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MRSA REMAINS A GREAT PRIORITY DUE TO THE TREMENDOUS MORTALITY --- A BIRD'S EYE VIEW

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ABSTRACT Methicillin-resistant Staphylococcus aureus (MRSA) is difficult to treat with methicillin, amoxicillin, penicillin, oxacillin, and other commonly used antibiotics because of its resistance. Staphylococcus organisms rapidly develop drug resistance as many as 50% of the domiciliary and 80% of the hospital strains are now penicillin resistant. Staphylococcus aureus also show multiple drug resistance. Therefore, Staphylococcal isolates should always be tested for antimicrobial sensitivity and chronic infection should be treated by more than one drug. Before 1960,when methicillin, is the first penicillin's-resistant penicillin's, was brought into use, about 1%of the strains of the Staphylococcus aureus were "methicillin resistant" and by 1970 in Britain their proportion has risen to about 5%.These strains are tolerant of, low therapeutic concentrations of methicillin, cloxacillin, benzyl penicillin and ampicillin.They do not destroy methicillin and cloxacillin, but most of them are penicillinase-producing as well as being "methicillin resistant" and therefore inactivate benzyl penicillin and ampicillin. Its resistance is uncertain since infections may be cured with a high dose of methicillin.

KEYWORDS : "pathobiont", Methicillin-resistant Staphylococcus aureus (MRSA), penicillin binding protein (PBP), Bacteraemia, TSS, Scaly skin syndrome, impetigo, cellulitis, folliculitis, and carbuncles

INTRODUCTION

Methicillin-resistant *Staphylococcus aureus* (MRSA) is Gram-positive bacteria that are genetically different from other strains of Staphylococcus *aureus*. *S. aureus* that has developed, through horizontal gene transfer and natural selection, multiple drug resistance to beta-lactam antibiotics. Beta-lactam (ß-lactam) antibiotics are a broad-spectrum group that include some penams (penicillin derivatives such as methicillin and oxacillin) and cephems such as the cephalosporins (1) S. aureus usually carried without symptoms. (2) MRSA is common in hospitals, prisons, people with open wounds, invasive devices such as catheters, and weakened immune systems are at greater risk of hospital-acquired infection. (3) Recent data shown a significant reduction in hospital-acquired methicillin-resistant *Staphylococcus aureus* (MRSA) bacteremia in the UK. (4) MRSA remains a high priority due to the high associated mortality. (5) Moreover, with specific strains of community-associated MRSA causing serious infections in previously healthy people without risk factors. (6) The prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA) in US continues to increase. (7) Throughout the 9-year study period 826 infectious complications were registered among 15,270 cardiac surgical patients (8) MRSA infections are less common than in the past, yet they still have a strong impact on the patients' outcome.(9)

Staphylococcus aureus is one of notorious microorganism that causes a wide variety of human diseases, from superficial skin infection to life threatening pneumonia, sepsis and endocarditis. Being a human commensal, it is difficult to eradicate and has a strong tendency to cause severe infection in both community as well as in hospitalized acquired patients. This increases morbidity as well as mortality and pose an enormous social and clinical burden on public health system in terms of treatment, hospital stay, equipment and isolation (10) Initially staphylococcus aureus responded well to the beta lactam group of antibiotics. Unfortunately, MRSA (methicillin resistance staphylococcus aureus) have been reported in a very short period of time. The global prevalence of hospital as well as community acquired MRSA infection continue to increase worldwide (11) Alteration in penicillin

binding protein (PBP) and production of autolytic enzymes are the two main mechanism of resistance seen in MRSA associated infections. Moreover, wide spread and irrational uses of antibiotics are its adding factors. (12) Hospitals are one of the major sources of MRSA stain dissemination that leads to MRSA outbreaks both epidemically and endemically. Prolonged hospital stay, wide spread use of antibiotics, nursing home exposure, immune suppression, improper antibiotic dosage, indwelling catheterization, invasive medical device, drug abusers, unsterilized instrumentations are another predisposing factors to MRSA spread. MRSA is important health issue in both developing & developed counties because it is contagious in nature and difficult to eradicate and treat (13) A study conducted by Khan et al showed 53.3% MRSA prevalence in two major hospitals of Rawalpindi- Islamabad (14) MRSA has a very high morbidity and mortality associated with it, most of it relating to emerging antibiotic resistivity (15) However, two studies which were conducted in Peshawar during 2012-2013 revealed very low MRSA prevalence (1-5.2%) (16) MRSA forms a major proportion of all hospital acquired infection (HAI) (17).

