

Community Associated Methicillin Resistant *Staphylococcus aureus* (MRSA): An Emergent Pathogen

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OBJECTIVES

- 1. Understand the role of Hospital-Associated MRSA in nosocomial infections, and recognize risk factors for HA-MRSA
- 2. Have an understanding of the emergence of Community-Associated MRSA in terms of
 - Clinical presentations
 - Unique microbiologic/molecular features
 - Epidemiology of recent outbreaks
 - Current knowledge of CA-MRSA incidence/prevalence in North America

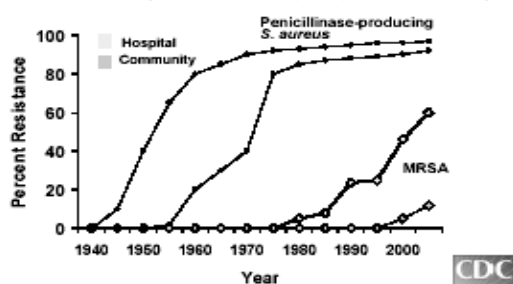
Introduction - MRSA

- That MRSA is now a predominant feature of nosocomial staphylococcal infections and a growing cause of community infections should not be surprising:
 - The first Penicillin resistant strains were reported within 2 yrs of the introduction of this agent in the 1940's, and within 6yrs 25% of hospital strains were resistant.
 - Within 15 years 25% of community isolates were penicillin resistant – studies in children under 10 found rates of 68%

Introduction - MRSA

- Similarly, the first isolates of Methicillin resistant *S.aureus* were reported within 1 year after the introduction of this agent in 1961.
- Hospital prevalence rates now exceed 25% for many regions in the US, and Canadian figures lag behind in this regard.
- In the last 5 years there has been an upsurge in MRSA cases arising in the community..

Trends in *S. aureus* Antimicrobial Resistance
(Chambers EID 2001, NNIS, Fridkin NEJM 2005)



Introduction - MRSA

- MRSA plays a significant role in nosocomial infections:
 - NNIS data show that MRSA makes up 50-60% of all *S.aureus* infections in ICU pts
 - Ventilator-associated pneumonias, catheter-related bacteremias, and surgical site infections
 - In the US 1999-2000 data show that 125,969 hospitalizations occurred with a diagnosis of MRSA infection – 3.95/1,000 discharges (Kuenert et al EID 2005)

Introduction - MRSA

- Risk factors for acquisition of Hospital – Associated MRSA are now well defined, and include, among others:
- Hospitalizations (obviously!)
- Recent surgery
- Dialysis
- Presence of indwelling medical devices such as catheters, gastrostomy tubes, tracheostomy)
- Residence in long-term care facilities

Community onset MRSA

- Initially, MRSA seen in the community had its origins in hospitals, even if diagnosis or isolation occurred in the community
 - Hence community onset.
 - Risk factors as outlined above often present.
 - A meta-analysis of both retrospective and prospective studies looking at MRSA in the community between 1996 and 2001 found that overall, the pooled MRSA colonization rate among community members was 1.3% (Salgado et al CID 2003)
 - Of these 85% had at least one healthcare associated risk factor
 - When healthcare contacts were excluded, the prevalence was 0.2%

Community onset MRSA

- A study in San Francisco looked at community prevalence amongst a population of inner-city urban poor (Charlebois et al CID 2002)
 - A prevalence of 2.8% was found
 - Most had contact with hospitals
 - IDU was also significantly associated with MRSA carriage OR 9.7
 - Molecular analysis indicated that the majority of isolates were identical to MRSA isolates endemic in the hospital

