Choices of Antibiotics for MRSA Infection in Malaysia

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Abstract

Methicillin-resistant Staphylococcus aureus (MRSA) are found to be common in many countries. A study was done in Hospital Universiti Sains Malaysia (HUSM) showed that there is a gradual reduction in MRSA infection rates from 2002 to 2006. Vancomycin, Linezolid, Daptomycin, Tigecycline, Rifampicin and Teicoplanin are the most common and popular antibiotics for treating MRSA infection in Malaysia. A study show that the patients that treated with Daptomycin achieve clinical success on day 3 (93%) compared to that having Vancomycin treatment (57%). Daptomycin showed 100% efficacy towards killing MRSA strains. In addition, only 10% of patients will complain about the adverse effects of vancomycin. The most common side effects associated with usage of Teicoplanin are hypersensitivity (2.6%), abnormal liver function (1.7%), fever (0.8%), abnormal renal function (0.7%) and ototoxicity (0.3%). Monitoring and dose adjustment should be carried out to reduce the side effects of the antibiotics used.

Introduction

Methicillin-resistant Staphylococcus aureus (MRSA) is one of the Gram-positive Staphylococcal strains which are resistant towards various kinds of drugs, including methicillin, oxacillin, penicillin and amoxicillin. There are generally 2 types of MRSA strains, which are Community-acquired and Nosocomial-acquired MRSA. Nosocomial-acquired MRSA is commonly found in healthcare settings. It will infect patients who have weakened immune system and stay in hospital for certain period of time while Community-acquired MRSA will affect those who have not exposed to health care environments previously. [Brandon, et al., 2008]

MRSA is commonly found to cause skin and soft-tissue infections. This is because Staphylococcus strains can be found on skin of healthy human. MRSA infection starts once the skin is injured when an opening is produced for the bacteria to invade. MRSA can also lead to some serious and life-threatening infections such as septicemia (blood infection). [Anon., 2011]

There are certain groups among community that are more prone towards MRSA infection. A person who had history of colonization of MRSA or had infected by Staphylococcus before is more prone towards infection. Considerations should be given to those who had close contact with MRSA infected patients such as family members and close friends. Moreover, patients having frequent antibiotic treatment and has recurrent skin diseases are more susceptible towards MRSA infection. A person who had undergone hospitalization, long-term care, end-stage renal failure, surgery, indwelling catheters and injection also can be infected by MRSA. [Anon., 2011]

Based on a cross-sectional study done in Hospital Kuala Lumpur (HKL), Hospital Tengku Ampuan Rahimah, Klang (HTAR) and the Bacteriology Division, Institute for Medical Research (IMR) of Malaysia, it was found that the occurrence of MRSA infection increase gradually with years, from 25.7% to 28.7% in 1996, 27.9% in 1998 and 33% in 2000. However, study done in Hospital Universiti Sains Malaysia (HUSM) recently shows that there is a gradual reduction in MRSA infection rates from 2002 to 2006. This might be due to improvement in quality of health care system in Malaysia. In this study, all MRSA strains isolated are resistant towards oxacillin and penicillin. There is an increase in resistance of MRSA strains towards Erythromycin, Gentamycin, Co-trimoxazole and Ciprofloxacin. However, some standard anti-MRSA antibiotics remain effective in treating the infections in HUSM such as Rifampicin, Fusidic acid and Vancomycin since Vancomycin-resistant Staphylococcus aureus is not yet detected in Malaysia. Thus, MRSA infection in Malaysia is still under control and to prevent resistance cases from increasing, the use of antibiotics should be restricted to cases where its usage is a necessary. [Al-Talib, Chan, Al-Jashamy and Hasan, 2010]

There are various types of antibiotics available for treatment of MRSA infection in Malaysia. But, in this review, we will only focus on 6 types of antibiotics available for treating MRSA infection in Malaysia, which are Vancomycin, Linezolid, Daptomycin, Tigecycline, Rifampicin and Teicoplanin. Both Linezolid and Tigecycline are considered to be
bacteriostatic agent and they inhibit protein synthesis of the bacteria [Slover, Rodvold and Danziger, 2007] while the others are bactericidal against MRSA. Linezolid can also be bactericidal in certain condition but usually, it is bacteriostatic. Both Vancomycin and Teicoplanin are bacterial cell wall inhibitor while Rifampicin is nucleic acid inhibitor.[Traczewski, Katz, Steenbergen and Brown, 2009] Daptomycin act by disrupt the function of bacterial plasma membrane.

