

T5.1: The Future Shape of MRSA Infection

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Abstract:

The appearance of methicillin-resistant *Staphylococcus aureus* (MRSA) in hospitals has led to a rise in mortality there, and to financial costs caused by longer hospitalisation and more use of antibacterial agents. The future prospect is that MRSA will be brought under control in hospitals by the development of vaccines for at-risk groups, better hygiene, and the use of antibiotics in ways that do not encourage further resistance to emerge. But MRSA will spread into the wider population, via humans and animals, and some of the strains that emerge may be highly toxic. The ageing population and the general increase in the number of people with compromised immune systems will increase this hazard. Non-hospital settings with vulnerable populations, such as long-term care homes, are especially at risk. Better screening and detection technology to detect MRSA in the general population and to allow it to be treated without encouraging resistance are under development.

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Methicillin-resistant *Staphylococcus aureus* (MRSA) has evolved from *Staphylococcus aureus*, which was previously resistant only to penicillin. Penicillin resistance itself appeared among strains of *S. aureus* soon after penicillin was discovered in 1929 and used in therapy from 1939–40. But the mechanism whereby *S. aureus* developed resistance to these two agents is different. Penicillin resistance is due to an enzyme, penicillinase, which attacks the key component for a large group of antibiotics. With MRSA, on the other hand, a modified penicillin-binding protein called PBP2 is produced which is rendered immune to attachment by methicilin. This allows cell-wall synthesis to proceed even in the presence of the antibiotic, defeating its intended effect. Different genes are responsible for the expression of each of these resistance mechanisms.

That this can occur in one and the same bacterium is testament to the ability of some bacteria to evolve in response to the environmental stress caused by antibiotics, especially in healthcare facilities. MRSA infection in humans is superimposed on that caused by methicilin-sensitive *S. aureus* (MSSA) (but which is probably resistant to other antibiotics).

The impact of infections due to *S. aureus* has been studied in terms of its cost: 77% of the cost is for extra days spent in hospital, 21% for the antimicrobial agents used in treatment and 2% for additional laboratory investigations. Another study has reported that *S. aureus* infection doubled the length of stay, morbidity and mortality as well as medical costs. There have also been comparisons between MRSA and MSSA in terms of added costs. There appears to be a roughly three-fold increase in costs for treatment of MRSA bacteraemia. This increase was attributed to higher antimicrobial agent costs and prolonged hospitalisation. These and several other studies provide a consensus view that *S. aureus*, and MRSA in particular, is a major factor in the costs attributable to hospital-acquired infection. Therefore strategies which lead to significant decreases in hospital-acquired infection are more likely to be cost-effective if they are directed against MRSA and MSSA.

One area where some improvement in diagnostic microbiology has been productive is in terms of the time taken to isolate MRSA from clinical samples. Several manufacturers of culture media have now developed selective media that will yield colonies identifiable within 18–24 hours as MRSA, as distinct from MSSA and *S. epidermidis*. This reduces somewhat the time that elapses before a patient suspected of carrying or being infected with MRSA is identified and appropriate isolation or treatment is instigated. It is still not quick enough to prevent possible cross-infection and dispersal of MRSA. But it provides the microbiologist with an earlier culture on which to determine antibiotic susceptibilities and thereby provide earlier therapeutic choices for the clinician. Staphylococcal release by colonised or infected individuals is almost instantaneous and can result in a considerable degree of dispersion.

MRSA has not taken the place of MSSA, which shows that *S. aureus* continues to be an effective parasite of man (and to a lesser extent animals and birds) capable of causing disease even in normal individuals. The increase in numbers of immunocompromised patients in our hospitals, and the

ageing population in our long-term care facilities, have provided the staphylococcus with an even more susceptible population in which to cause infection. This change over the last 25–30 years is likely to continue as more and more sophisticated medical treatments are developed. With the continuing rise in incidence of HIV infection worldwide, especially among the poorer socio-economic groups, there is likely to be fertile ground in which MRSA can breed.

