EDITORIAL

MRSA - A BACTERIOLOGIST'S VIEW

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Staphylococcus aureus remains an important bacterial pathogen in hospital infection because of the continuing emergence of methicillin resistance. Methicillin-resistant *Staphylococcus aureus* (MRSA) has been the major nosocomial pathogen at the Singapore General Hospital (SGH) for the past four years. The importance of MRSA in hospital infections is shown by the increasing use of vancomycin, still the drug of choice for life threatening infections. SGH saw an increase of 59% in the consumption of vancomycin for 1989 as compared to 1988. In the Diagnostic Bacteriology section of the Department of Pathology which serves SGH, government and restructured hospitals, 8.8% of laboratory isolates of *Staphylococcus aureus* for the first quarter of this year were multiply-resistant including resistance to the penicillinase-resistant penicillins (PRPs) as represented by methicillin.

Strains of intrinsically methicillin-resistant *S. aureus* are usually resistant to multiple antimicrobial agents including the aminoglycosides. They have been found to possess a new penicillin-binding protein (PBP) PBP2a or PBP2' which has a reduced affinity for the beta-lactam antibiotics. PBPs are involved in the formation of the bacterial cell wall and they are the sites where beta-lactams bind to exert their effect. Possession of this altered PBP, PBP2a which is coded for on the bacterial chromosome, results in resistance to beta-lactams. Though PBP2a is produced constitutively it is also inducible by the beta-lactams[1]. Hence the rational use of antibiotics, especially the beta-lactams is so vital. It is commonly assumed that the extremely high MIC (minimal inhibitory concentration) for MRSA strains seen as no zone of inhibition with the oxacillin disk diffusion test is related to this PBP2a.

Some *Staphylococcus aureus* with "borderline" or "intermediate" in-vitro resistance to the PRPs (Methicillin MIC of 2 to 4 ug/ml) are not due to the PBP2a. There are at least two mechanisms involved here: 1) There are strains in which there is overproduction of beta-lactamase so that PRPs are now hydrolysed and rendered ineffective[2,3]. We are beginning to see this in our laboratory and are calling these strains "beta-lactamase hyperproducers" to differentiate them from the multiply-resistant MRSAs as they are seldom multiresistant to drugs other than beta-lactams. Whether these strains are clinically resistant to the penicillinase-resistant penicillins is still not known. They are sensitve in vitro to the beta-lactamase inhibitor combinations like Augmentin and Unasyn. 2) Tomasz et al were able recently to identify a new resistance mechanism that seems to involve some modification of normal antibiotic binding by some normal PBPs. They termed them MOD (modified) strains and proposed that they have been selected by direct antibiotic pressure in a manner that has been shown to occur during exposure of susceptible staphylococci to increasing concentrations of beta-lactam antibiotics in the laboratory[3]. It is most likely that clinically, selection for this type of resistance mechanism is already happening. The emergence of these MOD strains may eventually lead to strains with substantially higher MICs with therefore potential clinical implications.

Kobayashi et al demonstrated the different synergistic in-vitro effects of beta-lactams combined with beta-lactamase inhibitors clavulanic acid and sulbactam against MRSA. They found that sulbactam has a lower PBP2a-inducing activity than clavulanic acid and that it suppresses the induction of PBP2a by other beta-lactams. Also, sulbactam has a higher affinity for PBP2a than clavulanic acid and inhibits the expression of PBP2a-induced resistance in MRSA strains[4]. How this will apply to therapy in the clinical situation has not been elucidated.

MRSA has now become the bane of the infection control practitioners in acute care general hospitals in Singapore and in many medical centres abroad. Control measures are typically multifaceted. However if we remember to enforce good handwashing practice and proper isolation measures it would easily be half the battle won.

References

1. Hackbarth CJ, Chambers HF: Methicillin-resistant Staphylococci: Detection methods and treatment of infections. Antimicrob Agents Chemother 1989; 33:995-9.
2. McDougal LK, Thornsberry C: The role of beta-lactamase in Staphylococcal resistance to penicillinase-resistant penicillins and cephalosporins. J Clin Microbiol 1986; 23:832-9.
3. Tomasz A, Drugeon HB, Lencastre HM, Jabes D, McDougal L, Bille J: New mechanisms for methicillin resistance in *Staphylococcus aureus*: Clinical isolates that lack the PBP2a gene and contain normal penicillin-binding proteins with modified penicillin-binding capacity. Antimicrob Agents Chemother 1989; 33:1869-74.
4. Kobayashi S, Arai S, Hayashi S, Sakaguchi T: In Vitro effects of beta-lactams combined with beta-lactamase inhibitors against methicillin-resistant *Staphylococcus aureus*. Antimicrob Agents Chemother 1989; 33:331-5.

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