

# Disclosure

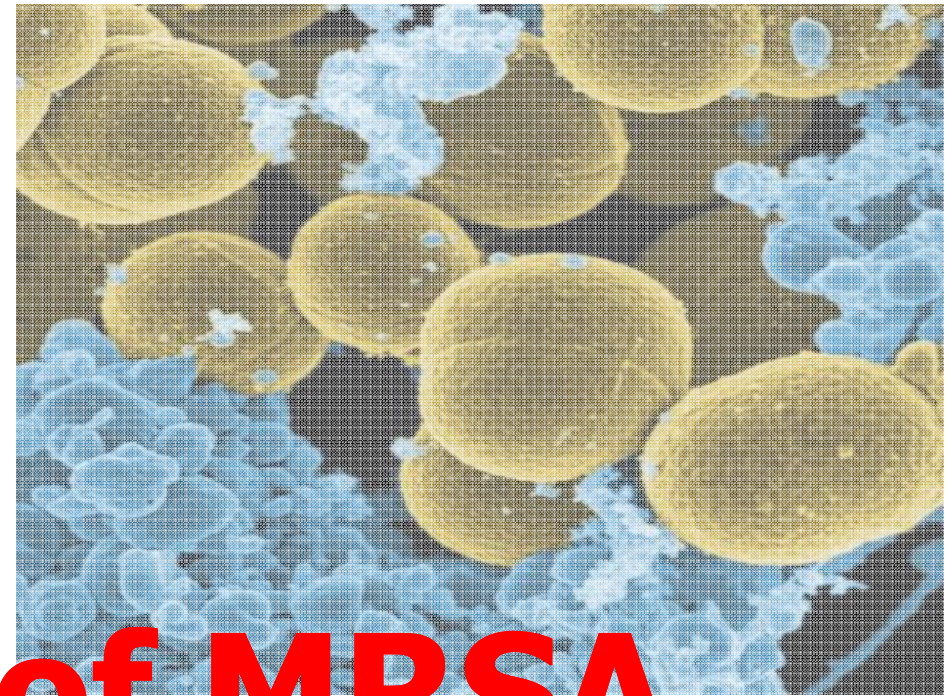
- Director for Clinical R & D & Medical Affairs, GSK Philippines



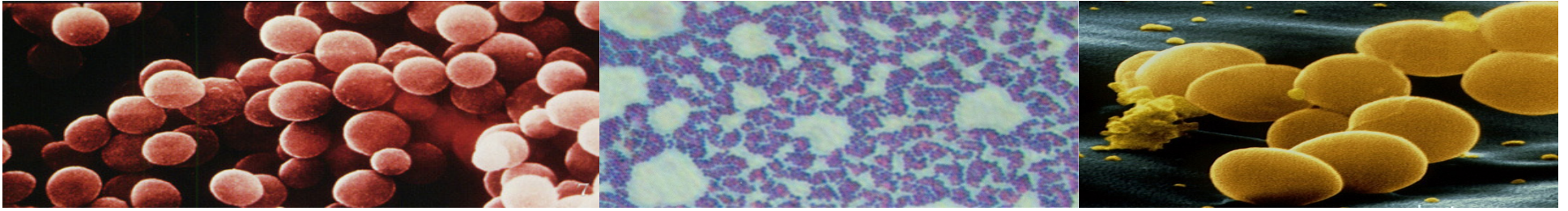


# Menace of MRSA

Salvacion R. Gatchalian, MD  
FPPS, FPIDSP, FPSMID

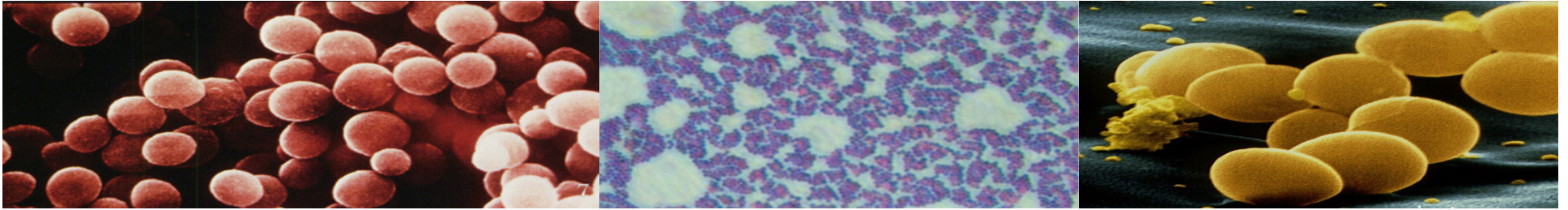






# The Organism

- **Commensal**
- **Colonizes nares, axillae, vagina, pharynx, and/or damaged skin surfaces**
- **Infection occur w/breach of skin or mucosal barriers**
- **Major cause of invasive infections**
- **Major cause of healthcare associated (HA) and community associated (CA) Infections**

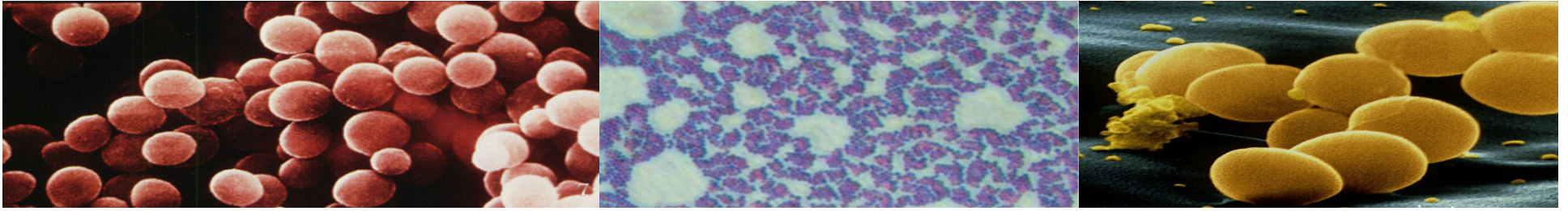


# The Organism

- **Emergence of drug-resistant strains in 1960s, MRSA**
  - ✿ **Therapeutic challenge**
- **Account for >50% of all strains causing clinical disease**
- **MRSA is etiologic agent for common skin infections to more serious manifestations**
- **Molecular Diagnostic Techniques**
  - ✿ **Rapid identification**
- **Newer antimicrobials not established as safe and effective in children**
- **Limited pharmacokinetic data**

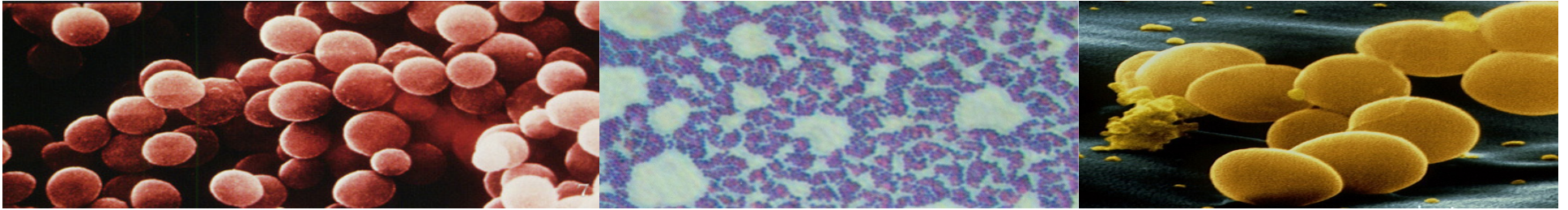
Boucher et al CID 2010:51 (Suppl2) pp 183-197

