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Pendidikan:
- SMA: Kolese KANISIUS, 1994
- Dokter Umum: FK TRISAKTI, 2001
- Spesialis Penyakit Dalam (Internist): FKUI, 2009
- Konsultan Penyakit Tropik & Infeksi: FKUI, 2013

Pekerjaan:
- Anggota PETRI (Perhimpunan Peneliti Penyakit Tropik & Infeksi Indonesia)
- Staf Pengajar Bagian Ilmu Penyakit Dalam, FK TRISAKTI, Jakarta
- Dokter RS PONDOK INDAH – PURI INDAH, Jakarta

Emerging cSSTIs Problem: Focus on MRSA Treatment

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Staphylococci Associated with Human Disease
- S. aureus
- S. epidermidis
- S. saprophyticus
Gram (+)ve Bacteria

<table>
<thead>
<tr>
<th>Organism</th>
<th>Carrier</th>
<th>Infections</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coagulase-positive Gram (+)ve</td>
<td>Skin</td>
<td>Skin infections: skin folliculitis, impetigo, furuncles, cellulitis, carbuncles, postoperative wound infections</td>
</tr>
<tr>
<td>Coagulase-negative Gram (+)ve</td>
<td>Nasopharynx</td>
<td>Nasopharynx infections: meningitis, sinusitis, mononucleosis, arthritis, pneumonia, osteomyelitis, septicemia, multiple organ failure</td>
</tr>
<tr>
<td>Staphylococcus epidermidis and others</td>
<td>Genitourinary tract</td>
<td>Genitourinary tract infections: prostatic, cardia, vascular, genitourinary, urinary tract infections, nosocomial urinary tract infection</td>
</tr>
<tr>
<td>Coagulase-negative Gram (+)ve</td>
<td>Ear canal</td>
<td>Ear canal infections: meningitis, sinusitis, mononucleosis, arthritis, pneumonia, osteomyelitis, septicemia, multiple organ failure</td>
</tr>
<tr>
<td>Coagulase-positive Gram (+)ve</td>
<td>Vagina</td>
<td>Vagina infections: skin folliculitis, impetigo, furuncles, cellulitis, carbuncles, postoperative wound infections</td>
</tr>
</tbody>
</table>

What is MRSA?

Definition: oxacillin minimum inhibitory concentration (MIC) >= 4 microgram/ml
- Resistant to methicillin
- Resistant to betalactam: Penicillin, cephalosporin, carapenem and betalactamase inhibitor/betalactam combinations

Staphylococcus Character Changes

The meca gene encodes for a 78-kDa penicillin-binding protein (PBP) 2A, which has unusually low affinity for all β-lactam antibiotics—a property that translates to the virtually complete resistance of MRSA strains to the entire β-lactam family of antimicrobial agents

Pinho MG et al. PNAS 2001;98:10886-10891
Skin and Soft Tissue Infections

Major pathogens*

<table>
<thead>
<tr>
<th>Rank</th>
<th>USA</th>
<th>France</th>
<th>Germany</th>
<th>Italy</th>
<th>Spain</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Enterococcus (24.9%)</td>
<td>S. aureus (29.2)</td>
<td>S. aureus (18.8)</td>
<td>S. aureus (24.2)</td>
<td>Enterococcus (18.1)</td>
</tr>
<tr>
<td>2</td>
<td>S. aureus (23.7)</td>
<td>CoNS (13.5)</td>
<td>Enterococcus (10.5)</td>
<td>E. coli (14.5)</td>
<td>P. aeruginosa (16.1)</td>
</tr>
<tr>
<td>3</td>
<td>CoNS (11.1)</td>
<td>Enterococcus (10.3)</td>
<td>E. coli (14.5)</td>
<td>P. aeruginosa (16.1)</td>
<td>CoNS (13.1)</td>
</tr>
<tr>
<td>4</td>
<td>E. coli (8.8)</td>
<td>E. coli (9.9)</td>
<td>CoNS (11.8)</td>
<td>CoNS (12.6)</td>
<td>E. coli (12.7)</td>
</tr>
<tr>
<td>5</td>
<td>P. aeruginosa (8.7)</td>
<td>P. aeruginosa (8.3)</td>
<td>P. aeruginosa (8.3)</td>
<td>E. coli (7.8)</td>
<td>P. aeruginosa (8.4)</td>
</tr>
</tbody>
</table>

* TSN (The Surveillance Network) study in 2001

Diabetic Foot Infections: Microbiology

- Predominant pathogens
  - Aerobic gram-positive cocci *Staph. aureus* and *β* hemolytic strep (esp GBS)
- Chronic wounds
  - Complex flora: Enterobacteriaceae, enterococci, obligate anaerobes, *Pseudomonas aeruginosa*
- Resistant pathogens: MRSA, VRE

