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EDITORIAL

Melioidosis: a clinical model for gram-negative sepsis

The recently published study of recombinant human activated protein C (drotrecogin-α, Eli Lilly, Indianapolis, IN, USA) in severe sepsis makes welcome reading. At last a clinical trial of an augmentative therapy in severe sepsis has managed to show a mortality benefit from the trial agent [1]. Most studies of augmentative treatments in serious sepsis have failed to show clear benefit. Sepsis studies commonly involve a syndrome caused by a myriad of organisms, occurring in a very heterogeneous group of patients, who may be enrolled in one of several centres. This introduces multiple confounding factors. A good model for clinical sepsis studies would ideally cause disease in a relatively homogeneous population, be acquired in a community setting, present in large numbers to a single institution, be caused by a single organism, and ordinarily result in a substantial mortality rate. These are, of course, difficult criteria to meet.

A recent issue of *Critical Care Medicine* published two papers on the use of meningococcal sepsis as a model (of gram-negative sepsis) for treatment studies [2, 3]. Both agreed that this disease is a good model but bemoaned the rarity of the disease, which makes good studies logistically difficult. Neither author discussed other possible models. Meningococcal disease has been used recently to study the potential for the endotoxin-binding agent bactericidal-permeability increasing (BPI) protein to reduce mortality in severe sepsis [4]. No reduction in mortality was demonstrated, although there were benefits seen in secondary outcome measures. This disease does fulfil one of the criteria for a good clinical sepsis model outlined above – a single causative agent. However, its rarity means that, as with the above study, a multi-centre study is required to recruit sufficient numbers of patients. This introduces the 'centre effect', whereby error is introduced as a result of inter-centre variability in recruitment or disease management. Such errors may overwhelm the possibly small advantages to be gained from use of the trial agent.

Melioidosis is rarely mentioned – it is usually ignored as a disease of the tropics, which very few doctors in either Europe or North America ever see, and which is therefore presumably of very minor importance. This is a very myopic view, which must be challenged. I propose that melioidosis provides many advantages as a clinical sepsis model over the current heterogeneous clinical trials. Our knowledge of melioidosis and its causative organism, *Burkholderia* (formerly *Pseudomonas*) *pseudomallei*, has expanded considerably over the last 15 years. Melioidosis was originally described in Myanmar (then Burma) in 1911 and came to prominence during the Vietnam conflict, when French and American soldiers became infected. It has been described in most countries of south-east Asia, including the Peoples Republic of China and the Lao PDR [5], but Thailand has the greatest reported disease burden [6]. It is also endemic to northern Australia [7]. Understanding of the epidemiology of the disease has been improved by the demonstration of two phenotypically similar but genetically distinct biotypes in the environment [8], only one of which appears to be virulent [9]. Further understanding of the organism will inevitably result from the *B. pseudomallei* genome-sequencing project currently being undertaken by the Sanger Centre in the UK.

During the rainy season, between 100 and 200 patients with severe melioidosis are admitted to the provincial hospital in Ubon Ratchathani in north-east Thailand. Similar numbers are admitted to the University teaching hospitals in Khon Kaen. It is the leading cause of community-acquired septicaemia during the months June to November [10]. Many of these patients present with sepsis – *c*. 60% have positive blood cultures on admission to hospital. This means that large trials can be conducted quickly. Several large therapeutic clinical trials have already been conducted in these hospitals. These have demonstrated that ceftazidime (with or without co-trimoxazole) [11, 12], co-amoxiclav [13] and imipenem [14] are each effective in acute severe disease but, despite their introduction, in-hospital mortality is still *c*. 40%. Long-term patient follow-up is also possible in this population. It became apparent early in these studies that relapse rates were high unless maintenance treatment was continued for several months [15]. Further studies are continuing, but new antibiotics and novel anti-sepsis agents are urgently required if any further reduction in mortality is to be achieved.

Pathogenesis studies in melioidosis have already enabled considerable advances to be made in our understanding of gram-negative sepsis. Several of these

studies have been published recently. The importance of both interleukin-12 (IL-12) and IL-18 (and possibly IL-15) as mediators of interferon-γ production has been demonstrated, as has the production of two chemokines which have a role in T-cell activation [16, 17]. Plasma IL-6 concentrations have been shown to be predictive of mortality in melioidosis, independent of APACHE II scores, which may be useful for patient stratification in future sepsis studies [18]. High plasma levels of granzymes, reflecting activation of cytotoxic T lymphocytes and NK cells, have also been demonstrated for the first time in gram-negative sepsis [19]. Endotoxin release following the start of antibiotic therapy has been studied, with convincing evidence that much higher plasma concentrations of endotoxin occur after the first dose of ceftazidime (which binds to penicillin-binding protein 3 – PBP-3), when compared with imipenem, which binds preferentially to PBP-2 [20]. Interestingly, this was not reflected in increased mortality in the ceftazidime arm of the study.

There has been some interest in pathogenesis studies from large pharmaceutical companies, but generally these have not come to fruition. The one exception to this was a study of the platelet-activating factor antagonist lexipafant, which proved to be disappointing, although it is arguable that the study was underpowered [21]. There has also been discussion of trialling drotrecogin-α in melioidosis. However, even the therapeutic studies mentioned above have been problematic, not for the anticipated logistic reasons of working in the rural tropics, but because the necessary antibiotics are all expensive. Glaxo, SmithKline Beecham and MSD have each provided free drug, but other companies have preferred to concentrate on their more lucrative markets, as the return from a disease of impoverished rice farmers in south-east Asia is (presumably) unlikely to be large. These problems, and geography, should not be enough to deter clinical investigators from considering studies of new agents in melioidosis.

If our understanding of gram-negative sepsis is to advance quickly, well-powered pathogenesis studies must be conducted using diseases that are not uncommon. It is time that melioidosis was considered seriously.

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