Long et al Expert Rev Anti-infective Ther 2012:8(2); 183-185



## **Antibiotic Resistance to *S. aureus***

- **Decade after introduction of Pen in 1950s, antibiotic resistance present in hospitals in US**
- **First case reported in UK after introduction of semi synthetic penicillins**
- **In US, 7 years later case of MRSA documented**
- **Mid 1980s, MRSA seen in large urban medical centers**
  - ✿ **Prevalence rate 5 – 10%**
  - ✿ **Smaller community hospitals, 20%**
  - ✿ **Larger urban centers, 40%**



## Incidence of MRSA Infections

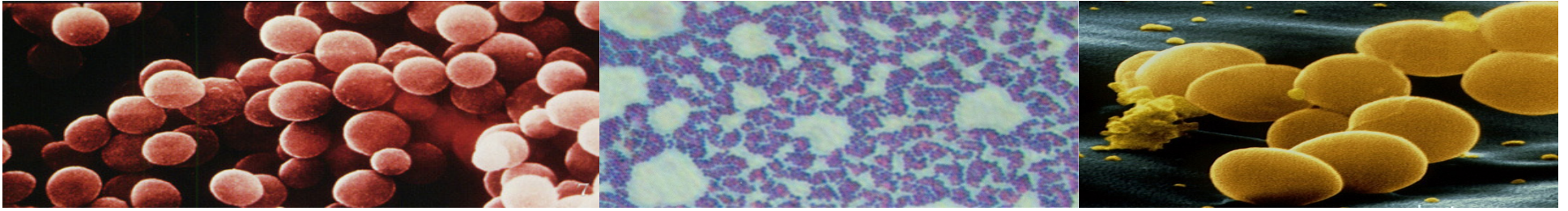
- **EU MRSA affects >150,000 patients annually**
- **Pan-European Surveillance data on bloodstream infections**
  - ✱ **Marked variability among EU member states on proportion of *S. aureus* that is MRSA**
    - **<1% - >50%**
- **Initially nosocomial pathogen limited to healthcare facilities**
- **Emerged as major community associated organism**
- **Initial cases of MRSA in non-hospitalized adults associated with:**
  - ✱ **Drug abuse**
  - ✱ **Previous antimicrobial therapy**
  - ✱ **Prior hospitalization**

Long et al Expert Rev Anti-infective Ther 2012;8(2); 183-185

Koch et al Euro Surveil 2010;15 (41); Oct 2010

Boucher et al CID 2010;51 (Suppl2) pp 183-197



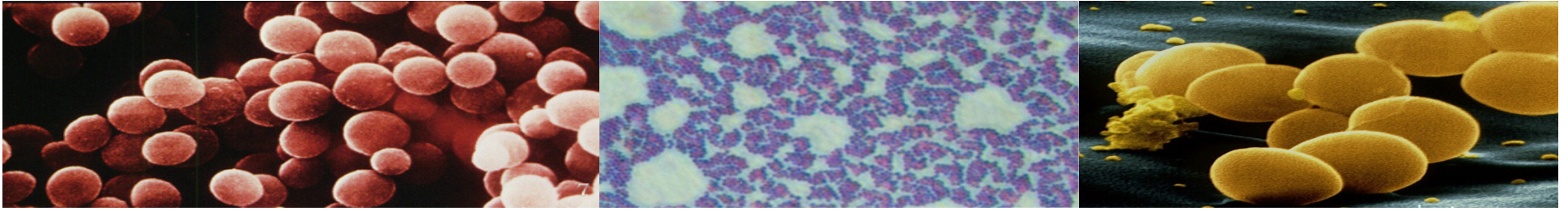


## Incidence of MRSA

- **1990s, CA-MRSA no identified risk factors in children**
- **Retrospective Study demonstrated**
  - ✱ **Prevalence of CA-MRSA w/o identified factors increased from 10 per 100,000/admission in 1988 - 1990 to 259/100,000 in 1993 – 1995 urban hospital**
- **Rapid development of resistance**
- **Resistance to Pen noted a year after introduction**
- **1950s 75% of strains in large hospitals Pen resistant**

