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On the Infection of Methicillin-Resistant *Staphylococcus aureus*

1. Introduction

When methicillin was first used in 1959 to treat infections induced by penicillin-resistant *Staphylococcus aureus*, the initial effect was remarkable. Two years later England first reported cases of methicillin-resistant *Staphylococcus aureus* (MRSA) in areas where methicillin had never been used[1,2]. Fortunately, these strains represented only 1% of all *Staphylococcus aureus*[3] The number of these strains, however, increased in the late '60s and early '70s, and the strains were identified in other places such as Australia, Belgium and the United States (US)[4-6]. In the late '70s and early '80s, MRSA was to be found in almost every continent of the world. Though the proportion, varied from area to area the trend of increase aroused serious alert for clinicians.

MRSA refers to the resistance of *Staphylococcus aureus* to methicillin, oxacillin or nafcillin. Clinically, MRSA often causes diseases such as bacteremia pneumonia osteomyelitis and endocarditis, thus extending days of hospital stay, increasing mortality rates and resulting in waste of medical care resources and manpower. Furthermore, MRSA in a hospital setting often induces nosocomial infection in the neo-natal Intensive Care Unit (ICU), Burn Units and nurseries. The disease is difficult to control once it begins to spread, for contacts between medical care personnel and patients in these Units are frequent, and antibiotics are used in quantity. Most of these antibiotics, however, cannot inhibit MRSA which therefore becomes a problem for both patients and medical care personnel.

2. Epidemiological Studies of MRSA

In a 17-year-long study of all hospitals in the US, the Atlanta Centers for Disease Control (CDC) in 1992 reported that the proportion of MRSA to all *Staphylococcus aureus* increased from 2.4% in 1975 to 29% in 1991; particularly after 1985, the increase was logarithmic[7]. This phenomenon was significantly greater in larger hospitals (more than 500 beds) than in hospitals of smaller sizes (200–499 beds, or

fewer than 200 beds).

In Taiwan the rate of MRSA infection has also reportedly been increasing to the rate being around 25 to 30% in large teaching hospitals[8]. Studies by the Nosocomial Infection Control Committee of this Hospital showed that between 1985 and 1989, MRSA strains were about 22% of all *Staphylococcus aureus* strains, a rate close to that in the large teaching hospitals. However, after 1990, the rate increased sharply from 33 to 47% in 1992, even reaching as high as 58% in 1991. Nosocomial infections induced by MRSA have also increased. Hospital findings show that in the last three years, the average rate of MRSA-induced nosocomial infections represented around 70.8% of all hospital *Staphylococcus aureus* infections, particularly infections in the blood. Medical care personnel, thus, must be particularly attentive to this issue.

A study by the Kaohsiung Medical College (KMC) showed that MRSA nosocomial infections significantly extended the days of hospitalization stay. Compared with MRSA infections in the community (21.6 days), the days of hospital stay for MRSA nosocomial infections were twice as many (48.6 days)[9]. MRSA infections in hospitals tend to attack the respiratory tract (60%) and surgical wounds (32%). The study also showed that infections are probably related to the invasive medical care measures often administered in hospitals: particular risk factors are the use of trachea tubes, in tracheotomy and with extensive use of antibiotics. Notably, the study showed that three MRSA strains (one nosocomial, and two community, infections) had already developed resistance to vancomycin (VRSA). These three so-called VRSAs have not yet been confirmed by either the EXPAND THIS (MIC) method nor by health authorities the accuracy of the finding remains to be proved. Lastly, the study also showed that the mortality rate from nosocomial MRSA infections is higher than from community MRSA infections (51.4% vs. 18.4%; $p<0.001$). Based on these data. Chang et al., of KMC, recommended that unnecessary use of antibiotics for out-patients and chronic patients be reduced[9]; that programs for nosocomial infection control and surveillance of in-patients be established; days of hospital stay and frequency of invasive medical care measures be reduced. They further urged that use of only reasonable and effective antibiotics be encouraged . . . all of these steps to be taken as measures to reduce the high mortality rate from MRSA infections.

