STAPHYLOCOCCAL SEPSIS IN THE NEWBORN

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INTRODUCTION

At a symposium on perinatal and neonatal infections in 1978 Dr. David Harvey reported that staphylococcal infection was much less common than a decade before (Harvey, 1979), but recently there has been resurgence of staphylococcal problems. Clinical infection increased in many hospitals where hexachlorophane was discontinued, multiresistant staphylococci have emerged as a major problem in some countries and *Staphylococcus aureus* has been implicated as the aetiological agent in toxic shock syndrome (tampon shock). This paper reviews the nature and incidence of staphylococcal infection in neonates, the transmission and prevention of spread and the treatment of sepsis.

COLONISATION

The fetus in utero is sterile, but the skin and mucosal surfaces of the newborn rapidly become colonised. Serial cultures show that babies are colonised with *Staphylococcus epidermidis* within a few days of birth and some babies acquire *S. aureus* in the neonatal period. The flora is derived in part from the mother, both during delivery and postanatal but also from medical and nursing staff and on occasions other mothers and babies.

Many staff members are carriers of *S. aureus* at some time, but phage typing of all isolates would suggest that only a few are responsible for infections in babies under their care. Staphylococci are relatively resistant to dessication and in theory have the potential for airborne spread. How important is spread by this route from staff carriers and other patients? A number of studies in the early sixties would suggest that airborne spread is much less important than manual transmission.

Mortimer *et al.* (1962) carried out studies in which spread, from a baby colonised with a known phage type of *S. aureus* to other babies was monitored. In these the colonised baby was handled by nurses when they started duty, prior to handling other babies. Rates of colonisation were 76% in babies when there was no handwash and 30% when a 10 second disinfectant handwash was performed following the initial handling of the coloniser baby. In this study there was a control group of babies who were not handled by the nurses and whose exposure was only by the airborne route. Only 15% of the control babies became colonised and colonisation was delayed. These figures suggest that in 80% of colonised babies spread was by the manual route if handwashing was absent.

Does this apply also to colonisation of babies by staff carriers? Wolinsky *et al.* (1960) carried out studies in a unit in which two nurses had been responsible for infection with two separate phage types of *S. aureus*. During the study 54% of the babies handled by one nurse became colonised by her strain of *S. aureus*

even though airborne spread was prevented by nursing the babies in isolettes. This phase of the study demonstrated the importance of hands in transmission. In further experiments the nurse was made to sit unmasked in the nursery for eight hours daily over a two week period. No babies became colonised with her strain during this period, whereas up to 46% of babies became colonised in each two weeks period when she worked normally. It could be argued that airborne spread might have occurred if the nurse had moved around rather than remaining seated, as this would increase the chances of dispersal, especially from perineal shedding, and would reduce the distance between some of the babies and the carrier.

In my own experience paediatric medical staff, who have been the cause of staphylococcal outbreaks, have almost without exception handled the babies that become colonised with their strain. In recent years we have experienced nine outbreaks of staphylococcal infection which were traced to paediatric staff. It is notable that these staff handled large numbers of babies, most of whom did not become colonised or infected with their strain. Closer analysis reveals that the babies who became colonised or infected usually required resuscitation following delivery. It could well be that the close contact and complex manipulations which occurred at a time when the baby had not established a flora accounts for the transfer of the organism of these babies. It is not our practice to routinely swab all nursing or medical staff to detect the carrier state, but we do swab the noses of the paediatric staff, working in our maternity unit, when they join our staff, because of this observation. Isolates of *S. aureus* from these staff and from patients are routinely phage typed.

Over a 10 year period I have noticed clusters of staphylococcal infection at Birmingham Maternity Hospital (BMH), involving two to six babies over a short space of time, due to the same phage type. Analysis of records reveals that these relate to the same postnatal ward and often the same cubicle. These small outbreaks probably involve baby to baby spread.

