to other biomarkers, and how they perform for differing clinical diagnoses.

Research consortia have begun to address some of these issues[63]; however the scope of the challenge calls for an international collaboration that is open access and non-proprietary, iterative in process, and rigorous in methodology—ambitious but not impossible. Such an approach transformed the field of oncology and a template for creating core outcome measure sets across a broad spectrum of medical disciplines provides useful insight into the necessary steps to achieve consensus on the optimal domains for a model.[64] Within the realm of critical care, efforts are ongoing to test the most recent Berlin criteria for ARDS in large diverse patient cohorts, and provide further evidence of the plausibility of large scale data-driven collaboration.

Conclusion

PIRO is not a robust and fully developed staging system, nor even, necessarily, the optimal architecture to create such a system. Rather it is a challenge—to understand critical illness as a complex and multidimensional process that need correspondingly sophisticated diagnostic tools to facilitate its optimal management, and to the global community of critical care investigators to collaborate to build the concepts and collect the data that will enable the development and validation of these tools.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

References

1. Williams GR. Presidential Address: a history of appendicitis. With anecdotes illustrating its importance. Ann Surg 1983; 197:495-506; PMID:6342553; http://dx.doi.org/10.1097/00000658-198305000-00001
2. Hansson J, Körner U, Khorram-Manesh A, Solberg A, Lundholm K. Randomized clinical trial of antibiotic therapy versus appendicectomy as primary treatment of acute appendicitis in unselected patients. Br J Surg 2009; 96:473-81; PMID:19358184; http://dx.doi.org/10.1002/bjs.6482
3. Shindoh J, Niwa H, Kawai K, Ohata K, Ishihara Y, Takabayashi N, Kobayashi R, Hiramatsu T. Diagnostic power of inflammatory markers in predicting severity of appendicitis. Hepatogastroenterology 2011; 58:2003-6; PMID:22234068
4. Gospodarowicz M, Benedet L, Hutter RV, Fleming I, Henson DE, Sobin LH. History and international developments in cancer staging. Cancer Prev Control 1998; 2:262-8; PMID:10470455
5. Sobin LH. TNM: evolution and relation to other prognostic factors. Semin Surg Oncol 2003; 21:3-7; PMID:12923909; http://dx.doi.org/10.1002/ssu.10014
6. Northcott PA, Shih DJ, Peacock J, Garzia L, Morrissy AS, Zichner T, Stütz AM, Korshunov A, Reimand J, Schumacher SE, et al. Subgroup-specific structural variation across 1,000 medulloblastoma genomes. Nature 2012; 488:49-56; PMID:22832581; http://dx.doi.org/10.1038/nature11327
7. Ribic CM, Sargent DJ, Moore MJ, Thibodeau SN, French AJ, Goldberg RM, Hamilton SR, Laurent-Puig P, Gryfe R, Shepherd LE, et al. Tumor microsatellite-instability status as a predictor of benefit from fluorouracil-based adjuvant chemotherapy for colon cancer. N Engl J Med 2003; 349:247-57; PMID:12867608; http://dx.doi.org/10.1056/NEJMoa022289
8. Sadanandam A, Lyssiotis CA, Homicsko K, Collisson EA, Gibb WJ, Wullschleger S, Ostos LC, Lannon WA, Grotzinger C, Del Rio M, et al. A colorectal cancer classification system that associates cellular phenotype and responses to therapy. Nat Med 2013; 19:619-25; PMID:23584089; http://dx.doi.org/10.1038/nm.3175
9. Marshall JC, Sweeney D. Microbial infection and the septic response in critical surgical illness. Sepsis, not infection, determines outcome. Arch Surg 1990; 125:17-22, discussion 22-3; PMID:2294878; http://dx.doi.org/10.1001/archsurg.1990.01410130019002