NEJM 1955;253: 909-22

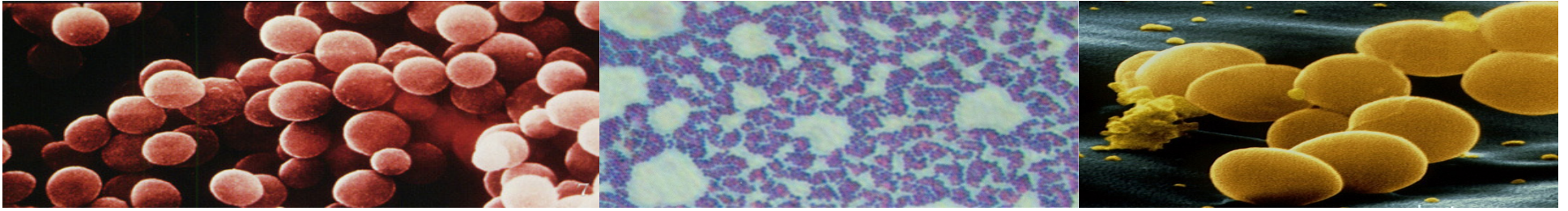
Herold et al JAMA 1998; 279:593-8



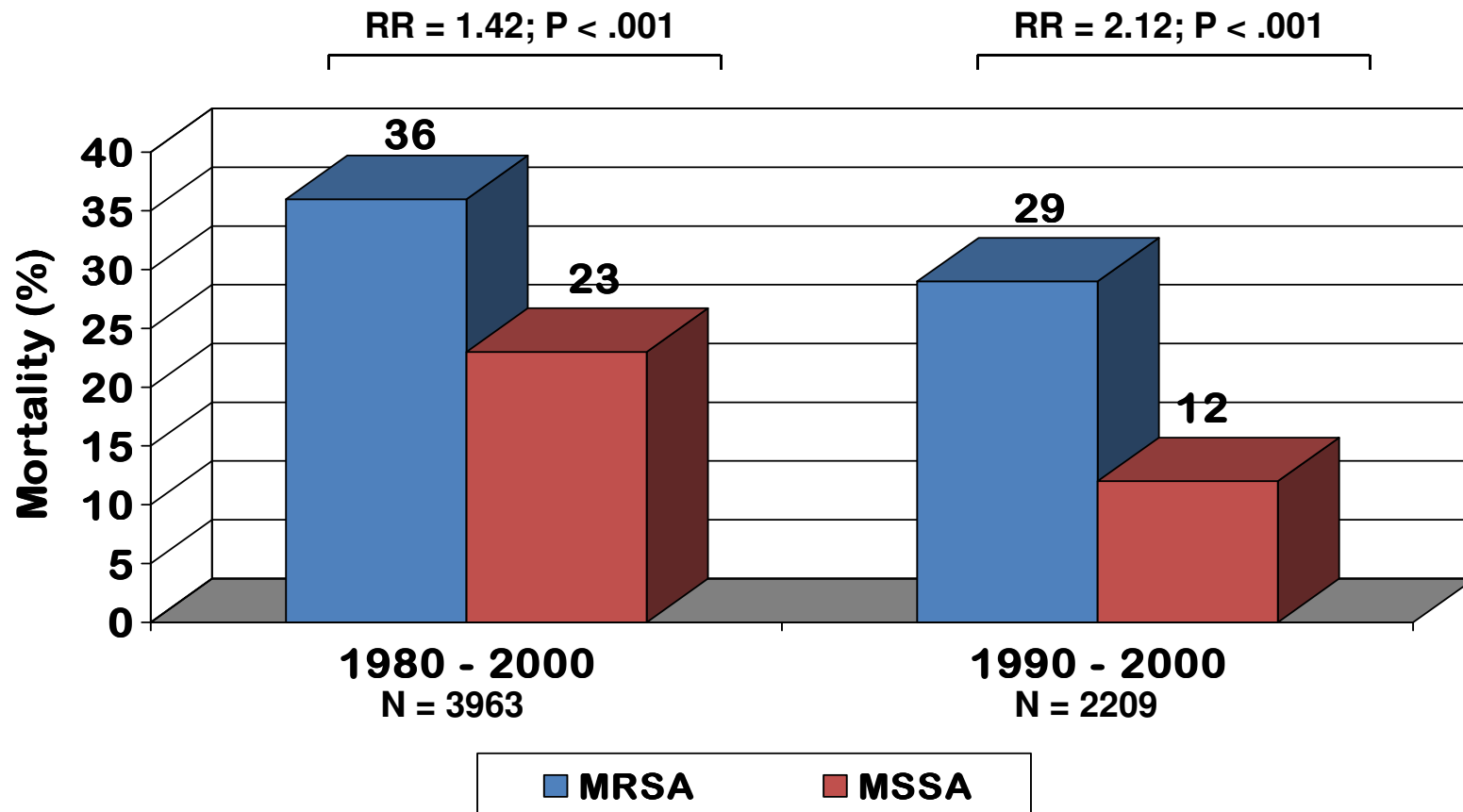
## Incidence of MRSA

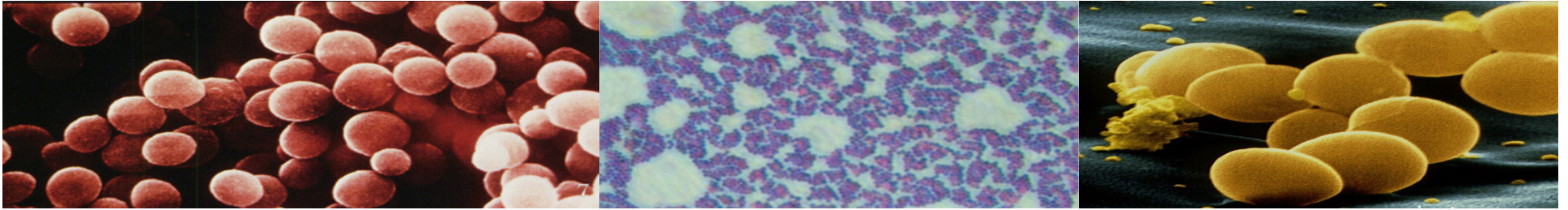
- **Currently, MRSA accounts for 60% of clinical *S. aureus* from ICU**
- **Retrospective study by Aragon et al Jan 2007-Dec 2008**
  - ✿ **Reviewed 219 records**
  - ✿ **40.64% had MSSA**
  - ✿ **15.07% had CA MRSA**
  - ✿ **44.3% had HA MRSA**
  - ✿ **Prevalence of CA MRSA is 7 per 1000 admissions**