Chronological Record Of Significant Events

MRSA began to be described in the 1970s (18) It is found that MRSA bacteremia to have a higher mortality than methicillin-susceptible S. aureus (MSSA) bacteremia (19).

Background

Since most hospital patients with septic lesions were treated systematically with penicillin-sensitive *strains* would tend to be eliminated both from their lesions and carriage sites, and that the lesions and carriage sites would thus become susceptible to replacement infection with a penicillin resistant strain from a hospital source. The high carriage rate of resistant strains by healthy hospital staff must have had another explanation, because high rate was observed at a time when many of the carriers had no previous therapy with penicillin, Hospital staff are, however ,frequently exposed to air borne penicillin-containing dust produced from penicillin accidentally slit in wards sand pharmacies, and penicillin excreted by patients under therapy, and it has been demonstrated that staff may inhale sufficient amount of this dust in to their noses to eliminate penicillin sensitive Staphylococcus and allow their replacement by penicillin resistant ones. Before 1960,whenmethicillin,the first of the penicillinase-resistant penicillins,was brought into use, about 1%of the strains of Staphylococcus aureus were "methicillin-resistant" and by 1970 in Britain their proportion had to about 5%.These strains are tolerant of, low therapeutic concentrations of methicillin,cloxacillin, benzyl penicillin. They do not destroy methicillin and cloxacillin,but most of them are penicillinase producing as well as being "methicillin -resistant and therefore inactivate benzylpenicillin and ampicillin. (20)

Research On Genomics And Molecular Biology Of *S. Aureus*

Staphylococcus aureus has been extensively studied as a model pathogen. (21) Recent genomic studies revealed extensive variation in populations of pathogenic bacteria (22) Meticillin resistant *S. aureus* (MRSA), pose an especially serious health risk (23) *Staphylococcus aureus* causes a variety of diseases in humans.(24) High level of inter strain variation in genome content was found recently (25) Among the 18 large chromosomal regions identified, (RD13) is bigger.(26) RD13 corresponds to the exotoxin gene-containing regions of genomic islands SaPIn2 and SaPIm2.(27)

Research On Pathogenesis Of Staphylococci

Staphylococci particularly, *S. epidermis*, are present on skin, respiratory and gastrointestinal tracts. Nasal carriage of *S. aureus* occurs in 40-50 % of humans. Staphylococci found on clothing, bed linens and other fomites of human environment. *S. aureus* is most common in the vaginal region of a female child. It is the most likely the cause of bacterial pneumonia complicated by abscess formation. It causes gastritis, Enterocolitis, Respiratory infections like tonsillitis, pharyngitis, pneumonia, lung abscess, empyema.The CNS infections are meningitis, brainabscess. It causes bone and joint infections like. Osteomyelitis and septic arthritis. It also produces cardiac infections like acute endocarditis, pericarditis, and haematogenous infections, pyaemic abscesses. Skin infections like rashes, pustule,boil, pemphigusneonatorum, sepsis in wounds and burns. TSS, Scaly skin syndrome, impetigo, cellulitis, folliculitis, and carbuncles. These are the important cause of hospital acquired infections. Wound infections, catheter infections lead to endocarditis' *S.epidermidis* is-the most common flora of the skin. *S.epidermidis* causes catheter infections, prosthetic valve infection, and prosthetic joint infection. It is mostly hospital acquired infection. *S. saprophyticus* causes UTI in sexually active women. In newly married women it causes honeymoon cystitis Pathology of Staphylococcus research Groups of S.aureus established in a hair follicle lead to tissue necrosis. *S. aureus* may cause pneumonia, meningitis, empyma, endocarditis (28).

Hospital Acquired Mrsa (ha-mrsa)

Approximately a decade after HA-PRSA had been identified, Methicillin and Vancomycin became approved for treating Staphylococcus aureus infections. Within 2 years the first case of MRSA would be reported. HA-MRSA surged in the 1990s and peaked around 2005. CA-MRSA infections would first be described in the early 1990s, this spike would increase the use of Vancomycin that was typically used as the last line of defence. HA-VRSA would first be identified in 2002 and has remained recently steady at approximately 20% of resistant strains.(29,30) The stabilization and decrease in HA-MRSA and CA-MRSA resistance may be the result of higher national and international vigilance participation of hospitals as well as awareness of the medical community at large, use of other newer antibiotics .

