Meeting report

The PIRO Concept: R is for response

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This report is based on the transcript of a roundtable debate held at the 23rd International Symposium on Intensive Care and Emergency Medicine (ISICEM), Brussels, Belgium, 18–21 March 2003. The participants of the debate were Jean-François Dhainaut (Paris, France), Stephan Harbarth (Geneva, Switzerland), Konrad Reinhart (Jena, Germany), John C Marshall (Toronto, Canada) and Mitchell Levy (Providence, USA).

[Herwig Gerlach] We will now continue with the 'R'. The R is for response. We had the definition from SIRS [systemic inflammatory response syndrome], which has been discussed, and SIRS was a stratification. Now we're discussing R as a new possibility to quantify the response, and this would be my first, maybe a little bit provocative, question.

We've heard that the grade of response is not always predictive of outcome; for instance, you might remember the cartoon in the *New England Journal of Medicine* by Hotchkiss, where he said that patients who are not responding are obviously clinically more at risk than those with a very visible response. So my question is, is it necessary to quantify response or do we need to find a new way of stratification, of qualifying response, or not?

[Mitchell Levy] That's very interesting – I think it has to be both. The whole purpose of PIRO is to stratify rather than quantify, and I think that as a hypothesis-generating model the idea is, can we figure out how to stage sepsis more accurately and precisely so that we might be able to time our interventions better. Right now, for instance, the agents that we use that have been shown to improve survival are for severe sepsis. Well, severe sepsis is such a crude definition because you have to wait until there's frank organ dysfunction. So if we could get a better stratification model that allowed us, based on biomarkers, for instance the 'R', to identify what patients are at risk for developing organ dysfunction, and then test that hypothesis to see if interventions reduce the degree to which organ dysfunction develops, then that is an important stratification. The actual quantification is necessary in order to create the model; how much IL-6, how much TNF [tumour necrosis factor], etc., is important, but more important is the stratification of profiles for biomarkers.

[HG] But this would consider that we have the conclusion that the higher the response the higher the risk. But is this really the case?

[John C Marshall] I agree, the intent here is to stratify rather than quantify the severity. But the other concept behind PIRO that I think is important is an attempt to deconstruct sepsis, because we've kind of regressed to a mindset where we're talking about a single large definable, homogeneous population of patients. So is it important to measure the

CRP = C-reactive protein; IL = interleukin; PCT = procalcitonin; SIRS = systemic inflammatory response syndrome; TNF = tumour necrosis factor.

response? That depends on the circumstances, and I think we need to define it by what we're going to do. If our intervention is continuous veno-venous haemodialysis, then it doesn't matter what the temperature is, it doesn't matter what the IL-6 is – we're treating renal failure as a component of the syndrome of sepsis. If our intervention is an antibiotic then it's probably going to work better in patients who don't have a really dramatic response, because those will tend to be patients in whom the disease is driven by the effects of the organism. On the other hand, if our intervention is an anticoagulant then clearly the response we want to look at is whether there is evidence of a coagulopathy that might stratify that patient into a more homogeneous population with response to therapy we're going to give.

Taking the notion, which I think is reasonable, that there are some patients who are sick because they are hyperresponsive and some patients who are sick because they are hyporesponsive, clearly if we lump those together we're never going to see a benefit for any therapy because it's going to help half the patients, harm half the patients, and the net effect will be zero. But if our intervention is something that is going to boost the immune response then it's critical that we define the response and we explicitly define it as hyporesponsiveness, just as Annane *et al*. showed that patients who are relatively steroid adrenal insufficient are those that respond to corticosteroids.

[Konrad Reinhart] I think this comes to the point of biological plausibility of the markers that we are measuring. As you said, if you want to treat with an anticytokine it might be wise to look for cytokines, and there IL-6 would be appropriate as a surrogate marker. And in fact this is the only marker so far that has identified a higher risk of dying because, in these two large studies, patients who had higher IL-6 levels had a clearly higher mortality, and the question is, why are we measuring response? Is it to titrate a specific therapy, or to have prognostic information? That's why we should not only talk about appropriate markers for the response but also discuss the cause of the response. What we all know from studies is that a person with a persistently high procalcitonin (PCT) is very unlikely to survive. We can discuss new markers like pro-ANP [pro-atrial natriuretic peptide] that has a high likelihood for predicting outcome very early and maybe also BNP [brain natriuretic peptide], so this response issue has to be looked at for the reasons that are relevant to our therapy. There may be markers that have a high potential for prognosis and maybe other markers to tell us how successful we are with therapy, or specifically predict how the patient might respond. Also, we must use not just immunosuppressive therapies but also immunoaugmentive therapies, where we should look at IL-10 or other anti-inflammatory mediators. We have some data but we should do further work.

