Meeting report

The PIRO concept: I is for infection

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Published online: 7 May 2003 *Critical Care* 2003, **7**:252-255 (DOI 10.1186/cc2194)
This article is online at http://ccforum.com/content/7/3/252

Keywords infection, organ dysfunction, PIRO, predisposition, response

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 Steven Opal (Pawtucket, RI, USA), Antonio Torres (Barcelona, Spain), Marc Bonten (Utrecht, The Netherlands), Jonathan Cohen (Brighton, UK), and Richard Wunderink (Memphis, TN, USA).

[Jean-Louis Vincent] 'I' stands for infection, and now we would like together to try to characterize the extent of or the severity of infection based on infection criteria. We will not discuss the temperature or C-reactive protein or procalcitonin because they will be the topic of the next discussion, but let us rather focus on at least four aspects.

The first in my mind is the source of the infection. Of course, in all our studies we record the source of infection but, for instance, are urinary tract infections associated with a better prognosis than pulmonary infections or infections coming from other sites? The second question I have in mind is about the degree of infection and how we can characterize it – just as in the tumor/nodes/metastases classification the size of the tumor is very important. We all know that appendicitis is less severe than generalized purulent peritonitis, so how can we quantify that? The third aspect concerns hospital-acquired infection versus community-acquired infection – how will this influence the prognosis? And finally, what about the type of organism – *Pseudomonas* versus other microorganisms against *Candida* against others.

So let us start with the first question. What about the source of infection – how will it influence our assessment and, in particular, our assessment of the severity of the disease state?

[Marc Bonten] Well, I confess I am a PIRO-naïve person but I think one of the distinctions that must be made is whether the infection is intensive care unit (ICU) acquired.

[JLV] We are talking about source first.

[MB] It depends how you define it. The most important source is the respiratory tract; if you want to come to staging of severity, it comes to staging of your diagnosis. If you base your diagnosis of ICU-acquired pneumonia on just a tracheal aspirate, the outcome will be much better for the group than if you have a much more specific diagnostic tool, taking only patients with much more severe pneumonia. So if you want to say something about the severity of one certain type of infection related to one source, it depends how you diagnose it. I think that is my first impression.

 ICU = intensive care unit.

[Antonio Torres] The source may be related to the outcome and to the severity as well, and it could be classified – I am PIRO naïve as well – as abdominal, lung, urinary, central nervous system. Then the second thing to be taken into account with each of these sources is invasive or noninvasive, localized or generalized? This is the second step in the subclassification and is related to the prognosis. So in the lung, for example, pneumococcal pneumonia with or without bacteremia. Also, as you said, urinary tract infections have not such a bad prognosis as lung infections. So this is clear to me.

[JLV] That is actually a question that could be added to the list: Does bacteremia by itself carry a worse prognosis?

[Richard Wunderink] I think that is a very important thing – probably one of the best examples of this has already been made by the surgeons, where the Surgical Infection Society put together a way to classify intra-abdominal infections. They did some clinical trials based on this, and it was based on a different prognosis if you have diffuse peritonitis versus a localized infection, and I think that kind of concept would be good to start to apply to different types of infection. Obviously, with urinary tract infections it makes a difference whether you are talking about simple cystitis versus pyelonephritis – those are clearly distinctions that we ought to make when we are classifying patients – but I agree it comes back to definitions. What does it require for you to say that it is pyelonephritis rather than a urinary tract infection. So I think more work has to be done on correct classification and correct diagnosis.

Can I jump ahead to the question about bacteremia? I'm not sure that that is necessarily true – if you look at bacteremic pneumococcal pneumonia, we have some outpatients with bacteremia but that does not by itself mean it is a more severe infection. And in fact, going back to the P concept, it might be predisposed to not localizing infection but not having a severe response. So I think that bacteremia is going to have to be studied a lot more – I do not think we have definitively proved that it carries a worse prognosis in all infection.

[Jonathan Cohen] I think we intuitively believe that the source of infection has an impact on outcome, and what we have to ask ourselves is what data are there to support that intuition? At one level I think the data are there – in fact, more than in other areas of PIRO actually – so if you look at specifically the population of patients you are interested in, the septic patient on the ICU, and you look at all the clinical studies that have been done, and you correlate mortality with site of infection, you can generally say that, let us say, lung infections have a higher mortality than urinary or urosepsis-related infections. Many studies address this – there is a very old paper by Roberts in *Clinical Infectious Diseases* in which he looked at all different sorts of infections and looked at the rates of progression to severe outcome, and it was very clear that you can draw Kaplan–Meier curves to show how quickly the patient deteriorates, and so on. So I think at that level there are data that would say, yes, the site of infection has an effect on outcome.

But one has to be careful because it is not as simple as that. Take bacteremia as an example: bacteremia caused by *Pseudomonas aeruginosa* is clearly a different disease to bacteremia caused by *Staphylococcus epidermidis*. So to simply take location or source of infection in isolation, without a wider context – a grid if you like, in which you are trying to establish what is the overall risk associated with the infection– is I think hazardous. So yes, source of infection is part of the equation but cannot be taken in isolation.