10. Marshall JC, Cook DJ, Christou NV, Bernard GR, Sprung CL, Sibbald WJ. Multiple organ dysfunction score: a reliable descriptor of a complex clinical outcome. Crit Care Med 1995; 23:1638-52; PMID:7587228; http://dx.doi.org/10.1097/00003246-199510000-00007
11. Levy MM, Fink MP, Marshall JC, Abraham E, Angus D, Cook D, Cohen J, Opal SM, Vincent JL, Ramsay G; International Sepsis Definitions Conference. 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. Intensive Care Med 2003; 29:530-8; PMID:12664219; http://dx.doi.org/10.1007/s00134-003-1662-x
12. Sørensen TI, Nielsen GG, Andersen PK, Teasdale TW. Genetic and environmental influences on premature death in adult adoptees. N Engl J Med 1988; 318:727-32; PMID:3347221; http://dx.doi.org/10.1056/NEJM198803243181202
13. Barreiro LB, Quintana-Murci L. From evolutionary genetics to human immunology: how selection shapes host defence genes. Nat Rev Genet 2010; 11:17-30; PMID:19953080; http://dx.doi.org/10.1038/nrg2698
14. López C, Saravia C, Gomez A, Hoebeke J, Patarroyo MA. Mechanisms of genetically-based resistance to malaria. Gene 2010; 467:1-12; PMID:20655368; http://dx.doi.org/10.1016/j.gene.2010.07.008
15. Chapman SJ, Hill AV. Human genetic susceptibility to infectious disease. Nat Rev Genet 2012; 13:175-88; PMID:22310894
16. Khor CC, Chapman SJ, Vannberg FO, Dunne A, Murphy C, Ling EY, Frodsham AJ, Walley AJ, Kyrieleis O, Khan A, et al. A Mal functional variant is associated with protection against invasive pneumococcal disease, bacteremia, malaria and tuberculosis. Nat Genet 2007; 39:523-8; PMID:17322885; http://dx.doi.org/10.1038/ng1976
17. Khor CC, Vannberg FO, Chapman SJ, Guo H, Wong SH, Walley AJ, Vukcevic D, Rautanen A, Mills TC, Chang KC, et al. CISH and susceptibility to infectious diseases. N Engl J Med 2010; 362:2092-101; PMID:20484391; http://dx.doi.org/10.1056/NEJMoa0905606
18. Mira J-P, Cariou A, Grall F, Delclaux C, Losser M-R, Heshmati F, Cheval C, Monchi M, Teboul JL, Riché F, et al. Association of TNF2, a TNF-α promoter polymorphism, with septic shock susceptibility and mortality: a multicenter study. JAMA 1999; 282:561-8; PMID:10450718; http://dx.doi.org/10.1001/jama.282.6.561
19. Nakada TA, Russell JA, Boyd JH, Walley KR. IL17A genetic variation is associated with altered susceptibility to Gram-positive infection and mortality of severe sepsis. Crit Care 2011; 15:R254; PMID:22026963; http://dx.doi.org/10.1186/cc10515
20. Thair SA, Walley KR, Nakada TA, McConechy MK, Boyd JH, Wellman H, Russell JA. A single nucleotide polymorphism in NF-κB inducing kinase is associated with mortality in septic shock. J Immunol 2011; 186:2321-8; PMID:21257964; http://dx.doi.org/10.4049/jimmunol.1002864
21. Thompson CM, Holden TD, Rona G, Laxmanan B, Black RA, O'Keefe GE, Wurfel MM. Toll-Like Receptor 1 Polymorphisms and Associated Outcomes in Sepsis After Traumatic Injury: A Candidate Gene Association Study. Ann Surg 2013; (Forthcoming); PMID:23478521; http://dx.doi.org/10.1097/SLA.0b013e31828538e8

22. Zeng L, Gu W, Zhang AQ, Zhang M, Zhang LY, Du DY, Huang SN, Jiang JX. A functional variant of lipopolysaccharide binding protein predisposes to sepsis and organ dysfunction in patients with major trauma. Ann Surg 2012; 255:147-57; PMID:22167001; http://dx.doi.org/10.1097/SLA.0b013e3182389515
23. Zhao Y, Tao L, Jiang D, Chen X, Li P, Ning Y, Xiong R, Liu P, Peng Y, Zhou YG. The -144C/A polymorphism in the promoter of HSP90beta is associated with multiple organ dysfunction scores. PLoS One 2013; 8:e58646; PMID:23516526; http://dx.doi.org/10.1371/journal.pone.0058646
24. Martin GS, Mannino DM, Eaton S, Moss M. The epidemiology of sepsis in the United States from 1979 through 2000. N Engl J Med 2003; 348:1546-54; PMID:12700374; http://dx.doi.org/10.1056/NEJMoa022139