Community Acquired Mrsa (ca-mrsa)

The 1990s a new aggressive form of MRSA appeared in the community, CA-MRSA. These clones had evolved to infect an atypical population of young and healthy individuals (31). As its previous ancestors it would rapidly develop resistance peaking in the mid-2000s and slowly decreasing since. The evolution of CA-MRSA has yielded populations of microorganisms that are capable of increased morbidity and mortality. The newest and most dangerous trend is CA-MRSA insurgence of more aggressive epidemic strains back into the hospital settings. (32) HA and CA-MRSA can now be found in each other's niche (33) Turner N (2019) emphasizes the great heterogeneity of MRSA infections across the world causes the emergence of pockets of infections with the predominant strains. This variability only complicates the scope of any future research, and newer epidemic strains should be expected. (34)

Development Of The Infection

S. aureus methicillin resistance happens because of a mutation of a penicillin-binding protein (PBP), a chromosome-encoded protein. This is transferred between the S. aureus organisms by a bacteriophage(35) Staphylococcus aureus had developed several mechanisms to resist and evade methicillin such as that the S. aureus expression of methicillin-hydrolyzing β lactamase or the expression of an altered form of PBP2 that binds to methicillin with lower affinity and the release of methicillin release at higher rates; in other words, lowers the affinity of the S. aureus to bind to the beta-lactam antibiotics. .The most prevalent mode of methicillin resistance is due to the presence of the mecA gene sequence, which generates a transpeptidase PBP2a.(36,37)

Risk Factors

In 1959, Beecham, a United Kingdom pharmaceutical company, introduced methicillin, but after a few years, less than a decade after, 20 patients in the area of Boston were identified with MRSA and with evidence of patient-to-patient spread. Since then, the incidence and prevalence of the disease has been increasing dramatically across the United States and world.(38,39,40)

Commonly Associated Risk Factors For Mrsa Infections

1. Recent or prolonged hospitalization
2. Intensive care unit admission
3. Recent use of antibiotics
4. MRSA colonization
5. Invasive procedures, hemodialysis, or open wounds
6. HIV infection
7. Admission to nursing homes
8. Discharged with long-term central venous access or a long-term indwelling urinary catheter
9. Health care worker, military personnel, homeless individuals
10. Older than 65 years of age
11. Living or admitted to an area or hospital with high prevalence of infection

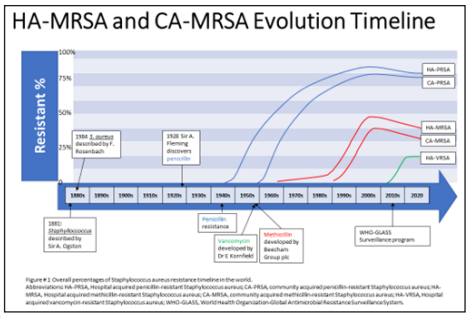
Clinical Presentation

The signs and symptoms of an infection with MRSA depend on the location of the body. The most common presentations being the skin and subcutaneous tissue, followed by invasive infections (osteomyelitis, meningitis, pneumonia, lung abscess, and emphyema). Infective endocarditis with MRSA an IV drug abuse history increases the morbidity and mortality.(41)

Spectrum of MRSA infection	
Common	Uncommon
1. Skin and soft tissue infections 2. Bone and joint infections 3. Central IV-line infections 4. Native-valve endocarditis or in prosthetic valve endocarditis 5. CNS shunt infection and meningitis or brain abscess	1. Skin and soft tissue abscesses 2. Intra-abdominal abscesses 3. Perinephric and intranephric abscesses 4. Pelvic abscesses 5. Lung abscess 6. Ventilator-associated pneumonia

MRSA infection	
Hospital acquired	Community acquired
1. Hospital-acquired pneumonia 2. Ventilator-associated pneumonia 3. Catheter related bacteremia or related to UTI 4. Bone and joints infections 5. Endocarditis	1. Necrotizing skin infection, pneumonia or fasciitis 2. Cellulitis or abscess 3. Bone and joint infections 4. Septic thrombosis

(42)



43 ,44)

