MRSA 2008
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Objectives

1. Discuss impact of MRSA colonization and infection in the US.
2. Describe keys to understanding MRSA epidemiology.
3. Discuss clinical presentation of MRSA.
4. Discuss detection methods for MRSA and its impact.
Crude death rate* for infectious diseases — United States, 1900–1996†

*Per 100,000 population per year.
Living species total 1413000

- Insect 7510000
- Protozoa 30800
- Higher plants 248400
- Algae 26900
- Fungi 69000
- Monera (Bacteria etc) 4800
- Viruses 1000
- Other animals 281000
Staphylococcus aureus

- Staphylococcus - bunch of grapes
- aureus - gold
- all intermittently colonized - skin, nares, vagina, rectum, clothing
Gram stain
Hans Christian Gram
Staphylococcus aureus
Penicillin
THIS STORE CAN NOW SERVICE THE PUBLIC THROUGH THE MEDICAL PROFESSION WITH PENICILLIN.

WE HAVE PENICILLIN IN STOCK.
PCN WW-II
# Classification of *Staphylococcus aureus*

<table>
<thead>
<tr>
<th>Type of <em>S. aureus</em></th>
<th><em>mecA</em> Gene</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methicillin-susceptible (MSSA)</td>
<td>–</td>
<td>Susceptible to methicillin, oxacillin, nafcillin, cephalosporins, and other β-lactams</td>
</tr>
<tr>
<td>Borderline-resistant (BRSA)</td>
<td>–</td>
<td>Borderline oxacillin MICs (1 to 2 µg/mL) due to hyperproduction of β-lactamase or abnormal PBPs</td>
</tr>
<tr>
<td>Methicillin-resistant (MRSA)</td>
<td>+</td>
<td>Methicillin MICs usually $\geq$ 16 µg/mL due to low-affinity PBP (PBP-2')</td>
</tr>
<tr>
<td>Glycopeptide-intermediate (GISA)</td>
<td>+(^a)</td>
<td>Vancomycin MIC 8 µg/mL (most <em>S. aureus</em> have MIC $\leq$ 2 µg/mL); also resistant to teicoplanin</td>
</tr>
</tbody>
</table>

\(^a\) All GISA described to date have been MRSA
S Aureus

- 1928 all PCN sensitive
- 1942 first PCN resistant
- 1960’s MRSA
- 1990’s VISA and VRSA
Penicillinase producing S aureus
Staph aureus
MSSA and MRSA
PCN resistance

- Penicillinase 90% of current isolates
- Gene for beta-lactamase part of transposable gene located on a large plasmid
- blaZ gene
Penicillinase production

- Beta-lactams
- Resistance gene is blaZ
- Gene product is beta-lactamase
- Mechanism is enzymatic hydrolysis
- Location plasmid: transposon now 80-90 of all strains carry
MRSA

• mecA gene is part of a mobile gene found in all MRSA strains
• mecA is part a genomic island called staphylococcal cassette chromosome mec
• only a limited number of clones involved in spread of disease
• is clear evidence for evolution of species
Beta-lactamase induction and Methicillin resistance
MRSA

- Beta-lactam antibiotics
- resistance gene is mecA
- gene product is PBP2a
- Mechanism is reduced affinity for PBP
- Location is chromosome via a cassette insertion mechanism from Staph epi strains
- evolution in few strains and now community
MRSA Background

- The spread of oxacillin (methicillin)-resistant *Staphylococcus aureus* (MRSA) is a major concern in healthcare settings, where human “carriers” can spread MRSA and can fall victim to infections.

- Carriers are colonized in the human nares, skin, vaginal mucosa, and rectum.

- Aggressive infections have caused deaths in both hospitalized patients and otherwise healthy individuals.¹
MRSA Impact

• Since 2003, MRSA has accounted for more than 60% of all *S. aureus* healthcare-associated infections (HAIs) reported in US hospitals.²

• The National Healthcare Safety Network (NHSN), part of the Centers for Disease Control (CDC), estimates that:
  – Hospitalized patients in the United States acquire 2 million HAIs (largely MRSA) each year, with:
    • 90,000 associated deaths; and
    • $4.5 billion in excess healthcare costs.³
MRSA Guidance: Timeline

- 2003: National guidelines from the Society for Healthcare Epidemiology of America (SHEA) recommended “active surveillance”.4

- 2005 / 2006: CDC’s Healthcare Infection Control Practices Advisory Committee (HICPAC) issued recommendations for reporting and managing multidrug-resistant organisms in healthcare settings 5,6, with detailed approaches for reducing MRSA infections in healthcare facilities.7

- January 2007: A memo from the Department of Veteran’s Affairs requested compliance for MRSA prevention in all facilities.