I have already discussed the role of airbone spread between colonised babies, but the situation may differ when there is frank sepsis. It is known that patients with staphylococcal pneumonia disseminate large numbers of organisms into the environment. I have isolated the offending strain from air in a cubicle of a neonate who had severe staphylococcal toxic epidermal necrolysis. How frequently airborne spread occurs when there is frank skin sepsis is unknown but where there is major sepsis or where particularly virulent strains are suspected (see infection section) the patient should be isolated. Staff with frank skin sepsis should be excluded from the unit.

PREVENTION OF COLONISATION

Isolation of patients with overt sepsis and appropriate barrier nursing techniques should prevent spread of virulent strains once recognised. However, I believe our aim should be to reduce colonisation with all strains of *S. aureus* and hence reduce the number of primary cases of sepsis. Two procedures have been adopted.

The first is the application of antibacterial compounds to the skin of the neonate either in the form of talcs or emulsions or by wholebody bathing.

Hexachlorophane and chlorhexidine are the two agents which have been most widely used in recent years. The umbilical cord is one of the earliest sites to colonise and both agents reduce the rates of colonisation with *S. aureus* (George, 1976; Alder *et al.*, 1980).

Antibacterial talcs are most commonly applied to the axillae, groin and umbilical cord but some units also powder the trunk and a few the buttocks as well. Following the implication of hexachlorophane as the cause of brain damage and death, studies have been undertaken to ascertain whether there is a continuing need for their use and whether the compounds are safe. Plueckhahn (1980) studied the influence of antibacterial compounds on neonatal sepsis due to staphylococci over the period 1959-1979. Annual sepsis rates varied between 0.5% and 1.8% in the periods when antisepsis with hexachlorophane compounds was practiced but rose to 6.3% in 1978 when these were not used. The sepsis rate fell to 1.4% in 1979 when hexachlorophane talcs was reintroduced. Other units have had similar experiences.

Studies of safety have included animal experiments to observe degenerative changes in the brain and studies of the absorption of compounds through the skin of neonates. Plueckhahn (1980) measured blood levels of hexachlorophane in 1,100 babies, weight 2.11-5.26 kg, who were treated with either 0.5% hexachlorophane talc or bathed with emulsions containing 0.75% or 3% hexachlorophane. Levels were well below those which produce degenerative changes in animals and much lower than levels reported in neonates with brain damage due to accidental overdosage. Blood levels were higher in the group bathed in 3% emulsion, than in the group treated with 0.5% talc. Greater absorption occurs in preterm infants and levels approaching those which cause damage have been reported in babies who are bathed regularly in hexachlorophane solutions (Curley *et al.*, 1971; Kopelman, 1973; Tyrala *et al.*, 1977). Nachman *et al.* (1971) reported that the skin of preterm infants is more permeable and Aggett (1981) showed a direct correlation with gestational age. There is no doubt that hexachlorophane has the potential for toxicity, although the number of cases of reported toxicity is small. My advice based on published work and my own experience is to use hexachlorophane talcs in preference to emulsions or whole body bathing. Healthy babies are soon discharged from hospital and I feel should not continue treatment with this agent at home. In hospital the talc should be applied to the umbilical cord, axillae and groin but not the buttocks, and should be discontinued after separation of the cord (usually four to eight days). Taking into account the demonstration of accumulation in some studies, I would recommend that hexachlorophane containing agents are not continued for longer than 10 days.

Although the absorption of hexachlorophane is greater in preterm infants the incidence of staphylococcal problems is higher. More than 50% of our epidemic strains of *S. aureus* are from babies in our special care baby unit, and staphylococcal septicaemia is commoner also in this group. This is a reflection of more frequent

spread due to frequent handling and dependence on staff rather than the mother. Once colonised, infection is more likely because of invasive procedures and the poorly developed immune system. Because of the higher risk of infection I believe the use of hexachlorophane talc is justifiable until an effective alternative agent becomes available, but would confine applications to the umbilical area only in these babies.