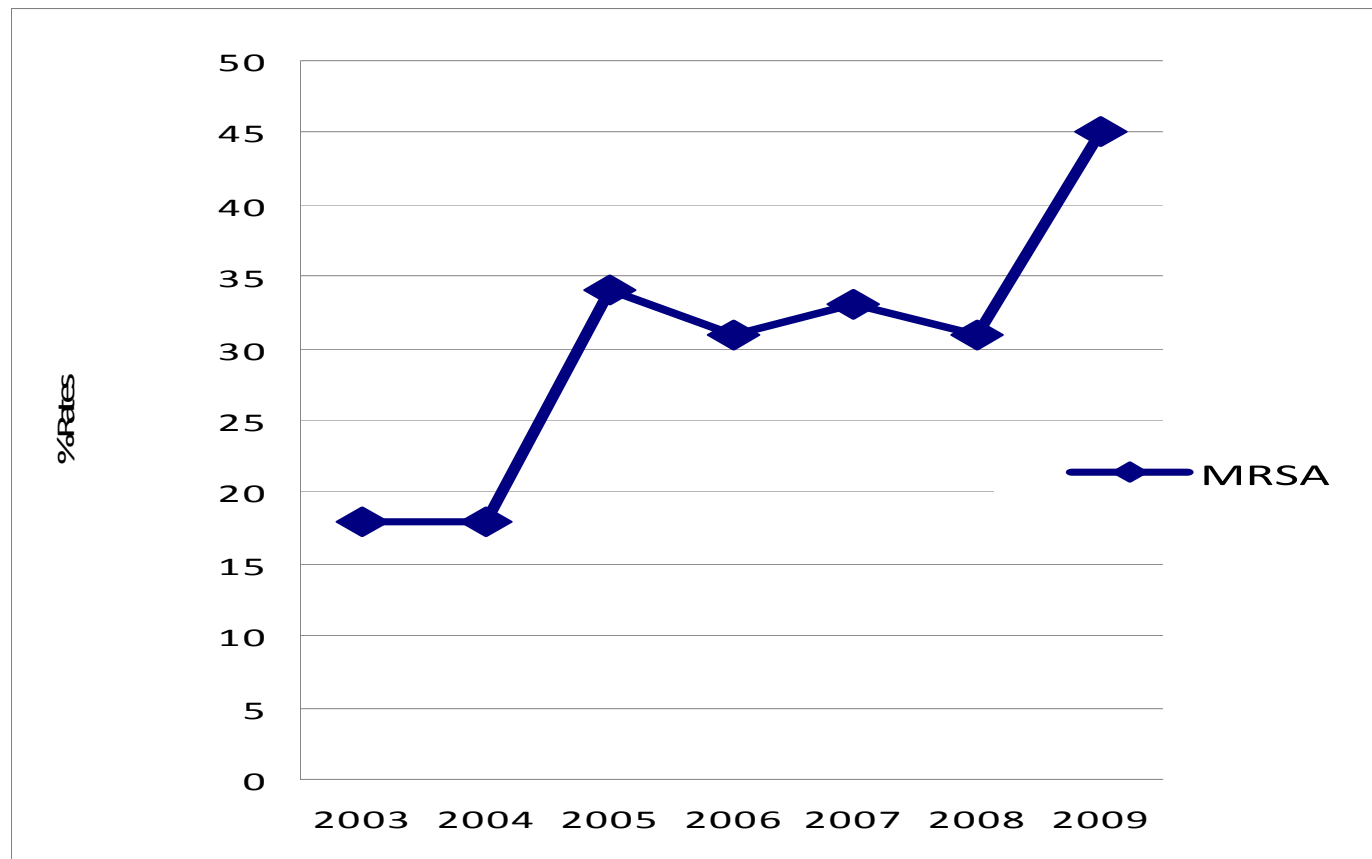


# Mortality of MRSA and MSSA



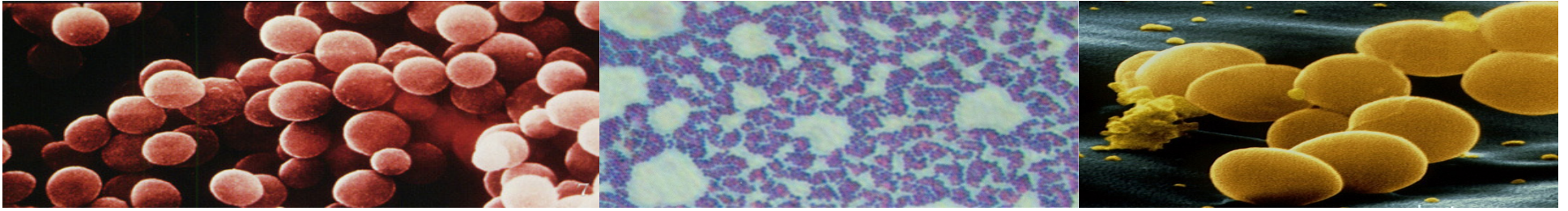


## MRSA SURVEILLANCE RATES 2003-2007: ANTIMICROBIAL RESISTANCE SURVEILLANCE PROGRAM (ARSP)

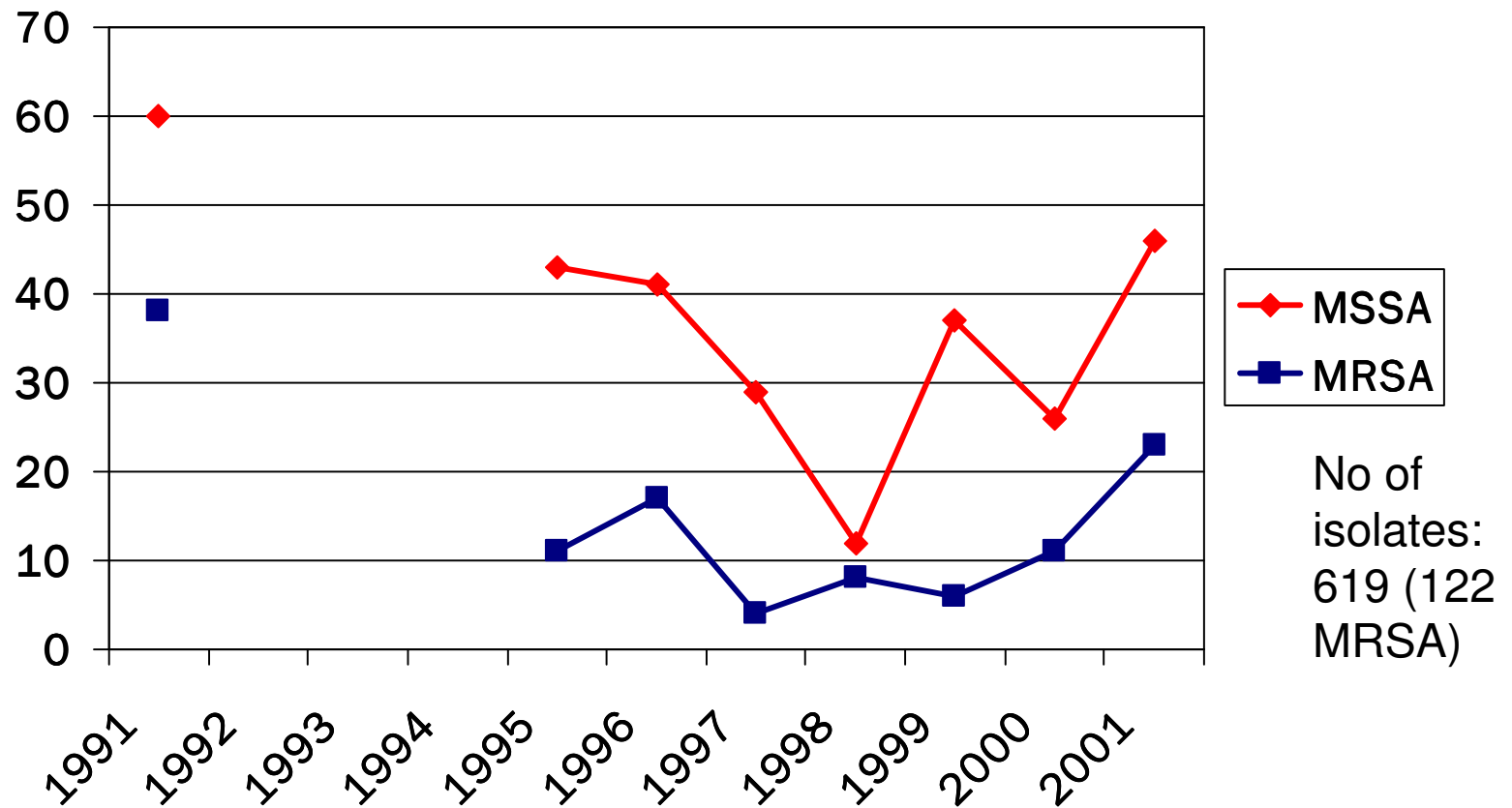


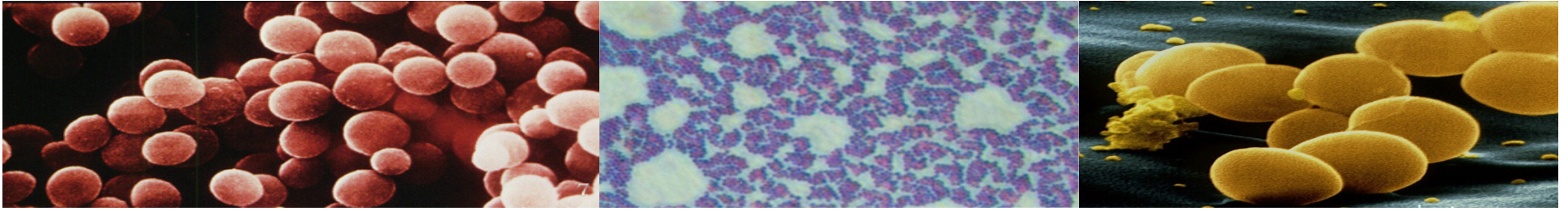
Carlos C, ARSP



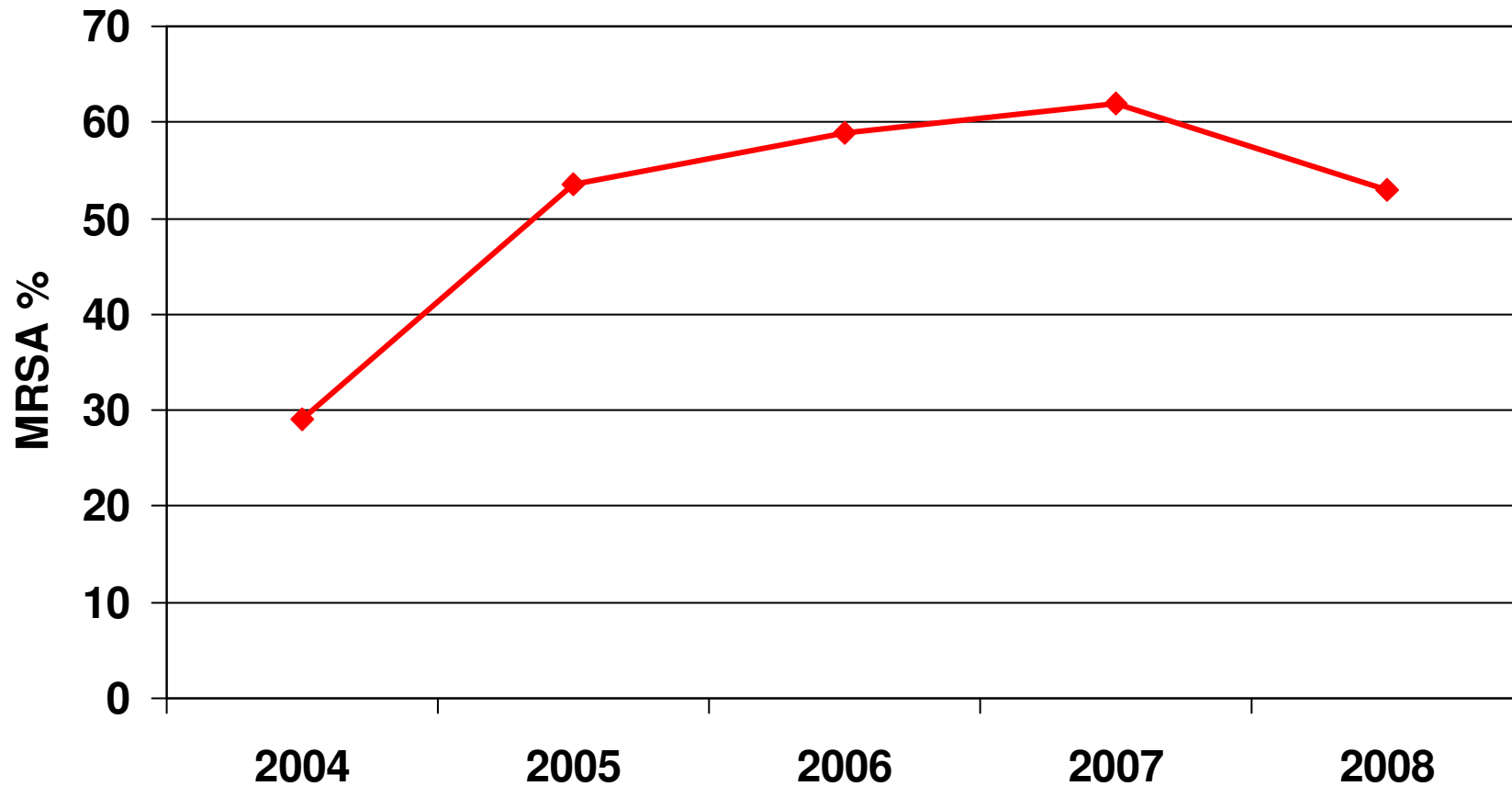


## PCMC Data: Selected Years



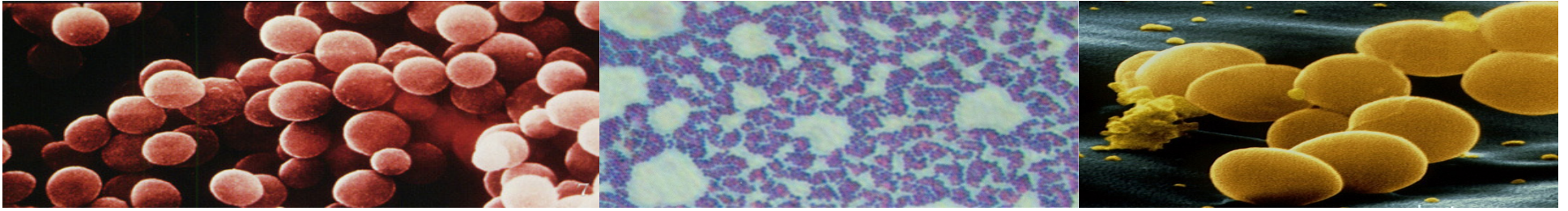


## Percentage of MRSA over total *S. aureus* isolates at PCMC from 2004-2008



Source: ICC, PCMC





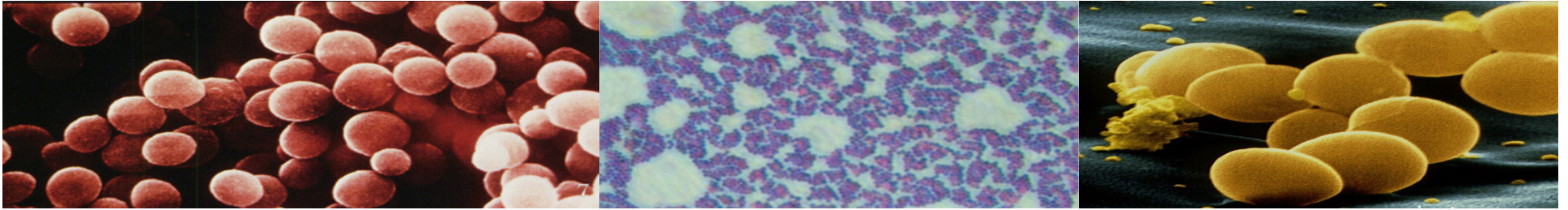
## What are MRSA'S?

- **oxacillin MIC  $\geq$  4 mcg/mL\***
- **MIC's of 4 to 8 mcg/mL : borderline or low level resistance**
- **resistant to all beta-lactams, including cephalosporins**
- **mediated by mecA gene, found in all resistant strains, which codes for PBP2a\*\***
- **mecA is part of mobile Staphylococcal cassette chromosome or SCCmec (5 types)\*\*\***

\*Clinical and Laboratory Standards Institute 2006

\*\*Inglis et al, J Gen Microbiol 1988 ; Tesch et al, Antimicrob Agents Chemother 1988

