Community Acquired Methicillin Resistant *Staphylococcus aureus*

**WHO, WHAT, WHEN**

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**Objectives**

1. To define what is considered CA-MRSA based on both clinical and molecular platforms
2. To understand the pathogenesis of Ca-MRSA and its role in public health
3. To evaluate the current surveillance or "lack of" hard statistical data surrounding current CA-MRSA carriage rates

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**Staphylococcus aureus (S. aureus)**

A gram positive cocci, known to appear in clusters on gram stain slide
- (image courtesy of CDC)

It is also, an organism well adapted to colonize humans

But – only some individuals are carriers over a long period of time
 Carrage is asymptomatic – so really not a problem ... or is it
- Risk of autoinfection
- Spread to other individuals

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**Not in Kansas anymore**

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**University of Alaska Anchorage**

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Methicillin Resistant S. aureus (MRSA)

Looks the same

But, antibiotic resistant:

MRSA is defined when Staphylococcus aureus shows resistant to:
- All beta-lactam agents, including cephalosporins and carbapenems (*)
- Oxacillin and methicillin
- * But may be susceptible to MRSA-active cephalosporins (ceftaroline)

Late 19th century

Staphylococci was known to be responsible for furunculosis
But, why some people were infected without being exposed was not understood

Clearer picture emerges.....

In 1932 Norwegian dermatologist discovered that 22/24 patients with recurring furunculosis had staphylococci with the same biochemical properties both in the nose and the lesions. He is the first to mention of an "autoinfection"

This discovery was repeated in 1948 (Moss et al. Lancet) along with the notion that nasal vestibule was the primary site of S. aureus carriage

In 1963, Williams further determined the anterior nares to be the most frequent site (Williams Bact.Rev)

However, in 2000 the Norwegian Institute of Public Health suggests a broader screen of MRSA from additional sites groin and throat, along with nares.

How does S. aureus “hang around”

Commensal bacteria have to balance the "lifestyle" of efficient surface adherence (so has not to be removed by cleaning) and also not recognized by our immune system (innate/adaptive)

Urban outbreak – hospital centered

From the 1960-1990s MRSA become entrenched as an endemic pathogen in large urban university hospital
- Particular in ICU units
- Increasing from 2.4% in 1975 to 29% in 1991

However there were also reports of MRSA colonization and infection in patients who had had no recent contact with health care facilities.

But, this was considered a non-issue compared to the uncontrolled hospital acquired MRSA infection rate.

So, if it has been around for so long..... where did MRSA come from?

1961, soon after the introduction of methicillin the first beta-lactamase resistant Staphylococcus aureus was identified in the United Kingdom

1965 MRSA was then seen in Sydney Australia

In 1968 the first outbreak was seen in United States (Boston)
This strain was identified as being resistant to
- Trimethoprim-sulfamethoxazole
- Erythromycin
- Chloramphenicol
- Tetracycline
- Gentamicin
Early epidemiology of MRSA

Epidemiology limited to health care facilities.

Risk factors prior to the mid-1990s included:
- Exposure to the health care system
- Residence in a long term care facility
- Residence in an acute rehabilitation unit
- Presence of an indwelling line or catheter
- Surgical wounds
- Chronic liver, lung or vascular disease
- Malnutrition
- Recent exposure to antibiotics
- Intrauterine drug use
- ICU admission
- Exposure to a patient with any of these risk factors for MRSA

Characteristics

<table>
<thead>
<tr>
<th>Nosocomial acquisition</th>
<th>83 (74.8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Community acquisition</td>
<td>28 (25.2)</td>
</tr>
<tr>
<td>Comorbidities</td>
<td>53 (47.7)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>24 (21.6)</td>
</tr>
<tr>
<td>Malignancy</td>
<td>12 (10.8)</td>
</tr>
<tr>
<td>End-stage renal failure</td>
<td>10 (9.0)</td>
</tr>
<tr>
<td>Cerebrovascular accident</td>
<td>8 (7.2)</td>
</tr>
<tr>
<td>Heart failure</td>
<td>7 (6.3)</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>5 (4.5)</td>
</tr>
<tr>
<td>HIV infection</td>
<td>2 (1.8)</td>
</tr>
<tr>
<td>Past history of MRSA</td>
<td>21 (18.9)</td>
</tr>
<tr>
<td>Previous hospitalization</td>
<td>20 (18.0)</td>
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</tbody>
</table>

Clinical characteristics of 111 patients with methicillin-resistant Staphylococcus aureus (MRSA) infection or colonization (data taken 1998)

In 2000: MRSA and *S. aureus*

MRSA was diagnosed in 125,969 hospitalizations.