- February 2008: per the Association for Professionals in Infection Control (APIC), 25 states require MRSA reporting to their State Dept. of Health.
The MRSA Infection Prevention and Patient Protection Act proposes a requirement for national reporting of infection rates.

The Protecting Workers from Infectious Agents Act proposes creation of a new OSHA standard to protect workers at risk of exposure to infectious agents and drug-resistant infections, such as MRSA.
Accredited healthcare institutions may find it prudent to take action to prevent MRSA by instituting infection prevention programs, such as
- hand hygiene campaigns
- universal gloving practices
- active surveillance programs using a variety of laboratory methods. \(^8\text{-13}\)

Laboratory assessment and understanding of MRSA detection methods are essential.
MRSA Active Surveillance Programs

- Assign “MRSA carrier status”, based on laboratory results; then institute isolation precaution practices.

- Delays in identifying status may hinder the operational effectiveness and cost-benefit of active surveillance programs; so most programs use a rapid laboratory detection method.

- Methods include:
  - Selective differential agar (based on chromogenic detection of expression of genomic-based antimicrobial resistance)
  - MRSA Polymerase Chain Reaction (PCR)
MRSA

• Methicillin resistance in S. aureus is defined as an oxacillin minimum inhibitory concentration (MIC) $\geq 4$ mcg/mL. Isolates resistant to oxacillin or methicillin also are resistant to all beta-lactam agents, including cephalosporins.
MRSA
Community versus Hospital

— MRSA has traditionally been classified into healthcare-associated (HA-MRSA) and community-associated (CA-MRSA) methicillin-resistant Staphylococcus aureus. However, the HA-MRSA and CA-MRSA classifications are no longer distinct. HA-MRSA can spread to community contacts, and CA-MRSA is becoming a significant cause of healthcare-associated infection. Thus, some authorities, including the U.S. Centers for Disease Control and Prevention Active Bacterial Core (CDC ABC) Surveillance System subdivide HA-MRSA according to the setting of onset (hospital or community).
HA-MRSA infections —

• Healthcare-associated MRSA is usually defined by MRSA infection in a patient with one of the following risk factors
  – Presence of an invasive device at the time of admission
  – History of MRSA infection or colonization
  – History of surgery, hospitalization, dialysis, or residence in a long-term care facility in the 12 months preceding culture
Nosocomial MRSA

- **Hospital-onset** — The CDC ABC Surveillance System defines invasive hospital-onset (nosocomial) HA-MRSA as cases with positive culture result from normally sterile site obtained >48 hours after hospital admission. These cases might have one or more of the risk factors for HA-MRSA, described above.
CA-MRSA infections

- Community-associated MRSA (CA-MRSA) usually is defined as an MRSA infection with onset in the community in a patient who is without risk factors for HA-MRSA, although the defining risk factors have varied from study to study.
Nosocomial infection

• The prevalence of HA-MRSA among hospitalized patients varies geographically. It is generally high in the United States, Japan, and southern Europe (eg, >30 percent in Spain, France, and Italy) but is very low (<1 percent) in Scandinavia and Switzerland.
Staphylococcus aureus

1. Entry
   (nasal or mucosal, wounds, I.V. drug abuse)

2. Spread

3. Diseases
   - Stye
   - Boil, carbuncle
   - Impetigo
   - Endocarditis
   - Pneumonia
   - Emesis
   - Diarrhea
   - Toxic shock and bladder infections
   - Rash (scalded skin syndrome)
   - Osteomyelitis

4. Exit

Genito-urinary
CA-MRSA

- The following manifestations of CA-MRSA have been observed:
  - Skin and soft tissue infection, including necrotizing fasciitis
  - Wound infections
  - Otitis media and otitis externa
  - Osteomyelitis
  - Urinary tract infection
  - Endocarditis
  - Sepsis (with or without Waterhouse-Friderichsen syndrome)
  - Necrotizing pneumonia
Soft Skin Tissue Infections