This article is done in order to know the choices of antibiotics available in Malaysia for treatment of MRSA infection. Besides, the efficacy and the safety aspects of different types of antibiotics used for treating MRSA infection are compared. Various journals are adapted from Science Direct and Google Scholar to search for more information. We obtained some of the online informations from a webpage known as Rx List, The Internet Drug Index.

**Efficacy of Antibiotics for MRSA**

Different clinical studies had been carried out by parties all around the world in order to compare the efficacy of different types of antibiotics available for treatment of MRSA infection. We had chosen some of the related studies for reviewing purpose and below are some of the information related to the comparison of effectiveness of Vancomycin, Linezolid, Daptomycin, Tigecycline, Teicoplanin and Rifampicin in treating patients infected by MRSA.

The efficacy of antibiotics can be classified according to Minimum Inhibitory Value (MIC) and the hospital length of stay of patients treated with different types of antibiotics. MIC is the minimum concentration of antimicrobial that can totally inhibit the growth of microorganisms. [Islam, 2008] The lower the value of MIC, the more effective the antibiotic is. Besides, the shorter the hospital length of stay of patients treated with particular antibiotics, the higher the efficacy of that particular antibiotic.

A study was performed to evaluate the effectiveness of Daptomycin therapy for hospitalized patients suffering from complicated skin and skin structure infections. This study was conducted in Detroit Receiving Hospital, Detroit, Michigan. A total of 265 patients involved in this study, where 53 patients undergone Daptomycin therapy while 212 received Vancomycin.

The results obtained from the study showed that all patients undergoing treatments are cured no matter which type of antibiotics are being used. However, it is found that a higher proportion of patients treated with Daptomycin achieve clinical success on day 3 (93%) compared to that having Vancomycin treatment (57%).

Besides, the day of clinical cure for Daptomycin-treated patients who achieve complete resolution is a median of 4 days compared to those treated with Vancomycin, a median of 7 days. The duration of inpatient Vancomycin therapy (8 days) is also longer than that of Daptomycin therapy (4 days).

Although both antibiotics can cure MRSA infection effectively, it seems that Daptomycin is having slightly higher efficacy than Vancomycin since patients recovered faster and the duration of antibiotic therapy is shorter compared to Vancomycin. [Davis, et al, 2007]

A randomized study was carried out at various health centers to study and compare the efficacy of Tigecycline and Vancomycin in hospitalized patients suffering from MRSA infection. The study showed that the efficacy of monotherapy using Tigecycline for treating MRSA infection is almost same as that of Vancomycin where the percentages of patients cured by either type of antibiotics do not differ much. However, the mean duration of therapy for Tigecycline is shorter (11.4 days) than Vancomycin (13.1 days) and this suggests slightly higher efficacy of Tigecycline compared to Vancomycin. [Florescu, et al., 2008]

A pooled analysis of 5 randomized studies is carried out to compare the efficacy of Linezolid and Vancomycin. A total of 3228 patients were involved in the 5 randomized studies. From the analysis conducted, the duration of intravenous therapy using Linezolid and Vancomycin are different where the duration of Linezolid treatment (8.6 days) is shorter compared to Vancomycin therapy (11.7 days). The analysis also showed that approximately 67% of Linezolid-treated patients survived from MRSA infection while 65% of Vancomycin-treated patients survived. This proves that Linezolid has almost the same or even higher efficacy compared to Vancomycin for treating MRSA infection. [Shorr, Kunkel and Kollef, 2005]

In order to compare the efficacy of Teicoplanin and Vancomycin in treating systemic infection caused by MRSA, a systematic review and meta-analysis of randomized controlled trial are carried out. A total of 2332 patients are involved and the randomized controlled trial was conducted from 1986 to 2007. From the trials reviewed, there is no significant difference in all-cause mortality of Teicoplanin and
Vancomycin (95%). On the other hand, Teicoplanin therapy is less associated with side effects. This means Teicoplanin has lower rate of adverse effects' occurrence compared to Vancomycin. This further proves that Teicoplanin's efficacy is not inferior to Vancomycin and it causes lesser side effects than Vancomycin. [Svetitsky, Leibovici and Paul, 2009]

There is another study conducted to investigate and evaluate the in vitro activity of Daptomycin and comparator agents against clinical isolates of *Staphylococcus aureus* in four Latin American countries. The study had been carried out for over five years. A total of 6031 *Staphylococcus aureus* isolates were collected from 10 medical centers in Argentina, Brazil, Chile and Mexico.