Ibiotic Resistance Mechanisms

Bacteria prevent the entry of antibiotics in its cell. The bacteria produce pumps. These pumps sit on bacterial cell walls are called efflux pumps. These efflux pumps will allow only certain signal molecules and nutrients into the cell. The efflux pumps restrict the entry of antibiotics. The efflux lowers the antibiotic concentration in the cell. Under certain conditions, the bacterial DNA produces more efflux pumps. As a result of it, resistance is increased. Similarly, the bacterial cell membrane produces certain changes to restrict permeability of antibiotics into the bacteria. In one sense the entry of antibiotics is under the control of bacterial cell membranes. However certain amount of antibiotics will enter into bacteria. The bacteria secrets certain enzymes. These enzymes inactivate the antibiotics. For instance Beta Lactamase that destroys the Beta Lactam ring of penicillins. Bacteria that produce extended-spectrum ß-lactamases, so called ESBL-producing bacteria, can degrade a wide spectrum of ß-lactam antibiotics. Some bacteria are capable of producing alternative proteins instead of the ones that are inhibited by the antibiotic. The new penicillin-binding protein has low affinity to ß-lactam antibiotics and is thus resistant to the drugs, and the bacteria survive treatment. This type of resistance is the basis in MRSA (methicillin-resistant *Staphylococcus aureus*). Diagnosis Staphylococcus aureus are gram positive, non-sporing, non -motile aerobic and normally facultatively anaerobic cocci. Cluster formation occurs.On nutrient agar most stains produce deep golden yellow pigment,some may produce creamy orange or yellow pigment.On blood agar colonies are almost similar to those on nutrient agarThey produce a beta type hemolysis ,which is best seen with rabbit or sheep blood.Uniform turbidity is produced in nutrient broth.Staphylococci can tolerate 5-10 % sodium chloride, lithium chloride,tellurite and polymyxin Salt containing agar and broth are used for isolating S.aureus from samples,such as feces containing large number of bacteria.OnMacConkey agar,the colonies are very small and pink due to lactose fermentation.Catalase and coagulase are positive in S.aureus. S.epidermis is gram positive,catalase positive and coagulase negative. It is sensitive to novobiocin test. *S. saprophyticus* is gram positive, coagulase negative, catalase positive and gamma hemolytic.

Laboratory Diagnosis

Specimens are collected from pus, CSF, blood, vomit or faeces. Examination of Gram stain. Specimens show Gram positive cocci. Specimens inoculate on blood agar or Manitol agar (Selective medium for Stahylococcus) Coagulase positive strain is identified. Phase typing and antibiotic susceptibility pattern are tested for tracing sources of *Staphylococcus aureus* infections.

Recent Advances In Diagnostic Technology

Community acquired –Methicillin resistant *Staphylococcus aureus(*CA-MRSA) different from Health care associated Methicillin Resistant *Staphylococcus aureus*. Automated Culturing walk away specimen processor unit(WASP) which can inoculate a plate using or 1 of 3 metal loops (1 μL, 10 μL, and 30 μL) and the BD Kiestra TLA system which uses magnetic beads to inoculate and streak liquid specimens Elisa Direct, competitive and sandwich are the main assays formats used to detect whole cell MRSA and secreted enterotoxins. Usually MRSA can be detected in 20 – 26 hours using chromogenic agars, at which point results can be reported and plates discarded. Mass spectrometry with advancement, soft ionization technique such as matrix assisted laser desorption ionization (MALDI-TOF.Whole cells, proteins as well as DNA possible Nucleic Acid Amplification Technologies(NAAT): PCR FOR mecA/C gene detection: RT-PCR assays with subsequent confirmation using a staphylococcal cassette chromosome mec element (SCCmec)-orfX-based real time PCR assay (GeneOhm MRSA

assay). The selectivity, sensitivity and accuracy of M-PCR improves depending on the number of targets that are screened this has resulted in numerous groups employing triple, quadruplex q (PCR) and more recently heptaplex PCR Optical sensing many types of label free refractive index sensors detect MRSA. Bandara et al. recently showed that an optical fiber long period grating conjugated with PBP2a monoclonal antibodies can detect 36 strains of MRSA. A variety of optical techniques such as Raman, infrared, fluorescence, absorption, reflection, biochemical luminescence, refractive index (RI) and surface enhanced Raman spectroscopy (SERS) have been employed in the detection of MRSA. Electrochemical Sensing addition Wang et al. detected the mec A gene via a novel electrochemical DNA (e-DNA) based on displacement polymerization reaction (ISDPR). A micro-electrochemical sensor (mECS) to detect specific mecA gene sequences Integrated Sensing Platforms multiplex able autonomous disposable nucleic acid amplification tests (MAD NAAT) on 2D paper networks Rapid MRSA detection Several FDA approved real-time multiplex PCR kits are now commercially available. BD Gene Ohm MRSA ACT is similar in principle to the original assay, but includes ACT (achromopeptidase) lysis and a more simplified procedure.