3. Pathogenicity of *Staphylococcus aureus*

Staphylococcus aureus is one of the normal micro-organisms on the skin, in nasal and oral cavities and in the intestinal tracts of humans. Individuals more vulnerable to the infection are: 1) patients physically weakened by diabetes, cancer and alcoholism; 2) patients infected by viruses such as measles and influenza; and 3) patients, long-term users of antibiotics in whom normal micro-organisms in the intestinal tract may have been killed, for whom the *Staphylococcus aureus* increases and enteritis may result.

That surface antigens of *Staphylococcus aureus* such as protein A may develop

resistance to the phagocytosis of the white blood cells of the hosts is the initial deciding factor whether an individual will be infected. In addition, *Staphylococcus aureus* also produces the following enzymes and toxins to intensify its pathogenicity. 1) coagulase can dissolve fibrinogens (the coagulant in blood) into fibrins to make blood plasma coagulate; in this way, the bacteria are protected from being killed by phagocytes or drugs; 2) lipase can dissolve fat and oil, thus permitting bacterial penetration into normal skin and the sub-cutaneous layers to cause skin infections such as folliculitis; 3) hyalouronidase, in which around 90% of all *Staphylococcus aureus* produce, can dissolve hyalogens in the connective tissues, to spread the infection; 4) penicillinase can dissolve antibiotics of the penicillin group to make them ineffective; 5) staphylokinase can dissolve fibrogens to allow bacteria to spread and attack other sites; 6) nuclease: about 96% of *Staphylococcus aureus* produce deoxynuclease to destroy deoxynucleic acid of the host; 7) hemolysis: alpha-hemolysis destroys the red blood cells, while betahemolysis destroys the sphingomyelin of the host; 8) leukocidin destroys polymorphonuclear psuedomembrous and phagocytes; 9) enterotoxin causes food poisoning and enteritis in man; and 10) exofoliative toxin causes skin diseases such as the staphylococcal scalded-skin syndrome.

It is obvious that *Staphlococcus aureus* is a strong pathogenic agent. Its pathogenicity permits it to successfully penetrate the protection and immunity of a host. It has developed resistance to penicillin and methicillin (oxacillin in Taiwan), and seems to be developing resistance to vancomycin. Individuals concerned are thus alerted to take preventive measures against VRSA infections. Otherwise, the mortality rate may rise even higher.

4. Mechanism of Resistance of MRSA

MRSA develops resistance to methicillin, not because the beta-lactamase destroys the structure of antibiotics, rather by the intrinsic mechanism of drug resistance; that is, resistance does not come from other micro-organisms, but the micro-organisms themselves already carry genes-of-resistance. Although all methicillin-resistant strains carry homogeneous genes-of-resistance, most strains express drug resistance by their heterogeneity[10]. That is, in a colony of 10^4 to 10^8 micro-organisms, one micro-organism may express high resistance and still grow in a culture of 50 g/ml methicillin[11]. The mechanism that causes either homogeneous or heterogeneous resistance is as yet unknown[12]. The expression of resistance of heterogeneous strains is affected by temperature, osmosis, pH value, light and ion concentration. For instance below a temperature of 30°C, or with the addition of NaCl, heterogeneous resistance is intensified[13]; however, under 43°C or a pH value of 5.2, the resistance disappears[14]. Therefore, all microbiology laboratories should carefully consider the environmental conditions in which sensitivity tests are conducted, therefore avoiding the reading of resistant strains as sensitive, causing a delay in treatment. Homogeneous resistant strains are not affected by these environmental changes.