In this study, Minimum Inhibitory Concentration (MIC) is used to find out the susceptibility of MRSA towards antibiotics. Based on this study, Daptomycin showed 100% efficacy towards killing MRSA strains. The MIC50 (Minimum Inhibitory Value-50) and MIC90 (Minimum Inhibitory Value-90) of Daptomycin were 0.25 and 0.5mg/ml respectively. [Biedenbach, 2010]

A study conducted at tertiary care hospital in north India aims to determine the in vitro susceptibility of Gram-positive and Gram-negative bacteria towards Tigecycline. A total of 21 isolates of MRSA were tested for susceptibility towards Tigecycline. Since the main purpose for this assignment is to study on the choices of antibiotics that act on MRSA, thus, only the efficacy of Tigecycline on MRSA strains is taken into consideration.

Minimum Inhibitory Value (MIC) is also used in this study where resistance is defined as MIC ≥ 8 µg/ml and zone size ≤ 14 mm. From the result obtained from this study, all MRSA isolates were sensitive towards Tigecycline. MIC50 of MRSA isolates was 0.25 µg/ml, whereas their MIC90 was 0.38 µg/ml. Therefore, this shows that MRSA is sensitive towards Tigecycline. [Behera, 2009]

Another study was carried out in Bangladesh for 1 year (from July 2006 to June 2007). Clinical MRSA samples were collected from Mymensingh Medical College Hospital, Mymensigh. 10 MRSA strains were obtained from 40 clinical isolates of *Staphylococcus aureus*. In this study, various types of antibiotics were used for testing, such as Penicillin, Oxacillin, Vancomycin, Rifampicin and Cloxacillin. If the MIC value of particular antibiotic is less than or equal to 2 µg/ml, it was categorized as Susceptible (S). In the meanwhile, if the MIC value for that antibiotic is more than or equal to 4 µg/ml, then it was categorized as Resistant (R).

From the result obtained from this study, Rifampicin and Vancomycin were found to have 100% effectiveness against MRSA strains. This means the MIC values of Rifampicin and Vancomycin were less than or equal to 2 µg/ml. [Islam, 2008]

In terms of efficacy, Vancomycin, Tigecycline, Linezolid, Daptomycin, Teicoplanin and Rifampicin show very high efficacy towards treating MRSA infection. Among the 6 types of antibiotics available in Malaysia for MRSA infection treatment, it is found that Vancomycin is actually the most commonly prescribed and most famous drug when a patient is suspected to be infected by MRSA.

Pharmacokinetic and Clinical Indications of Antibiotics for MRSA

In treatment of MRSA infection, there are several types of antibiotics that have the privilege to fight against it. Some common antibiotics classes that are frequently used to treat MRSA infection in Malaysia are Tigecycline, Vancomycin (Vancomycin Chloride), Oxalizidonones (Linezolid), Teicoplanin, Daptomycin, and Rifampicin (Rifampicin). All of these antibiotics are proven to be effective in combating against Methicilin-resistant *Staphylococcus aureus* (MRSA) infections.

Each antibiotic listed above have their distinct features and pharmacokinetic profiles. The comparison between the properties of antibiotics may lead to discovery of which antibiotics' preferential use is more important. Information obtained from comparisons might be useful for treatment of MRSA infection in certain cases and can also be used to determine their compatibility with the patients' conditions.