The shift to Community Associated MRSA

- So far so good – limited prevalence of MRSA in the community, most with epidemiologic links to healthcare settings, and shown to be identical genetically to hospital clones
- BUT....
- Pediatric studies were telling a different story
 - Daycare studies in Dallas found colonization rates of up to 24% in children with no risk factors for MRSA (Adcock JID 1998)
 - In Chicago pediatric rates of MRSA rose 15 fold over 1990-1997 - predominantly community in origin
 - Finally studies in Houston found 50% of pediatric S.aureus infections were due to MRSA in 2000, and by 2004 this figure had risen to 76% (Kaplan et al CID, 2005)

The shift to Community-Associated MRSA

- These isolates were from children without traditional risk factors for HA-MRSA
- In addition, this new version of MRSA was leading to high numbers of skin and soft tissue infections – 95.6% of isolates in the Houston series were from soft tissue infections
- Then: Startling cases of 4 pediatric deaths due to necrotizing pneumonia caused by MRSA in previously healthy children (MMWR 1999)

Community – Associated MRSA

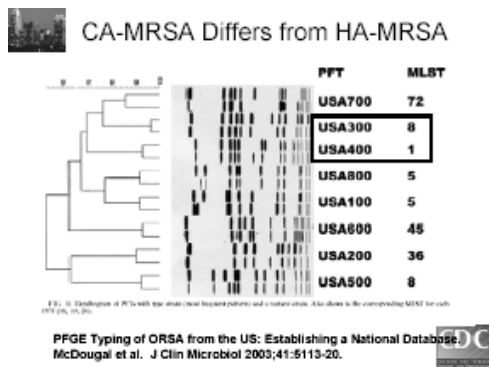
- A re-definition of community MRSA was required:
- Community-Associated (CA-MRSA)
- In addition to the lack of epidemiologic risk factors Unique features are present:
 - 1. Unique clonal type
 - By PFGE – USA 300/400
 - 2. Unique Genetic elements
 - SCC mec IV
 - 3. Common carriage of unusual toxin genes
 - Panton-Valentine Leukocidin PVL
 - 4. Retention of sensitivity to non B-lactam antibiotics

1. Clonality

- Molecular techniques allow identification of MRSA strains to the clonal level
- Initially a variety of differing techniques were used:
 - Pulsed-field Gel Electrophoresis (PFGE)
 - Common technique, able to discriminate well between clones, gel-sharing software exists for comparison
 - Multilocus Sequence Typing (MLST)
 - Studies the sequences of seven neutral loci
 - Staphylococcal protein A typing (spa typing)

1. Clonality

- PFGE endorsed and validated by group at the CDC
- 8 lineages identified
- Now common nomenclature:
 - USA300 and USA 400 are CA-MRSA strains/clones
 - HA-MRSA strains are commonly USA 100, 200
- Mulvey et al have typed Canadian strains with CMRSA10 = USA 300



1. Clonality

- USA 300 has become a widespread clone
 - The Houston Pediatric study found that 90% of the isolates were USA300
 - Common in other outbreaks (see later)
- USA 400 was the strain found in the fatal necrotizing pneumonia cases (MMWR 1999)

2. Unique genetic elements

- The Staphylococcal cassette chromosome (SCC) is a mobile DNA element able to control its integration and excision from loci in the genome
 - When it contains the Methicillin resistance gene (*mec*) it is known as *SCCmec*
 - 5 *SCCmec* types are currently described
 - I- V
 - Some have additional antibiotic resistance cassettes encoded

2. Unique genetic elements

- HA-MRSA isolates contain predominantly *SCCmec* types I–III.
 - These are large 34-67 Kb
 - Contain multiple drug resistance genes
- CA-MRSA is defined by the presence of *SCCmec* IV
 - Small usually 20-24Kb
 - ? Allows rapid replication vs other MRSA ie. More fit
 - Possible ease of transfer
 - No other genes for resistance

3. Toxin production

- A common feature of CA-MRSA is additional production of toxins
 - The necrotizing pneumonia strain from the pediatric cases in 1999 (MW2) was found to produce 19 virulence genes not seen in HA-MRSA
 - Among them was Panton-Valentine Leukocidin
 - PVL is a pore-forming cytotoxin that damages host defense cells such as PMN's.
 - Effect is due to synergistic action of 2 proteins; LukS-PV and LukF-PV