MRSA control should be based on vigorous cleaning, frequent use of surveillance cultures, isolation of colonised patients, eradication of colonisation, ward closure as appropriate, and an educational programme regarding infection control procedures including hand washing and the use of an alcohol hand gel or an alternative that is as effective.

Hygiene, or the lack of it in certain circumstances, has allowed MRSA to become indigenous in UK hospitals and therefore a major cause of hospital-acquired infection. The extensive use of antibiotics to treat infection has precipitated the development of resistance mechanisms in a variety of hospital pathogens, some of which have subsequently been able to transfer their resistance mechanism (or the genes responsible) to different bacterial species including *S. aureus* and its close relative, *S. epidermidis*. Since both are normal commensals of human skin and nostrils, the chances of genetic exchange between them are increased, expanding the antibiotic-resistant population that is carried by the host and is capable of causing infection.

S. aureus has changed almost continuously since its discovery. Even in its more recent past, since the 1960s, it has successfully transformed itself in terms of its spectrum of susceptibility to a range of antibiotics, its ingenuity in terms of expression of new virulence factors, and its proclivity to co-exist with its human host in the carrier state. These changes have resulted in a pathogen that is likely to remain with us for some considerable time. It will not be restricted to hospitals and nursing homes but will expand into the wider community as penicillin-resistant strains did 40 years ago.

While the routes of infection are easily defined within hospitals, the determinants of susceptibility to infection in the community are not understood and are not going to be easily recognised. It is likely that a combination of alterations in innate susceptibility to infection, together with the development of more aggressive virulence, will increase the threat of infection. Since the 1960s, several new toxins have been discovered in *S. aureus* including exfoliatins A and B and toxic shock syndrome toxin, and others have been rediscovered, as with Panton Valentine leukocidin. In addition, novel features of the cell's structure have been shown to play an important part in developing and maintaining staphylococcal pathogenicity in hitherto normal individuals.

It is clear that the range of MRSA infections is expanding. Given the combination of antibiotic resistances that may accompany resistance to methicillin, the variety of strains that may become endemic or even epidemic is likely to change with time. The UK currently has two epidemic strains, EMRSA 15 and EMRSA 16, in roughly a 2:1 proportion. Both have been present for the last 10 years with little or no change in their distribution. The advent of

community MRSA not related to either will in due course affect the distribution of EMRSA 15 and EMRSA 16 in our hospitals. The rate of change will depend to some extent on the relative ease with which the gene controlling methicillin resistance, the *scc mecA* gene, is spread amongst strains of *S. aureus* or whether another variant of this gene emerges and becomes more dominant. Already there are five *scc mecA* complexes, so the evolution of another one is quite likely. The spread of MRSA to the community, including an association with pets, livestock and wild birds, will provide the organism with an ever-expanding habitat in which to evolve new methods of survival and spread.

While considerable effort is being expended on reducing the incidence of MRSA in hospitals in the UK, significant reductions in the incidence of infection will take up to 10 years, especially if the selective pressure exerted by continued antibiotic usage is not significantly reduced. Infection still does need to be treated with appropriate antibiotics. The development of significant new antibiotics to treat infections due to MRSA and other Gram-positive bacteria is taking place. Three have appeared in the past three years and three more are due to appear within the next three years. Some of these, importantly, have novel structures and novel modes of action, which may limit the development of resistance in MRSA. This should extend their shelf-life as agents in the treatment of MRSA infection. The pharmaceutical industry is addressing the problem and provided that some prudence is applied by clinicians in their prescriptions, these agents might reverse the incidence of antibiotic resistance among staphylococci in our hospitals. The use of these new agents will need to be restricted to hospitals to avoid the danger of indiscriminate use in general practice leading to resistance.

It remains to be seen whether these new antibacterial agents (daptomycin, tigecycline, linezolid, oritavancin and dalbavancin) will really change the picture. Antibiotics *per se* will not solve the problem of drug resistance in *S. aureus*. History shows us that no antibiotic lasts for ever.