Vancomycin is a well-known drug used for treating MRSA infections. It is indicated for initial therapy when MRSA is suspected to be the cause for a particular infection. It has a trade name of VANCOMYCIN HYDROCHLORIDE™ and is considered to be a narrow spectrum antibiotic. It can mostly act on Gram-positive bacteria, mainly on Gram-positive cocci. Linezolid, another choice of antibiotic for MRSA infection treatment, is also considered to be narrow spectrum since it is very active against a wide variety of Gram-positive bacteria including Penicillin-resistant *Streptococcus pneumonia* and Vancomycin-resistant *Enterococci*, but not on Gram-negative bacteria. Linezolid belongs to the Oxazolidinones antibiotic class with a trade name of ZYVOX™.
Besides, there are another 3 types of antibiotics that only act on Gram-positive bacteria, which are Teicoplanin, Rifampicin and Daptomycin. Teicoplanin is an antibiotic used in prevention of development and treatment of serious infections caused by Gram-positive bacteria, including MRSA and Enterococcus faecalis. It also acts as an alternative for patients who are unable to tolerate Vancomycin since Teicoplanin has lowered a toxicity level. It has a trade name of TARGOCID®. Rifampicin or Rifampin, with a trade name of RIFADIN™, can also act effectively against MRSA. [Biedenbach, Bell, Sader, Fritsche, Jones and Turnidge, 2007][Traczewski, Katz, Steenbergen and Brown, 2007] Although Daptomycin has a limited spectrum of activity where its activity is restricted to Gram-positive organisms (highly resistant MRSA, Vancomycin-resistant Staphylococcus aureus (VRSA) and Vancomycin-resistant enterococci (VRE)), it is active against some anaerobes and also aerobes. This feature makes it slightly different from the previous four antibiotics. It has a trade name of CUBICIN™. [Tedesco and Rybak, 2004]

On the other hand, Tigecycline have broader spectrum of activity when compared with Vancomycin, Linezolid, Teicoplanin, Rifampicin and Daptomycin as they only act on Gram-positive bacteria. Tigecycline is a glycycline antibiotic with broad spectrum of activity against Gram-positive and Gram-negative bacteria, no matter whether the bacteria are aerobic or anaerobic organisms. Moreover, they also act on atypical bacterial species. Its spectrum of activity towards Gram-positive bacteria extends to clinically relevant susceptible strains of Staphylococcus aureus, Streptococcus pneumoniae, Vancomycin-resistant Enterococci, and Enterobacteriaceae. It is marketed under the trade name of TYGACIL™. [Meagher, Ambrose, Grasela and Ellis-Grosse, 2005]

Vancomycin cannot be administered via the oral route because it cannot be absorbed effectively by the gastrointestinal tract. However, it can be given parenterally, either as injection or infusion. The usual daily intravenous dosage for vancomycin is 2 g and it is administered either as 500 mg every 6 hours or 1 g every 12 hours for patients with normal renal function and 40 mg/kg in three or four divided doses for children. Similarly, Tigecycline also has a low bioavailability following oral administration and hence it is available as intravenous infusion formulation. 100 mg of it is administered as loading dose, followed by 50 mg every 12 hours.

Both Teicoplanin and Daptomycin are also administered parenterally. Teicoplanin cannot be absorbed via the gastrointestinal tract but intravenous and intramuscular administrations are well tolerated. For patients on haemodialysis, 3 loading doses of 6 mg/kg at 12-hour intervals followed by maintenance doses every 72 hours are administered. [Lortholary, Tod, Rizzo, Padoin, Biard, Casassus, Guillemin and Petitjean, 1996] Daptomycin is only available as intravenous formulation since its gastrointestinal absorption is very low. The approved dosing regimen for Daptomycin is 4mg/kg in intravenous injection once daily.

In comparison, Linezolid and Rifampicin can be administered orally. Linezolid has complete oral bioavailability and its absorption from gastrointestinal tract is unaffected by food intake. The excellent oral absorption characteristic of linezolid is particularly effective since the enteral route is increasingly used by clinicians to administer both nutrition and drug therapy to hospitalized as well as long-term care residents in lieu of the parenteral route. [MacGowan, 2003][Meagher, Forrest, Rayner, Birmingham and Schentag, 2003] Moreover, it can also be given as intravenous infusion for treatment of serious infections. The oral dosage of Linezolid is 600 mg every 12 hours. [Zyvox Clinical Pharmacology, (Anon., 2011)] Rifampicin is absorbed readily from the gastrointestinal tract which makes it active orally. Nevertheless, it can also be given in intravenous infusion. Oral dosage for Rifampicin is 600 mg daily.