The mechanism of beta-lactam antibiotics is to inhibit enzymes such as transpeptidase, endopeptidase or cargoxypeptidase needed by the cell walls of bacteria. These enzymes

exist primarily on the cell membrane of bacteria to make the peptidoglycan polymer of the cell walls form a crossed network to maintain the hardness of the cell walls, and are also essential to the growth and fission of bacteria. Enzymes which can join with beta-lactam antibiotics are called "penicillin-binding proteins" (PBPs). PBPs are important to the growth and survival of bacteria. The major difference between MRSA and methicillin-sensitive *Staphylococcus aureus* is the content of their PBPs[12]. Presently, the known resistance mechanism is induced by PBP2a which is not produced by the methicillin-sensitive *Staphylococcus aureus*. The molecular weight of PBP2a is about 78KD; PBP2a has a lower affinity for the beta-lactam antibiotics. This is the major mechanism which causes methicillin-resistance, making PBP2a the major factor in the resistance mechanism of methicillin. The resistance gene of methicillin (mec) has been chosen and cloned; its molecular weight (carrying 37×10^3 acid base) and gene chart are known. The genes which comprise PBP2a are a part of mec, carrying only 2.1×10^3 deoxynuclei acid base[15]. Therefore, mec should also carry other genes such as those which control the synthesis of PBP2a and the transposase genes which enable mec to infiltrate chromosomes. In addition to PBP2a's inducing resistance in *Staphylococcus aureus* methicillin by the homogeneous and heterogeneous expressions of strains, there must be other, still unidentified, mechanisms such as bacteria which automatically dissolve the enzyme systems. Through what mechanisms these genes control the synthesis of enzymes to prevent *Staphylococcus aureus* from being dissolved is a subject for future study.

5. Control of MRSA Infections

The only 100% effective antibiotic currently available to control MRSA infections is vancomycin. With the yearly increase of MRSA infections in the States, use of vancomycin has also increased. This practice, however, has caused many enterococci and coagulase-negative staphylococci to become resistant to the drug[16,17] though, as late as 1991, US CDC had not yet officially received reports from hospitals of vancomycin-resistant *Staphylococcus aureus* infection cases. Once the infection occurs, even in the US there will not be any new drug available for the treatment. Hence, MRSA infections should be very strictly surveyed. Their control will be extremely difficult once they spread within hospitals.

Currently measures available for surveillance and control of MRSA infections in hospitals are: 1) reviewing of the micro-biological test findings of all hospitalised patients; 2) periodical review of information from high-risk groups; 3) adequate isolation of patients with MRSA strains after admission to hospital, with clear alerts entered on their records; 4) special precautions required for medical care personnel working with such patients: wearing gloves when handling patients, and especially thorough washing of hands after with patient secretions; 5) identified cases of MRSA should be moved to single rooms for cohort nursing; 6) MRSA carriers should be discharged immediately; 7) medical care personnel at risk for exposure to MRSA patients and environment should receive micro-biological cultures and, when testing positive, should be immediately treated and given follow-up.

Boyce, in a study of 360 members of the American Epidemiology Association stationed in various hospitals, says that most members interviewed agreed, after reviewing micro-biological test findings of hospital patients, that the following control measures should be routinely practiced: medical care personnel should wear gloves for, practice hand-washing after, working with patients; MRSA patients should be placed in single rooms; patients not requiring further treatment should be immediately discharged from hospital units or wards with high MRSA infection to effectively control cross infection of MRSA[18].

6. Discussion

MRSA infections, either community or nosocomial, can cause serious consequences, and may even increase the infection and mortality rates of hospital patients. Both international and national survey reports show that ratios of MRSA in either clinically-isolated micro-organisms or pathogenic agents of hospital infection have greatly increased. Furthermore, the mechanism of resistance to MRSA is extremely complex with expressions which are very specific, both homogeneously and heterogeneously. Automatic dissolution systems require further study to understand through what mechanism the micro-organism controls the genes which dissolve the synthesis of enzymes and thus prevent some *Staphylococcus aureus* from being dissolved by the immune system of the host.

All individuals concerned with nosocomial infection control should establish a surveillance system; early detection of MRSA infections can mean early control. If carriers or patients with MRSA infections can be identified earlier, adequate control measures can help reduce cross infection among various units of hospitals, and effectively reduce both infection and mortality rates from MRSA. Hospital units concerned should also control the use of antibiotics, particularly vancomycin. Once many strains of *Staphylococcus aureus* become resistant to vancomycin, the infection rate and mortality rate will predictably rise. Hospital staff should be alerted to, and reminded of, this fact.

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