By 2003 MRSA accounted for 51.6% of ICU isolated *Staphylococcus aureus*, but ALSO 42% of non-ICU *Staphylococcus aureus* isolates.

As a natural reservoir for *S. aureus* 30-50% of healthy persons are nasally colonized.

Colonization and infection

Long term asymptomatic carriage
- Opportunistic acute infections
- Persistent chronic infections

Much of what we know about *S. aureus* evolution in the host comes from studies of chronic infections (Cystic Fibrosis patients who are often persistently colonized with *S. aureus*).

Nosocomial infection – where did it come from

Strain of *S. aureus* causing nosocomial infection is of the same strain carried in the nose of the infected individual.

So then, what is the potential for an asymptomatic carrier to develop infection?

Is it possible mutational events in commensal isolates confer a more invasive phenotype?

There are sub-populations of commensal *Staphylococcus aureus* which have greater pathogenic potential.
Not just in hospitals

MRSA, resistant to all available penicillins and other beta-lactam antimicrobial drugs, once confined largely to hospitals and other health care environments, was now everywhere.

By mid 1990s an explosion of individuals testing positive for MRSA lacked the risk factor of exposure to health care system.

Community Acquired MRSA

This increase became associated with the term:

Community Acquired MRSA CA-MRSA

CA-MRSA is now considered responsible for an increasing disease burden in this last decade.

Soon spreading

This new strain of CA-MRSA rapidly disseminated among the general population in most areas of the United States.

Began to affect patients with and without exposure to the healthcare environment.

Which is Which

MRSA now has to be differentiated as to the origin of infection

Hospital acquired (HA-MRSA)

Community acquired (CA-MRSA)

HA-MRSA vs CA-MRSA

The terms CA-MRSA and HA-MRSA have been used to call attention to the:  
- genotypic differences of certain MRSA isolates 
- epidemiological and clinical features of the infections that they cause

An essential component of epidemiological studies has been:
- To define the clinical burden of CA-MRSA and HA-MRSA isolates 
- Both of which circulate in the community

This interchange of terms has created confusion.

Defined by the CDC in 2000

Created a definition based on physical exposure and/or potential risk factors:

An MRSA infection diagnosed for an outpatient or within 48 hours of hospitalization AND the patient lacks: 
- hemodialysis 
- surgery 
- residence in a long term facility 
- hospitalization during the previous year 
- presence of an indwelling catheter 
- previous isolation of MRSA

4/4/2017
Then came another definition

Community-onset MRSA

All infections occurring among outpatients or among inpatients with an MRSA isolate obtained earlier than 48 hrs after hospitalization (came in with it)

Infections meeting either of these temporal criteria are sometimes referred to as "Community-onset" MRSA (CO-MRSA) infections

Everything else is considered HA-MRSA

What does it matter CA-MRSA or HA-MRSA

CA-MRSA isolates have typically been susceptible to most non-beta-lactam antimicrobial drugs including several orally available agents.

Allowing clinicians to have a number of options when selecting antibiotic treatment for CA-MRSA infections.

CA-MRSA isolates are usually susceptible to clindamycin in the United States

Problems with case definition

If the CDC case definition were used in acute-care setting to aid in selection of empiric antibiotic therapy:

- many people who could be managed with clindamycin
- would be unnecessarily treated with intravenous antimicrobial drugs

because they have an illness caused by a CA-MRSA and not a multiply resistant HA-MRSA

Define by molecular

MRSA can be pedigreed by:

1. Antimicrobial susceptibility (what we do know after culture)
2. DNA fragment patterns upon pulsed-field gel electrophoresis
3. Carriage of Panton-Valentine leukocidin (PVL) gene (determines virulence)
4. Multi-locus sequence typing (MLST)
5. Type of SCCmec element carried
HA-MRSA molecular
1. HA-MRSA carry a relatively large staphylococcal chromosomal cassette mec (SCCmec) belonging to type I, II, or III.
2. These cassettes all contain the signature mecA gene, which is nearly universal among MRSA isolates.

CA-MRSA molecular
CA-MRSA carry smaller SCCmec elements, most commonly SCCmec type IV or type V.
These smaller elements also carry the mecA gene.
They are resistant to fewer non-beta-lactam classes of antimicrobials.
Frequently carry PVL genes.