Vancomycin is widely distributed in the body. It can be found in tissues and body fluids such as bile, breast milk and joints. Besides, it can pass through the placenta and might influence the foetus. Vancomycin does not readily diffuse through normal meninges into the spinal fluid. Only when the meninges is inflamed, penetration into the spinal fluid will occur. Approximately 7-30% of simultaneous serum concentrations are achieved if meningeal infections are present. [Vancomycin Hydrochloride Clinical Pharmacology (Anon., 2011)] Although Linezolid is rapidly and extensively absorbed after oral dosing, it cannot pass readily through the blood-brain barrier and thus cannot be found in the cerebrospinal fluid. Maximum plasma concentration is reached approximately 1 to 2 hours after dosing, and its absolute bioavailability is 100%. [Zyvox Clinical Pharmacology, (Anon., 2011)] Linezolid is also widely-distributed in well-perfused tissues.

Daptomycin has a lower volume of distribution in the extracellular fluid due to its high percentage of protein bound (90%) compared to the 2 drugs mentioned previously. The high level of protein binding of daptomycin and the lack of proteins in the interstitial fluid were probably the most likely explanations for the
fact that the apparent volumes of distribution of daptomycin were lower than the estimates of the extracellular fluid volume (0.157 to 0.187 liter/kg). However, its ability in penetrating cerebrospinal fluid has not been characterized. On the other hand, tigecycline is proven to distribute rapidly and has large volume of distribution. Moreover, it has very long half life. [Meagher, Ambrose, Grasela and Ellis-Grosse, 2005][Hoffmann, DeMaio, Jordan, Talaat, Harper, Speth and Scatina, 2007]

90% of Teicoplanin will bind to plasma proteins in human body. Its volumes of distributions are 0.07 to 0.11 L/kg at initial phase, 1.3 to 1.5 L/kg at distribution phase and 0.9 to 1.6 L/kg at steady phase. [Wilson, 2000] This shows that it has very low volumes of distribution. However, it has longer half-lives when compared to others and is able to penetrate into tissues, skin, fats and bones. Besides, it has high concentrations in the kidney, trachea, lungs, and adrenals. It does not readily penetrate into the cerebrospinal fluid. In comparison, Rifampicin is widely distributed in the body tissues and able to enter the cerebrospinal fluid. 80% of it will bind to plasma proteins where most of the unbound fraction is unionized and therefore, diffuses freely into tissues. [Rifadin Clinical Pharmacology, (Anon., 2011)] In a healthy adult, the mean half-life for Rifampicin is 3-4 hours after a daily oral dosage of 600 mg but increases up to 5-7 hours with a daily dosage of 900 mg.

Metabolisms of Vancomycin, Daptomycin and Teicoplanin in the human body are not significant. Only a small proportion of vancomycin will undergo metabolism. Teicoplanin also has a low metabolism rate. Approximately 2 to 3% of an intravenously administered Teicoplanin is metabolized by human body. Metabolism process of Daptomycin is slightly different from Vancomycin and Teicoplanin because based on the results obtained from in vitro studies, it was found that Daptomycin is not metabolized by human liver microsomes. This means it does not undergo any metabolism in liver. On the other hand, Vancomycin and Teicoplanin both can be metabolized by human body but only a very low percentage of them will undergo the process. [Cubicin Clinical Pharmacology, (Anon., 2011)]

