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Infection associated with burns

E. J. L. LOWBURY
D.M., F.R.C.Path., M.R.C.P.

Bacteriologist, Medical Research Council Burns Unit, Birmingham Accident Hospital

Introduction

Infection was recognized by some 19th and early 20th century workers to be an important and potentially lethal complication of severe burns (Lustgarten, 1891; Stockis, 1903). The bacterial flora of burns were studied by Pack (1926), Aldrich (1933), Cruickshank (1935), Colebrook, Duncan & Ross (1948) and others before and during the second World War, but their pathogenic importance was commonly disregarded at a time when the main interests of clinicians treating burns were directed towards shock caused by fluid loss and the more nebulous 'toxaemia' attributed to products of thermal injury. In the 1950s some of the illness loosely described as 'toxaemia' was seen to be due to bacterial infection; with the introduction of methods that were successful in the control of shock, sepsis became recognized as the main cause of death in severely burned patients (Jackson, Lowbury & Topley, 1951; Markley *et al.*, 1957; Tumbusch *et al.*, 1961).

These fluctuations can be understood when we recall that severe burns cause a complex range of local and general pathological effects, including necrotic changes in the skin and underlying tissues which often make it hard to distinguish the added changes caused by microbial infection. At the same time it is well known that heavy colonization of most burns may occur without apparent sepsis; when sepsis does occur the patient is often very ill from other complications as well, and the infection is apt to be classed as 'opportunist'; this view is supported by the fact that some of the main pathogens (notably *Pseudomonas aeruginosa*) are organisms relatively harmless to healthy subjects and healthy tissues. It might be argued that extensively burned patients in this state are likely to die whether they become infected or not; but the mortality from severe burns has been reduced by successful control of such infections (Bull, 1971) showing that the presence of such infection can tip the scales against survival.

The bacteria of burns: sources and modes of transfer

Since bacteria as well as epithelial cells are destroyed by the heat which causes the burn, few or no bacteria are at first present on the burned area. Unless efficient protective measures are used, the burn quickly becomes colonized with bacteria, some being acquired from the patient's skin, gut and mouth, but most coming from external sources. In hospital, these sources are mainly other patients. Infected burns are a particularly profuse source of such organisms, and the uninfected burn, with its surface of defenceless necrotic tissue, is a particularly vulnerable 'catchment area'.

The bacteria which appear in burns treated in hospital include *Staphylococcus aureus*, other staphylococci and micrococci, diphtheroid bacilli, streptococci (including *Strep. pyogenes* sporadically), clostridia, and a wide range of Gram-negative bacilli, including *Pseudomonas aeruginosa*, *Proteus* spp., *Escherichia coli*, *Klebsiella* spp., *Acinetobacter anitratum*, *Enterobacter* and other species. The Gram-negative bacilli are particularly abundant where there is moist slough; they are less abundant on the outer surface of exposed slough than inside (Lowbury, Crocket & Jackson, 1954), and also less abundant on granulating surfaces exposed after separation of slough than in the slough itself. Gram-positive cocci are able to colonize the necrotic tissue, but unlike the Gram-negative bacilli they often multiply vigorously in granulation tissue exposed after separation of slough.

Staph. aureus in the burns of patients in hospital is usually resistant to various antibiotics—from which it can be inferred that they are acquired in hospital (Lowbury, 1960). *Ps. aeruginosa* has sometimes been thought to come by self-infection from the intestinal flora, but most patients in our experience have not carried *Ps. aeruginosa* on admission; direct evidence that cross-infection is the main source of *Ps. aeruginosa* in burns was obtained from serological and phage typing of strains isolated in the two wards of our burns unit; this showed that the type of *Ps. aeruginosa* acquired by a patient was usually the same as that previously found in the burns of other patients in the same ward, but different from the types found in patients in the other ward (Davis, Lilly & Lowbury, 1969).

Pathogenicity

Infection is of no importance in superficial burns, but potentially important in burns of full skin thickness or deep partial skin thickness; the latter may be converted to full skin thickness loss by infection.

Of the various bacteria isolated, *Streptococcus pyogenes* is unique in causing the complete failure of skin grafts almost whenever it is present on a grafted burn; it no longer tends to cause *invasive* infection for which in former times it was notorious. By contrast, *Pseudomonas aeruginosa* usually colonizes burns without causing obvious ill-effects, though it may cause some graft failure, with consequent delay in healing, and in severely burned patients it can colonize the living tissues adjacent to the burn, and the walls of small blood vessels, where it may be present in enormous numbers (Teplitz *et al.*, 1964); it causes septicaemia more often than the other bacteria of burns, sometimes associated with characteristic focal haemorrhagic necroses which break down to give ecthymatous ulcers. Other bacteria, including *Staph. aureus*, *Klebsiella* spp., *Proteus* spp. and *Serratia marcescens*, have also been found to cause invasive infection in some severely burned patients; with the successful control of Gram-positive cocci and, recently, of *Ps. aeruginosa*, *Candida* spp. and other fungi have been reported by some workers to be presenting new hazards of invasive and potentially dangerous infection (Pruitt & Curreri, 1971).

The mechanism by which bacteria invade burns has been most extensively studied in respect of *Ps. aeruginosa*. A defined culture medium in which these organisms were grown, fractionated by gel filtration through Sephadex G200, was found to contain toxic components one of which (F1 fraction) found in avirulent as well as virulent strains had lethal and immunizing properties, while another (F3 fraction), which was more abundant in virulent strains, contained proteolytic and other enzymes (Carney & Jones, 1968; Jones, 1968); it seemed probable that both factors were involved in burn sepsis, the enzymes facilitating invasion of tissues and blood vessels by bacteria colonizing the slough.

