the budget in March 2005 to rise to 37% by 2008, assuming that projected economic growth will be achieved.

The *Financial Times* published an article this spring suggesting that the Office for National Statistics (ONS) was about to reclassify PFI projects.[8] Although ONS issued a rebuttal, stating that it "has not taken any decision to change the treatment of Private Finance Initiative schemes in the public finances" as "the element of PFI debts that should be recorded within Public Sector Debt, is an extremely complex and difficult matter," it acknowledged that "ONS has recognised for some time that estimates need to be made and we have been continuously expanding our ability to cover PFI activities and explore possible sources of information."[9]

This is important because funds for PFI are treated as "off balance sheet" financing and appear as "additional expenditure" to public sector expenditure and are not currently included in the government balance sheet calculations of net debt. Should the Office for National Statistics change the rules, a major component of capital spending under these contracts could be reclassified as debt. This could easily lead to a breach of the second rule, removing the main justification for the PFI model.

If the private finance initiative dies in the United Kingdom it may still have a life beyond these shores. Rather like general practice fundholding, it has created a cadre of experts who can now offer their services to the rest of the world. The United Kingdom may, once again, be at least as successful in exporting its failures as its successes.

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Staphylococcus aureus, Panton-Valentine leukocidin, and necrotising pneumonia

A rare but often lethal cocktail that can complicate flu

Panton-Valentine leukocidin (PVL) is one of many toxins produced by *Staphylococcus aureus*. Structurally similar to γ haemolysin, this leukocidin comprises two subunits (F and S) that together are leukocidal and dermonecrotic.[1] Intermixing of γ haemolysin and the subunits of PVL produces toxin molecules with varying cellular affinities and destructive capability, even when the staphylococci may be otherwise sensitive to antibiotics such as methicillin. The death of a fit young soldier in the United Kingdom earlier this year from toxicity to PVL illustrated the extent of that capability.[2]

Infection with PVL producing staphylococci is rare. Fewer than 2% of clinical isolates of *S aureus* examined in the United Kingdom in 2002-3 had the genes to produce the leukocidin, although it was found in 4.6% of samples from infections of skin and soft tissue.[3] Furthermore, "pure" disease caused by those *S aureus* bacteria that produce PVL is rarely life threatening. It presents as recurrent furunculosis or abscesses, it may be either sensitive or resistant to methicillin, and it can be difficult to eradicate among carriers. Three new and more virulent staphylococcal syndromes associated with the leukocidin—purpura fulminans, skin sepsis, and necrotising pneumonia—have been recognised recently, however.

Purpura fulminans due to PVL producing methicillin sensitive *S aureus* (MSSA) has a mortality of 60% despite such sensitivity.[4] Skin sepsis due to community acquired methicillin resistant *S aureus* (MRSA) occurs in patients without recent contact with healthcare facilities or known risk factors for such infection. Transmission during close physical contact causes outbreaks in prisoners, military personnel, schoolchildren, and athletes.[5] Although these bacterial strains are resistant to methicillin, they are, at least, usually sensitive to more antibiotics than hospital strains.

The third manifestation of more serious disease caused by PVL is necrotising pneumonia, which is often lethal. It has been reported in America, Australia, Europe, and the Far East. The pneumonia often arises from bloodborne spread of organisms from infected tissue and can follow viral respiratory infections, especially influenza.

Strains of *S aureus* that produce PVL have a particular affinity for basement membrane exposed by desquamated ciliated epithelium, and they rapidly

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establish themselves in the lung, producing the leukocidin. Membrane piercing PVL then destroys newly recruited polymorph cells, liberating inflammatory mediators.[6] Alveolar macrophages, with depleted phagocytic ability owing to viral infection, then allow unhindered bacterial multiplication: at postmortem examination usually few neutrophils are found. Necrotising vasculitis with massive areas of pulmonary infarction and haemorrhage follows. Sheets of staphylococci cover ulcerated remnants of tracheal and bronchial epithelium.

Mortality due to such necrotising pneumonia is nearly 75%.[1] The first British case of necrotising pneumonia associated with PVL was in 2003,[7] and I am aware of six cases managed by colleagues in the UK in the past nine months. Because postmortem specimens are rarely cultured and the disease is not notifiable, its true incidence remains unknown. No particular strain of *S aureus* predominates,[3] and there is no predictable pattern of geographical variation.

Early diagnosis of necrotising pneumonia is very difficult, especially in young, fit people. Pyrexia, myalgia, chills, and occasionally diarrhoea imply non-specific viral illness but, equally, can indicate the production of other staphylococcal toxins. Typically, a previously young, fit patient, presents in the community with a recent flu-like illness. Classically he or she has a fever of >39°C; tachycardia of >140 beats per minute; and marked haemoptysis, hypotension, and leucopenia. Very high serum concentrations of C reactive protein (>400 g/l) may occur too, reflecting gross tissue destruction, thrombosis, and sepsis. Multilobular alveolar infiltrates are usual and, unlike in hospital acquired MRSA pneumonia, the lungs often cavitate. Effusions commonly develop.[1 4]

The initial management of necrotising pneumonia is supportive, with intensive care and aggressive treatment with antibiotics. In addition to routine infection control precautions, it may be advisable to use masks when clearing patients' airways with suction because infection among close contacts has been reported.[8] Having said that, screening of close contacts for PVL positive *S aureus* has not been recommended to date.

In the face of such high mortality, treatment with high doses of potent, penetrating, anti-staphylococcal antibiotics is justifiable to try to block the production of toxins. Conventional doses of vancomycin produce inadequate lung concentrations to kill MRSA in many patients, and vancomycin will not suppress toxin formation. Empirical therapy must cover MRSA, since 47% of PVL positive clinical isolates of *S aureus* from various sources were resistant to methicillin.[3] Furthermore, isolates of *S aureus* that seem to be resistant to erythromycin but sensitive to clindamycin should be checked ("D tested") to exclude inducible resistance to clindamycin. Clindamycin and linezolid have the advantage of switching off toxin production, and linezolid is also active against MRSA. This combination may be synergistic and has been used as initial therapy, pending the results of testing for antibiotic sensitivity. With no evidence based guidelines for treating necrotising pneumonia, and no dosage recommendations for intravenous dosages of clindamycin in this situation, 1.2 g given at six hourly intervals seems reasonable. This is similar to the regimen recommended for streptococcal necrotising fasciitis.

Rifampicin, flucloxacillin, and cephalosporins have also been used, with varying degrees of success.[6 9] Intravenous immunoglobulin, 2 g/kg, may have a beneficial immunomodulatory action, especially in toxic shock, neutralising superantigens, and circulating toxins.[10] Anecdotal reports indicate a possible role for activated protein C. The key to improved survival may be the inactivation of the toxins that continue to drive the necrosis even after the bacteria have died. Potential treatments needing further research include nebulised immunoglobulin, glycerol monolaurate,[11] staphylococcal vaccination, and it may be worth revisiting old treatments such as leukocidin toxoid.[12]

Depressingly, even with what seems to be appropriate initial treatment with antimicrobial drugs, the maximal survival from necrotising pneumonia is 30%.[9] During the 1919 influenza outbreak in Fort Jackson in the United States, when hundreds of troops were dying—almost certainly of PVL related necrotising pneumonia—doctors reported that "the treatment of *Staphylococcus aureus* infection of the lung is extremely ineffectual."[13]

Until the toxins and inflammatory intermediaries responsible for the necrosis can be neutralised earlier, the outlook will remain bleak.

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