[HG] So may I conclude that there is a necessity for quantifying? So let's look at how we can do this – starting with clinical features. Do you think that it's necessary or good and useful to measure fever and white blood count – the traditional markers used in the SIRS criteria?

[Jean-François Dhainaut] I think first it's very important to understand that the response depends not only on the infectious process, for instance the white blood cells for haematologic patients, heart rate in patients with cardiac disease or patients taking drugs that interfere with this cardiac response. Responses can also be very different in the elderly; often their responses are a bit lower, and sometimes you have no fever, white blood cells are not so high, and also regarding the markers. As an example, in the PROWESS trial elderly patients usually had relatively inflammatory symptoms, taking into account the coagulation and inflammatory biomarkers. Likewise, patients with some underlying disease may have lower inflammatory and coagulation responses.

So the question is, how important is it to quantify the response regarding the clinical side or the biological side? I think a single measurement may not be so important but its time course is more interesting because we can modify it with treatment.

[A participant] I would take an extreme stance. First of all, I think that the R is the most important part of PIRO, and I think that the clinical signs and symptoms will fall by the same way as SIRS criteria fell, because I think that most of us assume that clinical signs and symptoms of infection are surrogates for biomarkers. We certainly know that about fever and IL-1, and I think that over the next 5–10 years – and it's already happening – clinical trials are adding proteonomic arms and collecting large volumes of biomarker data, sequentially, over time. I predict, or hope, that once we have the ability to get profiles of those biomarkers for identification of patients in the early phases, for identification of patients who are progressing, and then respond to therapy, we won't be looking at clinical signs and symptoms any more.

[Stephan Harbarth] I wouldn't completely throw away SIRS since it has a high sensitivity to detect septic patients. If there is something particular useful in SIRS it has probably to do with the white blood count (WBC) and left shift. We saw in a couple of studies that if you take into account leukocytosis plus the left shift and you add, perhaps, procalcitonin or lactate – something that is easily available at the bedside – I think for the next couple of years this may remain a pretty good marker for response. After all, we have been talking about all these cytokine cocktails for 10 years and look what's really used at the moment. I remind you that in the USA, they've just introduced CRP [C-reactive protein]; something that most European critical care physicians don't understand is that for 10 years CRP was not available in most U.S. hospitals. So let's get practical, and let's speak about what's really going to be important in the next

2–3 years. I think we should consider blood gases, pH, lactate, differential WBC and procalcitonin as markers for systemic response

[JCM] I just wanted to make a big-picture comment, and that is how to approach this whole notion of thinking about a stratification system for sepsis. We can all talk about what are our favourite markers for sepsis, or how we see a complex disease process, but I would hope that what we can generate here is a whole series of good questions to ask and evaluate in clinical trials. Something as simple as what you're asking, Herwig, is: is fever important? The way you'd transfer this into a research question is, does the patient's temperature at onset of therapy alter response to therapy? Another question is, is the response to therapy reflected in an alteration in temperature? The important one for the PIRO model is, is temperature a stratification variable that will define, for example, relative increased success of therapy with a broad-spectrum carbapenem in a patient with ventilator-related pneumonia? So it's thinking of a whole series of contingent questions that can be answered. It's fairly simple database-driven observational studies that we should be working on, rather than trying to *a priori* impose our particular view of the world on a process that we clearly don't understand very well right now.

[HG] One problem was that SIRS was a black and white stratification – it was never evaluated over time. So this leads of course to parameters or any variables that are feasible to monitor the state of the patient, and why do you think there are so many differences between the US and Europe, for example, in PCT, CRP [C-reactive protein]? Do you have any idea why this is the case?

[JCM] As a Canadian – someone who is neutral in this issue – I think it actually gets back to the 'P' of the PIRO model. There are some very important cultural differences that define the way we institute therapy, and it's clear to me that North Americans don't believe in CRP and PCT in part because they originated in Europe, and I suspect there are probably similar views among Europeans about things that originated in North America. And more power to you!

[SH] There are some North Americans who have some consideration for PCT or who are pretty curious about PCT, and I think that, just coming back to what's practical nowadays, some studies have shown that PCT may be a good surrogate marker for the other cytokine cocktails going on. High PCT levels are well correlated with TNF levels and other marker levels. So my suggestion for future clinical trials is to add PCT and test the hypothesis that by stratifying according to PCT one may predict outcomes.