The remaining 3 types of antibiotics, which are Linezolid, Tigecycline and Rifampicin can undergo metabolism to form metabolites. Both Linezolid and Tigecycline are metabolized in liver. Linezolid undergoes metabolism in the liver when the morpholine ring, one of the components of its chemical structure, is oxidized. [Zyvox Clinical Pharmacology, (Anon., 2011)] The major metabolic pathways of Tigecycline that had been identified are glucuronidation and amide hydrolysis of the parent drug, followed by N-acetylation to form a metabolite known as N-acetyl-9-aminominocycline. [Hoffmann, DeMaio, Jordan, Talaat, Harper, Speth and Scatina, 2007] Rifampin or Rifampicin undergoes progressive deacetylation and the metabolite resulted has some antibacterial activities. The metabolites are mostly found in the bile. The average half-life of Vancomycin is about 4 to 6 hours in human with normal renal function. In the first 24 hours, about 75% of an administered dose of vancomycin is excreted in urine via glomerular filtration. [Vancomycin Hydrochloride Clinical Pharmacology (Anon., 2011)] Linezolid has longer mean half life than Vancomycin Hydrochloride. It has a half-life between 5-7 hours and it is also excreted by glomerular filtration through renal pathway. The renal clearance of linezolid is quite low (average 40 mL/min) and this suggests occurrence of net tubular reabsorption. [Zyvox Clinical Pharmacology, (Anon., 2011)] Daptomycin is also excreted via renal route and since its metabolism is not significant, 60% of the drug excreted as parent drug in urine. Teicoplanin, having the same route of elimination as Vancomycin, Linezolid and Daptomycin, is excreted predominantly by the kidneys. It has longer half-lives compared to the other 3 antibiotics and its total clearance is 11 ml/h/kg. On the other hand, both Tigecycline and Rifampicin undergo biliary excretion. Tigecycline is found to be eliminated through feces, primarily as unchanged drug. Rifampicin which excreted via bile may undergo intestinal reabsorption. However, since it can be metabolized by deacetylation process, its intestinal reabsorption is greatly reduced and elimination facilitated. About 30% of a dose of Rifampicin is excreted in urine, with about half of this being unchanged drug. [Rifadin Clinical Pharmacology, (Anon., 2011)]

Each drug has their clinical indications. Vancomycin, due to its inability to be absorbed orally, is used for treatment of gastrointestinal tract infection when taken orally. This is because it will remain in gastrointestinal tract for prolonged time and thus will have longer duration to act on the bacteria. Since it is excreted through renal route, its dosage should be monitored for patients suffering from renal insufficiency to prevent accumulation of Vancomycin that may lead to toxicity. It can also act as prophylaxis against endocarditis in penicillin-allergic patients who have congenital heart disease when these patients undergo dental procedures or surgical procedures of the upper
respiratory tract. It can also be used to treat pseudomembranous colitis, an acute inflammation of the colon caused by *Clostridium difficile*.

Beside treatment for MRSA infection, Teicoplanin is also indicated for some other treatments such as treatment of multidrug-resistant Gram-positive infection. It can be used to treat infections caused by *Enterococcus faecium* and prosthetic device infection caused by coagulase-negative staphylococcus. Moreover, it can act on serious Gram-positive infection in patients allergic to other antibiotics and as prophylaxis or treatment of endocarditis. Rifampicin is indicated for another two main treatments apart from treatment of MRSA infections. It can be used to treat tuberculosis and for treatment of asymptomatic carriers of *Neisseria meningitidis* in order to wipe out meningococci from the nasopharynx. [Rifadin Clinical Pharmacology, (Anon., 2011)]

Tigecycline is used for treatment of complicated intra-abdominal and skin-structure infections. It also show high effectiveness in inhibiting MRSA organism embedded in biofilm when compared to Vancomycin and Linezolid. Thus, it is more suitable in treating infections caused by catheter-related Methicillin-resistant Staphylococcus infections. [Raad, Hanna, Jiang, Dvorak, Reitzel, Chaiban, Sherertz and Hachem, 2007]

Linezolid can penetrate blood-brain barrier and it is distributed in cerebrospinal fluid. Hence, it can be used to treat infections of central nervous system, but not meningitis. Besides, it is widely distributed in lower respiratory tract and thus is suitable to treat pneumonia. It can also be prescribed for septicemia, skin and soft tissue infections. [Herrmann, Peppard, Ledeboer, Thesefeld, Weigelt and Buechel, 2008] Another antibiotic that has been approved for treatment of soft and skin tissue infection is Daptomycin. Dose adjustment of Daptomycin should also be done if it is used to treat patients with renal dysfunction. [Salidar, Andes and Craig, 2004]

### Side Effects and Management of Side Effects

The adverse effects encountered by patients that taking vancomycin are only about 10% and most of the reactions are minor. Vancomycin is a glycopeptide drug and poorly absorbed by gastrointestinal tract due to the sugar moieties that attached to it and for that reason vancomycin need to be administered by injections. Hence, vancomycin can cause phlebitis which is the inflammation of the vein due to the insertion of intravenous catheters at the site of injection. However, phlebitis only causes a minor inconvenience to the patients and it is consider being less serious side effect. [Kantor, 2005]

