

M R S A N E W S



Prague/Czech Republic, May 1–4, 2004

PRAHA 14th ECCMID

14th European Congress of Clinical Microbiology and Infectious Diseases



ECCMID convention

Introduction

The European Congress of Clinical Microbiology and Infectious Diseases (ECCMID), held under the auspices of the European Society of Clinical Microbiology and Infectious Diseases (ESCMID, www.escmid.org), took place between 1–4 May 2004 in Prague, Czech Republic, with over 6,300 attendees. Held during a momentous weekend, when the Czech Republic entered the European Union, the meeting mirrored this coming together, with experts from a multitude of specialties from more than 90 countries sharing information and exchanging the latest research against the background of Prague's beauty and charm.

One of the prevailing themes throughout ECCMID 2004 was the continually increasing challenge of MRSA. The sessions held during the meeting which focused on this crucial aspect of microbiology and infectious diseases are reported in this newsletter.

The next ECCMID meeting will be held in Copenhagen, Denmark, between 2–5 April 2005 (www.escmid.org/eccmid2005).

Setting the scene



Professor Roger Finch

Introducing the topic of MRSA in a personal interview given to MRSA News, Professor Roger Finch, Past President, ESCMID, put the UK MRSA situation into perspective.

Professor Finch said:

MRSA presents a major challenge to healthcare systems. The increasing prevalence of MRSA

worldwide has reached epidemic proportions in the UK compared with the rest of Europe.

MRSA is currently the Number 1 hospital pathogen. It has become a primary causative agent for several severe hospital infections, including bloodstream infections, nosocomial pneumonia and skin and soft tissue infections. The clinical and economic impact of such infections are considerable and require timely, appropriate management as well as prevention through infection control.

Traditionally considered a hospital-based infection, MRSA has now spread into the community, notably affecting nursing home residents. However, there are also increasing reports of primary community-acquired infection, including those expressing the Panton-Valentine leukocidin. This was widely discussed during the meeting.

Recent media stories highlight the fact that MRSA is big news for the general public. Addressing this issue, the UK Government has introduced league tables with mandatory notification of MRSA bacteraemias. In addition, this year sees the requirement of performance standards to judge the quality of infection control performance in hospitals.

Compared with the situation 10 years ago, MRSA now colonises widely and spreads rapidly and has the ability to cause serious disease. However, we must not give up this battle and clinicians remain positive that the 'MRSA epidemic' can be controlled by prompt recognition, timely management and high standards of hygiene.

MRSA

- an endemic challenge for hospital clinicians

Introducing the symposium entitled 'MRSA - an endemic challenge for hospital clinicians', co-Chairman Dr Gary French from London, UK, said "The foundation of any MRSA infection control programme is a clear understanding of the epidemiology of MRSA, including routes of transmission and risk factors for these life-threatening infections." He continued "The next challenge is the efficient and accurate diagnosis of MRSA infections within the time and cost constraints of the prevailing healthcare system and the third element is the optimal treatment of correctly diagnosed infections." Co-Chairman Dr Jiri Benes from Prague, Czech Republic, added "In order to achieve this, the clinician must balance the immediate clinical needs of the patient with the longer-term needs of future patients and the limitations in available healthcare resources."

Clinical and economic impact of MRSA

Discussing the clinical and economic impact of MRSA, Professor Hartmut Lode from Berlin, Germany, stressed that *S. aureus* is a serious nosocomial pathogen which is commonly (25-30%) carried on the skin or nose.¹

In many European hospitals and laboratories, 20-40% of *S. aureus* isolates are now resistant to methicillin and many other classes of antibiotics² (see pages 4 and 5).

MRSA infections can be severe and include:

- Bacteraemias
- Surgical site infections
- Skin and soft tissue infections (SSTI)
- Ventilator-associated pneumonia (VAP)

MRSA infections are of such concern since they cause substantial:

- Prolonged hospitalisation/increased length of stay
- Increased morbidity
- Increased risk of mortality
- Increased costs

Professor Lode noted that the increased costs associated with MRSA in hospital are not due to the increased cost of antimicrobials but rather are driven by the increased length



Panel at symposium

of stay. In the UK, the total cost of hospital acquired infection to the hospital sector is estimated at £930 million per annum and hospital costs are 2.9 times greater for infected compared with non-infected patients.³

Professor Lode also noted that both early and late hospital-acquired pneumonia are associated with increased mortality, with MRSA being responsible for 17.9% and 21.1% respectively.⁴ Bacteraemic infections due to MRSA are associated with nearly a two-fold increase in mortality compared with MSSA ($p < 0.001$)⁵ at an extra cost of 2,500 Euros per infection episode.

MRSA is almost always spread by direct or indirect physical contact with MRSA patients. Such contact is due, in part, to:

- Poor hygiene/lack of infection control
- Overcrowding
- Inappropriate use of broad spectrum antibiotics
- Reduction in nursing/support staff

"It is only by addressing each of these causes of spread that MRSA can be controlled," said Professor Lode.