Prophylaxis

My colleagues and I in Birmingham have, for many years, been studying methods of preventing infection of burns; these methods can be regarded as forming two lines of defence (Lowbury, 1967). The first line consists of methods aimed at keeping the burns free from bacteria—by excision and grafting of full skin thickness burns, by the use of antiseptic applications, and by physical methods of excluding bacteria; the second line of defence consists of methods which prevent invasion of the tissues and the blood-stream by bacteria that have succeeded in colonizing the burn, for which purpose antibiotics, vaccines, immune sera, and other methods which support natural resistance against infection (e.g. control of diabetes) are used.

Primary excision of slough and application of autografts is an ideal barrier in the first line of defence, but it cannot be used on the more extensive burns, which are, of course, the ones most liable to septic complications. Antiseptic methods have been highly effective; one example is the use of 0·5% silver nitrate solution, a method introduced in 1965 by Moyer *et al.* (1965) at St Louis, Missouri. In our controlled trial of this method (Cason *et al.*, 1966) the frequency of isolation of *Ps. aeruginosa* from burn swabs was very low (3%) when silver nitrate was used, compared with the frequency of its appearance in burns treated with penicillin cream (70%). Other bacteria (apart from *Proteus* spp.) were not so well controlled by silver nitrate compresses, but the clinical benefits from the control of this most dangerous of the pathogens were shown in a significantly lower mean temperature and respiration rate of silver nitrate-treated patients in the trial, and in a significantly reduced mortality following the subsequent introduction of silver nitrate as a routine prophylactic measure for extensive burns. Pseudomonas sepsis became very rare.

Many other methods have been tested, and alternatives to silver nitrate compresses are required, because this treatment does not suit all patients; among the most effective have been 11% mafenide ('Sulfamylon') (Lindberg *et al.*, 1965) acetate cream, and 1% silver sulphadiazine cream (Fox, 1968). Recent trials in severely burned patients have shown 0·5% silver nitrate solution to give better prophylaxis in fresh burns than mafenide or exposure in warm dry air (Lowbury *et al.*, 1971). Local chemoprophylaxis is effective only if, as in the examples cited, resistant variants do not emerge; for this reason agents such as gentamicin, against which resistance can emerge, should not be used for topical prophylaxis, but should be reserved for therapy of established infection.

Physical methods have had some effect—e.g. an isolator, which reduces access of bacteria by air and by contact; but unless all supplies, including food, are sterilized, this method has limited value. In a controlled trial on patients whose supplies were not sterilized, the use of an isolator reduced the incidence of *Ps. aeruginosa* infection significantly (from 65 to 11%), but the effect against *Staph. aureus* was marginal, and there was no effect against *Proteus* spp., *Escherichia*, *Klebsiella* and other coliform bacilli which are probably acquired most often by self-infection (Lowbury, Babb & Ford, 1971).

The second line of defence may prove useful when the first has failed. Though systemic chemoprophylaxis fails to prevent colonization of burns with

Gram-negative bacilli, it may have some value in preventing invasion. Burned mice were completely protected by antiserum and by certain antibiotics (gentamicin and carbenicillin) against fatal invasive infection with *Ps. aeruginosa* (Jones, Jackson & Lowbury, 1966; Feller, 1966). Because of the risks of anaphylaxis with animal sera and the difficulty of obtaining human immune serum, passive immunization seems impracticable (though it has been used with some apparent success) (Jones & Lowbury, 1967).

At first sight, the prospects for using active immunization seem poor, because of the expected delay in the appearance of antibodies; but recent studies have shown that a very early resistance, apparently 3 or 4 days after the first immunizing dose, can be obtained on injecting burned mice with an antigen obtained from cultures of *Ps. aeruginosa* (Jones, 1971; Jones, Lilly & Lowbury, 1971). By the use of a multivalent vaccine the whole range of serotypes of *Ps. aeruginosa* can be covered by such early immunity, which is shown to be associated with the IgM fraction of serum protein.

Chemotherapy

Controlled trials have shown that *Strep. pyogenes* can almost always be removed from burns by 3 or 4 days of systemic treatment with cloxacillin or erythromycin (Lowbury & Miller, 1962), (not by benzylpenicillin, which is destroyed by penicillinase from other bacteria on the same burn) and *Staph. aureus* can often be removed from covered burns by systemic cloxacillin or fusidic acid (Lowbury *et al.*, 1962). The results of chemotherapy for Gram-negative bacilli have been much less satisfactory; and though *Ps. aeruginosa* can sometimes be removed from burns by local application of polymyxin, gentamicin, mafenide or silver sulphadiazine (apparently not by silver nitrate), such treatment is highly imperfect, and systemic treatment usually fails to remove the organism from the burns, even when the strain is sensitive; resistance (including transferable resistance) is a problem with many of the burn bacteria (Lowbury *et al.*, 1969; Roe, Jones & Lowbury, 1971). Systemic therapy may suffice to prevent invasion, even if the surface remains colonized; but our experience has shown that even if the treatment is started as soon as possible, irreparable damage may by that time already have occurred through invasive infection with *Ps. aeruginosa* (Jones *et al.*, 1966). For such reasons we regard prophylaxis as having a special importance in burns; prevention in this case is not only better than cure but much more likely to be achieved.

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