Chlorhexidine talcs are not yet commercially available but have been shown to reduce staphylococcal colonisation (George, 1976; Alder *et al.*, 1980). This compound has a low potential for toxicity and studies of absorption in term and preterm babies (Alder *et al.*, 1980; Aggett *et al.*, 1981) suggest it is safe. In some centres chlorhexidine is applied, to the umbilicus as an aqueous or alcoholic solution. Skin permeability is increased by alcohol and the pharmacological activity of absorbed alcohol and toxic potential of methyl alcohol must be remembered, especially in premature babies.

Good hand disinfection should reduce the spread of bacteria. Figure 1 shows the number of bacteria surviving at intervals in three experiments I performed. In these experiments standardised inocula of microorganisms were prepared, and applied to the finger tips. Fingers were then sampled after varying intervals of total inactivity. It will be seen that *S. aureus* survives better than *Escherichia coli* or *Candida albicans* and 1% of the original inoculum was viable one hour after application. Disinfection of hands with antiseptics containing chlorhexidine or povidone iodine substantially reduces the microbial counts of the skin and there is a residual effect even after rinsing and a cumulative reduction in count occurs with repeated washings. Repeated washings with antiseptics as occurs in special care baby units frequently leads to sore hands. Because of this we have substituted an alcoholic hand rub between babies, instead of routine washing in our special care baby unit, except when there is soiling of hands with faeces or secretions. Colonisation and infection with *S. aureus* is less frequent in term babies nursed in our postnatal wards, which may reflect the less frequent handling by staff. Handwashing with soap appears adequate for most purposes in these areas, when antiseptic talcs are being applied to the babies.

We have discontinued the use of face masks and caps in the labour ward for routine deliveries in recent years. We also allow parents and siblings to visit our special care baby nuit and they do not gown. Despite these changes we have not observed an increase in staphylococcal sepsis nor has there been evidence of more frequent cross infection.

CLINICAL INFECTIONS

Cutaneous infection may manifest itself as minor pustules, bullous impetigo or toxic epidermal necrolysis. The latter condition is also known as Ritter's disease or staphylococcal scalded skin syndrome. More than one of these forms of lesion may be present in the same child. Mastitis is a less common soft tissue infection, but is more frequent than septicaemia, pneumonia or osteomyelitis due to *S. aureus*.

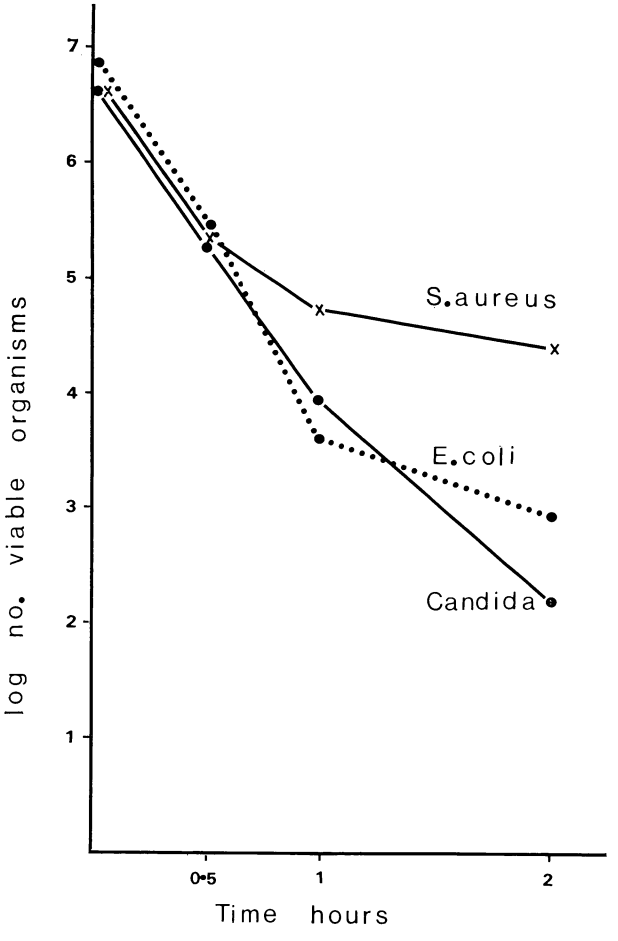

Fig. 1.