MRSA Risk Factor

- Predominant risk factors should increase suspicion for CA MRSA in patients presenting with compatible signs and symptoms:
  - History of MRSA infection or colonization in patient or close contact
  - High prevalence of CA MRSA in local community or patient population
  - Recent skin disease
  - Crowded living conditions (e.g. homeless shelters, military barracks)
  - History of incarceration
  - Participation in contact sports
  - Skin or soft tissue infection with poor response to β-lactam antibiotics
  - Recent and/or frequent antibiotic use
  - Injection drug use
  - Member of Native American, Pacific Island, Alaskan Native populations
  - Child under 2 years of age
  - Male with history of having sex with men
  - Shaving of body hair

EPIDEMIOLOGY OF MRSA

- *Staphylococcus aureus* commonly carried on skin or in nose (25%-30%)\(^1\)
- Most MRSA infection arises in the hospital or healthcare setting, particularly among elderly or sick patients\(^1\)
- MRSA infections include skin infections, bone infections, pneumonia, and bloodstream infections\(^1\)
- MRSA is almost always spread by direct or indirect physical contact with MRSA patients\(^1\)

1. Available at: http://www.cdc.gov/ncidod/hip/Aresist/mrsafaq.htm

The Prevalence of Methicillin-Resistant *Staphylococcus aureus* (MRSA) is Rising in Many European Countries

<table>
<thead>
<tr>
<th>MRSA Prevalence</th>
<th>Key countries (blood isolates)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1990-1991(^1,2)</td>
<td>1990-1991(^1,2)</td>
</tr>
<tr>
<td>11.9%</td>
<td>42</td>
</tr>
<tr>
<td>1.5%</td>
<td>37</td>
</tr>
<tr>
<td>10.1%</td>
<td>36</td>
</tr>
<tr>
<td>5%</td>
<td>22</td>
</tr>
<tr>
<td>4.1%</td>
<td>22</td>
</tr>
<tr>
<td>4.5%</td>
<td>9</td>
</tr>
<tr>
<td>0%</td>
<td>0</td>
</tr>
</tbody>
</table>

1. Mean prevalence in key countries. Monthly data. 1994-13/06-05
<table>
<thead>
<tr>
<th>Range</th>
<th>Isolates</th>
<th>% OXA resist</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jul – Sept 2007</td>
<td>30</td>
<td>39.3</td>
</tr>
<tr>
<td>Oct – Dec 2007</td>
<td>43</td>
<td>39.5</td>
</tr>
<tr>
<td>Jan – Mar 2008</td>
<td>46</td>
<td>28.3</td>
</tr>
<tr>
<td>Apr – Jun 2008</td>
<td>17</td>
<td>50.0</td>
</tr>
<tr>
<td>Jul – Sept 2008</td>
<td>52</td>
<td>19.2</td>
</tr>
<tr>
<td>Oct – Dec 2008</td>
<td>50</td>
<td>36.0</td>
</tr>
<tr>
<td>Jan – Mar 2009</td>
<td>35</td>
<td>37.1</td>
</tr>
<tr>
<td>Mar – Jun 2009</td>
<td>58</td>
<td>27.6</td>
</tr>
</tbody>
</table>

Loho T, Astrawinata DAW. 2009

Methicillin-resistant *Staphylococcus aureus*

Type of Infection

- Total No. of MRSA cases: 12,553
  - Nosocomial MRSA: 10,906 (86.9%)
  - Community-acquired MRSA: 1,647 (13.1%)
- Higher incidence in young children (< 2YO)
- Type of infection: SSTI (77%), Wound infection (10%), UTI (4%), Bacteremia (2%), Pneumonia (2%), Osteomyelitis (1%)


How to Diagnose cSSTIs by MRSA?

Risk Factor +
Clinical Appearance:

- PVL+
  - Severe, frequently SSTIs
  - Progressive
Microbiologic Diagnosis of MRSA Infection

- Inadequate susceptibility to betalactam AB

Definite Diagnosis
Mec A Gene +

MRSA, is it Colonization or Infection?

**COLONIZATION:**
- Culture: +
- Symptom: +

MRSA de-colonization therapy can be defined as the administration of topical antimicrobial or antiseptic agents, with or without systemic antimicrobial therapy, to MRSA-colonized persons for the purpose of eradicating or suppressing the carrier state.


**INFECTION:**
- Culture: +
- Symptom: ++++
  (Severe, progressive)

MRSA AB-TREATMENT
AREA, POPULATION AND REGIMEN

- Health care workers
- Patients with nasal colonization without skin implant-related devices
- Patients with skin lesions or implanted devices or multiple site infections
- Presence of MRSA colonization

When to Start the MRSA Empirical Treatment in cSSTI?