Of rather more promise is the early-phase development of agents whose antibacterial activity is quite unlike those of traditional antibiotics. In this context, we can include agents such as bacteriophages which can either directly target living *S. aureus* cells, or indirectly deliver a lethal gene product to susceptible cells. These include naturally accruing antibacterial peptides present either within host defence cells or in plant, animal or reptile products, as well as a range of humanised monoclonal antibodies. In each case, it is expected that these agents would be used in concert with a recognised antibiotic, potentiating its activity to result in shorter therapeutic regimens and less likelihood of the emergence of resistance during therapy.

Elimination of carriage

Considerable reliance has been placed in the past on eradication therapy and, in particular, the use of mupirocin in the control of epidemic, if not endemic, MRSA. The use of mupirocin in eradicating mupirocin-susceptible strains from the nose is well established. In early studies before the description of resistance, about 85% of nasal carriers were cleared, although relapse did occur. Carriage in the nose alone is more likely in staff than in patients, the

latter often having soft tissue lesions. Clearance of nasal *S. aureus* with mupirocin is associated with clearance of hand carriage, which may be important in the control of outbreaks.

Careful consideration should be given to whether reliance should be placed on the use of mupirocin to aid control of endemic MRSA, although it is undoubtedly useful in outbreaks in low-prevalence environments. The use of blind intranasal mupirocin in an outbreak may be effective, but increased exposure to the drug may make it less useful in future if it selects resistant strains and its use is repetitive or prolonged. The increasing prevalence of mupirocin-resistant strains (EMRSA 16) in some areas, although not apparent generally in the UK, means that eradication treatment with mupirocin should now only be considered in especially vulnerable patients, such as those undergoing joint replacement, stent placement, vascular and cardiothoracic surgery or where MRSA has a low prevalence. Levels of mupirocin resistance may require testing to predict clearance.

One innovation that could make a big difference to our perception of MRSA as a main player in hospital-acquired infection would be the introduction of a different form of the 'search and destroy' policy used in the Netherlands and Scandinavia. A number of initiatives being developed by some of the smaller bio-pharmaceutical companies may alter our treatment of staphylococcal carriage. In particular, there is interest in 'rediscovering' lysostaphin – an enzyme first described 40 years ago which acts by causing rupture of the staphylococcal cell wall – as an agent that might reduce nasal carriage of *S. aureus* and thereby reduce infection rates. Lysostaphin is specifically active against *Staphylococcus aureus* and does not interfere with the normal commensal flora. Early clinical trials have shown that it is effective. Extension of studies to at-risk patients about to undergo surgery, for example, might reduce the risk of subsequent MRSA infection.

An alternative strategy would be the use of humanised monoclonal (or polyclonal) antibodies as adjunctive therapy for serious life-threatening *S. aureus* infections. In a 60-patient phase II clinical trial, favourable results were observed in the composite end-point of mortality, relapse rate and infection-related complications, and at a number of secondary end-points including progress in the severity of sepsis and length of stay in the intensive care unit. The study compared the use of humanised monoclonal-antibodies as a single dose alongside antibiotic therapy to antibiotic therapy alone.

Vaccination may provide an alternative solution. But any vaccine will need to be taken up by over 85% of the susceptible population in order to achieve any herd immunity. To achieve such a figure is unrealistic for staphylococcal infection. More limited use of the vaccines for at-risk patient groups attending hospital for special surgical or other medical procedures offers greater possibilities for the control of infection. However, such vaccines need to provide protection against all the strains to which the patients are likely to be exposed. The vaccine developers will need to consider the emergence of new strains of MRSA.

The combination of better hygiene standards, more appropriate use of antibiotics, and the introduction of effective and protective vaccines for at-risk groups is likely to drive down the levels of endemic MRSA in our hospitals. But their place may be taken by another bacterial pathogen, resulting in somewhat similar problems.