Professor Lode concluded "MRSA has become an increasing challenge in hospitals and is associated with an increase in morbidity and mortality. Understanding the clinical and economic issues associated with MRSA is of increasing importance for clinical and healthcare resource planning." He added "Infection control measures are crucial to limit transmission and control the healthcare costs associated with this problem."

The evolutionary history of MRSA

"*Staphylococcus aureus* is a remarkably versatile pathogen causing a wide spectrum of diseases of varying severity," according to Dr Mark Enright from Bath, UK. Dr Enright continued "This versatility reflects the organisms adaptation to antibiotic use which has resulted in the global spread of MRSA."

Studies have shown that pandemic MRSA clones belong to one of only five lineages, also called clonal complexes. Examination of 101 vancomycin-intermediate *S. aureus* (VISA) isolates from nine countries shows that decreased vancomycin susceptibility has evolved in all five of these lineages. "This is a clear cause for concern," said Dr Enright.

SCCmec is responsible for transferring methicillin resistance between isolates. Addressing the issue of how often we may see the movement of *mecA* to create new clonal strains, Dr Enright noted "They may even occur daily." Dr Enright stressed "When many patients have MRSA in hospital, we must consider whether this is a true outbreak of one strain or whether we are seeing various different strains. If it is the latter, it is important to identify the strain."

Addressing the issue as to why EMRSA-15 and -16 strains are uncommon outside of the UK, Dr Enright said "This is due to the fact that spread of this isolate occurs slowly but it will occur."

Spread of resistant isolates is now also occurring in the community (see page 7), with 70% of isolates in some areas now being resistant to all beta-lactam antibiotics. Dr Enright noted "Community-acquired MRSA can be more virulent than the strains seen in hospitals due to the Panton Valentine leukocidin (PVL) toxin (see page 7)." Indeed, the re-emergence of an early hyper-virulent strain has recently been reported as true community-acquired MRSA in the United States.

"The significance of MRSA is certainly set to increase," summarised Dr Enright.

Diagnostic challenges of ventilator-acquired pneumonia (VAP)

Dr Gary French from London, UK, said "There is no gold standard for diagnosing VAP and no single set of criteria for its diagnosis. It is difficult to diagnose clinically due to the poor sensitivity and specificity of clinical and microbiological criteria and remains a challenge for microbiologists, particularly since it is associated with a higher mortality and morbidity."

Dr French clarified the definitions of hospital-acquired pneumonia (HAP) and ventilator-acquired pneumonia (VAP) (Figure 1).

Figure 1. Definitions of HAP and VAP

- HAP – pneumonia that develops 48 hours or more after admission and was not present or incubating at admission
- VAP – HAP that develops more than 48 hours following endotracheal intubation and mechanical ventilation

Explaining the natural history of VAP, Dr French said that patients begin with underlying disease that requires their admission to ICU. Colonisation of the upper airways occurs as normal clearance mechanisms are circumvented. "In these cases, sputum is a poor microbiological specimen since the infection is deep in the lungs," explained Dr French. Invasive techniques, such as bronchoalveolar lavage (BAL) can get specimens from the lower respiratory tree. Devices such as the protected specimen brush (PSB) can be used to avoid contamination of the sample as it is brought up through the upper tract and pharynx.

Dr French advised that there is some confusion between late- (>4 days) and early-onset (<4 days) VAP. "Late-onset VAP is nearly always from hospital-acquired multi-drug resistant organisms, including *S. aureus*," he said.

It is important to distinguish colonisation from infection since only 10% of patients with positive cultures will actually have an infection. Quantitative bacteriology of BAL and PSB specimens are proposed by some as a way of identifying true infection but not all studies have shown a correlation of quantitative results with post-mortem histology. "What is clear is that there is a need for standardisation in the diagnosis of VAP," said Dr French. Indeed, diagnostic criteria have been described.^{6,7} "We are getting better results although even in autopsy we are still identifying VAP which was previously undiagnosed."

Outcome studies


"Outcome studies are key to identifying VAP since the response to specific therapy can help to confirm clinical and microbiological diagnosis," said Dr French.

Comparing studies using invasive and non-invasive (clinical) management of suspected VAP, Dr French presented one study⁸ in which invasive management was associated with significantly fewer deaths, less antibiotic use (and, therefore, less spread of resistance) and earlier improvement in organ dysfunction. "It is important to balance necessary treatment and unnecessary squandering of antibiotics," said Dr French.

In summary, Dr French said "Although VAP is difficult to diagnose clinically and it is difficult to distinguish colonisation from infection, appropriate clinical and x-ray signs together with positive quantitative/invasive bacteriology provide guidance for therapy." Outcome studies with directed therapy can help confirm true infections with organisms such as MRSA.

Treatment challenges of nosocomial and ventilator-acquired pneumonia in the ICU

"Whilst the major focus of treatment protocols and recommendations for nosocomial pneumonia, especially VAP, is to ensure that a high percentage of patients receive



appropriate initial antibiotic therapy, mortality rates are not decreasing," stated Dr Richard Wunderink from Chicago, Illinois, USA.