- No culture results
- Severe infection (sepsis)
- Clinical profile, prior treatment of antibiotic, disease progressivism
- Risk factors
- Presence of MRSA colonization

Antimicrobial Treatment for MRSA

<table>
<thead>
<tr>
<th>Glycopeptide</th>
<th>Vancomycin (500 mg q8h OR 1 g q12h)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Teicoplanin (400 mg IV, then 200 mg/d IV/IM)</td>
</tr>
<tr>
<td>Oxazolidinones</td>
<td>Linezolid (600 mg q12h IV/PO)</td>
</tr>
<tr>
<td>Streptogramin</td>
<td>Quinupristin-Dalfopristin</td>
</tr>
<tr>
<td>Glycylcycline</td>
<td>Tigecycline (100 mg IV, then 50 mg IV q12h)</td>
</tr>
<tr>
<td>Alternative</td>
<td>Cotrimoxazole, Minocycline, Fluoroquinolones, Rifampicin</td>
</tr>
<tr>
<td>Combination</td>
<td>Cotrimoxazole + Rifampicin</td>
</tr>
<tr>
<td></td>
<td>Minocycline + Rifampicin</td>
</tr>
</tbody>
</table>

Treatment of MRSA

Based on Microbiological and susceptibility test Staph.Aureus resistant to methicillin or oxacillin (MIC > 4 ug/ml)

Antibiotic for MRSA:
- Glycopeptide: Vancomycin, Teicoplanin
- Oxazolidinones: Linezolid
- Strepnotomycin-Dalfopristin
- Gyacycline: Tigecycline
- Alternative: Cotrimoxazole, Minocycline, Clindamycin, Fluoroquinolones, Rifampicin, Tetracycline
- Combination treatment: Cotrimoxazole + Rifampicin, Minocyclin + Rifampicin


Susceptibility                   First choice                                         Alternative

Methicillin(oxacillin) resistant  Vancomycin 1g bid i.v.   Vancomycin 50-100 mg/kg/day in single dose 2-4x a day
(MRSA)                         Teicoplanin 3 mg/kg (high infection) 10 mg/kg (endocarditis) bid i.v. for the first 3-5 day followed by
                                3-5 mg/kg qd i.v. 7,5 mg/kg bid or tid iv
Quinupristin-Dalfopristin 7.5 mg/kg bid or tid

Oxacillin resistant  Vancomycin intermediate  Quinupristin-Dalfopristin 7.5 mg/kg bid or tid
VISA                                 Linezolid 600 mg bid or oral


MRSA Treatment UK Guidelines 2008

bacteremia, osteomyelitis, abscesses, endocarditis

First line
- Vancomycin (1 g i.v. / 12 hour)
- Teicoplanin (400i 800 mg i.v./24h)
- PLUS gentamicin (6.7 g/kg i.v. once daily/ rifampicin (300 mg po twice daily/ Na-fusidate (3x500 mg po)

Second line
- Linezolid (2x600 mg i.v/po)

Alternative
- Daptomycin (1x4 mg/kg i.v.)
- Tigecycline (100 mg loading dose followed by 50 mg i.v.)
**In vitro susceptibility pattern**

- **MRSA**: 85% Vancomycin, 85% Teicoplanin, 70% Linezolid
- **MSSA**: 95.5% Vancomycin, 88.6% Teicoplanin, 88.8% Linezolid
- **MRSE**: 94.6% Vancomycin, 92.9% Teicoplanin, 92.9% Linezolid
- **MSSE**: 94.6% Vancomycin, 92.9% Teicoplanin, 92.9% Linezolid
- **Strep. pneumoniae**: ND, 100% Teicoplanin, 100% Linezolid
- **Strep. viridans**: ND, 92.9% Teicoplanin, 92.9% Linezolid
- **Strep. Non Group A**: ND, 80% Teicoplanin, ND Linezolid
- **Strep. Non Hemolytic**: ND, 89.7% Teicoplanin, 71.1% Linezolid

**Cipto Mangunkusumo Hospital Jan-June 2007 (Sensitivity Pattern)**

- **Staph. aureus**: 88 isolates
  - MRSA: 40%
- **Staph. epidermidis**: 371 isolates
  - MRSE: 66%

<table>
<thead>
<tr>
<th>Bacteria</th>
<th>Vancomycin</th>
<th>Teicoplanin</th>
<th>Linezolid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Staph. aureus</td>
<td>72</td>
<td>55</td>
<td>86</td>
</tr>
<tr>
<td>Staph. epidermidis</td>
<td>86</td>
<td>52</td>
<td>87</td>
</tr>
</tbody>
</table>
CONCLUSION

- Methicillin Resistant Staphylococcus aureus (MRSA) is a Staphylococcus aureus with oxacillin minimum inhibitory concentration (MIC) \(\geq 4\) microgram/ml based on Clinical Laboratory Standart Institute (CLSI) criteria. This pathogens genotype is identified as a betalactam resistant.

- MRSA infection arises both in the hospital and community setting.

- Complicated Skin and Soft Tissue Infections (cSSTIs) is the most frequent event of MRSA infections and usually has severe and progressive clinical outcome.

- Proper narrow spectrum AB for Gram-positive bacteria is the first choice of therapy after bacterial culture is obtained. A few kind of antibiotics such as: glycopeptide or oxazolindinone is the drug of choice of MRSA infection.

The Power of Anti-infection

THANK YOU