

Meeting report

The PIRO concept: P is for predisposition

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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, Brussels, Belgium, 18–21 March 2003. The participants of the debate were David Burgner (Perth, Australia), Richard Wunderink (Memphis, TN, USA), Jean-Paul Mira (Paris, France), Herwig Gerlach (Berlin, Germany), Christian J Wiedermann (Innsbruck, Austria) and Jean-Louis Vincent (Brussels, Belgium).

[Derek C Angus] As you know, in 1991 the American College of Chest Physicians and the Society of Critical Care Medicine convened a consensus panel to come up with some operational definitions for sick septic patients that would, in particular, facilitate the standardized enrolment of patients into clinical trials. At that time it was proposed to be 'infection' plus two or three out of the four systemic inflammatory response syndrome (SIRS) criteria that were believed to be related to the infection. If you also had acute organ dysfunction, it was believed that you had severe sepsis. That was published in 1992 and served as the basis for enrolment entry criteria into about 30 large randomized, controlled trials, but it rarely did much in terms of patient management – people were not necessarily using it to care for patients.

In December 2001, the American College of Chest Physicians, the Society of Critical Care Medicine, the European Society of Intensive Care Medicine, and several other sponsoring organizations – the American Thoracic Society – decided to convene another conference with at least one of the purposes being to explore how people felt about the robustness of the existing severe sepsis criteria. During that meeting SIRS came under heavy attack, and it was largely disbanded as not being very useful because the criteria identified lots of patients who were not sick and because there were sick patients who did not necessarily have SIRS.

At the same time, during that meeting there was considerable discussion about a new concept that had been proposed predominantly by John Marshall, from Toronto. He suggested that we could think about severe sepsis in a way that might be analogous to cancer – where you stage cancers by tumors/nodes/metastases, the TNM classification, and perhaps you can consider thinking of sepsis in the same way.

This gave birth to the concept of PIRO, which is thinking about severe septic patients across four domains. P for 'predisposition', predisposing factors that would make

someone more likely to become infected or to suffer organ dysfunction. I for 'infection', and/or insult if you apply it to trauma; in that way, you would categorize the type of infection, what the organism was, the site of infection, and so on. R for 'response'; there was a lot of debate about whether this would be a beneficial response, but it is something that would be characterizing the inflammatory cascade, the innate immune response, that was being turned on in response to infection, trying to understand how systemic it was, and so on. Finally, O for 'organ dysfunction', which largely incorporated all the adverse sequelae of developing infection and then having this overly exuberant inflammatory response to infection.

So this was PIRO, and perhaps around PIRO you could have different grades – grades of P, grades of I, grades of R, grades of O – that might actually be a way to come up with a better understanding of which patients were distinct from each other and which were similar to each other, and it might even inform better choice of interventions. It might also allow us to select patients that were more likely to benefit from a particular therapy, and so on.

[John Marshall] I think the notion is simply that sepsis is a complex disease like cancer – and oncologists learn very early on that you cannot just evaluate a therapy in a patient with cancer, you have to look at distinct aspects of that cancer. What staging systems in cancer have done is to stratify patients according to the probability that they will die, that they will have an adverse outcome – but also according to the probability that they will respond to particular therapy. So this is not a staging system; in essence, what we are looking at is a template that hopefully at some point will help us to develop a stratification system. And by looking at the P part, you are looking at the predisposing factors that might modulate the potential to respond to therapy for a particular clinically important outcome.

[Herwig Gerlach] If we take this analogy to TNM classification, there are different TNM classifications for each type of cancer, and this might explain why there are different Ps. P1I2R2O1 might be totally different in a meningococcal sepsis than it is in a long-term sepsis, so this we must keep in mind – just as with cancer TNM, there are many different TNMs for different cancers with totally different prognostic factors.

[David Burgner] I come at this from a genetic predisposition point of view, and obviously the priority for me is to identify the gene that makes us think of all these acronyms! I think genetics has always been perceived as a bit too difficult, a bit too esoteric, and probably a bit irrelevant to clinical medicine. I think that is the perception – obviously I do not think it is true. But I think we are coming to the end of that era, and I think one of the first areas that will see genetic predisposition coming into clinical practice will be, I hope, critical care

medicine. This is for a number of reasons. First, you are dealing with very extreme phenotypes, you have a very high-risk population with very poor outcomes. The other reason is that you have very good and very beautiful studies of epidemiology, and genetic epidemiology is only a small step from the epidemiology – and the epidemiology to me suggests a genetic predisposition. Obviously, in this population you cannot do twin studies or sibling studies, but the fact that you have a male excess of mortality and ethnic differences that seem to stand up to multiple corrections would seem to me to point strongly to genetic factors being important. Some of the simple genetic tests that we could do are almost at the point where you would want to screen your patients for common and simple genetic variants that seem to have really profound effects on mortality. I think the challenge would be to have studies that are big enough to give you pure-enough phenotypes that you can look at in a clean, scientific way.