Inappropriate antibiotic therapy remains an issue, with significant numbers of patients receiving inadequate antibiotics for VAP and this is associated with increased mortality.⁹ "We need to use regimens which cover the most likely pathogens, for instance MRSA and pseudomonas," noted Dr Wunderink. In a study assessing the benefits of implementing clinical guidelines for the treatment of VAP, initial administration of adequate antimicrobial treatment was statistically greater during the 'after' period compared with the 'before' period (94.2% vs. 48.0%; $p < 0.001$).⁹ In addition, this study showed that guideline adherence significantly shortened the duration of antimicrobial treatment from approximately 15 to 9 days and also significantly reduced the likelihood of a second episode of VAP from 24.0% to 7.7%.⁹

Issues associated with non-response in ICU-acquired pneumonia

Since the micro-organisms associated with ineffective VAP therapy are the same as those associated with inappropriate initial therapy, the correct initial empiric antibiotic choice may not result in lower mortality. Just as the original diagnosis is challenging, identifying ineffective therapy can be difficult. In addition to inappropriate therapy, other causes of non-response to antibiotics in VAP include inadequate doses and the development of resistance during therapy.

"A further important issue in the treatment of VAP is tissue penetration," said Dr Wunderink. He added "There is a fairly consistent pattern throughout the literature that vancomycin fails in 40% of cases or more." Whilst vancomycin was probably the appropriate antibiotic for some MRSA infections, in VAP the drug levels achieved at the site of infection do not appear to be sufficiently effective¹⁰ due to a low area under the inhibitory curve (AUC) leading to clinical failure. "High AUCs are required to treat MRSA pneumonia," noted Dr Wunderink.

Another issue with vancomycin is the understandably cautious tendency to underdose, particularly in patients

with renal insufficiency. In a study of 119 critically ill patients, vancomycin-associated nephrotoxicity occurred in 20% of cases especially when patients were also taking concomitant nephrotoxic drugs¹¹ and is 'Number 7' on the list of drugs causing patient harm.¹² "Since there are significant problems with vancomycin, we may increasingly need to use another agent," said Dr Wunderink.

Alternative antibiotics

Linezolid is associated with significantly higher clinical success rates compared with vancomycin in MRSA HAP (59% vs. 35.5%)¹³ and MRSA VAP (62.2% vs. 21.2%).¹⁴ "Linezolid also confers a significant survival advantage [OR 95% CI 2.2; $p = 0.05$] compared with vancomycin with patients twice as likely to survive," said Dr Wunderink.

One reason for this significant improvement in survival may be due to the good lung penetration of linezolid. Even 24 hours after a 600mg dose of linezolid, the mean concentration in the epithelial lining fluid (ELF) was significantly higher compared with the plasma levels.¹⁵

Getting it right

Dr Wunderink noted that it is important that there are several choices of treatment. "If vancomycin is used, both peak and trough levels should always be checked. Alternatively, linezolid should be considered," he said. We are already putting selection pressure on vancomycin and seeing it fail due to the increase in resistance to this agent. "Perhaps we should consider rotating vancomycin and linezolid more often to prevent putting pressure on either agent," suggested Dr Wunderink.

Focusing on VAP, he continued "Appropriate initial therapy is necessary but this alone may still not necessarily lead to a decreased mortality in VAP. The greatest barrier to improved treatment is an overestimation of the efficacy of vancomycin. It should be remembered that the dose of vancomycin may be inadequate in MRSA VAP."

Dr Wunderink concluded "Linezolid offers an alternative to vancomycin. I would use linezolid first-line in patients with renal insufficiency with evidence of Gram-positive infection."

Let the battle commence – MRSA vs. man

Two eminent microbiologists debated whether it is possible to fight the MRSA epidemic by describing the situation in their particular countries; the UK, a country with extremely high levels of MRSA, and the Netherlands, a country still with low levels of MRSA.

a. Is the UK losing the battle?

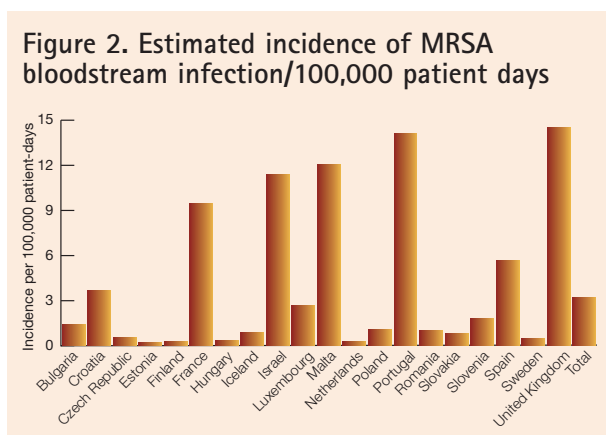
MRSA continually makes headline news in the UK. On 6 December 2003, the front page of *The Times* screamed '*Hospitals losing fight against antibiotic superbugs*'. However, at present, only 15% of all clinically significant in-patient isolates in the UK are MRSA.

