

False-coloured transmission electron micrograph of MRSA. Biomedical Imaging Unit, Southampton General Hospital / SPL

MRSA is constantly in the news. **Simon Foster** questions how well we are coping with living with this public enemy.

S. aureus: a 'superbug'

Be afraid, be very afraid? *Staphylococcus aureus* is most well known as its antibiotic-resistant form, MRSA, a scourge of modern medicine and a major public enemy. MRSA (meticillin-resistant *S. aureus*) is quite rightly feared as it causes considerable death and suffering in the UK, and around the world. To an extent this is a calamity of our own making as a result of over

use of antibiotics and non-ideal clinical practices. In some countries such as Denmark and Sweden the incidence of MRSA is much lower due to a variety of measures, including stringent screening and isolation of MRSA carriers.

Can things get worse?

Up to now MRSA has been primarily associated with nosocomial (hospital-acquired) infections. However, recently the spread of community-acquired MRSA (CA-MRSA) is particularly disturbing, as these organisms are becoming endemic in the wider population. A number of these strains produce Panton-Valentin leukocidin, which is

controversially associated with a rare but often fatal pneumonia. In the last few influenza pandemics, *S. aureus* infection was a common complication. Perhaps if bird 'flu jumps the species barrier then *S. aureus* might find a world of susceptible hosts awaiting infection. CA-MRSA strains also produce high levels of a newly discovered set of cytolytic peptides, able to lyse human neutrophils, our main cellular defence against *S. aureus*.

But enough of scaremongering, we can always rely on the drugs, can't we? For several years vancomycin has been used as a fallback drug when others have failed. Recently, resistance even to this has appeared, which has led to the spectre of VRSA (vancomycin-resistant *S. aureus*). Whilst not a common problem, this highlights the inevitability of development of resistance to all new drugs.

It can't be that bad?

It is all too easy to fear and loathe *S. aureus* and with such antipathy, to gloss over the special relationship which has evolved between us and one of our most faithful microbes. We all have a high titre of circulating antibodies against *S. aureus* and so we must be challenged subclinically on a regular basis. Getting a serious *S. aureus* infection is actually remarkably difficult and mostly requires immense effort on our part via injury, surgery, indwelling medical devices, etc. *S. aureus* is an opportunist pathogen for which many of the diseases it causes are distinctly inopportune for the bacterium. Endocarditis and other deep-seated infections give little chance for reintroduction into the environment. Superficial and minor skin lesions are the primary infections caused by *S. aureus* and the flow of golden pus gives relief to the host and the prospect of dispersal to the pathogen.

That is not to say that the interaction between *S. aureus* and the human host during infection is not exquisite and highly evolved. *S. aureus* has a myriad of surface and secreted components able to react in the most intricate ways with almost every facet of the human immune and other bodily systems. The organism is also extraordinarily adaptable in being able to cause a wide range of different infections. *S. aureus* has a large arsenal of virulence determinants, including toxins, enzymes and adhesins. Apart from a very few specific syndromes (such as toxic shock) it is impossible to label individual components as primary virulence determinants. It is more the skilful wielding and interplay of a variety of determinants drawn from its repertoire that allows *S. aureus* to succeed so well across different infections. This in itself requires extraordinary powers of regulation in response to the host environment. Many regulators have been identified but how these interact, particularly in response to the host environment has remained largely elusive.

Living in harmony?

The primary niche for *S. aureus* is as a commensal living in our noses, on our skin and in the nasopharynx. In fact 20 % of the human population are permanent carriers and 60 % are transient carriers, which attests to the highly successful