Current Treatment

Choice Of Antibiotic For Therapy

Since different strains of Staphylococcu aureus differ in sensitivity to different vantibiotics, the choice of antibiotic for use in treatment of a patient should be based on the result of sensitivity tests made on a culture of strain. Pending the receipt of the results the treatment of severe infections suspected of staphylococcal, should begin with cloxacillin or a cephalosporin or with combination of cloxacillin and benzylepencillin. If the patient is hypersensitive to pencillin, another drug should be used eg. gentamycin, vancomycin, fucidin in combination with erythromycin. Serious multiple skin infections like acene, furunculosis, the staphylococci liberates fatty acids from lipids, and thus cause tissue irritation.Tetracyclines are used for long term treatment. Abscesses are treated by drainage and antimicrobial therapy. However it is difficult to eradicate Staphylococci from infected persons. Hyperbarrieic oxygen and application of vascularized mucocutaneous flaps have aided healing osteomyelitis. If *Staph. pyogene* is isolated , treatment must be modified in accordance with the result of sensitivity tests. Resistance to pencillin may be due to production of pencillinase,and such infections can usually be controlled by combination of benzylepencillin (600 mg) and floxacillin (250-500 mg 6 hourly). Flucloxacillin (250-500) by mouth) or gentamycin (80mg) or cefuroxime (750mg)-8 hourly by intra muscular or intravenous injuction, may be indicated.

Prevention Of MRSA

There are a number of prevention strategies to prevent the infection and transmission of MRSA and they depend if the infection was acquired in the hospital or community, but they both have one thing in common which is hand washing and alcohol-base hand sanitizer. The prevention and control of MRSA infections include a strict hand-washing policies and adequate contact precaution.

1. Hand washing policy with soap and water
2. Use alcohol-base hand sanitizer when water and soap is not available.
3. Contact precautions: gowns, gloves, face masks.

Other Recommendations:

1. Keep the wounds clean and cover.
2. Avoid touching the wounds or bandages.
3. Avoid sharing personal items.
4. Isolate the patient from other individuals.(45)

Research Programs To The Next Generation World

The CDC are supporting five investigations to better under a stand how to detect, prevent, and respond to MRSA and to protect people from MRSA infections. At Rush University Medical School, a one-year study where researchers will use the whole genome sequencing (WGS) to understand the spread of MRSA between healthcare workers and community setting in Cook County Health and Hospital System in Chigaco, IL in the year 2018.The University of California Irvine: 2018 study that evaluates what percentage of MRSA carriers being discharged from the hospital have a community-associated strain. REDUCE MRSA: The decolonization with chlorohexidine, and mupirocin, which can be used to reduce the amount of MRSA on patients carrying it, in intensive care units (ICUs) in 43 U.S. hospitals. (46).

Control Of MRSA

Prevention is very difficult. Patients with discharging lesions should be neutralized as sources of infection by the use of antibiotic therapy. Surgeons, nurses, anaesthetists who have an open infected lesion on any part of the body, even if the lesion is small, eg. paranychia, a discharging pustule, or a patch of secondarily infected psoriasis, or who have a lesion of hand or arm, even if it is not discharging, should not attend patients, until healing is complete. Carriers among patients and staff may be detected by nasal and perineal swabbing and treated with twice daily application of neomycin-chlorohexidine cream to the carrier site. Judicious use of antibiotics. In hospitals, the areas at highest risk for severe Staphylococcal infections are the new born nursery, intensive care units, operatingrooms, and cancer chemotherapy wards. Massive introduction of pathogenic Staphylococcus.