Dr Nick Brown from Cambridge, UK, said that it is this environment in which the NHS is currently battling. MRSA is taking up an ever-increasing amount of time in UK hospitals and the severity of the situation has not eased.

Dr Brown clarified that MRSA is no longer an epidemic in the UK, as it is in most of Europe, but rather is now endemic.

As illustrated in the latest EARSS data,² the estimated incidence of MRSA bloodstream infection/100,000 patient days is higher in the UK than in any other European country (Figure 2).

For this reason, Dr Brown explained that the methods for handling MRSA are very different from how they would be if the UK was still in an epidemic situation.



However, data collected by the Health Protection Agency in the UK¹⁶ suggest that the proportion of *S. aureus* bacteraemias due to MRSA may be stabilising at around 40%.

MRSA history in Addenbrooke's Hospital, Cambridge

Describing the course of MRSA in Addenbrooke's Hospital, a 1,000 bed tertiary referral centre, Dr Brown noted that

Addenbrooke's is somewhat unusual in the UK as it has a high number of ICU beds, 154 single rooms and a high referral rate from other hospitals.

EMRSA-16 was first isolated in Addenbrooke's in 1992. However, there were a low number of introductions and little within-hospital spread. The hospital was able to cope with the isolation required and the relatively low number of ward closures needed.

In 1994, EMRSA-15 was first isolated at Addenbrooke's and this led to an increased use of isolation rooms and significant ward closures. However, at the same time there was a significant increase in workload pressures that meant that wards had to be reopened.

The result was a dramatic increase in MRSA, from around only 50 new cases over a six-month period previously to 500-600 new cases over a six-month period. Such an outbreak could be due to failure of infection control or the high number of patients. Dr Brown felt that, in Addenbrooke's, it was due to the latter reason.

Selection pressure may also have had an impact in Addenbrooke's since quinolones replaced cephalosporins as the antibiotic of choice. "Since EMRSA-15 is resistant to quinolones, this may have contributed to its selection," added Dr Brown.

Currently, around 10% of the population at Addenbrooke's Hospital (around 100 patients) is MRSA positive at any one time. Dr Brown explained that this is due to the lack of capacity within the hospital system to move patients into isolation units and/or close wards as needed. "This is the sign that the epidemic is now endemic," he noted.

In Addenbrooke's, screening is aggressive for all admissions from other hospitals, overseas patients and ICU patients. However, it is not possible to routinely screen staff in an endemic situation; only in an acute situation.

Other issues affecting the UK

Bed occupancy rates

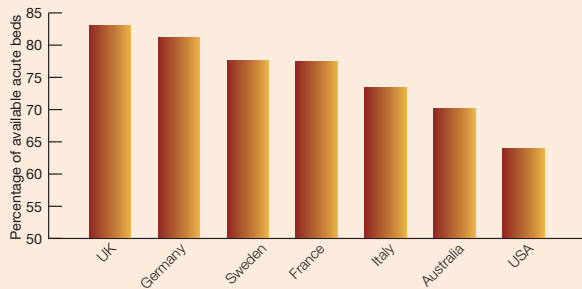
In the UK, these currently stand at 83%,¹⁷ (Figure 3), this rate being higher than many other European countries. In fact, bed occupancy in the Netherlands is currently around 62%, "A significant difference in terms of pressures on the hospital system and a significant factor in a hospital's ability to control MRSA," noted Dr Brown.

Screening policies between different hospitals

Dr Brown said "When attempting to control MRSA, a co-ordinated approach is needed not only locally but also regionally and nationally to allow for comparisons and accurate referrals."



Figure 3. Bed occupancy across Europe¹⁷



Workload

This has increased, putting additional strain on the system.

Mandatory reporting

In April 2001, MRSA reporting became mandatory in the UK, meaning that data from all UK hospitals can now be compared, hopefully with some degree of accuracy. This data, which can be viewed at www.hpa.org.uk, shows the variety of different strains in different parts of the UK.

Contact tracing

On average, medical patients visit 5.5 wards per stay, which makes contact tracing impractical.

Battle line

Dr Brown summarised his overview of the UK situation by saying "Different interventions are required in endemic and outbreak situations. Efforts should always be targeted as a priority to areas where they will be most effective, for example, the ICU and haematology/oncology units, where data show that the incidence of MRSA and MRSA bacteraemia is highest." He added "Not only are interventions required in the most problematic areas but they must be sustainable." Dr Brown believes that the 'search and destroy' strategy is appropriate if there is an outbreak. However, countries and units overwhelmed by MRSA, such as the UK, should concentrate their activities on the areas in which they can have the greatest impact.

Addressing the issue of whether the UK could reverse the MRSA situation, Dr Brown felt that this was no longer possible due to the lack of capacity to take measures which are needed to make this feasible. "There are too few staff, too few side rooms and too many patients to make this possible," said Dr Brown. Whilst Dr Brown felt that we might be able to have some effect on reducing the plateau, he said that there was currently an insufficient evidence base to show which interventions are most effective.