In terms of whether bacteremia carries a worse prognosis, I think we need to look at the data – and it is actually quite interesting. If you look at bacteremia caused by different organisms, you get different answers, and there is a great danger here of trying to oversimplify something that is actually rather complex. I am all in favor of oversimplification, but only when it makes sense. So the answer to your question is, exactly as Richard said, if you take the specific context of community-acquired pneumonia with *Streptococci pneumoniae*, there are data out there. If you look at the specific context of candidemia, yes there are data out there. But if you simply say, generally, does bacteremia have an impact on outcome, you can probably get an answer – but it probably is not a very meaningful answer because it is not rich enough in information.

[Steven Opal] I totally concur with what Cohen just mentioned. I would say about bacteremia that many of our patients have catheter-related bacteremia, and that is an entirely different set of problems from someone who has secondary bacteremia from an uncontrolled, localized infection. So if you look at those patients who have bacteremic pneumonia or bacteremia associated with intra-abdominal sepsis, you can show in a number of studies if you look at large enough numbers that there is an adverse outcome associated with bacteremia, probably as a manifestation of two things. One is that you are getting quantitative information about how heavy the infection is in the localized area, and also how well the host is dealing with the problem. If they are not dealing with the problem well they will be bacteremic and likely to die, or if they have a massive infection (undrained abscess, for example) and they are bacteremic they are likely to do worse as well. However, if you throw into that equation bacteremia from catheter-related infection, particularly from coagulase-negative *Staphylococci*, where the attributable risk of mortality associated with that is in some studies zero, it can very substantially affect the predictive value of bacteremia *per se* as an endpoint.

So I think what has been said is true but with the caveats that you have to look at the origin of the bacteremia and what the host has attached to the bacteremia as well.

[JLV] Let us jump perhaps on the tide of microorganisms because time, of course, is very limited. So if I was showing to you a big database, like the Sepsis Occurrence in the Acutely ill Patients (SOAP) studies, what kind of analyses would you like to do on the microbiologic data, again trying to find a link between type of organisms and outcome – would you take *Candida*, would you take resistant organisms, methicillin-resistant *Staphylococcus aureus* versus methicillin-sensitive *Staphylococcus aureus*.

[AT] This is very clear – for instance, take the lung as this is my field – it is very clear that patients with community-acquired *P. aeruginosa* pneumonia have a worse prognosis. The second thing is that for *Pseudomonas* they will receive a very different empirical treatment – that is very important to know for *Pseudomonas*. Resistance is important as well – methicillin-resistant *Staphylococcus aureus* pneumonia has a worse prognosis than methicillin-sensitive *Staphylococcus aureus*, for example. The other issue is the concentration of bacteria in the site, because this is related to the inflammatory response – it has been shown in animal models and in humans as well, at least in the lung.

[MB] I think you should consider the combination of the bacteria and the therapy that has been given. If you have a bacteria considered to be a low-pathogenic bacteria that is treated with the wrong antibiotics, the outcome may be worse than for a high-pathogenic bacteria treated with the right antibiotics. So I do not think that you can see them separately from each other.

[RW] I am not sure that methicillin-sensitive *Staphylococcus aureus* is different to methicillin-resistant *Staphylococcus aureus*, because you are looking at very different patient populations when you look at those two microorganisms – at least in ventilator-associated pneumonia, not so much in community-acquired pnemonia. So I think there clearly needs to be some distinction between Gram-positive and Gram-negative microorganisms; I would tend to want to split the Gram-negative into *Pseudomonas* versus *Enterobacteriaceae* – I am not sure there is a significant difference between an *Escherichia coli* and a *Klebsiella*, and even *Serratia*.

[Derek C Angus] It seems to me that one of the things we want to do with PIRO is use it, either in trials or in clinical practice. So I can imagine that maybe we could know the genetic predisposition ahead of time, but one of the things that concerns me is that 'I' is going to be critical, and 'I' needs to be assigned within 2–3 hours of seeing the patient, while administering therapy.

My question is simply about the timeliness of assigning the 'I' – it seems to me that you have a preliminary 'I', upon which you have to make a treatment decision, and then later when the cultures come back you might have another 'I'. So this is another issue: the notion of how PIRO will actually work.

[JC] There are some data that it makes some difference whether it is Gram-positive or Gram-negative, and there are several levels of that. First of all there are some interesting and pretty obvious clinical data – the fact is that if you thought you had someone with classic tampon-associated staphylococcal shock syndrome, then you would use a different kind of treatment and enroll them in a different kind of trial than if you thought, on purely clinical grounds, that they had a Gram-positive nosocomial pneumonia. I mean, that is basic stuff. So in that sense it is obviously different. It is also different in that we and others have published data to show that there are different immunologic responses according to whether it is Gram-positive or Gram-negative, and interestingly it is now becoming increasingly clear that there are different pathogenetic pathways. So even the basic stuff – whether this is a round blue thing or a long pink thing – may indeed have some impact on the kind of treatment you do and on the way in which you enroll patients in a trial.

