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A COMPARATIVE ANALYSIS UPON PERFORMANCE OF METHICILLIN RESISTANT STAPHYLOCOCCUS AUREUS: A CASE STUDY OF ORTHOPAEDIC PATIENTS

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A Comparative Analysis upon Performance of Methicillin Resistant Staphylococcus Aureus: A Case Study of Orthopaedic Patients

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Abstract – Methicillin resistant Staphylococcus aureus (MRSA) is now a threat to both the hospitalized patients and community globally. This work was aimed at detecting molecularly, methicillin resistant Staphylococcus aureus from the orthopaedic patients. Conventional biochemical methods were used to identify the isolates while API STAPH identification test kit further characterized the isolates to species level. The susceptibility test was carried out using disc agar diffusion method while beta – lactamase production was tested for using nitrocefin. Methicillin resistance was detected phenotypically using cefoxitin 30 µg disc and oxacillin agar screen test. Multiplex polymerase chain reaction (PCR) was used to detect mecA gene, the gene coding methicillin resistance and blaZ gene, the gene coding for beta-lactamase production with 16SrRNA gene being the internal control.

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INTRODUCTION

Staphylococcus aureus is commonly carried on the skin or in the nose of healthy individuals. It is an important pathogen in human infections causing illness ranging from minor skin infections and abscesses to life - threatening diseases such as pneumonia, meningitis, endocarditis, toxic shock syndrome and septicaemia which may be rapidly fatal (Holmes et al., 2005). Bacterial resistance to antibiotics has been recognized since the first drugs were introduced for clinical use. Penicillin was first introduced in 1941, when less than 1% of Staphylococcus aureus strains were resistant to its action. By 1947, 38% of hospital strains had acquired resistance and currently over 90% of Staphylococcus aureus isolates are resistant to penicillin. Increasing resistance to antibiotics is a consequence of selective pressure (Power, 1998). Methicillin was the first penicillinase - resistant semisynthetic penicillin to be derived from the penicillin nucleus, 6- aminopenicillanic acid (6-APA) (Figure 1). Initially, it was used widely, but because of its toxicity it was gradually replaced with other penicillinase-resistant penicilins such as nafallin, oxacillin etc.

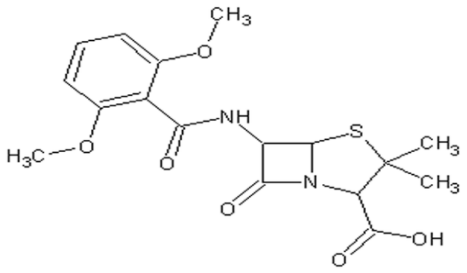

Figure 1: Structure of Methicillin

Ever since the beginning of the use of antibiotics, bacteria have become very adept at becoming resistant to different antibiotics. Methicillin- resistant S. aureus (MRSA) was first discovered in 1961; they are isolates of S. aureus which have acquired genes encoding antibiotic resistance to all penicillins including methicillin and other narrow spectrum β lactamase resistant penicillin antibiotics. Since then hospitals worldwide have reported varying proportion of MRSA among S. aureus isolates (Foster, 2006). Thus MRSA has become a real clinical and therapeutic problem.

MRSA infections can be classified into two major groups: Hospital-acquired MRSA (HA-MRSA) and Community-acquired MRSA (CA-MRSA). HA-MRSA is responsible for post-operative wound infections, or infections resulting from implanted devices such as catheters, that are acquired within the healthcare setting. Typically, patients infected with HA-MRSA

are immune-compromised and the resulting infections are generally more invasive. CA-MRSA typically manifests itself as skin infections, such as pimples or boils, and is classified as being acquired outside of any type of healthcare setting. These infections are typically more serious than minor skin irritation and affect otherwise healthy individuals (Raygada and Levine, 2009).

LITERATURE REVIEW

The Staphylococci –

Staphylococci are Gram-positive bacteria, with diameters of 0.5 – 1.5 µm and characterised by individual cocci, which divide in more than one plane to form grape-like clusters. To date, there are 32 species and eight sub-species in the genus Staphylococcus, many of which preferentially colonise the human body (Kloos and Bannerman, 1994), however Staphylococcus aureus and Staphylococcus epidermidis are the two most characterised and studied strains.

The staphylococci are non-motile, non-spore forming facultative anaerobes that grow by aerobic respiration or by fermentation. Most species have a relative complex nutritional requirement, however, in general they require an organic source of nitrogen, supplied by 5 to 12 essential amino acids, e.g. arginine, valine, and B vitamins, including thiamine and nicotinamide (Wilkinson, 2007). Members of this genus are catalase-positive and oxidase-negative, distinguishing them from the genus streptococci, which are catalase-negative, and have a different cell wall composition to staphylococci. Staphylococci are tolerant to high concentrations of salt (Wilkinson, 1997) and show resistance to heat. Pathogenic staphylococci are commonly identified by their ability to produce coagulase, and thus clot blood. This distinguishes the coagulase positive strains, S. aureus (a human pathogen), and S. intermedius and S. hyicus (two animal pathogens), from the other staphylococcal species such as S. epidermidis, that are coagulase-negative (CoNS).