\*\*\*Oliveira et al , Microb Drug Resist 2001 ; Ito et al, Antimicrob Agents Chemother 2004



## Classification of MRSA

### ■ HA-MRSA\*

- 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

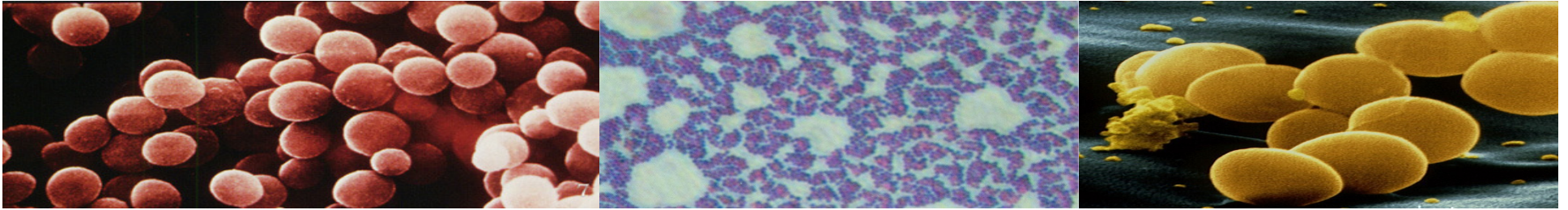
### ■ CA-MRSA\*\*

- onset in the community in a patient who is without risk factors for HA-MRSA

\*Klebens et al, JAMA 2007; Fridkin et al, N Engl J Med 2005

\*\* Fridkin et al, N Engl J Med 2005; Gorwitz RJ, Pediatr Infect Dis J. 2008





## Microbiological Differences

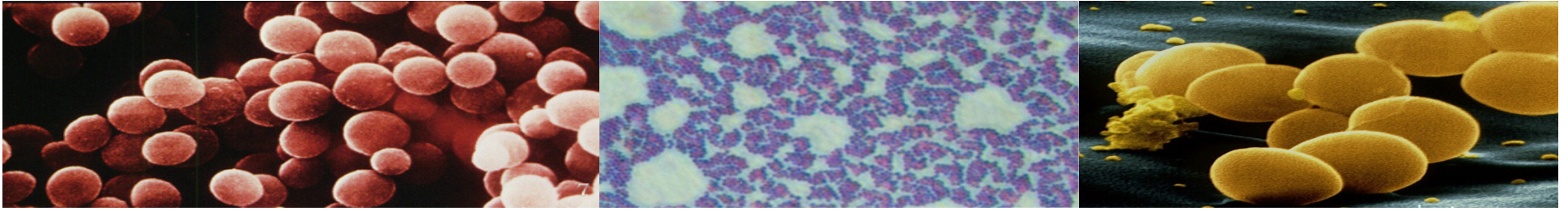
### HA-MRSA

- **mostly associated with SCCmec types I, II, and III**
- ***multidrug resistant (usu. to 3 or more agents)\****

### CA-MRSA

- **associated with SCCmec type IV and, sometimes, type V**
- ***often not multidrug resistant to non-beta lactam agents e.g. clindamycin, fluoroquinolones, tetracyclines, mupirocin\****
- **many are PVL + : **increased morbidity in children with osteomyelitis and mortality in *S. aureus* pneumonia\*\*****
- ***resistance increasing***