[Audience member] It is important to underline that if we do not find the source of the infection the prognosis may actually be worse, perhaps because we cannot cure the patient as well as when we identify the source.

[Audience member] I think the practical use of this would be that you could say, 'I' will be L for Lung, U for microorganism unknown on day 1, and next day it is L 'pseud' or whatever the code is for *Pseudomonas* plus/minus whether it is bacteremic plus/minus whether it is appropriate or inappropriate antibiotic therapy. So I think if the purpose of this is to try and speak a language that everybody understands, to classify patients so that you can group them together in clinically relevant ways, then I think you are going to have to consider both source and microorganism.

[Audience member] Would it be possible to quantify it in any way?

[JC] Yes, one of the things that Tony mentioned in passing is that one simple way in which you could do this, which is analogous to the tumors/nodes/metastases thing, is to say clearly it makes a difference as to whether you think this organism is simply colonizing or whether it is causing a real infection. So you could imagine you might say 'I0' is colonization, 'I1' is local infection, 'I2' is deep infection, and 'I3' is systemic infection plus/minus toxin production. That would be a practical approach that would be informative, but would also be easily applicable.

[Audience member] But that comes very close to the systemic inflammatory response syndrome and severe sepsis classification.

[JC] No, because it refers specifically to what your interpretation of that particular organism is in that patient.

[Audience member] But if you have to make that judgment at the bedside, you just look at clinical criteria.

[SO] I only want to point out that many of our patients have polymicrobial infections, and that is where the PIRO system might start to break down. We know now from a number of experimental studies that some of these bacteria synergize with each other in causing abscess formation, and one organism might protect the other organism from antibiotic exposure but also affect the immune response in a way that allows the other to exist – so polymicrobial infection is another topic that does not necessarily lend itself easily to a nice easy source of classification.

[Audience member] I like this 'I' also because it is the only way to remain connected to the real disease. It is not only the microorganism, it is a microorganism in a site; and this is the real disease – pneumococcal pneumonia with septic shock – so it is far better to describe things like 'severe pneumonia with septic shock due to *Pneumococcus*'. This 'I' is the only way for us to remain in the real world. The 'I' is both microorganism and the organ.

[Audience member] I just wondered whether we are trying to achieve two things with the same system? It has got to the point now where you want a system to enroll people into studies, and at the other end you want a system where you have more data, like the genetics, like the patient history, like the microbiological evidence. So maybe we need a late PIRO score or a different system where we can construct better analyses of our data.

[JLV] Do not forget that this is a quite flexible system and you can adapt it to your own needs – whether it is to characterize patients in your own ICU or for enrolling patients in a clinical trial.

Now, the next question will be about community-acquired infection versus ICU-acquired infection. In our clinical trials, we enroll patients sometimes when they come in with severe sepsis and sometimes when they develop sepsis after 10 days in the ICU – and my next question will be about how different these are.

Data from the SOAP study showed that the prognosis is about the same whether sepsis is present upon admission or whether it develops after more than 48 hours. We were surprised to find this, although immediately after that we saw the results of the French EPISEPSIS study, where the same kind of data came out in a study population that had more than 3000 patients. So my question is, do hospital-acquired infections – or at least infections acquired after at least 2 days in the ICU – have the same prognosis globally as severe sepsis on admission? Of course it will depend on the type of microorganism involved, but perhaps we could have your reaction to these data, which are rather new.

[SO] I think that it is generally true that if you look at global mortality statistics in nosocomially acquired infection versus severe community-acquired infection, they are not a whole lot different, but there are probably important differences in the patient population. Patients in the community are reasonably healthy and, in order to become septic, you have to have bumped into a fairly virulent organism – whereas nosocomially acquired patients are a surrogate for disease severity, and these are typically abnormal patients, and the bacteria that are now required to cause disease in these patients can be substantially less virulent. So when you add those together you wind up with similar mortality statistics – so I am not surprised by those results.

[AT] I am not surprised about the results at 48 hours, but I think that we should consider what happens later on – 7 days later it may be completely different. So the host is different, a hospitalized patient in the ICU mechanically ventilated with lots of antibiotics and some kind of immunosuppression is a different type of host, although the response is probably the same – just not the outcome.

[JLV] Can one expect that the attributable risk due to sepsis is higher in community-acquired sepsis than in nosocomial sepsis?

[RW] That is a very good question. I think if you look at it, it is much much much easier to separate attributable mortality in community-acquired infections – there you are talking about this is the reason for admission, and yes they may have underlying diseases but they are dying of infection. When you talk about nosocomial pneumonia, and they have their fifth episode of nosocomial pneumonia, they have had two line infections with multiple different microorganisms, I think it is incredibly difficult to have an attributable mortality. So it is almost like comparing apples and oranges; I would say this issue is more relevant to the 'P' discussion – this is past, or predisposition – that is where you have to put this issue. Has this patient been hospitalized, have they been ventilated for a long period of time? Nosocomial pneumococcal pneumonia has roughly the same mortality as community-acquired pneumococcal pneumonia but it occurs in very different populations.