Understanding and Fighting
Methicillin-Resistant Staphylococcus Aureus
“MRSA”

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Methicillin-Resistant Staphylococcus Aureus
“MRSA”

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PharmCon is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education.
Speaker: Michael Barton, MD has served as the chairman of the Infection Control Committee at a community hospital in Pittsburgh for the past 2 years. While continuing to care for patients in the emergency department, he has developed a fascination for community-associated MRSA and a growing concern over the rapid spread of this "superbug". Dr. Barton is a graduate of The Pennsylvania State University with a B.S. in Biology and earned his medical degree at Temple University School of Medicine. His post-graduate training was in Emergency Medicine at Allegheny General Hospital in Pittsburgh.

Speaker Disclosure: Dr. Barton has no actual or potential conflicts of interest in relation to this program

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Understanding and Fighting Methicillin-Resistant Staphylococcus Aureus
“MRSA”

**Target Audience:** Pharmacists, Pharmacy Technicians, Nurses, and Physicians

**Program Overview:** In the battle of man vs. bacteria, a new enemy has emerged as the most feared “superbug” of 2008. Forget West Nile and bird flu – Methicillin Resistant Staphylococcus Aureus (MRSA) is suddenly all over the media. This well deserved media spotlight highlights the increasing danger associated with MRSA infections. This program will review the most recent guidelines for the diagnosis and management of pneumonia and skin and skin-structure infections caused by MRSA. The program includes information on pharmacological treatments, patient counseling, and a question/answer period.

**Objectives:**
1. Identify the epidemiology and differences between CA-MRSA and HA-MRSA, including virulence factors and antibiotic susceptibilities.
2. Outline the virulence mechanism of methicillin resistance in Staphylococcus aureus.
3. Explain the modes of action, efficacy, and advantages and disadvantages of currently available pharmacological therapies for both HA-MRSA and CA-MRSA.
4. Review the conventional actions necessary to prevent MRSA infections in both the clinical and community settings.

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Understanding and Fighting MRSA

1. What is MRSA?
2. Why is it such a problem today?
3. What is Community-associated MRSA?
4. Is it really that serious?
5. How is it treated?
6. How can we prevent it?
What is MRSA?

Methicillin-resistant Staphylococcus aureus
Staph aureus

- Transient skin flora
- Most common cause of skin infections
- Various strains with variety of virulence factors
  - Encoded by phages, plasmids, pathogenicity islands and SCC
- Virulence factors
  - Leukocidin (kills WBC)
  - Exfoliatins (scalded skin syndrome)
  - Toxic shock toxin TSS T1 (Toxic shock syndrome)
  - Enterotoxins (food borne illness)
History of S. aureus Resistance

- 1941 - Introduction of Penicillin into treatment of infectious disease
- 1944 - S. aureus becomes Pen resistant
- 1959 - Methicillin introduced
- 1960’s - MRSA strains emerge
- 1968 - First case found USA
- 1970/80’s - Problem in hospitals (ICU, burn units)
History of S. aureus Resistance

- 1988 2% MRSA
- 1991 29% MRSA
- Today ~ 70% of S. aureus in USA is MRSA
Prevalence of MRSA Colonization

- Carriage rates in the general population range from 2 to 10%.
- Recent pediatric study: 36% s. aureus in nares (9% were MRSA).
- Higher rates among certain populations:
  - Old (nursing home residents)
  - Sick (hospitalized, dialysis)
  - Health care workers (ICU, surgical wards)
    - One study showed up to 70% colonized.
Prevalence of MRSA Infection

- 18-25 cases/100,000 noted in 2001/02 study from CA, GA, and MN
  - Majority SSTIs (77%)
  - 73% resistant to initial antibiotics

- Proportion of Post-op infections with MRSA from 1992 to 2002 increased from 9.2% to 49.3% (NNSI/CDC)
Invasive MRSA Infection Incidence

- For every 100,000 people living in the U.S. there were 32 cases of invasive MRSA in 2005.
- MRSA was responsible for an estimated 94,000 life-threatening infections and 18,650 deaths in 2005.

(CDC report; Oct 17, 2007 *The Journal of the American Medical Association*)
What happened?

Community-associated MRSA
**CA vs. HA MRSA**

**CDC definitions**

- **“Community-associated”**
  - In prior year no hospitalizations, NH, dialysis, surgery, or permanent indwelling devices

- **“associated” vs. “acquired/onset”**
  - Community-acquired = diagnosed in outpatient setting or w/in 48hrs of stay
CA MRSA

- Responsible for dramatic increase in incidence of MRSA
  - Increased rates of invasive MRSA infections
  - Increased skin and soft tissue infections in Emergency Departments
  - Increased mortality among MRSA-related infections
“Four Pediatric Deaths from Community-Acquired Methicillin-Resistant \textit{Staphylococcus aureus} -- Minnesota and North Dakota, 1997-1999”
The Culprit!