25. Sakr Y, Elia C, Mascia L, Barberis B, Cardellino S, Livigni S, Fiore G, Filippini C, Ranieri VM. The influence of gender on the epidemiology of and outcome from severe sepsis. Crit Care 2013; 17:R50; PMID:23506971; http://dx.doi.org/10.1186/cc12570
26. Dombrovskiy VY, Martin AA, Sunderram J, Paz HL. Occurrence and outcomes of sepsis: influence of race. Crit Care Med 2007; 35:763-8; PMID:17255870; http://dx.doi.org/10.1097/01.CCM.0000256726.80998.BF
27. Pietropaoli AP, Glance LG, Oakes D, Fisher SG. Gender differences in mortality in patients with severe sepsis or septic shock. Gend Med 2010; 7:422-37; PMID:21056869; http://dx.doi.org/10.1016/j.genm.2010.09.005
28. Baker MG, Barnard LT, Kvalsvig A, Verrall A, Zhang J, Keall M, Wilson N, Wall T, Howden-Chapman P. Increasing incidence of serious infectious diseases and inequalities in New Zealand: a national epidemiological study. Lancet 2012; 379:1112-9; PMID:22353263; http://dx.doi.org/10.1016/S0140-6736(11)61780-7
29. Esper AM, Martin GS. The impact of comorbid [corrected] conditions on critical illness. Crit Care Med 2011; 39:2728-35; PMID:22094497; http://dx.doi.org/10.1097/CCM.0b013e318236f27e
30. Christiansen CF, Christensen S, Johansen MB, Larsen KM, Tønnesen E, Sørensen HT. The impact of pre-admission morbidity level on 3-year mortality after intensive care: a Danish cohort study. Acta Anaesthesiol Scand 2011; 55:962-70; PMID:21770901
31. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. Crit Care Med 1985; 13:818-29; PMID:3928249; http://dx.doi.org/10.1097/00003246-198510000-00009
32. Metersky ML, Fine MJ, Mortensen EM. The effect of marital status on the presentation and outcomes of elderly male veterans hospitalized for pneumonia. Chest 2012; 142:982-7; PMID:22459780; http://dx.doi.org/10.1378/chest.11-3183
33. Frost DW, Cook DJ, Heyland DK, Fowler RA. Patient and healthcare professional factors influencing end-of-life decision-making during critical illness: a systematic review. Crit Care Med 2011; 39:1174-89; PMID:21336127; http://dx.doi.org/10.1097/CCM.0b013e31820eacf2
34. Erridge C. Endogenous ligands of TLR2 and TLR4: agonists or assistants? J Leukoc Biol 2010; 87:989-99; PMID:20179153; http://dx.doi.org/10.1189/jlb.1209775
35. Seok J, Warren HS, Cuenca AG, Mindrinos MN, Baker HV, Xu W, Richards DR, McDonald-Smith GP, Gao H, Hennessy L, et al.; Inflammation and Host Response to Injury, Large Scale Collaborative Research Program. Genomic responses in mouse models poorly mimic human inflammatory diseases. Proc Natl Acad Sci U S A 2013; 110:3507-12; PMID:23401516; http://dx.doi.org/10.1073/pnas.1222878110
36. Xiao W, Mindrinos MN, Seok J, Cuschieri J, Cuenca AG, Gao H, Hayden DL, Hennessy L, Moore EE, Minei JP, et al.; Inflammation and Host Response to Injury Large-Scale Collaborative Research Program. A genomic storm in critically injured humans. J Exp Med 2011; 208:2581-90; PMID:22110166; http://dx.doi.org/10.1084/jem.20111354
37. Lorente JA, Marshall JC. Neutralization of tumor necrosis factor in preclinical models of sepsis. Shock 2005; 24(Suppl 1):107-19; PMID:16374382; http://dx.doi.org/10.1097/01.shk.0000191343.21228.78
38. Greenman RL, Schein RMH, Martin MA, Wenzel RP, MacIntyre NR, Emmanuel G, Chmel H, Kohler RB, McCarthy M, Plouffe J, et al.; The XOMA Sepsis Study Group. A controlled clinical trial of E5 murine monoclonal IgM antibody to endotoxin in the treatment of gram-negative sepsis. JAMA 1991; 266:1097-102; PMID:1865542; http://dx.doi.org/10.1001/jama.1991.03470080067031
39. Opal SM, Laterre PF, Francois B, LaRosa SP, Angus DC, Mira JP, Wittebole X, Dugernier T, Perrotin D, Tidswell M, et al.; ACCESS Study Group. Effect of eritoran, an antagonist of MD2-TLR4, on mortality in patients with severe sepsis: the ACCESS randomized trial. JAMA 2013; 309:1154-62; PMID:23512062; http://dx.doi.org/10.1001/jama.2013.2194