Staphylococcus aureus –

Staphylococcus aureus is a major pathogen of increasing importance due to the rise in antibiotic resistance. It is distinct from the CoNS (e.g. S. epidermidis), and more virulent despite their phylogenic similarities (Waldvogel, 1990; Projan and Novick, 1997).

The species named aureus, refers to the fact that colonies (often) have a golden colour when grown on solid media, whilst CoNS form pale, translucent, white colonies. To date the S. aureus genome databases have been completed for 7 strains, 8325, COL, MRSA, MSSA, N315, Mu50, and MW2. The average size of the S. aureus genome is 2.8Mb (Kuroda et al., 2001).

S. aureus has three well characterised global regulators of virulence determinant production, agr, and sae that regulate the expression of surface proteins, exoproteins, and other proteins essential for growth. Studies have shown that the accessory gene regulator (agr) up-regulates the production of many exoproteins, including TSST-1, enterotoxin B and C, and V8 protease (sspA); and down-regulates the synthesis of cell wall associated proteins, including fibronectin-binding proteins, and fibrinogen-binding proteins during post-exponential and stationary growth phase (Foster et al., 1990; Lindberg et al., 1990).

Pathogenesis of MRSA –

S. aureus pathogenesis is reviewed before the discussion of the pathogenesis of MRSA, because MRSA virulence factors are generally not unique to MRSA. Nonetheless, certain MRSA strains appear to contain particular factors or genetic backgrounds that enhance their virulence or enable them to cause particular clinical syndromes.

Colonization and disease - S. aureus is both a commensal organism and a pathogen. The anterior nares are the main ecological niche for S. aureus. Approximately 20% of individuals are persistently nasally colonized with S. aureus, and 30% are intermittently colonized. However, numerous other sites may be colonized, including the axillae, groin, and gastrointestinal tract. Colonization provides a reservoir from which bacteria can be introduced when host defenses are breached, whether by shaving, aspiration, insertion of an indwelling catheter, or surgery. Colonization clearly increases the risk for subsequent infection. Those with S. aureus infections are generally infected with their colonizing strain. In a study of bacteremia, blood isolates were identical to nasal isolates in 82% of patients. Colonization also allows S. aureus to be transmitted among individuals in both health care and community settings. The basis for S. aureus colonization is complex and incompletely understood but appears to involve the host's contact with S. aureus (e.g., other carriers) and the ability of S. aureus to adhere to host cells and to evade the immune response.

Methicillin resistant S. aureus (MRSA) –

Staphylococcus aureus continues to be a dangerous pathogen for both community-acquired as well as hospital-associated infections. S. aureus resistant to methicillin were reported soon after its introduction in October 19601. Methicillin resistant S. aureus (MRSA) is now endemic in India. The incidence of MRSA varies from 25 per cent in western part of India2 to 50 per cent in South India3. Community acquired MRSA (CA-MRSA) has been increasingly reported from India4.

A network of microbiology laboratories (Indian Network for Surveillance of Antimicrobial Resistance - INSAR) at premier medical colleges and hospitals in

India was formed with support from the World Health Organization. The network aims to monitor antimicrobial resistance and to review the magnitude of its problem in India. Initially, a few organisms of public health importance have been chosen for monitoring their prevalence and antimicrobial resistance patterns, with S. aureus being chosen among the Gram-positive organisms. All participating laboratories shared their antimicrobial susceptibility data and provided technical support to other members. The present study provides a national level initiative to understand emerging trends of antimicrobial resistance among clinical isolates of S. aureus and provides a platform to initiate epidemiological studies for staphylococcal infections.

ORTHOPAEDICS -

The term orthopaedics is derived from two Greek words: ‗ortho' means ‗straight', ‗pais' means ‗children' together meaning ‗straight children'. As in all branches of medicine no condition can exist in true isolation thus there is a defined linking system between general diseases and orthopaedic problems as well as the specifically linked components (e.g. shoulder/arm/elbow etc) found in the limbs. An understanding of these inter-relationships is an essential diagnostic and therapeutic feature of orthopaedics.

MRSA INFECTION IN ORTHOPAEDIC SURGERY

Nearly half of the entire surgical site infectionsirrespective of the speciality- are caused by staphylococci, of which 81% are Staph. aureus, of these, 63% are resistant to methicillin. The incidence of methicillinresistant Staphylococcus aureus (MRSA) infection is increasing. The incidence of MRSA varies from region to region, and depends to great extent on the policy for infection control. The rate of methicillin resistance is higher in orthopaedic units compared to other medical specialities. MRSA produces biofilm and becomes more resistant to antibiotics. When caused by MRSA either because of resistance to antibiotic or biofilm formation, the treatment of orthopaedic infection becomes complicated and poses a higher economic burden.