USA300
CA MRSA Outbreaks

- Saint Louis Rams in 2003
- Fencers in Colorado
- Prison inmates (MS, GA, TX)
- Children in Tennessee
- Gay men in California
USA 300 MRSA Strain

- Originated in the community
- “A single clone of CA MRSA accounts for the majority of infections”

CA vs. HA MRSA Genetics

- **Community Associated**
  - USA300 and USA400 PF-types
  - Carry SCCmec IV gene

- **Healthcare Associated**
  - USA100 and USA200 PF-types
  - Carry the SCCmec types II and III

CA vs. HA Characteristics

- **CA MRSA**
  - “multi-drug susceptible”
  - Produce super-antigens (SEB, SEC, and TSST-1)

- **HA MRSA**
  - “multi-drug resistant”
  - Fewer toxins produced
CA MRSA in the hospital

USA300 accounted for 34% of MRSA BSI over a 7 mo period in 2004 at Grady Memorial Hospital in Atlanta

Methicillin-resistant S. Aureus

- More frequent development of symptomatic infections
- Skin and STI are most common
  - Furuncles, impetigo
  - Large, painful skin abscesses
MRSA in the ED

- MRSA the most common cause of SSTI among ED patients (76%)
- USA300 accounted for 97% of MRSA isolates and 31% of MSSA isolates

MRSA in the ED

SSTI
- 1993 1.2 million visits
- 2005 3.5 million visits
- After 2001 increasing use of antibiotics effective against MRSA
  - 51% TMP/SMX in 2005


“Increased US Emergency Department Visits for Skin and Soft Tissue Infections, and Changes in Antibiotic Choices, During the Emergence of Community-Associated MRSA"
How bad can it get?

- Higher fatality rates
  - 2X more likely to die from MRSA than MSSA
- Pyomyositis, necrotizing fasciitis, septic thrombophlebitis
- Necrotizing pneumonia
  - Lung necrosis, empyema
  - Rapid progression to death within 48 to 72 hours
MRSA Pneumonia

- Severe necrotizing pneumonia
  - Hemoptysis
  - Necrotic appearance on CXR
  - Recent influenza
MRSA Pneumonia

- S. aureus is most common cause of Hospital-acquired pneumonia
- MRSA nosocomial pneumonia has been associated with significantly poorer outcomes than MSSA pneumonia
Treatment of MRSA Pneumonia

Antibiotic Options

- vancomycin
- quinupristin/dalfopristin
- linezolid
- daptomycin
- tigecycline
Vancomycin

- 2g/day (15mg/kg q12hr)
  - Goal is trough concentration 15-20 mcg/mL
- Poor lung perfusion
- Failure rates up to 40% reported
Treatment of MRSA Pneumonia

- **Linezolid (Zyvox)**
  - Oxazolidinone
  - 100% bioavailability
  - Epithelial lining fluid levels exceed plasma concentrations
    - May benefit those with empyema/loculations/abscess
  - Aerobic gram positive organisms
Treatment of MRSA Pneumonia

- No definite superiority to vancomycin in studies to date

- Side effects
  - Serotonin syndrome (weak MOA inhibitor)
  - thrombocytopenia
  - neuropathies
Management of MRSA Infections

- Consider in all cases of skin and soft tissue infections
  - esp. abscesses and "spider bites"
- Consider in sepsis, osteomyelitis, septic arthritis, severe pneumonia, necrotizing fasciitis
- Culture all pus!
- Blood cultures?
  - Severe disease (sepsis, lymphangitis)
Management of SSTI Infections

**Recommendations:**

- **Culture all wounds!**
- **I&D alone may be adequate. Consider antibiotics on individual basis:**
  - severity and rapidity of progression
  - surrounding cellulitis (>5cm diam)
  - signs/symptoms of systemic illness
  - Co-morbidities (DM, malignancy, HIV)
  - extremes of age
  - unable to drain completely
Antibiotic Options

- **Bactrim**
  - Not FDA approved for use in staph but it works.
  - GAS commonly resistant (consider adding Beta-lactam if cellulitis)

- **Tetracycline/minocycline/doxycycline**
  - Limited studies to support efficacy in invasive infections
  - Not in children/pregnancy
  - Also need double coverage for Strep
Antibiotic Options

- **Clindamycin**
  - High level of resistance in HA strain
  - Increased incidence of C. diff colitis

- **Levaquin**
  - High prevalence of resistance
  - Not recommended first line
Vancomycin

- For severe infections requiring hospitalization
- Must be given IV
- “Red man syndrome”
- Ototoxic
- Thrombophlebitis
Newer Agents

- **Linezolid (Zyvox)**
  - VERY effective, but VERY expensive
  - Available orally
  - Resistance has been reported
  - Myelosuppression with prolonged use

- **Tigecycline (Tygacil)**
  - glycylcycline
  - FDA approved for complicated SSTI and intraabd infxns (not pneumonia)
  - Active against MRSA and VRE
Newer Agents

- **Quinupristin-dalfopristin (Synercid)**
  - Not approved for MRSA infections
  - Poor tolerability profile (arthralgias, myalgias, thrombophlebitis)
  - Need central line

- **Daptomycin (Cubicin)**
  - FDA approved in 2003 for MRSA – bactericidal
  - Dose dependant myopathy
  - Not for pneumonia, CNS or bone
Newer Agents

- Ceftobiprole
  - “fifth generation”
  - Phase III trials for treatment of nosocomial pneumonia
  - Phase II trials for complicated STTI
  - Bacteriocidal

Clin Infect Dis 2008;46:647-655, 656-658
The Problem

CA MRSA is spreading fast!
Controlling the Spread of MRSA

Graph showing the percentage of resistant cases from 1960 to 2002. The graph compares USA (ICUs) and Denmark (BSIs) with a gradual increase in resistant cases over time.
CA MRSA Risk Factors

- Crowding
- Person to person contact (athletes)
- Contact with wounds
- Poor hygiene
- Low socioeconomic status
- IVDA
- Homosexuals
- Prisoners
HA MRSA Risk Factors

- Previous antibiotic use
- >8.4 days in hospital
- Indwelling catheters/IVs
- Surgical procedures
- Dialysis
- Diabetes
- Nursing Home Residents
The Solution

Hygiene!

Antibiotic stewardship!

Education!
Questions?