CONCLUSION

It causes the skin, like rashes, pustules, and boil. TSS, Scaly skin syndrome, impetigo, cellulitis, folliculitis, and carbuncles. Most of the MRSA infections aren't serious, but some are life-threatening. Because it's hard to treat, MRSA is called a "superbug." A person colonized with MRSA may be transmissible for an indeterminate period of time. In accession, MRSA organisms can remain viable for about two to six months. MRSA is improvable and curable. If infection is severe or in the blood stream, patients need intravenous antibiotics. Staph skin infections, including MRSA, generally start as bloated, painful red bumps that look like spider bites. The affected area warms to the touch. Full of pus or other drainage. Staphylococcus aureus (also known as MRSA) will be destroyed. Lysol kills 99.9% of viruses & bacteria, including MRSA. Good hygiene prevents MRSA infection.

REFERENCES

1. Gurusamy, KurinchiSelvan; Koti, Rahul; Toon, Clare D.; Wilson, Peter; Davidson, Brian R. (2013-08-20). "Antibiotic therapy for the treatment of methicillin-resistant Staphylococcus aureus (MRSA) infections in surgical wounds". The Cochrane Database of Systematic Reviews (8): CD0097
2. Schenck, LP; Surette, MG; Bowdish, DM (November 2016). "Composition and immunological significance of the upper respiratory tract microbiota". FEBS Letters. 590(21): 3705–3720
3. Wollina, U (2017). "Microbiome in atopic dermatitis". Clinical, Cosmetic and Investigational Dermatology. 10: 51–56.
4. UK Health Protection Agency. Health protection report: Quarterly MRSA bacteraemia data (September to December, 2008) derived from mandatory surveillance, March 2009. Available at: http://www.hpa.org.uk/hpr/archives/2009/news1109.htm#mrsa (accessed July 17, 2009).
5. T.P. Lodise, J. Graves, A. Evans, E. Graffunder, M. Helmecke, B.M. Lomaestro, et al. Relationship between vancomycin MIC and failure among patients with methicillin-resistant Staphylococcus aureus bacteremia treated with vancomycin,Antimicrob Agents Chemother, 52 (2008), pp. 3315-3320
6. T.S. Naimi, K.H. LeDell, K. Como Sabetti, S.M. Borchardt, D.J. Boxrud, J. Etienne, et al. Comparison of community- and health care-associated methicillin-resistant Staphylococcus aureus infection JAMA, 290 (2003), pp. 2976-2984
7. MARA LAMBERT,IDSA Guidelines on the Treatment of MRSA Infections in Adults and Children, American Family physician,2011
8. AikateriniMastoraki, IoannisKriaras, EvangeliaDouka, SotiriaMastoraki, Georgios Stravopodis, StefanosGeroulanos Methicillin-resistant Staphylococcus Aureus Preventing Strategy in Cardiac Surgery, Interact CardiovascThoracSurg 2008 May;7(3):452-6.
9. MARINA PIERI, GIOVANNI LANDONI, MASSIMO ZAMBON, DAIANA TADDEO, ROBERTO ASCARI, MARCO COSTANTINI, FABRIZIO MONACO, ANNA MARA SCANDROGLIO, FEDERICO PAPPALARDO, TIZIANA BOVE,