It is likely that the next 10–15 years will witness a change in distribution of MRSA in the UK. There will be a gradual decrease in epidemic strains of MRSA (EMRSA 15 and EMRSA 16) in our hospitals to be replaced at least in the short term by community-acquired MRSA, which may or may not be related to the epidemic strains. In the meantime, the incidence of non-healthcare-associated infection with MRSA will increase, with the possible emergence of highly virulent strains expressing potent toxins. Such a scenario will place pressure on the development of early accurate diagnosis of infection and the rapid implementation of remedial effective treatments. The development of rapid microbiological detection methods will help control the spread of such staphylococcal infections in the community. It may be necessary to develop a simple, sensitive and specific screening method to detect very early the presence of MRSA in the community. Whether the cost of such surveillance can be recouped from savings in morbidity and mortality attributable to infection remains to be seen. However, the emergence of such 'superbugs' may bring with it a novel and easily distinguishable genetic marker that can be targeted specifically for detection purposes and may mark out carrier strains from 'normal' pathogens.

Such a surveillance system would need endorsement by general practitioners, and subsequent universal application to ensure that MRSA carriers are not missed. However, it may be that not all community MRSA are the same. The design of the molecular probe needs to recognise particular forms of *scc mecA*, *luk* and others as yet to be identified as key genes of community MRSA, capable of causing infection both in the community as well as the hospital. Together with such an 'ideal' primer, there has to be a cost-effective automated detection system based probably on the currently available light cycler or TacMan instruments. Such instrumentation needs to be cost-effective in order to gain credibility in the fight against MRSA.

The fact that any individual may or may not maintain carriage of the same MRSA strain provides a major drawback to such a surveillance system. Several investigators have shown that nasal carriage of MRSA, and for that matter MSSA, is transient, and that there is evidence of the transposition of one strain by another in some but not all individuals. In addition, one is faced with the problem of sampling efficiency. Different strains of *S. aureus* are likely to exist in micro-environments and therefore important strains might be missed on a routine basis. Certainly, it would not be economic to take multiple samples from every individual. Thus, the ideal may not be possible and perhaps should not even be attempted.

While community MRSA may emerge to strike previously healthy individuals in the next 5–10 years, the risk of vancomycin-resistant MRSA (VMRSA) is less serious since its appearance requires the transfer of a particular gene (*vanA*) from an enterococcus to an MRSA strain. Only when both bacteria are

present within the same habitat is this possible. To date, only four such strains have appeared and none has survived for any length of time. Nor have any of these strains been transmitted to another patient. Acquisition of the *vanA* gene clearly compromises the pathogenicity of *S. aureus*. Additional transcription of antibiotic-resistance genes clearly places a negative burden on the virulence and transmissibility of strains.

However, should such strains acquire the mobile form of *ssc mecA*, this burden might be lessened. This would allow VMRSA to pose a major threat and effectively remove one of the most effective therapies for MRSA. It would precipitate the use of some of the newer antibacterials prematurely and thereby reduce their shelf life.

This review has attempted to draw together the various factors that are going to influence the ability of the United Kingdom to manage the problem of MRSA in the future.

Among the key drivers, at least in the short term, are economies, in the context of funding restrictions or imbalances in where the money is spent within the National Health Service. Important in this respect is our dependence on ageing hospital building stock, contracting-out of cleaning services where profitability outweighs efficiency, and Government-led targets for patient treatment and bed occupancy rates. In addition, we have unfulfilled medical needs in terms of the application of modern practice techniques in inadequate surroundings (see Figure 1).

Improvements in infection control should be accompanied by improvements in our hospital working environment. Educational blind-spots need to be eliminated at all levels. The problem of MRSA has probably peaked, at least within our hospitals, but not elsewhere in the healthcare system. Our ageing population means greater susceptibility to infection in long-term care and residential homes. The emergence of MRSA in the community as a pathogen reminiscent of *S. aureus* in the 1960s brings a new dimension to the problem and, as with penicillin resistance from 1940–1960, is likely to continue to rise, governed to some extent by the genetic promiscuity of *S. aureus* itself.

All the reports and papers produced within the Foresight project 'Infectious Diseases: preparing for the future,' may be downloaded from the Foresight website (www.foresight.gov.uk). Requests for hard copies may also be made through this website.

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