When asked how a country knows when an epidemic has reached endemic proportions, Dr Brown advised "Continue the 'search and destroy' strategy for as long as is practicably

feasible. The end is near when you have exhausted your ability to place patients in single rooms and close wards. At that point, you lose control and MRSA takes control!"

b. Is the Netherlands winning the battle?

Dr Christina Vandenbroucke-Grauls from Amsterdam, the Netherlands, said "It is both worthwhile and feasible to fight MRSA." In her opinion, the Netherlands is managing to hold back MRSA, with the country still reporting low levels.

MRSA history in the Netherlands

In the Netherlands, there is a population of 16 million and there are 125 hospitals.

In the early 1980s, there were small localised outbreaks of MRSA. Dr Vandenbroucke-Grauls said that these were controlled immediately with stringent infection control measures, including patient isolation and search for carriers. It was noted that MRSA from repatriation from foreign hospitals was a problem and "Quick action was taken by following stringent infection control methods which made it possible to stop this."

At the same time, a National search and destroy policy was introduced which led to National Guidelines by the Working Party on Infection Prevention. These were updated in 2003 and are endorsed by the Health Inspectorate that compels all units to follow the guidelines (www.wip.nl.uk/). Also, the National Institute of Public Health and Environmental Protection (RIVM) set up a national surveillance scheme.

Regularly, since the 1980s, small to larger (2-100 cases) outbreaks have occurred which, according to Dr Vandenbroucke-Grauls, have been controlled by following national infection control measures.

In 1997, there were only 350 reported cases of MRSA, with many introduced from foreign hospitals; in 2002, there were 1,000 cases and, in 2003, it is predicted that 1,500 cases will be reported. Dr Vandenbroucke-Grauls noted "The rise in the 2002 cases is largely due to a single outbreak of around 500 cases from a low-level resistant strain which was detected late." Due to this growing issue of low-level detection, the Dutch Government acted immediately and introduced national guidelines for improved detection of MRSA. "The increase in the 2003 data could, therefore, be due to increased detection," noted Dr Vandenbroucke-Grauls. However, in the Netherlands, less than 1% of *S. aureus* is MRSA.

How the Netherlands fights MRSA

The national Dutch policy includes:

- Isolation and screening of all patients repatriated from foreign hospitals

- Strict isolation of all MRSA cases and screening of all contact patients and healthcare workers. If increase in cases, close wards to admissions and screen all.
- No direct patient contact for healthcare workers with MRSA
- Treatment with nasal mupirocin
- All units strictly follow national guidelines and surveillance policies

Battle line

Dr Vandembroucke-Grauls believes that it is indeed possible to keep the prevalence of MRSA low as, she believes, is

demonstrated in the Netherlands. She stressed the importance of considering carriers in infection control measures, of contact tracing and of strictly following national guidelines. Also, environmental issues must always be considered, e.g. filters. In the Netherlands, the national guidelines include room cleaning measures that are strictly adhered to.

However, it was noted that the ratio of nurses to patients is far higher in the Netherlands compared with most of Europe, in addition to the bed occupancy rates being significantly lower. There is also a lower use of antibiotics in both primary and secondary care in the Netherlands compared with the UK.

The modern gladiatorial arena: Gram-positive pathogens vs. new therapies



Dr Francesco Menichetti

Introducing the session entitled 'The modern gladiatorial arena: Gram-positive pathogens vs. new therapies', Professor Ian Phillips from London, UK, said "Serious Gram-positive infections have become increasingly difficult to treat due to the emergence of resistant bacterial strains."

Dr Francesco Menichetti from Pisa, Italy, went on to discuss the management of serious Gram-positive infections, which include streptococci, enterococci, staphylococci and complicated skin and soft tissue infections.

Currently, the treatment options for serious Gram-positive infections include beta-lactams, fluoroquinolones, glycopeptides, streptogramins and oxazolidinones. These

treatments attempt, with varying success, to target the numerous types of resistant organisms which have already been identified. These include MRSA, VRE, VISA, hetero-VISA, GISA, SARV, VRSA and penicillin-resistant *Streptococcus pneumoniae* which are continually increasing, presenting new challenges to clinicians. In April 2004, a new isolate of VRSA was identified in New York, USA, this being the third strain of VRSA identified to date¹⁸ after the Michigan and Pennsylvania strains (see page 9).

MRSA that have acquired the vancomycin resistant determinant from *Enterococcus* are difficult to detect phenotypically. Two of the three clinical isolates reported so far have escaped detection by automated methods for *in vitro* susceptibility testing. There is, therefore, a need for the development of detection techniques at the gene level, according to Professor Patrice Courvalin from Institut Pasteur, France. "There may be many more strains than we currently believe," noted Professor Courvalin.

MRSA and VRE remain the most worrying resistant strains due to their rapid increase. Dr Menichetti stressed that resistance with Gram-positive infections is significant, noting that the average level in Europe is 25% but the UK currently leads the European league table where it remains a "growing problem," with the current level being 45%.