Some strains of *S. aureus*, most commonly those sensitive to staphylococcal phages belonging to group two, produce the toxins exfoliatin A and B, which causes intra-epidermal splitting at the level of the stratum granulosum. Despite the production of toxin, affected babies do not always develop the full blown picture and for this reason clinical presentation cannot be used as a reliable method of detecting all babies who develop infections with an epidemic strain. Curran *et al.* (1980) reported an outbreak of infection due to an exfoliatin producing staphylococcus in 68 babies. Whilst 24 had toxic epidermal necrolysis, 34 manifested as bullous impetigo and 8 had a scarlatiniform rash without desquamation. This triad of lesions is sometimes referred to as the expanded scalded skin syndrome. I also observed this spectrum of disease when we had an outbreak of infection due to *S. aureus* phage type 3A/3C in 1978.

Invasive procedures and infection. Staphylococcal infection frequently follows invasive procedures. This is in part a reflection of the poorly developed immune system. In a group of 122 neonates who underwent surgery at Birmingham Children's Hospital (BCH), during a 12 month period, 10 developed staphylococcal wound sepsis. This was almost eight times more frequently than in a group of older children.

Over 90% of staphylococcal septicaemia at BCH occurs in babies in the special care baby unit. There is a clear association between the presence of intravascular catheters and staphylococcal septicaemia in many cases. *Staphylococcus epidermidis* is a frequent cause of cannula related septicaemia. Because the organism is of low virulence and is a normal part of the skin flora it can mistakenly be dismissed as a contaminant but culture of the catheter tip in these cases reveals the true significance of the organism. *S. epidermidis* is also a cause of infection of pressure reducing valves in children with raised intracranial pressure.

Osteomyelitis. Staphylococcal osteomyelitis is rarely reported in neonates in the UK. Group B streptococci are increasingly implicated as the cause in many cases in the USA (Edwards *et al.*, 1978; Memon *et al.*, 1979). Lauer and Altenburger (1981) reported five cases of *S. aureus* osteomyelitis involving the os calcaneus following heel prick collection of blood and three cases have been seen in Birmingham recently. The need for good handwashing and adequate disinfection of the heel is highlighted by these cases.

Chest infection. *S. aureus* pneumonia is now rare in the neonatal period. In recent years we have isolated *S. epidermidis* from the tracheal aspirates of numerous neonates who were intubated and in whom infection was clinically suspected. In many of these cases *S. epidermidis* was the only organism isolated and the child responded to therapy tailored to this organism having failed to respond to treatment with cefuroxime or penicillin combined with gentamicin. Whilst it is difficult to prove this organism was responsible for these children's condition, I believe that *S. epidermidis* is an important cause of respiratory infection in intubated neonates, especially the preterm.

Toxic shock syndrome. This recently described syndrome occurs mainly in adult women and is mainly associated with the use of tampons. However about 12% of cases are in other groups. The conditions is manifest by an acute febrile illness, hypotension, erythroderma which subsequently gives rise to diffuse desquamation and mucosal hyperaemia. The patient may vomit, have diarrhoea and myalgia or show signs of dysfunction of various organs. The condition is due to the production of a toxin, enterotoxin F, which causes amongst other actions cleavage of the epithelium. However the cleavage produced by enterotoxin F is at a deeper level than exfoliatin. Green and Lapeter (1982) reported a case of maternal shock 20 hours post partum associated with a rash, and the child developed a rash the following day. A staphylococcus, belonging to phage group 3, was isolated from mother and baby. It is probable that the child was suffering from this condition and definite that the mother had the syndrome.