Vancomycin has been the cornerstone of treatment of MRSA infection. It is considered that resistance to vancomycin is rare. Our aim in this retrospective study was to find out the prevalence of MRSA infection and the rate of vancomycin resistance in patients admitted to the orthopaedic wards.

Staphylococcus aureus (S aureus) is one of the most prevalent pathogen-causing skin and softtissue infections (SSTIs) that the orthopaedic surgeon encounters on a regular basis. These infections may require surgical incision and drainage (I&D) in the operating room, and patients are typically given antimicrobial agents as an adjuvant to the treatment. Beta-lactam antibiotics, including penicillins and cephalosporins, are the empiric medication recommended as the first line of treatment of S aureus. However, because of the rapid emergence of methicillin-resistant S aureus (MRSA) in the community setting, suspected staphylococcus infections

no longer can be treated exclusively with traditional □-lactam antibiotics.

The emergence of communityacquired MRSA (CA-MRSA) necessitates the need to rapidly identify the organism, determine its sensitivity, and develop new treatment protocols for suspected S aureus infections that orthopaedic surgeons can use to effectively treat this virulent pathogen.

In the orthopaedic setting, S aureus infection rates are low, yet methicillin resistance among infections is high.3,16 Fluit et al16 reported that approximately 3% of hospitalized patients with S aureus infections were orthopaedic patients; however, more than half of these orthopaedic patients had MRSA. Bach et al8 reported that cultures in 38 of 52 patients (73%) admitted to the hospital for hand infections were positive for CA-MRSA.

Screening and decolonization of MRSA among joint arthroplasty patients Staphylococcus aureus (S. aureus) is the most common organism responsible for orthopaedic surgical site infections (SSIs) after elective joint arthroplasty. Patients who are carriers for methicillin resistant S. aureus (MRSA) have a higher likelihood of having invasive MRSA infections.

Some reports have suggested that screening and decolonization of all patients having elective joint arthroplasty will decrease the incidence of postoperative infections. They believe that a prescreening program (nasal swab using polymerase chain reaction-based testing), followed by an appropriate eradication using a 5- to 14-d course of nasal mucopirocin (2% nasal ointment) will lower the rate of SSIs.

Although some have advocated screening and decolonization, it is unclear whether these efforts reduce SSIs. In other words, while some institutions and surgeons have implemented universal screening and decolonization on their patients undergoing elective arthroplasty, others remain unconvinced about the efficacy of this process.

The purpose of this paper is to revise the literature with the aim of answering the following three questions: 1) Is screening and decolonization of

MRSA effective in reducing the incidence of postoperative infection after elective joint arthroplasty? 2) Is decolonization cost-effective? 3) What is the durability of decolonization?

Regarding the efficacy of decolonization, a reduction of the incidence of postoperative SSI after elective joint arthroplasty has been found in the literature. The prevalence density rate (MRSA-positive cultures) of 1.23 per 1000 patient-days before decolonization dropped to 0.83 per 1000 patient-days after decolonization.

Preoperative MRS A screening and decolonization is strongly cost-effective (incremental cost-effectiveness ratio less than 86000 per quality-adjusted life year) from the third-party payer perspective even when MRSA prevalence was as low as 1%, decolonization success was as low as 25%, and decolonization costs were as high as $300 per patient.

A Markov decision analysis showed that universal S. aureus screening and decolonization for hip and knee arthroplasty patients' needs to result in only a modest reduction in the SSI rate to be cost saving.

Concerning the durability of decolonization, arthroplasty surgeons must be aware that a decolonization treatment does not guarantee that a patient will remain decolonized in the future. in a study, 33% of postoperative arthroplasty patients tested positive for MRS A colonization at 3 to 30 months after surgery despite preoperative decolonization.

In conclusion, the review of the literature found a tendency toward fewer MRSA SSIs after total joint arthroplasty when a screening and decolonization program was used. However, most of these studies were underpowered. Larger, randomized, controlled studies are needed to confirm the apparent efficacy of decolonization. Screening and decolonization is a cost-effective procedure. Regarding the durability of decolonization, one third of patients tested are positive for S. aureus at 3 to 30 months after surgery.

CONCLUSION

The presence of MRSA in orthopaedic patients' wound can cause delay in healing of the wound and patients' overstay in the hospital while the isolation of MRSA from the patients skin confirms that MRSA can colonize a healthy skin asymptomatically. The prevalence of MRSA isolates on patients' beds as discovered from this study is a great risk to both patients, patient relatives and hospital staff because they might become asymptomatic carriers of MRSA through contact with patients beds.

The phenotypic resistance to methicillin observed in this study may be due to plasmids carriage and/or the hyper-production of beta lactamase wherewith some S. aureus masquerade themselves as MRSA. In comparison with the use of cefoxitin and oxacillin discs, detection of mecA gene is still the gold standard for detection of methicillin resistance in S. aureus even though cefoxitin had higher specificity than oxacillin. Vancomycin was active against the two mecA gene mediated MRSA isolates, but since vancomycin is not readily available in this locality the use of gentamicin and ciprofloxacin can be explored in the treatment of MRSA infections since they are readily available.

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