40. Lee BH, Inui D, Suh GY, Kim JY, Kwon JY, Park J, Tada K, Tanaka K, Ietsugu K, Uehara K, et al.; Fever and Antipyretic in Critically ill patients Evaluation (FACE) Study Group. Association of body temperature and antipyretic treatments with mortality of critically ill patients with and without sepsis: multi-centered prospective observational study. Crit Care 2012; 16:R33; PMID:22373120; http://dx.doi.org/10.1186/cc11211
41. Marik PE, Zaloga GP. Hypothermia and cytokines in septic shock. Norasept II Study Investigators. North American study of the safety and efficacy of murine monoclonal antibody to tumor necrosis factor for the treatment of septic shock. Intensive Care Med 2000; 26:716-21; PMID:10945388; http://dx.doi.org/10.1007/s001340051237
42. Marshall JC, Reinhart K; International Sepsis Forum. Biomarkers of sepsis. Crit Care Med 2009; 37:2290-8; PMID:19487943; http://dx.doi.org/10.1097/CCM.0b013e3181a02afc
43. Pierrakos C, Vincent JL. Sepsis biomarkers: a review. Crit Care 2010; 14:R15; PMID:20144219; http://dx.doi.org/10.1186/cc8872
44. Panacek EA, Marshall JC, Albertson TE, Johnson DH, Johnson S, MacArthur RD, Miller M, Barchuk WT, Fischkoff S, Kaul M, et al.; Monoclonal Anti-TNF: a Randomized Controlled Sepsis Study Investigators. Efficacy and safety of the monoclonal anti-tumor necrosis factor antibody F(ab')2 fragment afelimomab in patients with severe sepsis and elevated interleukin-6 levels. Crit Care Med 2004; 32:2173-82; PMID:15640628
45. Rose C, Thorpe SM, Andersen KW, Pedersen BV, Mouridsen HT, Blichert-Toft M, Rasmussen BB. Beneficial effect of adjuvant tamoxifen therapy in primary breast cancer patients with high oestrogen receptor values. Lancet 1985; 1:16-9; PMID:2856949; http://dx.doi.org/10.1016/S0140-6736(85)90966-3
46. Piccart-Gebhart MJ, Procter M, Leyland-Jones B, Goldhirsch A, Untch M, Smith I, Gianni L, Baselga J, Bell R, Jackisch C, et al.; Herceptin Adjuvant (HERA) Trial Study Team. Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. N Engl J Med 2005; 353:1659-72; PMID:16236737; http://dx.doi.org/10.1056/NEJMoa052306
47. Nathens AB, Rotstein OD, Marshall JC. Tertiary peritonitis: clinical features of a complex nosocomial infection. World J Surg 1998; 22:158-63; PMID:9451931; http://dx.doi.org/10.1007/s002689900364
48. Clec'h C, Timsit JF, De Lassence A, Azoulay E, Alberti C, Garrouste-Orgeas M, Mourvilier B, Troche G, Tafflet M, Tuil O, et al. Efficacy of adequate early antibiotic therapy in ventilator-associated pneumonia: influence of disease severity. Intensive Care Med 2004; 30:1327-33; PMID:15197443; http://dx.doi.org/10.1007/s00134-004-2292-7
49. Bernard GR, Vincent J-L, Laterre PF, LaRosa SP, Dhainaut J-F, Lopez-Rodriguez A, Steingrub JS, Garber GE, Helterbrand JD, Ely EW, et al.; Recombinant human protein C Worldwide Evaluation in Severe Sepsis (PROWESS) study group. Efficacy and safety of recombinant human activated protein C for severe sepsis. N Engl J Med 2001; 344:699-709; PMID:11236773; http://dx.doi.org/10.1056/NEJM200103083441001
50. Moreno RP, Metnitz B, Adler L, Hoechtl A, Bauer P, Metnitz PG; SAPS 3 Investigators. Sepsis mortality prediction based on predisposition, infection and response. Intensive Care Med 2008; 34:496-504; PMID:18060541; http://dx.doi.org/10.1007/s00134-007-0943-1
51. Lisboa T, Diaz E, Sa-Borges M, Socias A, Sole-Violan J, Rodríguez A, Rello J. The ventilator-associated pneumonia PIRO score: a tool for predicting ICU mortality and health-care resources use in ventilator-associated pneumonia. Chest 2008; 134:1208-16; PMID:18779186; http://dx.doi.org/10.1378/chest.08-1106
52. Rello J, Rodriguez A, Lisboa T, Gallego M, Lujan M, Wunderink R. PIRO score for community-acquired pneumonia: a new prediction rule for assessment of severity in intensive care unit patients with community-acquired pneumonia. Crit Care Med 2009; 37:456-62; PMID:19114916; http://dx.doi.org/10.1097/CCM.0b013e318194b021