MARIA GRAZIA CALABRÒ, GIOVANNI MARINO, ALBERTO ZANGRILLO SIGNA VITAE Methicillin-Resistant Staphylococcus Species in a cardiac surgical intensive care unit2015; 10(2): 65-88
10. Tong SY, Davis JS, Eichenberger E, Holland TL, Fowler VG. Staphylococcus aureus infections: Epidemiology, pathophysiology, clinical manifestations, and management. ClinMicrobiol Rev. 2015; 28(3):603-61.
11. Bertrand X. Methicillin-resistant Staphylococcus aureus: An ever emerging threat. Therapy. 2010; 7(2):169-78.
12. Ippolito G, Leone S, Lauria FN, Nicastri E, Wenzel RP. Methicillin-resistant Staphylococcus aureus: the superbug. Int J Infect Dis. 2010; 14:S7-11.
13. McKinnell JA, Miller LG, Eells SJ, Cui E, Huang SS. A systematic literature review and meta-analysis of factors associated with methicillin-resistant Staphylococcus aureus colonization at time of hospital or intensive care unit admission. Infect Control HospEpidemiol. 2013; 34(10):1077-86
14. Khan S, Rasheed F, Zahra R. Genetic polymorphism of agr Locus and antibiotic resistance of Staphylococcus aureus at two hospitals in Pakistan. Pak J Med Sci. 2014; 30(1):172.
15. Ur Rahman K, Ahmad A, Aziz A, Daud M, Khan I. Antibiotic susceptibility patterns of methicillin resistant staphylococcus aureus at national institute of health sciences, Islamabad, Pakistan. World J Zool. 2015; 10(4):318-22.
16. Rafiq MS, Rafiq MI, Khan T, Rafiq M, Khan MM. Effectiveness of simple control measures on methicillin resistant staphylococcus aureus infection status and characteristics with susceptibility patterns in a teaching hospital in Peshawar. J Pak Med Assoc. 2015; 65(9):915-20
17. Amorim ML, Vasconcelos C, Oliveira DC, Azevedo A, Calado E, et al. (2009) Epidemiology of methicillin-resistant Staphylococcus aureus (MRSA) nasal colonization among patients and healthcare workers in a Portuguese hospital: a pre-intervention study toward the control of MRSA. Microb Drug Resist 15(1): 19-26.
18. Gurusamy, KurinchiSelvan; Koti, Rahul; Toon, Clare D.; Wilson, Peter; Davidson, Brian R. (2013-08-20). "Antibiotic therapy for the treatment of methicillin-resistant Staphylococcus aureus (MRSA) infections in surgical wounds". The Cochrane Database of Systematic Reviews (8): CD009726.
19. Blot SI, Vandewoude KH, Hoste EA, Colardyn FA (2002). "Outcome and attributable mortality in critically Ill patients with bacteremia involving methicillin-susceptible and methicillin-resistant Staphylococcus aureus". Arch Intern Med. 162 (19): 2229–35.
20. J P .Duguid,BP,Marmion,RHA.Swain,Mackie and McCartney Medical Microbiologyu,Vol-1Microbial infections,13 thedition,ELBS
21. Marcel Prax, Chia Y. Lee,Ralph, An update on the molecular genetics toolbox for staphylococci Microbiology. 2013 Mar; 159(Pt 3): 421–435.
22. J. Ross Fitzgerald, Sean D. Reid Eeva Ruotsalainen, Timothy J. Tripp, MengYao Liu, Robert Cole, Pentti Kuusela, Patrick M. Schlievert, Asko Järvinen, and James M. Musser, Genome Diversification in Staphylococcus aureus: Molecular Evolution of a Highly Variable Chromosomal Region Encoding the Staphylococcal Exotoxin-Like Family of Proteins, Infect Immun. 2003 May; 71(5): 2827–2838.
23. Levy S. B., Marshall B. (2004). Antibacterial resistance worldwide: causes, challenges and responses. Nat Med 10 (Suppl.), S122–S129 10.1038/nm1145
24. Dinges, M. M., P. M. Orwin, and P. M. Schlievert. 2000. Exotoxins of *Staphylococcus aureus*. Clin. Microbiol. Rev. 13:16-34.
25. Baba, T., F. Takeuchi, M. Kuroda, H. Yuzawa, K. Aoki, A. Oguchi, Y. Nagai, N. Iwama, K. Asano, T. Naimi, H. Kuroda, L. Cui, K. Yamamoto, and K. Hiramatsu. 2002. Genome and virulence determinants of high virulence community-acquired MRSA. Lancet 359:1819-1827
26. Fitzgerald, J. R., D. E. Sturdevant, S. M. Mackie, S. R. Gill, and J. M. Musser. 2001. Evolutionary genomics of *Staphylococcus aureus*: insights into the origin of methicillin-resistant strains and the toxic shock syndrome epidemic. Proc. Natl. Acad. Sci. USA 98:8821-8826