• Community outbreaks of SSTI have been reported in multiple settings, including native and aboriginal communities, sports teams, child care centers, military personnel, men who have sex with men, and prison inmates and guards.
Impetigo
Folliculitis
Staphylococcal scalded skin syndrome
Boils
Abscess
Reservoirs of MRSA

- Three major reservoirs of MRSA are:
  - patients,
  - healthcare workers, and
  - the inanimate environment.
- Patients are the greatest source of transmission in the healthcare setting.
Colonization

• Colonization can occur in the following ways:
  • Contact with contaminated wounds or dressings of infected patients
  • Contact with another individual's colonized intact skin
  • Contact with contaminated inanimate objects
  • Inhalation of aerosolized droplets from chronic nasal carriers
MRSA colonization

• The anterior nares is the most common site of MRSA colonization.

• The durability of MRSA colonization can vary from a few days or weeks to up to several years.

• In one report of patients requiring readmission to a hospital, the median length of colonization was 40 months.
The prevalence of nasal colonization with MRSA

- The prevalence of nasal colonization with MRSA varies depending upon the population, with rates of approximately 10 percent among healthy children in the United States attending health maintenance visits in 2004.
- <1 percent among hospitalized children in Switzerland and healthy schoolchildren in Germany.
Natural history of MRSA and MSSA colonization

• The natural history of MRSA and MSSA colonization was evaluated in a 10-week prospective observational study of 812 soldiers.
• Baseline colonization rates with MRSA was lower than MSSA (3 versus 28 percent), but subsequent development of infection was higher among those with MRSA than MSSA colonization (38 versus 3 percent).
• The rate of CA-MRSA colonization fell to under 2 percent at 10-week follow-up.
MRSA

- Methicillin-resistant Staphylococcus aureus (MRSA) has traditionally been classified into healthcare-associated (HA-MRSA) and community-associated (CA-MRSA). However, these classifications are becoming less distinct.
HA-MRSA

- HA-MRSA strains tend to have multidrug resistance and carry staphylococcal cassette chromosome type II (SCCmec type II) or SCCmec type III. HA-MRSA strains are typified by a USA100 or USA200 pulse-field gel electrophoresis (PFGE) pattern
CA-MRSA

• CA-MRSA strains are usually susceptible to nonbeta-lactam antibiotics, although local susceptibility patterns vary. CA-MRSA strains typically carry staphylococcal cassette chromosome type IV or V and have a USA300 or USA400 PFGE pattern. They also frequently carry genes for Panton-Valentine leukocidin.
MRSA strains

- MRSA strains isolated from children with risk factors for HA-MRSA and onset of infection in the community (CO HA-MRSA) share features of HA-MRSA and CA-MRSA. Similar to CA-MRSA, most CO HA-MRSA strains carry the SCCmec type IV cassette. However, they have greater diversity in PFGE patterns, are less likely to contain sequences for PVL, and more likely to be resistant to $\geq 3$ classes of antibiotics than CA-MRSA
CA-MRSA

• Risk factors for CA-MRSA include:
• skin trauma, crowding, frequent skin-to-skin contact, sharing potentially contaminated personal items or equipment, and frequent exposure to antimicrobial agents.
• However, they have a relatively poor ability to distinguish MRSA from methicillin-sensitive S. aureus infection
Clinical spectrum of MRSA

• The clinical spectrum of MRSA infection ranges from asymptomatic colonization, to skin and soft-tissue infection, to life-threatening invasive infection
HA-MRSA

- HA-MRSA has been a problem in hospital settings since the 1960s; there has since been a progressive increase in the prevalence of antimicrobial resistance in hospital-acquired S. aureus infections.
- In a United States surveillance report of over 24,000 cases of nosocomial S. aureus bacteremia, isolates with methicillin resistance increased from 22 to 57 percent between 1995 and 2001.
- Worldwide, HA-MRSA prevalence varies considerably, from <1 percent in Scandinavia to up to 40 percent in Japan, Israel, and elsewhere in Europe.
Staphylococcus aureus susceptibility Denmark

![Graph showing the percentage of resistance over years for different antibiotics in Denmark.]
MRSA

- MRSA is one of the few pathogens routinely implicated in nearly every type of nosocomial infection.
- This is probably related in part to the organism's capacity for biofilm formation on nosocomial foreign devices such as endotracheal tubes and urinary and endovascular catheters.
- Biofilm facilitates MRSA survival and multiplication on these surfaces, prolonging the duration of organism exposure to antibiotics as well as promoting the potential opportunity for transfer of antibiotic resistance genes between organisms.
CA-MRSA and HA-MRSA

• The CA-MRSA and HA-MRSA classifications are no longer distinct, since patients can develop MRSA colonization in one realm and develop manifestations of infection in another
CA-MRSA and HA-MRSA

• Hospital-acquired MRSA infections have been observed with increasing frequency among patients in community settings; such infections have been described as healthcare-associated MRSA with community onset.