3. Toxin production

- PVL has been shown to cause severe inflammation and skin necrosis in rabbits
- It is present in <5% of *S.aureus* in general, but is found in a majority of strains of CA-MRSA
- Clinical associations in humans show it is found in cases of necrotizing pneumonia and furunculosis (85% and 93% respectively in one series – Lina et al CID 1999)
 - PVL associated with necrotic lesions affecting the skin and mucosa

4. Sensitivity to non B-lactam antibiotics

- The presence of SCCmec IV is associated with a lack of additional resistance genes in CA-MRSA
- Commonly CA-MRSA remains susceptible to
 - clindamycin (94% in Houston isolates, 93% in Washington State Surveillance studies)
 - TMP-SMX (99%)
 - Doxycycline and rifampin (94-99%)
- Resistance to erythromycin and ciprofloxacin are high

Clinical features

- Classic associations are seen with skin and soft tissue infections
 - Furuncles
 - Abscesses
 - Often described as "spider bites"
 - Usually multiple
 - Cellulitis
 - Necrotizing pneumonia and necrotizing fasciitis have been described
 - Less commonly invasive infections – blood, urine etc

CA-MRSA Outbreaks

- Correctional Facilities (MMWR 2003)
 - Growing problem in prisons in the US
 - Multiple states have reported outbreaks (Texas, Georgia, California)
 - In largest Los Angeles prison – 20,000 inmates
 - Found 1,697 cases 2002- 2003
 - Risks of close contact, poor hygiene, sharing personal items and helping other inmates with wound care
 - Decreases in numbers with improved surveillance, improved laundry services and access to shower facilities

CA-MRSA Epidemiology

- 2 landmark studies in the growing epidemiology of adult CA-MRSA
 - Naimi et al Jama 2003
 - Prospective cohort study Jan-Dec 2000 in Minnesota
 - HA-MRSA defined using traditional risk factors
 - CA-MRSA defined purely epidemiologically
 - Outcomes were type of clinical infection, PFGE pattern, presence of exotoxin gene locus (ie PVL)

CA-MRSA Epidemiology

- 1100 MRSA infections
 - 12% CA-MRSA
 - 85% HA-MRSA
- Of the CA-MRSA
 - Median age was 23 vs 68 for HA-MRSA
 - 75% associated with skin and soft tissue infections vs 37%
 - Most of these treated with incorrect antibiotics initially

CA-MRSA Epidemiology

- On molecular testing
 - Found retained antibiotic susceptibilities to at least 4 drug classes
 - Clindamycin 83% sensitive (interestingly also had high rates of sensitivities to erythromycin and ciprofloxacin)
 - Clonal in nature
 - Contained SCCmec IV
 - Contained PVL genes
- Confirmed growing presence of CA-MRSA amongst healthy adults, warning sign for role of empiric B-lactam antibiotics

CA-MRSA Epidemiology

- Fridkin et al NEJM 2005
- Population based surveillance in three communities around US
 - Baltimore, Atlanta, Minnesota
- 2001-2002, ABC Surveillance Program
- Again epidemiologic risk factors to separate HA-MRSA from CA-MRSA

CA-MRSA Epidemiology

- CA-MRSA made up 8-20% of all MRSA
- Incidence rates of 25/100,000 in Atlanta
- 77% skin and soft tissue infections
- Most remained sensitive to clindamycin, rifampin, septria, tetracyclines. Varying rates of erythromycin and ciprofloxacin sensitivity
- But most people treated with incorrect antibiotic, and responded purely to drainage of wounds

CA-MRSA Epidemiology – Where are we Now?