27. Whole genome sequencing of meticillin-resistant Staphylococcus aureus. *Kuroda M, Ohta T, Uchiyama I, Baba T, Yuzawa H, Kobayashi I, Cui L, Oguchi A, Aoki K, Nagai Y, Lian J, Ito T, Kanamori M, Matsumaru H, Maruyama A, Murakami H, Hosoyama A, Mizutani-Ui Y, Takahashi NK, Sawano T, Inoue R, Kaito C, Sekimizu K, Hirakawa H, Kuhara S, Goto S, Yabuzaki J, Kanehisa M, Yamashita A, Oshima K, Furuya K, Yoshino C, Shiba T, Hattori M, Ogasawara N, Hayashi H, Hiramatsu K Lancet. 2001 Apr 21; 357(9264):1225-40.*
28. E. Jawetz,JL.Melnick,EA.Adelberg,Alange medical book.Review of Medical microbiology,seventeenth edition
29. Antimicrobial Susceptibilities Among *Staphylococcus aureus* From the SENTRY Antimicrobial Surveillance Program [published correction appears in Open Forum Infect Dis. 2019 May 20;6(5):ofz202. Zervos, Marcos [corrected to Zervos, Marcus]]. *Open Forum Infect Dis*. 2019;6(Suppl 1):S47-S53. Published 2019 Mar 15. doi:10.1093/ofid/ofy270
30. Rodvold KA, McConeghy KW. Methicillin-resistant Staphylococcus aureus therapy: past, present, and future. *Clin Infect Dis*. 2014;58 Suppl1:S20-S27. doi:10.1093/cid/cit614
31. Diekema DJ, Pfaller MA, Shortridge D, Zervos M, Jones RN. Twenty-Year Trends in Lakhundi S, Zhang K. Methicillin-Resistant Staphylococcus aureus: Molecular Characterization, Evolution, and Epidemiology. *ClinMicrobiol Rev*. 2018;31(4): e00020-18. Published 2018 Sep 12. doi:10.1128/CMR.00020-18
32. Kale P, Dhawan B. The changing face of community-acquired methicillin-resistant *Staphylococcus aureus. Ind J of Med Micr., Vol 34, issue 3, 275-285 (2016)*
33. Turner, N.A., Sharma-Kuinkel, B.K., Maskarinec, S.A. *et al.* Methicillin-resistant *Staphylococcus aureus*: an overview of basic and clinical research. *Nat Rev Microbiol*17, 203–218 (2019). https://doi.org/10.1038/s41579-018-0147-4
34. Lakhundi S, Zhang K. Methicillin-Resistant Staphylococcus aureus: Molecular Characterization, Evolution, and Epidemiology. Clin. Microbiol. Rev. 2018 Oct;31(4)
35. Stapleton PD, Taylor PW. Methicillin resistance in Staphylococcus aureus: mechanisms and modulation. *SciProg*. 2002;85(Pt 1):57-72. doi:10.3184/003685002783238870
36. Shahkarami F, Rashki A, RashkiGhalehnoo Z. Microbial Susceptibility and Plasmid Profiles of Methicillin-Resistant Staphylococcus aureus and Methicillin-Susceptible S. aureus. Jundishapur J Microbiol. 2014 Jul;7(7):e16984.
37. Landau R, Pharmaceutical innovation : revolutionizing human health. Philadelphia: Chemical Heritage Press; 1999.
38. BARBER M. Methicillin-resistant staphylococci. *J ClinPathol*. 1961;14(4):385-393. doi:10.1136/jcp.14.4.385
39. Methicillin-resistant Staphylococcus aureus at Boston City Hospital. Bacteriologic and epidemiologic observations.Barrett FF, McGehee RF Jr, Finland M N Engl J Med. 1968 Aug 29; 279(9):441-8.
40. https://www.cdc.gov/mrsa/community/index.html
41. Siddiqui AH, Koirala J. Methicillin Resistant Staphylococcus Aureus (MRSA) [Updated 2020 Jun 29]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK482221/
42. Klevens RM, Morrison MA, Nadle J, et al. Invasive methicillin-resistant Staphylococcus aureus infections in the United States. *JAMA*. 2007;298(15):1763-1771. doi:10.1001/jama.298.15.1763
43. Diekema DJ, Pfaller MA, Shortridge D, Zervos M, Jones RN. Twenty-Year Trends in Antimicrobial Susceptibilities Among *Staphylococcus aureus* From the SENTRY Antimicrobial Surveillance Program [published correction appears in Open Forum Infect Dis. 2019 May 20;6(5):ofz202. Zervos, Marcos [corrected to Zervos, Marcus]]. *Open Forum Infect Dis*. 2019;6(Suppl 1):S47-S53. Published 2019 Mar 15. doi:10.1093/ofid/ofy270
44. McGuiness WA, Malachawa N, De Leo F R. Vancomycin Resistance in Staphylococcus aureus. Yale J Bid Med. 2017; 90(2): 269-281. Published 2017 Jun 23
45. https://www.cdc.gov/mrsa/healthcare/inpatient.html
46. https://www.cdc.gov/mrsa/tracking/index.html