Promise from new agents?

Dr Pramod Shah from Frankfurt am Main, Germany, presented data on a potential new agent, daptomycin (Figure 4). Daptomycin is not licensed in Europe but received FDA approval in the USA in September 2003 for the treatment of complicated skin and skin structure infections (cSSSi) caused by Gram-positive bacteria. Data presented by Dr Shah on the activity of daptomycin in cSSSi show that it appears to be equally as effective as vancomycin in cSSSi in a variety of sites.¹⁹

Figure 4. Daptomycin*

- Novel cyclic lipopeptide
- Precise mechanism not completely understood
- Binds to cytoplasmic membrane resulting in efflux of potassium ions causing cell death not cell lysis, i.e. reduces activity in stationary phase
- Rapid concentration-dependent bactericidal activity
- Synergistic with gentamicin against MRSA and MSSA *in vitro* – clinical importance unknown
- Recommended dose = 4mg/kg once daily administered by intravenous infusion over 30 minutes
- At present, resistance has not been reported, possibly due to its limited use and/or its novel mechanism of action which suggests that multiple genetic steps may be required for the development of resistance
- Half life 8-9 hours
- No adjustment required in hepatic dysfunction
- In renal insufficiency (Cl <30ml/min), administer 4mg/kg post-dialysis then 4mg/kg 48 hourly (around 15% removed following 4 hours haemodialysis)

* Daptomycin is not licensed in Europe but received FDA approval in the USA in September 2003 for the treatment of complicated skin and skin structure infections (cSSSi) caused by Gram-positive bacteria

Into the future

Dr Shah noted that activity in the search for new MRSA sensitive agents is highlighted by the vast array of new compounds in the pipeline (Figure 5). Since many are analogues of existing structural classes, e.g. beta-lactams, he noted that they may suffer from the prevalence of existing resistance mechanisms.

There are also other considerations which were highlighted. For example, the quinolones are not generally active against MRSA and have reported clinical failures in pneumococcal infections; quinupristin/dalfopristin requires a slow infusion of a large volume and is not active against *E. faecalis*; telithromycin is not available as an intravenous agent unlike other agents such as linezolid; there have been isolated reports of resistance with linezolid; ramoplanin is only available as a topical preparation.

Dr Shah said "Solutions to the current problem of antimicrobial resistance include the prudent use of antimicrobial agents, appropriate use of combination treatments, prevention of bacterial infections and control and prevention of the dissemination of antimicrobial resistant organisms, in addition to on-going research into additional newer agents."

Figure 5. New compounds

Recently introduced agents

- Quinolones, e.g. levofloxacin
- Streptogramins, e.g. quinupristin/dalfopristin
- Ketolides, e.g. telithromycin
- Oxazolidinones, e.g. linezolid

Future compounds with existing modes of action

- Glycopeptides/peptides, e.g. oritavancin, ramoplanin
- Quinolones, e.g. garenoxacin, sitafloxacin, fandofloxacin
- Glycycyclines, e.g. tigecycline
- Dihydrofolate reductase inhibitors, e.g. iclaprim
- Beta-lactams, e.g. BAL-5788
- Lipated glycopeptides

Future compounds with new modes of action

- Mray inhibitors
- Lipopeptides, e.g. daptomycin

MecA gene on the move – emerging community-associated MRSA or hospital overspill?



Dr Fred Tenover

There was a great deal of discussion during the meeting concerning the issue of the observed increase in 'community-associated MRSA':

Dr Fred Tenover, Associate Director for Laboratory Science, Division of Healthcare Quality Promotion, Centers for Disease Control and Prevention, Atlanta, Georgia, USA, stressed that community-associated MRSA

is an important issue in the USA and is now emerging in Europe.

The key question raised with the presentations of this alarming data was the importance of clarification of the terminology used when describing 'community-associated MRSA'. It was questioned whether the pattern we are seeing is actually a further spread of hospital-acquired MRSA (HA-MRSA) being taken out into the community, hospital-acquired infection presenting later or 'true' community-associated MRSA (CA-MRSA) (Figure 6). It was stressed that true CA-MRSA is very different from hospital-acquired infection diagnosed in the community.

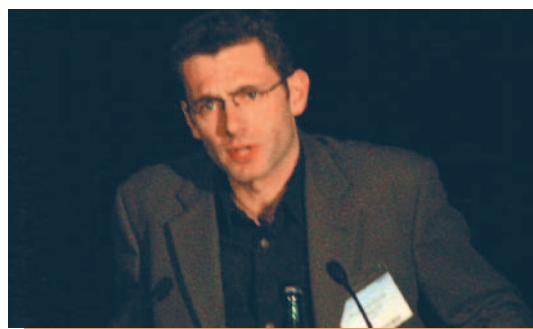
Figure 6. What might 'community-associated MRSA' be?