Vancomycin can cause two types of hypersensitivity reactions, which are the red man syndrome and anaphylaxis. However, the red man syndrome is more common with vancomycin users than anaphylaxis. Red man syndrome is an infusion-related reaction which causes the patients to endure an erythematous rash at the face and neck that can be characterized by pruritus due to itchiness felt by the patients. The condition can worsen by further development of headache, chills, fever and also chest pain. The effects happen due to a rapid infusion of vancomycin and it usually appears after the completion of the first infusion. The reaction results from the release of histamine when degranulation of mast cells and basophils occurs after the infusion and triggers the inflammatory response. [Sivagnana, et al., 2002]

Histamine released will trigger the blood vessels nearby to dilate and become more permeable to promote blood flow. The increase in the blood supply causes redness at certain part of the body. [Campbell, et al., 2008] Since vancomycin is time-dependent and not concentration-dependent, the red man syndrome can be avoided by prolonging the infusion period or increase the dose interval. Therefore, it is unnecessary to monitor the peak serum levels unless for patients having the treatment for more than five days. Patients who suffer from red man syndrome will have to stop the therapy and take another drug as alternative to vancomycin. Besides, pretreatment of antihistamines can also be carried out to increase patients' tolerance and reduce occurrence of red man syndrome. [Kondo, et al., 2002]

Linezolid which have great activity against many aerobic gram-positive bacteria including MRSA and VRE is considered to be a safe drug with few side effects for patients under this drug regimen. Side effect associated with patients undergoing Linezolid treatment is the disturbance of gastrointestinal tract (GIT) which can lead to nausea, vomiting and diarrhea. Diarrhea happen when the orally administrated drug is too concentrated in GIT and killed the normal flora living in the GIT. As a result of the disturbance, diarrhea will occur. The condition can become worse because the patients with diarrhea will be suffer from dehydration due to massive water loss and this further decreases the volume of distribution of the drug. High concentration of Linezolid can become toxic and will further induce the diarrhea. However, diarrhea is a common side effect for most of the drug and dose

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adjustment can help to overcome this problem. Only if the patients’ conditions become severe, the usage of the drug should be stopped and replace the treatment with another drug. The similar side effect also happens when a patient is undergoing Tigecycline treatment although Tigecycline can be considered as safe and effective drug for treatment of MRSA infection. [National Heart Lung and Blood Institute, 2011] The side effect can be inhibited by administration of Tigecycline with food or carboxymethylcellulose and the reduction of the dose of tigecycline. [Katzung, 2004] If the diarrhea condition becomes severe (watery and bloody diarrhea), the patient is advised to discontinue the Tigecycline’s therapy.

Other adverse effects cause by Linezolid are the reduction in number of platelets, red blood cells (RBCs) and white blood cells (WBCs) and these leads to the diseases known as thrombocytopenia, anemia and leucopenia respectively. These diseases can be diagnosed when the medical practitioners monitored the efficacy and safety of the drug. Complete blood count (CBC) is very important for the diagnose purpose. The normal number of platelets, RBCs and WBCs for normal person are between $1.5 \times 10^5 / \mu L$ to $4.0 \times 10^5 / \mu L$ where $4.8 \text{ million} / \mu L$ in females and $5.4 \text{ millions} / \mu L$ in males. A person with lower number of blood count than stated is most probably at risk of getting the side effect but the severity is different according to the condition of patient. [Tortora, 2009] A patient with prolonged time of Linezolid treatment (more than four weeks) has the highest risk of getting these adverse effects. [Beekmann, et al., 2008]

Discontinuation of linezolid is needed for patients who experienced thrombocytopenia, leucopenia and anemia. However, blood or platelets transfusion should be done if the condition becomes serious as this can threaten the patient’s life. [Utox Editor, 2002]

Side effect which is more significant with usage of Tetracycline is that it readily binds to calcium and can be deposited in newly formed bones and teeth of children. Besides, pregnant women should not take Tigecycline during the second and third trimester of the pregnancy because there is a high risk of the discoloration of teeth of the baby and also could lead to deformation or growth inhibition when tigecycline deposited at the bones. [Katzung, 2004] [Organization of Teratology Information Specialists, 2010] The discoloration of the teeth appeared to be permanent but once the patient stop taking the drug, the formation and development of the bones become normal.