\*Naimi et al, JAMA 2003; Deserinski, Clin Infect Dis 2005; Ma et al, Antimicrob Agents Chemother 2002; \*\* Baba, Lancet 2002; Diep et al, J Infect Dis 2006; Diep et al, Lancet 2006; \*\* Gillet et al, Lancet 2002; Martinez-Aguilar et al, Pediatr Infect Dis J 2004; Bocchini et al, Pediatrics 2006; \*\*\*Han et al, J Clin Microbiol. 2007; Styers et al, Ann Clin Microbiol Antimicrob. 2006



# Clinical Presentation



**MRSA**  
(Methicillin resistant *Staphylococcus aureus*)



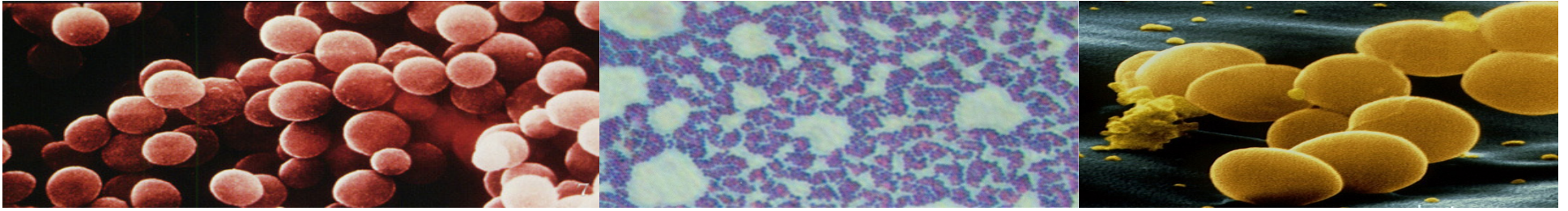
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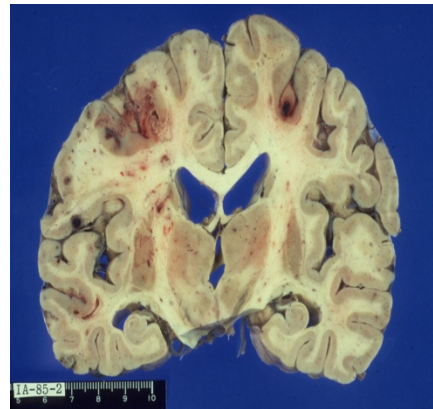
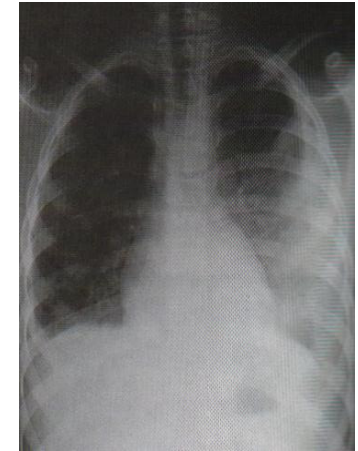
Photo Credit: Gregory Moran, M.D.





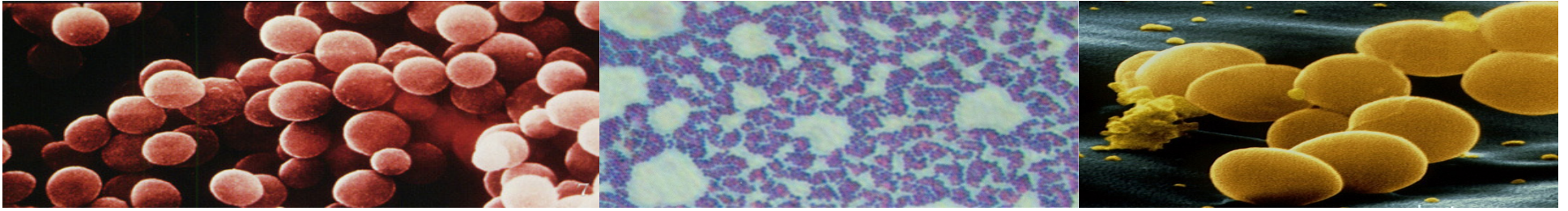


# Clinical Presentation



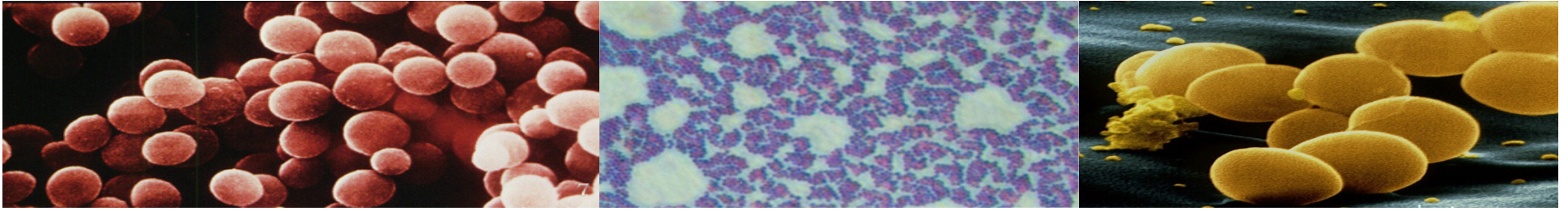
Mandell, Atlas of Infectious Diseases; cases from Phil. Children's Medical Center





## Management of MRSA

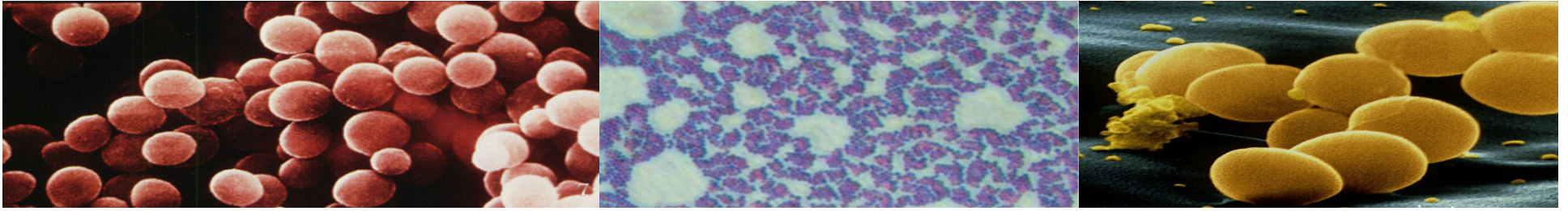
- Mainstay of treatment
- Vancomycin is 1<sup>st</sup> line therapy
- Efficacy in children limited
- IDSA has issued 1<sup>st</sup> Clinical Practice Guidelines for treatment of MRSA in adults and children
  - ✿ Synthesize current information
  - ✿ Address the management of a variety of clinical syndromes



# Clinical Practice Guidelines

**What is the management of skin and soft-tissue infections (SSTIs) in the era of community-associated MRSA (CA-MRSA)**

- **Cutaneous abscess**
  - ✱ **Incision and drainage**
- **Antibiotic therapy**
  - ✱ **Recommended for the following**
    - **Severe or extensive disease**
    - **Rapid progression in presence of associated cellulitis**
    - **Signs and symptoms of systemic illness**
    - **Associated comorbidities or immunosuppression**
    - **Extremes of age**
    - **Abscess in an area difficult to drain**