The final thing I want to say is to be able to bring together not only the human genetics, but the bacterial genetics and the gene expression profiling and the genetics involved in response to therapy, and I think that will be the challenge – to work as a whole. I guess that blurs the PIRO concept a bit, but I think it is important.

[Richard Wunderink] I actually favor this concept much more than the SIRS criteria, because in fact we have found that the original concept of SIRS was that this was a stepwise progression – you went from SIRS to severe sepsis to septic shock to death. In fact, many of the organ dysfunctions you see with SIRS probably have different genetic predispositions. Patients who get acute respiratory distress syndrome in response to an insult are different genetically to patients who get septic shock from the same insult – and there may or may not be overlap between septic shock and acute respiratory distress syndrome. So from that point of view I think, clearly, that genetics in starting with a predisposition is a better concept than that it is a progression from SIRS to severe sepsis.

I think the other thing that is going to be critically important is outside influences – simply, predisposition alcohol will change the phenotype very dramatically whatever your underlying genotype. So that kind of concept must be in there also – it is not just genetic predisposition, but also some of the other exposures that patients have.

This is complex. Patients who are tumor necrosis factor hyposecretors may actually be more prone to an infection but less prone to get septic shock when they get an infection. Or IL-10, or a variety of these kinds of mediators. This could explain some of the problems we see in simply measuring levels – there is a reason that we have tumor necrosis factor, it is a good reason, so to say that all tumor necrosis factor hypersecretion is bad is a wrong concept; I think it is wrong

in the wrong circumstances and good in the right circumstances.

[HG] I think this PIRO is very exciting and opens up new diagnostic tools, although I am a little skeptical to translate P always into genetics – I think we must look for all the environmental factors. There are so many data from epidemiologic studies, and we all know that, for example, male persons are more responsive to infections whereas females are more responsive to noninfectious inflammation (the ratio is 4:1) and to autoinflammatory diseases. So this is very simple information that you can get from the patient – smoking and nonsmoking habits, for example, in acute respiratory distress syndrome. There have been several studies, not all of which have been published – so I think these environmental factors and comorbidities are very important. So let me repeat that we must be a little bit skeptical and not look for the ‘holy grail’, but look for a genetic key to calculate or to predict whether this patient will get severe organ failure. I know that the data are very exciting and the results were very good, but the interpretation is still limited – it will take many years until we have the difference between prediction and association, and I think that most of the studies that have been done up until now have been associations.

[DCA] It sounds, then, like you are endorsing, at least from a conceptual standpoint, the notion of moving towards PIRO.

[Christian J Wiedermann] I will nevertheless stick to genetics because my relation is, first of all, that we all know that with infectious diseases genetics is more important than for cancer or cardiovascular diseases, so I also like the broadening of the concept and bringing in the genetic predisposition when we think about sepsis. The PIRO concept should be helpful not only for clinical routine, but for experimental hypothesis testing. We were interested in infectious diseases in relation to atherosclerosis, and we have reported that a mutation of the toll-like receptor 4 is associated with a higher frequency of acute bacterial infections. Therefore, I have put together some thoughts on what we have learned from genetic association studies in atherosclerosis as opposed to sepsis and infectious diseases. Genetic association studies have strength and limitations: they are simple to design, noninvasive sampling is possible, genotyping is reliable and cost-effective and statistics is uncomplicated, and they have the potential for clear interpretation and direct relevance to human biology.

But many factors undermine confidence in association studies. Lessons have been learned from atherosclerosis, where initial publications of a positive association were often followed by reports of nonreplication or refutation. There are many reasons identified for nonreplication, and an instance of the problematic nature of genetic association is, for example, that in atherosclerosis few DNA markers are routinely in use,

such as in risk stratification. Genetic association studies using single nucleotide polymorphisms or insertion–deletion variants are increasingly in the scientific literature. A MEDLINE search I performed for the terms “gene AND polymorphism AND atherosclerosis OR vascular biology OR thrombosis OR lipoprotein” turned out to have more than 3000 original publications. However, when “atherosclerosis” was substituted with the word “sepsis” or “bacteremia”, only about 160 articles could be found. This illustrates that association studies are just beginning in sepsis.