- Acquired from previous hospitalisations
- A real emerging community MRSA
- Community-based spread of hospital-acquired MRSA

Role of nursing homes in MRSA community spread

Dr Francois-Xavier Lescure from Amiens, France, discussed a longitudinal, case-control survey that researched the risk factors associated with the community acquisition of MRSA, concentrating primarily on medical and paramedical care in the community. The survey included 175 cases infected with MRSA and 173 controls infected with MSSA, admitted from the community between April 2002 and July 2003.

Presenting the results, Dr Lescure said that the multivariate analysis showed a strong and highly significant independent



Dr Francois-Xavier Lescure

association between MRSA infection at admission and:

- Prior home nursing procedures (OR=3.7, $p<0.0001$)
- Prior hospitalisation in a surgical ward (OR=2.3, $p=0.0003$)
- Transfer from another institution: hospital or nursing home (OR=2.3, $p=0.008$)
- Age >65 years (OR=1.6, $p=0.04$)

Dr Lescure noted that the risk of community-acquired MRSA increased as the number of home nursing procedures increased. The source of the MRSA may be MRSA carriers discharged from hospital and/or domiciliary nurses who may not be applying appropriate hygiene measures.

The results have important implications for the spread of MRSA. Information should be given to community workers about the prolonged carriage of MRSA when patients leave hospital. In addition, hand hygiene should be reinforced in hospital and community settings. Finally, selected screening of patients on the first day of hospitalisation was recommended.

True CA-MRSA – characteristics and spread

Dr Jerome Etienne from Lyon, France, listed the characteristics of 'true' community-acquired MRSA. "Patients with CA-MRSA typically have no known risk factors and are generally younger than healthcare associated MRSA patients. The MRSA strain more frequently carries the powerful toxin, Panton-Valentine leukocidin (PVL)," he said. CA-MRSA is primarily associated with skin and respiratory infection and is most commonly spread by skin-to-skin contact. "PVL-positive strains can be responsible for devastating disease," noted Dr Etienne.



CA-MRSA clones are spreading from one continent to another, with new clones emerging continually. In addition, PVL-positive MRSA isolates have been associated with hospital-acquired infections, to date in Greece and Algeria. "These have been particularly prevalent in post-partum women," noted Dr Etienne. In addition to PVL, other *S. aureus* toxins are now also associated with CA-MRSA clones, e.g. toxic shock syndrome toxin and exfoliatin A-positive MRSA.

Dr Etienne concluded "Not only are clones spreading across continents but they now also appear to be spreading in hospitals."

EMRSA-15 isolates carrying Panton-Valentine leukocidin (PVL) gene

Possible transmission of MRSA in the community was further suggested by Dr Giles Edwards from Glasgow, Scotland. Dr Edwards presented data from Scotland indicating that an EMRSA-15 (ST22) variant with distinct antibiogram and phage type acquired the PVL toxin gene and has been spreading in the community for several years. "Identical isolates have also been isolated from hospital patients with typical hospital infections but the community acquired isolates are associated with recurrent abscesses typical of the PVL toxin," Dr Edwards explained.

The picture across Europe

Dr Nienke Bruinsma presented data on MRSA reported through EARSS (European Antimicrobial Resistance Surveillance System, Figure 7) between 1999 and 2002 assessing variation over time and place.

Dr Bruinsma noted that this survey had been conducted due to the "Growing threat of MRSA for public health."

Figure 7. What is EARSS?

The remit of EARSS (European Antimicrobial Resistance Surveillance System, www.earss.rivm.nl) is to maintain a comprehensive surveillance and information system that links national networks by providing comparable and validated data on the prevalence and spread of major invasive bacteria with clinically and epidemiologically relevant antimicrobial resistance in Europe.

EARSS is a 'network of networks'. It collects data from around 700 laboratories from 28 countries from a population base of over 90 million.

The survey analysed data from 495 hospitals that reported results of more than 20 isolates. Of the data received by EARSS, 50,759 isolates were included in the analysis.

It was observed that the prevalence of MRSA differed largely and varied almost 100-fold in Europe from 0.5% to 44%. In general, a low proportion (<1%) was found in northern Europe and a high prevalence (>30%) was observed in southern Europe, Ireland and the UK.

During the survey period, MRSA proportions increased significantly in Germany (from 9 to 19%), the UK (from 31 to 45%), Ireland (from 39 to 45%), the Netherlands (from 0.4 to 1%) and Belgium (from 22 to 27%). Within countries, the prevalence of MRSA varied greatly between hospitals, with the highest variance in Germany and in other countries with a prevalence of between 5-18%.

The data showed that MRSA proportions vary substantially between countries and between hospitals. The findings of this study should serve to increase alertness in countries with increasing MRSA rates. "Hospitals with a low prevalence of MRSA in these countries should maintain their efforts to keep this prevalence low [see debate]," said Dr Bruinsma.

Detection of MRSA

Due to the costs currently associated with automated methods for detecting *S. aureus*, a commonly used method for the detection of MRSA in Europe remains disk diffusion.