• This was illustrated in a study of 209 patients discharged from hospitalized care; within 18 months following hospital discharge, 49 percent of new MRSA infections began outside the hospital.

• In another series of 102 patients with community acquired MRSA infections, 29 percent had molecular typing consistent with HA-MRSA.
Keys to understanding of MRSA testing

• MRSA can be isolated from a pure infection or found mixed within a population of MSSA (methicillin-susceptible S. aureus) and/or other microbes

• Historic Culture Methods
• Phenotype: S. aureus id, usually 24 hrs
• MRSA confirmation, >24-48 hrs
• Susceptibility Testing, >2-3 days

Cefoxitin 30ug induces PBP’2a
Keys to understanding of MRSA testing

- MRSA is identified by confirmation of:
  - the presence of a characteristic penicillin-binding protein, known as PBP2a’ from a bacterial isolate of *S. aureus* \(^{15-17}\)
  - The active site for binding antimicrobials is depicted by the area spanned by the red bar
CHROMAgar MRSA™

• Salt concentration (2.5%): MRSA strains grow in the presence of the cephalosporin antibiotic and produce “mauve”-color colonies, resulting from hydrolysis of the chromogenic substrates.

• Most MRSA are identified in 24 h; total incubation time may be as long as 48 h
  – Some results require extra incubation, and/or extra biochemical testing.

• Performance of CHROMagar vs. Oxacillin MIC, (product insert)
  Sensitivity 94.9%, Specificity 96.6%
Guidance for MRSA PCR

- Results may vary with previous antibiotic treatment. A positive PCR does not always indicate the presence of “viable” organisms.
- Does not detect the _mecA_ gene directly (detects interface of SCC mec cassette, etc.).
- Does not detect the PBP’2a encoded enzyme itself (just the presence of the gene interface).
MRSA & VRE

• The role of contamination of HCW’s hands
  – Semmelweis 1847
  – 42% of nurses gloves + after touching surfaces
  – VRE lives 60 minutes after acquiring on hand
  – Few do correct handwashing
MRSA

• The role of contamination of HCW’s clothes
  – 65% of uniforms MRSA
  – 32% of uniforms for VRE
  – Gowns protect clothes effectively
Contamination of equipment

• The role of contamination of equipment
  – Stethoscopes, tourniquets, otoscopes, pagers etc contaminated
Contamination of the environment

• The role of contamination of the environment
  – 73% of rooms with MRSA had surface colonization
  – 64% in burn units to 5% in low risk areas
Handwashing

• The role of handwashing and gloves and gowns
  – Handwashing impact difficult to determine
  – Gloves prevent hand contamination about 75% of time
  – Gowns prevent contamination of clothes
  – Maks ? Difficult to quantify but nares sites of colonization
Antibiotic control

- Antibiotic control
- Difficult to measure impact
- Difficult to enforce
SHEA guidelines

- Hand hygiene
  - Soap and water
  - Etoh based solutions
SHEA guidelines

- Gloves, gowns and masks
- Antibiotic stewardship
- Decolonization
- Educational programs
- Use hospital computer system for tracking
MRSA
Antibiotic choice

• Community acquired MRSA could use clindamycin first
• Nosocomial acquired need Vancomycin +/- rifampin
Treatment of serious Staphylococcal Infections

- Initial empiric Rx
- Life threatening - Vancomycin
- Non-life threatening - Naf/oxacillin or Cepazolin +/- clindamycin - Community
- Vancomycin for nosocomial
Staphylococcus aureus

- MSSA
- Nafcillin/oxacillin or cephalosporin
- Clindamycin
- Vancomycin for allergic Pt.
MRSA

- Nosocomial
- Multiresistant strains

- Vancomycin +/- gentamicin +/- rifampin
- Alternative Linezolid, Synercid, S/T and ? Quinolones (not cipro)
MRSA

- Community strain (not multidrug resistant)
- S/T or Clindamycin
- Vancomycin
Vancomycin
Ant & Fungus
The end