# Clinical Practice Guidelines

## ■ Antibiotic therapy

### ✱ Recommended for the following

- Associated septic phlebitis
- Lack of response to I & D alone

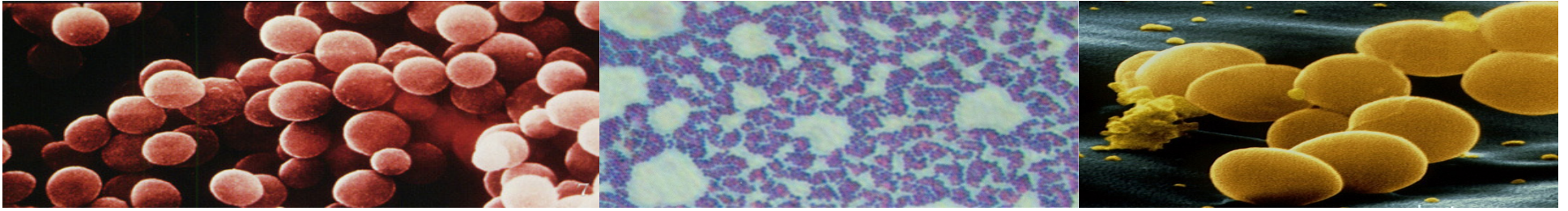
## ■ Purulent cellulitis

- ✱ Empirical therapy for CA-MRSA pending culture results
- ✱ Empirical therapy for  $\beta$  – hemolytic strep not necessary
- ✱ 5 – 10 days therapy recommended

## ■ Non-purulent cellulitis

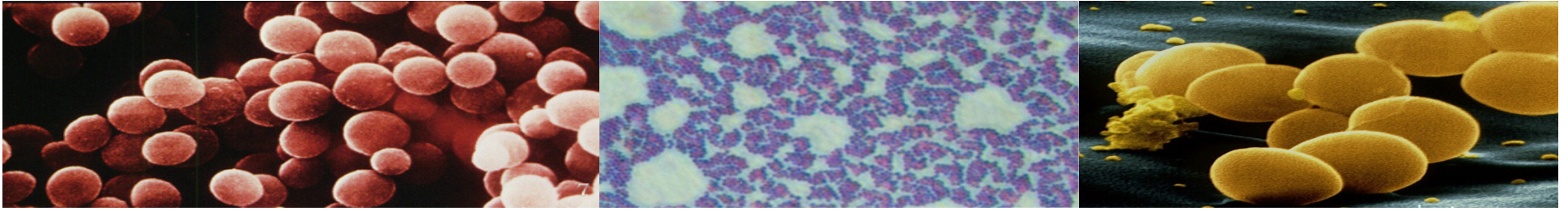
- ✱ Empirical therapy for  $\beta$  – hemolytic strep recommended
- ✱ Empirical coverage for CA-MRSA recommended if no response to  $\beta$  – lactam therapy





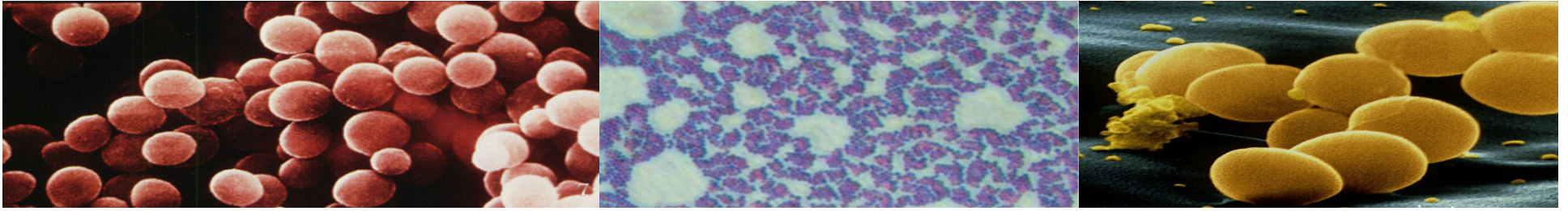
# Clinical Practice Guidelines

- **Non-purulent cellulitis**
  - ✱ Empirical therapy for  $\beta$  – hemolytic strep recommended
  - ✱ Empirical coverage for CA-MRSA recommended if no response to  $\beta$  – lactam therapy
  - ✱ 5 – 10 days therapy recommended
- **Empirical coverage of CA-MRSA with SSTI**
  - ✱ Oral antibiotic options
    - Clindamycin
    - TMP-SMX
    - Tetracycline
    - Linezolid



# Clinical Practice Guidelines

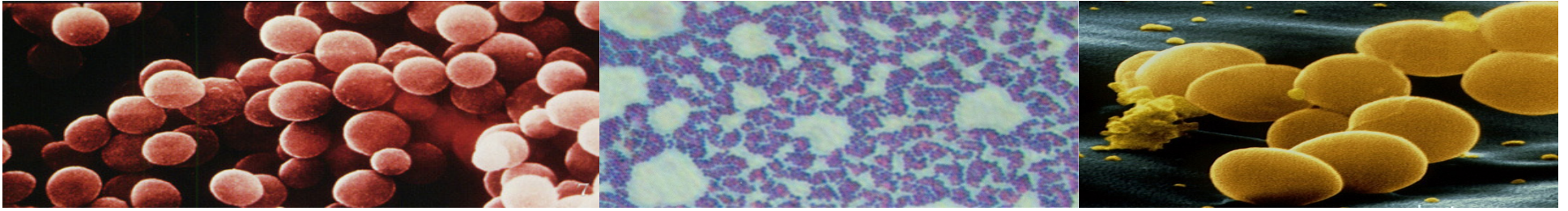
- **Empirical coverage of CA-MRSA**
  - ✿ **If  $\beta$  – hemolytic strep and CA-MRSA desired:**
    - **Clindamycin alone**
    - **TMP-SMX**
    - **Tetracycline +  $\beta$  – lactam**
    - **Linezolid alone**
- **Use of rifampin as a single agent or as adjunctive therapy for the treatment of SSTI is not recommended**



# Clinical Practice Guidelines

- Hospitalized patients with complicated SSTI
  - ✿ Surgical debridement and broad-spectrum antibiotics
  - ✿ Empirical therapy for MRSA considered pending culture data
    - Options include the following:
      - Intravenous (IV) vancomycin
      - Oral (PO) or IV linezolid twice daily
      - Daptomycin 4 mg/kg/dose IV once daily
      - Telavancin 10 mg/kg/dose IV once daily
      - Clindamycin 600 mg IV or PO 3 times a day
      - $\beta$ -lactam antibiotic (eg, cefazolin) may be considered in hospitalized patients with nonpurulent cellulitis with modification to MRSA-active therapy if there is no clinical response
      - Seven to 14 days of therapy is recommended but should be individualized on the basis of the patient's clinical response





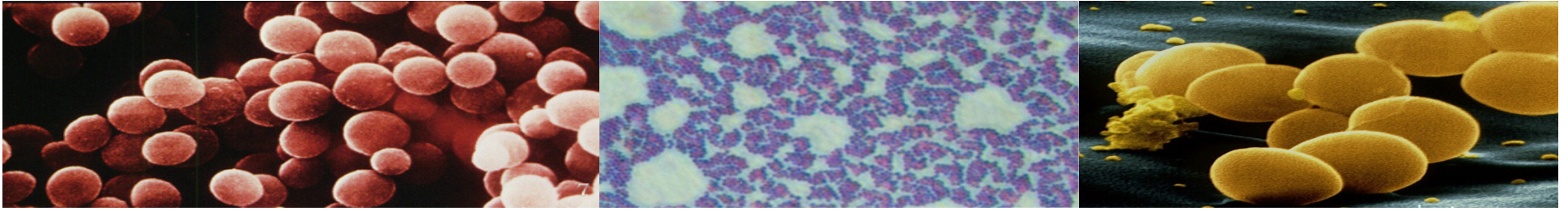
# Clinical Practice Guidelines

## ■ Cultures are recommended in the following:

- ✿ Antibiotic therapy
- ✿ Severe local infection
- ✿ Signs of systemic illness
- ✿ Not responded adequately to initial treatment
- ✿ Concern for a cluster or outbreak