<table>
<thead>
<tr>
<th>CA-MRSA</th>
<th>HA-MRSA</th>
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<tbody>
<tr>
<td>Common clinical syndrome</td>
<td>Skin/soft tissue infection, UTI, bloodstream, pulmonary (rare)</td>
</tr>
<tr>
<td>Antimicrobial susceptibility</td>
<td>Usually susceptible to: TMP/SMX, doxycycline, clindamycin, rifampin</td>
</tr>
<tr>
<td>PFE clone</td>
<td>USA300 or USA400</td>
</tr>
<tr>
<td>SCCmec type</td>
<td>IV (sometimes V)</td>
</tr>
<tr>
<td>PVL gene</td>
<td>Yes &gt;80%</td>
</tr>
</tbody>
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Compare: CDC model vs Molecular
University of Chicago in 2004-2005
The CDC definition would have classified 65.6% of MRSA patients as HA-MRSA.
But among these HA MRSA patients:
- 47% of the isolates carried SCCmec type IV,
- 35.9% were PVL positive and 40.1% were ST8 traits attributed to CA MRSA isolates.

If defined by molecular standards, HA-MRSA would have been 34.8%.

Blurred lines
Since 2003 the distinctions between CA-MRSA and HA-MRSA isolates have become increasingly blurred, which has been confirmed with molecular typing.
HA-MRSA isolates do circulate in the community especially among adults.
Along with demonstrated MRSA clones bearing SCCmec type IV cause nosocomial MRSA outbreaks and infections among patients with chronic illnesses.
Particularly USA300, the predominate CA-MRSA PFGE type now seen in the United States.

What does this mean in numbers
34% of nosocomial transmitted isolates of MRSA belongs to the USA300 CA-MRSA genotype.
Detroit Michigan from 2005-2007 USA300 accounted for 20% of nosocomial bloodstream infections.
San Francisco USA300 increased among MRSA isolates in a large long term care facility 11.3% in 2002 to 64% in 2006.
Complicated epidemiology

Some Community Onset MRSA (CO-MRSA) infections are caused by HA-MRSA related to exposure to HA-MRSA managed infections at home. MRSA in the community from this circulation or “feral” HA-MRSA in the general population.

What does this mean

Complex epidemiology of CA MRSA strains in health care settings and circulating of HA-MRSA strains in the community clear delineation between is not possible. CDC investigators have used a third category of MRSA infections called “health care-associated, community-onset” MRSA (HACO-MRSA). This category includes cases that would be HA-MRSA by history of health care exposure but have onset in the community.

Tripartite classification

HA-MRSA
CA-MRSA
HACO-MRSA

CDC Active Bacterial Core Surveillance Program: CDC 2014 data

<table>
<thead>
<tr>
<th>Epidemiologic Category</th>
<th>Estimated No. of Infections</th>
<th>Incidence Rate (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CA</td>
<td>16,522</td>
<td>5.18 (4.03 - 6.79)</td>
</tr>
<tr>
<td>HCA</td>
<td>44,627</td>
<td>14.01 (12.17 - 16.29)</td>
</tr>
<tr>
<td>HCA-HO</td>
<td>10,130</td>
<td>3.18 (2.33 - 4.40)</td>
</tr>
<tr>
<td>HCA-HACO</td>
<td>34,497</td>
<td>10.83 (9.26 - 12.81)</td>
</tr>
<tr>
<td>Overall</td>
<td>61,927</td>
<td>19.45 (17.16 - 22.18)</td>
</tr>
</tbody>
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Outpatient CA-MRSA is common

Outpatient and ED visits for CA-MRSA abscesses or cellulitis nearly doubled. In some regions CA-MRSA accounts for 75% of community associated S. aureus infections in children.
Carriage medical students

2008-2009 Medical students at the China Medical University

4.5% in 2008 11.7% in 2009

All MRSA strains were susceptible to vancomycin but resistant to oxacillin, cefoxitin, and erythromycin.
PVL positive CA-MRSA classified into strains which can differ from continent to continent.
In this study strains ST-1, 3, 30, 59, 88, 90 and 239 were identified.
10/22 strains were ST-88 and 6/10 were also PVL positive.
ST-88 has been found in Belgium, Portugal, Sweden, Nigeria.
ST-88 clone has been reported in both hospital and community settings in China.