53. Rubulotta F, Marshall JC, Ramsay G, Nelson D, Levy M, Williams M. Predisposition, insult/infection, response, and organ dysfunction: A new model for staging severe sepsis. Crit Care Med 2009; 37:1329-35; PMID:19242329; http://dx.doi.org/10.1097/CCM.0b013e31819d5db1
54. Granja C, Póvoa P, Lobo C, Teixeira-Pinto A, Carneiro A, Costa-Pereira A. The predisposition, infection, response and organ failure (Piro) sepsis classification system: results of hospital mortality using a novel concept and methodological approach. PLoS One 2013; 8:e53885; PMID:23349756; http://dx.doi.org/10.1371/journal.pone.0053885
55. Weiser MR, Landmann RG, Kattan MW, Gonen M, Shia J, Chou J, Paty PB, Guillem JG, Temple LK, Schrag D, et al. Individualized prediction of colon cancer recurrence using a nomogram. J Clin Oncol 2008; 26:380-5; PMID:18202413; http://dx.doi.org/10.1200/JCO.2007.14.1291

56. Myburgh J, Cooper DJ, Finfer S, Bellomo R, Norton R, Bishop N, Kai Lo S, Vallance S; SAFE Study Investigators; Australian and New Zealand Intensive Care Society Clinical Trials Group; Australian Red Cross Blood Service; George Institute for International Health. Saline or albumin for fluid resuscitation in patients with traumatic brain injury. N Engl J Med 2007; 357:874-84; PMID:17761591; http://dx.doi.org/10.1056/NEJMoa067514
57. Umićević Mirkov M, Cui J, Vermeulen SH, Stahl EA, Toonen EJ, Makkinje RR, Lee AT, Huizinga TW, Allaart R, Barton A, et al. Genome-wide association analysis of anti-TNF drug response in patients with rheumatoid arthritis. Ann Rheum Dis 2013; 72:1375-81; PMID:23233654; http://dx.doi.org/10.1136/annrheumdis-2012-202405
58. Endo S, Inada K, Yamada Y, Kasai T, Takakuwa T, Nakae H, Kikuchi M, Hoshi S, Suzuki M, Yamashita H, et al. Plasma tumour necrosis factor-alpha (TNF-alpha) levels in patients with burns. Burns 1993; 19:124-7; PMID:8471144; http://dx.doi.org/10.1016/0305-4179(93)90033-5
59. Roumen RMH, Hendriks T, van der Ven-Jongekrijg J, Nieuwenhuijzen GAP, Sauerwein RW, van der Meer JWM, Goris RJ. Cytokine patterns in patients after major vascular surgery, hemorrhagic shock, and severe blunt trauma. Relation with subsequent adult respiratory distress syndrome and multiple organ failure. Ann Surg 1993; 218:769-76; PMID:8257227; http://dx.doi.org/10.1097/00000658-199312000-00011
60. Aaltonen KJ, Virkki LM, Malmivaara A, Konttinen YT, Nordström DC, Blom M. Systematic review and meta-analysis of the efficacy and safety of existing TNF blocking agents in treatment of rheumatoid arthritis. PLoS One 2012; 7:e30275; PMID:22272322; http://dx.doi.org/10.1371/journal.pone.0030275
61. D'Haens GR. Top-down therapy for IBD: rationale and requisite evidence. Nat Rev Gastroenterol Hepatol 2010; 7:86-92; PMID:20134490; http://dx.doi.org/10.1038/nrgastro.2009.222
62. Ford AC, Peyrin-Biroulet L. Opportunistic infections with anti-tumor necrosis factor-α therapy in inflammatory bowel disease: meta-analysis of randomized controlled trials. Am J Gastroenterol 2013; 108:1268-76; PMID:23649185; http://dx.doi.org/10.1038/ajg.2013.138
63. Klein MB, Silver G, Gamelli RL, Gibran NS, Herndon DN, Hunt JL, Tompkins RG; Inflammation and the Host Response to Injury Investigators. Inflammation and the host response to injury: an overview of the multicenter study of the genomic and proteomic response to burn injury. J Burn Care Res 2006; 27:448-51; PMID:16819346; http://dx.doi.org/10.1097/01.BCR.0000227477.33877.E6
64. Williamson PR, Altman DG, Blazeby JM, Clarke M, Devane D, Gargon E, Tugwell P. Developing core outcome sets for clinical trials: issues to consider. Trials 2012; 13:132; PMID:22867278; http://dx.doi.org/10.1186/1745-6215-13-132