[KR] I think this is another good point – feasibility. I think for PCT the technical requirements have been improved rapidly. We have to learn to which of our various treatments that we apply in sepsis our biomarkers respond best. We often don't know whether it's due to the antibiotic that our patient gets better or if it's because we took out his catheter, which was contaminated, or even if it is because we have improved our oxygen delivery; data were recently presented that the serum of patients with a central venous O_2 pressure below 50% had a strong inflammatory response. If we learn which of these new biomarkers best reflect our various treatment strategies, then we can use this also for the response to therapy. But primarily it's a response to the insult.

[JCM] I agree. First, it's important to say that PIRO is really meant as a hypothesis-generating model. None of us are introducing it with the idea that tomorrow we'll go look at a patient and work out their PIRO score. Really it's a way of introducing the field to a new way of stratifying response to infection. So from that point of view, the R is clearly the response to infection, but as you intervene the R changes. So you could go from an R2 to an R3, based on how you define response; well, that's the response to therapy – but it's still R as the response to infection, but within that there's a response to therapy.

[Audience member] I agree with those comments, and the other thing to keep in mind is that this is a template that could be applied to virtually every disease in medicine. The reason we're doing it in the context of sepsis is that the questions we have to answer to study this entity are probably more complex than any other area of medicine. In cardiology, for example, the R could be a rapid heart rate in a patient with a supraventricular tachycardia, that's the patient you would treat with an antiarrhythmic, but you would anticipate that the R would also be the response – i.e. that the rate would come down.

A corollary of that is a huge mistake we've made in sepsis trials, which is thinking that we can enroll patients based on a certain group of entry criteria but that we wouldn't anticipate that these would get better. If they're important stratification variables to select patients for a trial then they should be altered by therapy, and if they're not then they're not useful for stratification.

Sepsis typically arises as a complication of other disease processes; one could even argue that it's a complication of a pneumococcal pneumonia rather than a pneumococcal pneumonia *per se*. So clearly that lead-time bias is intrinsically the entity of the disease, and part of the reason why we have to think about – Where did we start? What was the stimulus? What was the response? What has happened so far? – is that if the damage has already been done then trying to modify the initiating stimulus is unlikely to affect the outcome. We're going to have to focus on therapies that are going to modulate the subsequent response to that injury, to the damage that has been done, to the organ dysfunction.

[J-FD] Another point is the difficulty to separate the pro- and the anti-inflammatory process, and to assess the balance between the two. For example, IL-6 is a pro- and anti-inflammatory cytokine. When you correlate prognosis with a cytokine, it appears that IL-10 is better than TNF, or rather the balance between TNF and IL-10. There was a paper in *The Lancet* showing that patients who have an imbalance between TNF and IL-10 have a poor prognosis. It's the same for the coagulation process, where coagulation is activated and anticoagulant factors consumed. It is very difficult to influence the coagulation system because the two possibilities are rapidly inhibited, fibrinolysis and anticoagulation.

[ML] I think that's exactly why SIRS is inadequate because when we look at one clinical sign and symptom, or two out of four, it's the same thing as if you looked at just one cytokine. So as our understanding of the pathophysiology of the inflammatory response to infection deepens, we begin to realize you can't just look at IL-6, you can't just look at a proinflammatory or even just an anti-inflammatory marker. We need the constellation of response in terms of markers. So I think that's exactly why stratification is important.

[KR] It might well be that GSF [growth-stimulating factor] administration, which turned out to be negative, might have worked had we looked at it only in patients with leukopenia or who would have been immunosuppressed by other markers, and interferon-γ. One reason why I like PCT is that it helps me differentiate, for example, between patients with infection-related organ dysfunction and non-infection-related organ dysfunction. A fundamental question to me is whether I have the right antibiotic or not. So they are separate questions.

[Audience member] One of the things that I'm having a hard time with is, does it make any difference whether it leads to organ dysfunction, and especially in those who have the genetic factors responsible for greater release of IL-8 etc. What I'm hearing you say is that you need to specify a marker for the specific intervention that you're trying to study – that there needs to be some surrogate in there somewhere. From a practical standpoint, there are many markers with unclear relationships to specific disease.

[JCM] Let me give you an example of that. We did an analysis of patients in the MONARCH anti-TNF study, who'd had some sort of source control done. We did a blinded analysis of the adequacy of source control. Now, in that study patients were stratified on the basis of their IL-6 level, and what we found was that if you looked at the impact of adequate source control, there was a 16% survival improvement for patients who had adequate source control, even in the group with low IL-6 levels. But the benefits of adequate source control were less clear. There was no evidence that the adequacy of source control impacted on outcome in the patients with high IL-6 levels; it was an insignificant effect. What that means is that if the intervention we're looking at is, for example, a source control with surgical therapy and antibiotics, then we're probably going to see a maximum signal where we're going to want to exclude patients who have an activated response, or the disease process is now being driven by the response rather than by the original stimulus.