MRSA PVL+ SCCmec IV in Hospitals

2012 study Makkah: March – 5 major tertiary care hospitals:

50% of S. aureus were MRSA
18% SCCmec IV and of these 4% PVL positive.
29% of nearly 1/3 of MRSA could be considered CA-MRSA.

Nearly half contained the increased virulence of PVL positive gene.

Complications to increased virulence

Expensive to treat:
Limited antibiotics to treat massive course:
May become untreatable:
Poor patient outcome:

Neonatal risk factors

Neonatal MRSA cause of epidemic and endemic disease and a cause of infection in the first days of life among newborns in neonatal intensive care units.
Several neonatal MRSA outbreaks have been linked to CA-MRSA strains including USA300 and USA400 and have been associated with visiting fathers, maternal mastitis, health care workers.
This source of colonized or infection with MRSA implies a community source.

Pediatric epidemiology 2004-2006

Rates of MRSA in noninstitutionalized children ages: 1-19

Nashville 9.2%, Corpus Christi, TX 12.3%
Of these 66% carried SCCmec type IV and 50% were PVL positive.

Staphylococcus aureus carriage rate: (Bogart, 2004)

<table>
<thead>
<tr>
<th>Age</th>
<th>S. aureus carriage rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.5 months – 6 months</td>
<td>23.9%</td>
</tr>
<tr>
<td>1 year – 5 years</td>
<td>30%</td>
</tr>
<tr>
<td>6 years – 12 years</td>
<td>Up to 50%</td>
</tr>
<tr>
<td>12 years – 18 years</td>
<td>Stably declines until 25% at age 18</td>
</tr>
</tbody>
</table>

Pediatric concerns

Study done in University of Chicago and University of Illinois discovered an association of CA-MRSA genotypic USA400 strains PVL positive with severe sepsis in previous healthy children (Frank, Clin. Infect. Dis. 2000).

Pediatric hospitals:

Corpus Christi had 22% of pediatric patients with CA-MRSA (no previous hospital exposure)
one of the highest prevalence rates of MRSA in the US
74% carried SCCmec type IV and 62% PVL positive.
Many of these patients also had no day-care attendance, no household contact with a known risk factor, and no antibiotic use.
In 1990 there were no pediatric MRSA at this hospital. The year of this study there were 584
Outside the United States

Taiwan (2004) 13.2%
Taipei 8.1%
Seoul 6.1%

In South Wales 87 of 100 MRSA infections in children were caused by CA-MRSA and of these strains 67% caused SSTI and carried SCCmec type IV.

Community populations at higher risk

Sports participation.
\- Football is the highest incident
\- 1.8% to 15.8% isolate belonged to the USA300

Household contacts.
\- Transmission rates of 10% in the US

Exposure to HIV

Incarceration

Military

Indigenous Populations

Multiple indigenous populations
\- Native American
\- First Nation
\- Australian Aboriginal
\- Pacific Islander
\- Alaska Native

- High risk of infection with CA-MRSA strains.

ED visits

SSTI visits increased from 1.2 million in 1993 to 3.4 million in 2005

11 University affiliated ED found:
- MRSA accounted for 59% of the S. aureus SSTI
- And
- 97% of these isolates were USA 300

In TN MRSA isolated from 67.6% of adult and 79.7% of pediatric SSTI cultures in 2005

In Texas 68% of cultured abscesses were MRSA

Treatment Decisions

Physician needs to differentiate clinically between

Uncomplicated SSTI

and

Severe or complicated SSTI

This is problem solving:

Clinical conditions

Uncomplicated CA-MRSA SSTI typically presents as an abscess that may resemble a spider bite filled with purulent material

They present as folliculitis, paronychia, furuncle, felon, cellulitis

But clinically you cannot determine MSSA from MRSA

So – is it important to determine if it is CA-MRSA or HA-MRSA?

Is this a part of the "history and physical" if no molecular test is available

(tough to get PVL typing on a Saturday evening)
Clinical conditions

Severe invasive CA-MRSA disease in previously healthy patients has been reported from many centers to cause necrotizing fasciitis, necrotizing pneumonia, severe sepsis, and septic thrombophlebitis. This was rarely reported for healthy individuals prior to the emergence of CA-MRSA.

Mortality rate

Severe invasive CA-MRSA disease have a high mortality rate, even when optimal therapeutic regimens are used. Mortality rate for children has been as high as 50%.