Daptomycin is a lipopeptide anti-MRSA agent. Due to its bactericidal ability to inhibit the synthesis of DNA and RNA in bacteria, it becomes a favorable choice of antibiotics for treatment against Gram-positive aerobic and anaerobic organisms. Daptomycin usually prescribed as 4-6 mg/kg once daily due to its effective concentration-dependant and long-lasting post antibiotic effect. [Brauers et al., 2007]

Acute renal failure is referred to sudden decrease in the filtration ability of kidney. It can be detected when the concentration of serum creatine increases or when there is a rise in blood urea nitrogen level (azotemia). [Workeneh, 2011]

A study done in end of 2010 showed that for patients aged ≥ 66 years old, 2.2% of adverse effect reported was elevation in creatine phosphokinase (CPK) while 2.1% of them facing gastrointestinal disorders and only 0.8% with skin rashes. Patients, who develop the unexplained signs and symptoms of CPK elevation, should be monitored weekly. This is because an increase in creatine phosphokinase level might indicate the patient is suffering from acute renal dysfunction or nephrotoxicity. As daptomycin is mostly excreted through renal route (78%), patients with both renal impairment and CPK elevation should be monitored more than once a week. [D. D. DePestel et al., 2010] In addition, Vancomycin, Linezolid and Teicoplanin may also cause nephrotoxicity in patients suffering from renal impairment since they are excreted predominantly via renal route. Therefore, dosage for this kind of patients should be monitored regularly.

Although the chemical structure of Teicoplanin is similar to that of Vancomycin, it seldom causes red man syndrome. The most common reported side effects associated with usage of Teicoplanin is hypersensitivity (2.6%), abnormal liver function (1.7%), fever (0.8%), abnormal renal function (0.7%) and ototoxicity (0.3%). [Wilson, 1998]

In order to detect the adverse effects, analysis of blood culture should be carried out before and after administration of Teicoplanin. Besides, the creatine serum level should also be considered and audiometric testing can be performed so that patients suffering from ototoxicity can be detected easily. [Leport et al, 1989]

Rifampicin or Rifampin can cause some undesirable side effects. It may promote the increasing of hepatic cytochrome P450 in liver, and consequently will increase the metabolism of other drugs (liver enzyme-inducer). [R. A. Harvey, 2010] It can also lead to hepatotoxic reaction. The best way to detect occurrence of hepatotoxicity is by carrying out blood test. If there is an abnormal increase in liver enzymes that
circulate in bloodstream, especially the level of aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase and bilirubin, then, the possibility of patients suffering from hepatoxicity is very high. [AIDSMeds, 2011]

In addition, Tigecycline may also lead to occurrence of hepatoxicity as it is excreted through bile and hence, the dosage should be monitored when it is used to treat patients suffering from hepatic failure. Generally, in order to detect whether the side effects are caused by the drugs or other factors, rechallenge test can be carried out. Rechallenge test can be used to identified which drug are causing the side effects when the patients consume different types of drug at the same time. A patient suffering from particular side effect will stop consuming all the drugs for a period of time. After the side effect ceases, the drug suspected to be the one causing side effect will be re-administered by the clinician. If the side effects reoccur, then it is ascertain that the particular drug is the one causing the side effect. Besides, by carrying out blood test or urine test, side effects can also be identified.

Conclusion

There are 6 types of antibiotics available in Malaysia for treatment of Methicillin-resistant *Staphylococcus aureus* (MRSA) infections. Those are Vancomycin, Linezolid, Daptomycin, Rifampicin, Teicoplanin and Tigecycline. All the antibiotics are very effective in treating MRSA infections in Malaysia. However, the most commonly used antibiotics are Vancomycin and Linezolid. The antibiotics used will cause some side effects such as hypersensitivity, diarrhea and others. Thus, monitoring should be carried out in order to reduce the side effects caused by treatment using antibiotics and dose adjustment is used if the patients suffer from kidney, liver or other organs impairment.

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