Why is this? In 2001, the *Journal of Clinical Investigation* expanded its editorial criteria for rapid rejection of submitted papers to include “genetic association studies related to complex disorders including atherosclerotic heart disease”. So it will be difficult to publish association studies on patients with sepsis for the simple fact that this disease is quite complex. This policy is justified as eliminating false-positive publications but nevertheless I think there is hope for genetic association studies in sepsis. They have significant limitations but they sometimes represent the only practical approach to begin to address a particular biological hypothesis, as we tried to do with toll-like receptor 4. So for new genes, for example, this will be the only way to get a clear review, but I am not so sure whether we can think about designing clinical trials or getting help in routine bedside work with genetics.

I think you actually began to address one of the concerns, which is that PIRO may be long on concept but a little short on application. I think that everyone here likes many of the ideas behind it but the issue is how it is to be put into clinical practice.

[Jean-Paul Mira] I guess it is very important to look at other predisposing conditions to sepsis, and all the epidemiological studies that have been presented this morning show that comorbidity greatly increases the weight of infection in terms of prognosis. I guess the other predisposing or prognostic factor is how the patient was before – this is a major issue in terms of selecting a patient for a trial or adjusting treatment. We have the phenotype of sepsis, but when you look at a cellular level it will be completely different if the patient has, for example, no cardiac reserve to face a major or even minor insult, compared with someone with a normal heart. I guess all the other predisposing factors, like heart failure or liver cirrhosis, have to be weighed. It is difficult – you have hundreds of patients on your database and it would be very interesting to understand the relative weights of all these predisposing factors because it is impossible to give the same weight to all of them. Now we have lots of community databases – we have seen an American database and a French one earlier today – so we have the informatic tools to try to measure the weight of all these predisposing factors, compared with each other.

[Audience member] Once again, keeping with that concept, there is a genetic predisposition that goes totally outside of that. Conversely, there are issues with, say, smoking or alcoholism that may make a very big difference, or just the whole functional status, so you put your TNM with a functional status too. The P concept is not only a genetic predisposition, but also alcoholism, functional status, ejection fraction, and so on. One of the things I would like to emphasize is that perhaps the experts here think that genetics is important, and the people at the front of the room think it may be important, and people at the back a little less, and outside of the room even less – but no chart I have ever reviewed has had ‘familial history of predisposition to infection’, yet that has a greater prognostic significance. I think the simple thing – if we do nothing more in this concept than to say ‘genetics plays a role in infection’ and we start to look for that, because until we start to look we are not going to find it.

[J-PM] Maybe you can also divide into acquired and innate prognostic factors – because we know that very old people who have an acquired prognostic factor like cirrhosis or heart failure or immunosuppressive treatment required for some reason.

You are right that you do not have a way to detect genetic predisposition in your hospital, but your patients do not care. Some studies showed that some genetic variant of cytochrome is responsible for major bleeding after warfarin treatment. If you give this treatment to a patient who has this genetic predisposition and then develops an intracerebral hemorrhage, he/she may sue you – because there have been two papers in *JAMA* and *The Lancet*. I guess we have to think about that and try to develop ways to improve our knowledge. But you cannot say “I don’t care because I don’t have that in my hospital” because your patients want the best care, evidence-based. So you must be very careful. If you do not have a computed tomography scanner in your hospital and the patient has very severe head trauma, you may have to transfer the patient to another hospital.

[Jean-Louis Vincent] I think, for the record, it would be nice to have one word more about alcoholism and how it comes into play. In particular, should we sometimes make a distinction between chronic and acute alcoholism – are there some differences?

[RW] I think it is not only in trauma, but also in community-acquired pneumonia, as Antonio Torres has shown, that acute ingestion is much more significant in many ways than whether there is a history of drinking every weekend. If you have a measurable alcohol level when a patient presents with community-acquired pneumonia they are in real trouble, and as I mentioned before that covers any phenotypic manifestation that may be underlying the genetic predisposition. So I think that is clearly going to be important

in trauma, in community-acquired pneumonia, and there are others – active smoking changes which bugs you might have in pneumonia.

[DCA] I am going to say one other thing that we have not touched upon, and that is that when we developed the concept of SIRS and severe sepsis, it was a conceptual idea. Actually, in the 10–12 years since it was introduced, there was comparatively little evaluation of SIRS – although it was being used all the time in large expensive clinical trials, there were few studies of large cohorts of patients trying to understand how useful SIRS might be. I do not think that served us well – it is almost a shame that it took us 10 or 11 years to work out that we maybe should not be using SIRS because it was not particularly valuable.

So I think we have heard that people like at least the first letter of PIRO – conceptually, people like the notion of having predisposition that is genetic and everything else, and that affects the I, the R, and the O. But I would put it to all of you that we do not want to be waiting another 10 or 11 years to work out whether there is any value to this. I think that a lot of us could contribute to putting some ‘beef’ on the P by looking at inception cohorts or intensive care unit populations or hospital populations to try to understand the relative contributions, giving some shape and flavor to the P with data rather than just with roundtable expert opinion.