However, the ever-increasing number of identified *mec* types of *S. aureus* mean that traditional techniques using oxacillin discs are not detecting some of the newer strains. According to Fred Tenover from Atlanta, Georgia, USA, there are now at least 5 *mec* types of *S. aureus* with many different types of clones, e.g. clone V, NY/Japan clone and EMRSA-15 and -16.

Low-level oxacillin resistance in *S. aureus* is now a major problem. Dr Tenover stressed "It is important to understand that *S. aureus* is a dynamic organism, both in the hospital and community setting and our methods of detection must continually keep this in mind. It is now sometimes really difficult to find these organisms." He explained that studies in his unit have shown that some organisms that appear to be susceptible to oxacillin are not if the cultures are grown for longer. "This means that there are heterogeneous types which are being missed," he explained.

One newer method of addressing this is the use of cefoxitin disks, a method which has recently been described by the NCCLS (National Committee for Clinical Laboratory Standards). Christina Vandenbrouke-Grauls from Amsterdam, the Netherlands, confirmed, "Phenotypic detection of low-level methicillin-resistant *S. aureus* may fail when relying only on oxacillin susceptibility, regardless of whether determined by disk diffusion or by broth dilution. Cefoxitin MIC determination increases the rate of detection of low-level MRSA."

Cefoxitin discs require only 18 hours of incubation time, allowing a confirmatory test to be conducted a full 24-hours earlier compared with oxacillin discs. Dr Vandenbrouke-Grauls noted that, although not a foolproof method, agar disc diffusion with cefoxitin is an accurate, relatively rapid, easy and cost-effective method of MRSA detection.

It was noted that the MRSA ultra-rapid test, recently approved by the FDA, may ultimately have an effect on infection control in hospitals by significantly improving detection.

Further challenges in MRSA detection – small colony variants of MRSA

Dr Barbara Kahl from Munster, Germany, discussed the small colony variant (SCV) sub-population of *S. aureus*. "This colony presents further challenges to microbiologists since they are hard to detect," Dr Kahl noted. "However," she added "They are clinically relevant and so an important group to identify."

Specific characteristics of SCVs have now been identified. They are small, non-pigmented, slow-growing, non-haemolytic colonies. Dr Kahl hypothesised that one mechanism by which SCVs can survive in the host could be the uptake of SCVs by eukaryotic cells, thereby acquiring protection against antibiotic therapy and host defence.

Over the past seven years, a clinical syndrome typifying SCVs has been identified as persistent, recurrent and antibiotic-resistant staphylococcal infections.

SCVs have been isolated most commonly from the diseases listed in Figure 8.

Figure 8. Diseases most commonly associated with SCVs

- Persisting and relapsing osteomyelitis and septic arthritis
- Abscesses
- Recurrent and relapsing infections of prosthetic valves and pacemakers
- Gentamicin bead placement for osteomyelitis
- Persistent *S. aureus* infections in cystic fibrosis

Dr Kahl noted "SCVs are found in various locations, settings and infections. Due to the unusual colony morphology, slow growth, unusual behaviour in standard tests (e.g. catalase, coagulase) and possible atypical appearance in Gram staining, SCVs are easily missed or misdiagnosed in routine laboratory monitoring resulting in major reporting errors with regard to their presence and susceptibility profile."

There is no established treatment for SCVs although prolonged treatment with beta-lactam antibiotics and intracellular active antibiotics, such as rifampicin, are most frequently used.

Dr Kahl concluded "In persisting and recurrent infections, particularly when antibiotic therapy fails despite apparent *in vitro* activity, microbiologists should actively search for SCVs."



References

1. www.cdc.gov/ncidod/hip/Aresist/mrsafaq.htm
2. EARSS 2002 data, www.earss.rivm.nl
3. Plowman R et al. J Hosp Infection 2001;47:198-209
4. Ibrahim E et al. Chest 2000;117:1434-1142
5. Cosgrove et al. Clin Infect Dis 2003;36(1):53-59
6. Pugin J et al. Am Rev Respir Dis 1991;143:1121-1129
7. Wunderink RG. Chest 2000;117:191S-194S
8. Fagon J-Y et al. Ann Intern Med 2000;132:621-630
9. Ibrahim EH et al. Crit Care Med 2001;29(6):1109-15
10. Moise PA et al. Am J Health Syst Pharm 2000;15;57(Suppl 2):S4-9
11. Wysocki M et al. Antimicrob Agents Chemother 2001;45(9):2460-7
12. 2001 MedMarx Data, www.medmarx.com
13. Wunderink RG et al. Chest 2003;124(5):1789-97
14. Kollef MH et al. Int Care Med 2004;30:388-94
15. Conte JE et al. Antimicrob Agents Chemother 2002;46(5):1475-1480
16. CDR Weekly, 16 April 2004, Volume 14, No 16
17. OECD Health Data 2002
18. www.cdc.gov/mmwr/preview/mmwrhtml/mm5315a6.htm (MMWR Weekly, 23 April 2004;53(15):322-323)
19. Carpenter CF, Chambers HF. Clinical Infectious Diseases 2004;38:994-1000