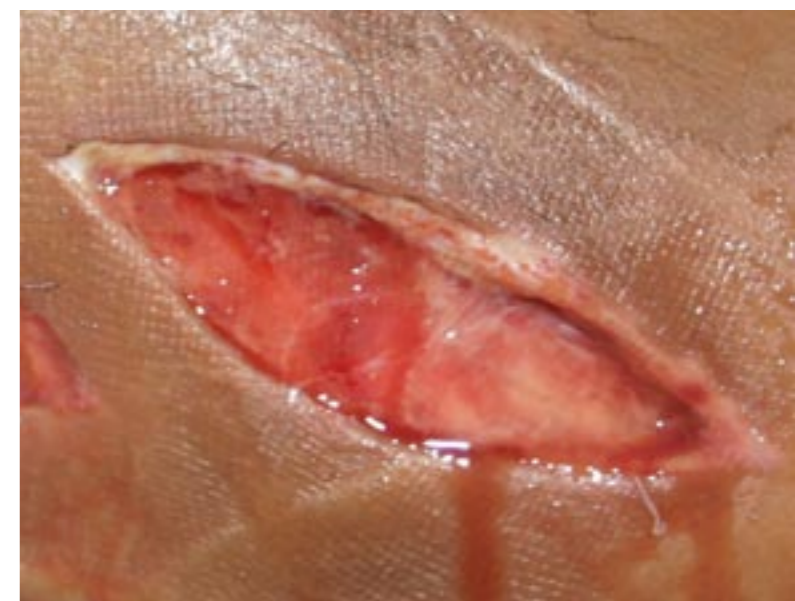
► *S. aureus* abscess. Emma Nickerson, Mahidol University

► Open incision to drain pus from a thigh in a case of *S. aureus* pyomyositis. Emma Nickerson, Mahidol University

nature of the bacterium. Some people actually carry the same strain of *S. aureus* for years and such a long-term commitment to a relationship is laudable. Carriage cannot be looked upon, however, as an easy life for *S. aureus* as it not only has to survive and proliferate in a rather harsh physical environment, but also resist human innate defences and compete with other microflora. Understanding the basis for carriage is beginning to not only define the roles for several *S. aureus* components, but also give us clues as to the host environment. Surface components such as wall teichoic acids and the proteins ClfB and IsdA are required for nasal carriage and act as adhesins to nasal squamous cells. ClfB and IsdA, like many other *S. aureus* surface proteins bind to more than one human ligand and so their true *in vivo* target cannot as yet be defined (if a single target actually exists). The *isdA* gene is only expressed under conditions of iron deprivation and so the nose must be iron-limited.

We also control *S. aureus* on our surfaces via the production of bactericidal fatty acids and peptides. IsdA is required for resistance to these factors and survival on live human skin. It is interesting that patients with atopic dermatitis often have altered fatty acid metabolism resulting in reduced levels of anti-staphylococcal fatty acids and this correlates with enhanced *S. aureus* colonization. In fact, application of anti-staphylococcal fatty acids results in reduced colonization in these patients. Thus by harnessing our own defence mechanisms we may reduce the prevalence of *S. aureus* carriage. The interaction of *S. aureus* and our skin fatty acids is even more intense, as at sub-growth inhibitory concentrations the fatty acids are able to inhibit virulence determinant production and so potentially allow survival of the organism but render it benign.

The nose and skin are also inhabited by a range of other flora (see the article by Farrar & Bojar on p. 14) and it is interesting to note that nasal carriage by *Staphylococcus epidermidis* or corynebacteria does not coincide with *S.*



aureus, suggesting that our resident flora is battling it out for the prize of a human host. Thus *S. aureus*, whilst it is a formidable foe, can be beaten by other lowly microbes.

Man against microbe

The golden age of antibiotic discovery is over and the inevitable rise in resistance levels does not bode well for the future. *S. aureus* soon acquires resistance to new drugs, including linezolid and daptomycin. However, antibiotics will always remain a key tool in our armoury against *S. aureus* and it is essential that industry is encouraged to keep new compounds flowing into the clinic. Alternative approaches such as vaccines and therapeutic/prophylactic antibody development have continued apace, but all Phase III trials so far have ended in failure. MRSA is high on the UK political agenda and the favoured approach for control rests on cleaner hospitals. In truth, there is no one measure that will remove the MRSA problem. It is by a concerted and integrated pack-

age of approaches for the present, and the future, that will at least alleviate some of the burden. *S. aureus* cannot be eradicated from the human environment and it does not seek to eradicate us. By understanding more of the basis of our interaction with *S. aureus* we are beginning to discover possible breakpoints to reduce the incidence of infections and also to treat those once established. Although *S. aureus* can be a killer, with associated suffering, one cannot but admire the tenacity and versatility of one of the most intimate cohabiters of the human body.

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Further reading

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