Vergeront *et al.* (1982) reported a maternal infection during which enterotoxin F was detected in breast milk, over an 11 day period. The mother subsequently developed antibodies to this toxin. However antibodies to this toxin are present in the serum of at least 80% of adults and these cross the placenta. Antibodies seem to protect adults from the toxic shock syndrome and it is likely that most neonates will be similarly protected. However this condition should be considered in cases of neonatal hypotension and staphylococcal infection either in the baby or the mother excluded.

ANTIBIOTIC RESISTANT STRAINS

In the last decade most strains of *S. aureus* producing infection in the neonate have been sensitive to a wide range of antibiotics, with the exception of penicillin and ampicillin. However strains which are resistant to methicillin and gentamicin have been frequently reported in the United States in the last few years and have also caused outbreaks in Australia, Ireland and Greece. In addition to difficulties in the selection of antibiotics for blind treatment of sepsis other problems have been reported with these strains. The ease with which these strains spread within units in highlighted in a number of reports. In the report by Dunkle *et al.* (1981) 70% of the babies in the unit became colonised and 25% had clinical infection. Spread has also been noted between hospitals and within the community outside hospital. Many different phage types have been reported to have methicillin/gentamicin resistance and outbreaks have occurred with several of these in some units. I would recommend isolation and barrier nursing of infants with these strains. Colonisation of staff with methicillin/gentamicin resistant *S. aureus* has occurred during some outbreaks, and this can be difficult to eradicate.

TREATMENT OF STAFF CARRIERS

When I have evidence that a staff carrier is responsable for an outbreack I recommend treatment to eradicate the carrier state. I treat the anterior nares with chlorhedixine and neomycin cream four times daily and recommend daily bathing with the addition of an iodophor (Steribath®) or 15 ml of a chlorhexidine detergent mixture (Hibiscrub®) to the bathwater. In addition, I prescribe twice weekly shampooing of the hair with either Hibiscrub or povidone iodine instructing that the agent is retained on the scalp for at least five minutes.

In my experience a number of staff fail to respond to two weeks treatment, but four weeks therapy is successful in almost all cases.

TREATMENT OF INFECTION

Minor pustules can be dried with chlorhexidine in spirit, which I prefer to triple dye. Prophylactic applications of hexachlorophane talc usually limit extension in the infection, but should not be applied to desquamating areas because of the dangers of absorption. Abscesses and mastitis should be drained. For these and

more severe forms of cutaneous infection a narrow spectrum agent such as flucloxacillin can be administered. Many eye infections respond to irrigation with saline or water but neomycin ointment is effective in more severe infections. I favour the use of neomycin ointment in preference to chloramphenical in situations where swabs cannot immediately be cultured for *Neisseria gonorrhoeae* or *Chlomydia trachomatis*, as the latter drug is likely to prevent culture of these pathogens.

When dealing with deep seated infections many clinicians choose a combination of a penicillin type antibiotic and an aminoglycoside, such as gentamicin, whilst they are awaiting laboratory results. In units where *Pseudomonas aeruginosa* or antibiotic resistant Gram-negatives are rare a β-lactamase stable cephalosporin is a suitable alternative. Most cutaneous infections respond to five to seven days treatment with flucloxacillin but I would recommend 12-14 days therapy for septicaemia and six weeks for osteomyelitis.

In case of septicaemia I recommend the changing of intravascular cannulae, when this is a possible source.

S. epidermidis is in my experience frequently multiply resistant and the choice of antibiotic therefore is dependent on sensitivity patterns. We have seen isolates which were sensitive to one or two antibiotics only, and these were drugs we would not have otherise prescribed. On occasion we have treated infections due to resistant strains with either clindamycin, fusidic acid or rifampicin and we routinely test resistant isolates to these drugs.

Staphylococcal infection is seldom fatal in the neonate if treated early with appropriate antibiotics. In recent years the only fatal cases we have seen were two children with *S. aureus* meningitis secondary to encephalocoeles. We have also noted terminal bronchopneumonia due to staphylococci in children with multiple severe congenital abnormalities.

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