CA MRSA necrotizing pneumonia

Methemephtysis
Leucopenia
Cavity lung lesions which require mechanical ventilation

The clinical presentation of CA-mrsa necrotizing pneumonia is reminiscent of rapidly progressive influenza cases during the 1918 pandemic. Necrotizing pneumonia often has a rapidly progressive fatal course and occurs most often in children and young adult patients. 50 cases of necrotizing community-acquired pneumonia caused by PVL+ Staph aureus mortality rate was 56% an with a median age of 14.5 years.

Complicated SSTI – risk factors

Large or rapidly growing lesion
Lesion with deep tissue penetration
Systemic inflammatory response syndrome
Leucopenia
Host characteristic – patient looks ill
Immunocompromised
Age younger than 6 months
Lack of reliable site for outpatient follow up care
Poor controlled comorbid conditions which may suggest hospitalization

Treatment for severe infection

Intravenous antibiotics same as for HA-MRSA
Vancomycin is still the primary agent for suspected invasive CA-MRSA but it has poor penetration into lung tissue, under dosing, reported treatment failure in cases of necrotizing pneumonia caused by PVL+CA-MRSA strains.

There is also an increasing low-level intermediate resistance and “MIC creep”
The adjunctive use of an antimicrobial agent interfering with bacterial protein synthesis such as clindamycin or linezolid has been suggested, although this has limited evidence support.

So how does MRSA go from annoying to really bad

What does this mean about the transformation between asymptomatic carrier to disease?
And what makes it go from just a wound infection to severe sepsis?
Does it change during infection?
Are there "rouge" populations that emerge under duress?
Horizontal gene acquisition

Most S. aureus infections are monoclonal in nature. Clonal lineages have distinct restriction modification systems which limit horizontal gene acquisition. However, when this occurs — a horizontal transfer of SCCmec during infection leads to the emergence of new methicillin-resistant Staphylococcus aureus (MRSA) strains.

VRSA (Vancomycin resistant S. aureus)

Vancomycin-resistant S. aureus resulting from a co-infection of S. aureus and E. faecalis in a foot abscess (diabetic).

VRSA strain acquired the horizontal transfer of the Tn1546 transposon encoding for the vancomycin resistant determinant (vanA).

Limited clonal expansion of VRSA has not been fully understood.

Mutations during treatment (VISA)

Molecular basis for emergence of antibiotic resistance during infection.

Reduced sensitivity to vancomycin during treatment (Vancomycin intermediate susceptible S. aureus).

Molecular evaluation with whole genome sequencing from initial to late stages of infection reveal the presence of 35 mutations in 31 loci in a time-dependent manner which correlated with the emergence of resistance to antibiotics which were being used to treat infections (rifampicin, beta-lactams, and vancomycin).

Resistance to daptomycin emerged during the infection even though it was not used on the patient.

Mutations from carrier to infection

Young et al. (2012) during a longitudinal study of Staphylococcus in asymptomatic nasal colonization had a volunteer develop a S. aureus infection over 12 months after joining the study.

The evolution of the S. aureus during the transition from commensal to disease-associated organism (86 isolates collected from early and late onset nasal and blood cultures).

They found an identification of loss-of-function mutations correlated with the development of bacteremia. Was this really a mutation as an adaptive evolution or a re-seeding by a latent population?

So — is it possible that there is considerable genetic diversity within colonizing and subsequent infection S. aureus populations. Whether this is done to make that jump from carriage to infection has yet to be determined.

Control the rise of CA-MRSA virulence

Immediate use of antibiotics for clinical S. aureus isolates is no longer a reliable treatment for empiric therapy.

Incision and drainage may be adequate without antimicrobial drug therapy.

Image credit: University of KS Medical School.
Antibiotic of choice

But there is no consensus to which patients can be treated with incision and drainage alone and which patients require adjunctive antimicrobial therapy.

But if it must be given in accordance with local institutional antibiotic susceptibility data, clindamycin, doxycycline, minocycline, and trimethoprim-sulfamethoxazole are often recommended for empiric treatments. With clindamycin as a mainstay of therapy.

But, really what is our problem?

Prevention – can we just do better?

Typical standard guidelines of:
- Isolation or cohorting of colonized individuals
- Active identification of MRSA carriage by surveillance cultures of high-risk populations
- Decolonization of MRSA carriers
- Environmental disinfection by chemical means or light
- Or even some combination of the above described interventions have failed to limit transmission or spread.

CA MRSA epidemic continues

Something needs to be done – at least we need to have continued community surveillance.

Questions?
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