- CA-MRSA now predominant cause of adult skin and soft tissue infections (SSI) in many centres
 - Surveillance of 389 Staphylococcal infections over 3 month period (2003) in Atlanta found that 63% due to CA-MRSA, and of these 99% belonged to USA300 (King et al An Int Med 2005)
 - Similarly over Aug 2004 422 patients with SSI at 11 University ER's found 76% due to S.aureus, with MRSA prevalence of 59%.
 - 97% of the MRSA was CA-MRSA = USA300 (Moran NEJM 2006)

CA-MRSA where are we now?

- In addition to SSI, CA-MRSA is emerging as a cause of bacteremias
 - Over 7 month period in 2004 Atlanta group found 132 MRSA bacteremias
 - Evaluation of 116 cases found that 34% of them were due to CA-MRSA (USA300)
 - Underlying risks were IDU with OR of 3.67, and concomitant SSI – OR 4.26
- Nosocomial spread of CA-MRSA now reported – NICU, maternity ward settings

CA-MRSA in Canada

- Outbreak in Calgary 2004
- 42 isolates of CA-MRSA (USA300) identified over Jan-Sept 2004.
 - 70% had risk factors of IDU, homelessness or recent incarceration
 - 98% SSI, 1 case necrotizing pneumonia

MRSA in BC

- Outbreaks reported in number of communities in province..
- We reviewed MRSA isolates at Providence Health over a 4 month period during 2005 (Hull et al AMMI 2006)
 - Only 1 isolate per patient was included, with preference given to sterile site isolates over surveillance screens

Table 1: Source of MRSA isolates
February – May 2005

Infection site/ Location at time of collection	Number n=493 (100%)
Wound	243 (50%)
Nasal/perineum screen	115 (23%)
Sputum	73 (15%)
Blood	33 (6.7%)
Urine	23 (4.6%)
Joint	6 (1.2%)
Emergency Room (ER)	148 (30%)
Non-ER	345 (70%)

Results – molecular testing

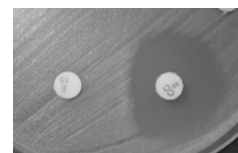
- 57/493 isolates were sent for molecular testing:
 - 68% were CA-MRSA (USA300)
- 150 isolates had full antibiotic susceptibility profiles recorded:
 - Isolates were uniformly sensitive to rifampin and fucidic acid – 97 and 100% respectively.
 - Isolates were uniformly resistant to ciprofloxacin and erythromycin – 98% and 99% respectively
 - CA-MRSA isolates were 100% susceptible to TMP-SMX and 79% susceptible to clindamycin

Therapeutic Options

- Not that much in the way of good data...
- Severely ill patients requiring admission should be treated with IV Vancomycin
- Oral options available for patients with moderate skin and soft tissue infections:
 - I+D likely curative for simple abscesses
 - Septra (2 DS PO BID), Clindamycin and doxycycline all options
 - Must be certain that Strep co-infection not likely

Therapeutic Options

- Clindamycin use may be limited by inducible resistance and this would not be picked up by standard automated susceptibility testing
 - Instead new test now instituted to look for this mechanism – double disk diffusion test, or D test



D test positive

Therapeutic Options

- Much debate (and no SSI evidence) regarding dual coverage:
 - Addition of rifampin or fusidic acid to therapy.
 - Not recommended as monotherapy
 - Certainly for recurrent infections may be worthwhile
 - Linezolid an option but limited by cost, ID restricted
 - Newer agents may also play a role:
 - Tigecycline – new glycylycline, FDA approved 2005, but limited IV formulation and associated nausea
 - Dalbavancin – new lipoglycopeptide. Long half life so IV administration D1,D8 (Jauregui CID 2005) – as efficacious as linezolid

Conclusions

- MRSA is no longer solely a nosocomial agent of disease
- Growing role of CA-MRSA in severe skin and soft tissue infections in patients lacking characteristic risk factors for MRSA
- CA-MRSA has defining characteristics both clinically, phenotypically and genetically
- Treatment options still need to be defined