## ■ Pediatric considerations

- ✿ Children with minor skin infections
  - ➔ Mupirocin 2% topical ointment can be used
- ✿ Tetracyclines not used in children < 8 years

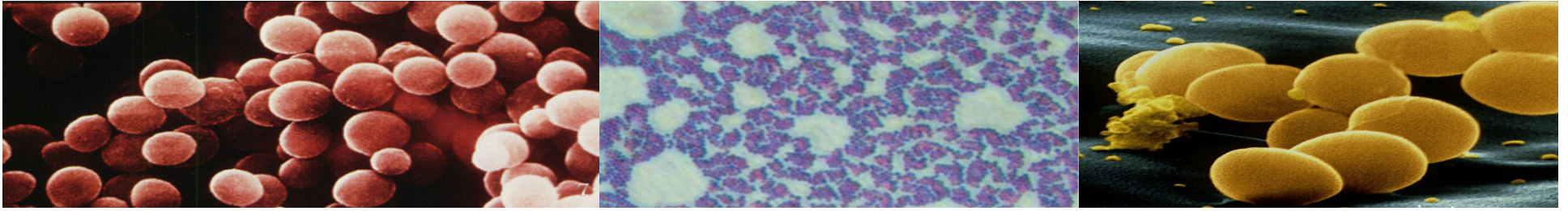


# Clinical Practice Guidelines

## ■ Pediatric considerations

### ✿ Hospitalized children with cSSTI

- Vancomycin recommended
- Empirical therapy with clindamycin 10–13 mg/kg/dose IV every 6–8 h is an option if the clindamycin resistance rate is low
- Linezolid 600 mg PO/IV twice daily for children  $\geq 12$  years of age and 10 mg/kg/dose PO/IV every 8 h for children  $< 12$  years of age is an alternative

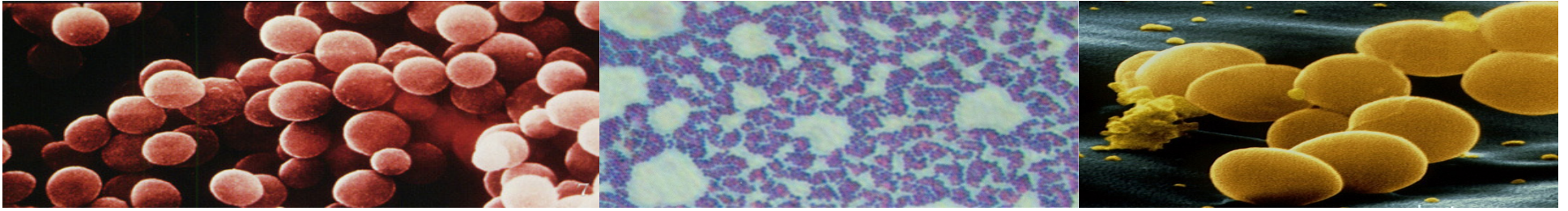


# Clinical Practice Guidelines

## What is the management of recurrent MRSA SSTIs

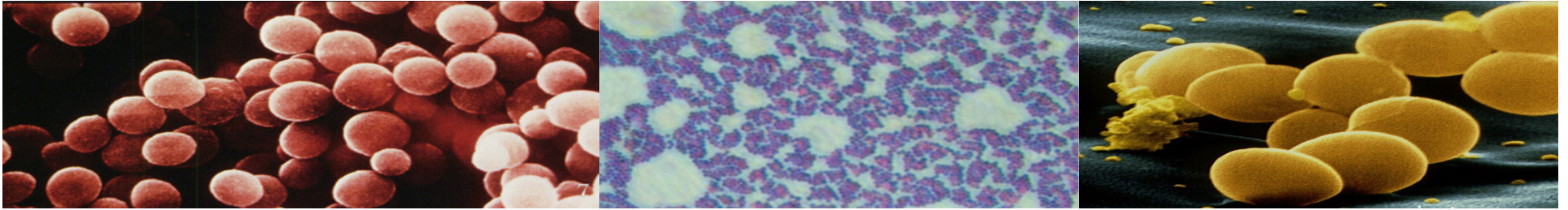
- Preventive education messages on personal hygiene
- Appropriate wound care
- Environmental hygiene measures
- Decolonization considered in selected cases if:
  - ✱ Develops a recurrent SSTI despite optimizing wound care and hygiene measures
  - ✱ Ongoing transmission in household
- Decolonization strategies offered
  - ✱ Nasal decolonization with mupirocin twice daily for 5–10 days





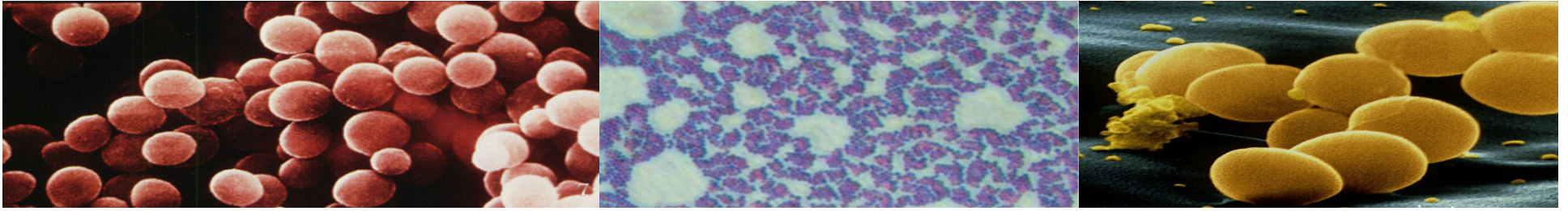
# Clinical Practice Guidelines

- Oral antimicrobial therapy recommended for the treatment of active infection
- An oral agent in combination with rifampin, if the strain is susceptible
- In cases where household or interpersonal transmission is suspected:
  - ✱ Personal and environmental hygiene measures
  - ✱ Contacts should be evaluated for evidence of *S. aureus* infection:
    - Symptomatic contacts should be evaluated and treated
    - Nasal and topical body decolonization strategies considered
    - Nasal and topical body decolonization of asymptomatic household contacts



## Clinical Practice Guidelines

- **Role of cultures in the management of recurrent SSTI is limited:**
  - ✱ **Screening cultures prior to decolonization not routinely recommended**
  - ✱ **Surveillance cultures following a decolonization are not routinely recommended in absence of active infection**

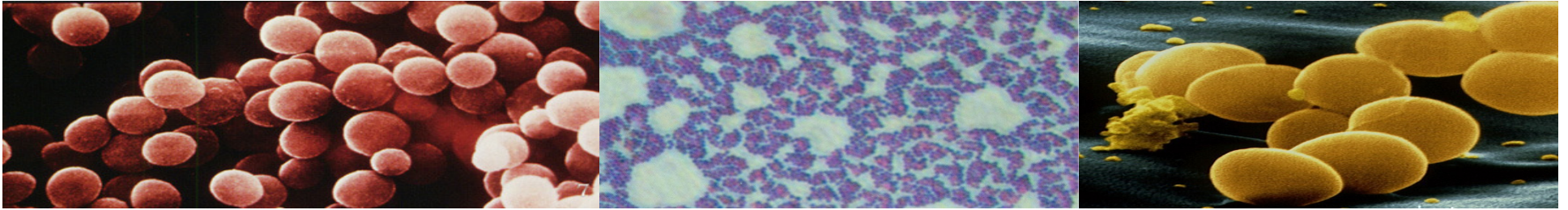


## Clinical Practice Guidelines

### What is the management of MRSA bacteremia and infective endocarditis

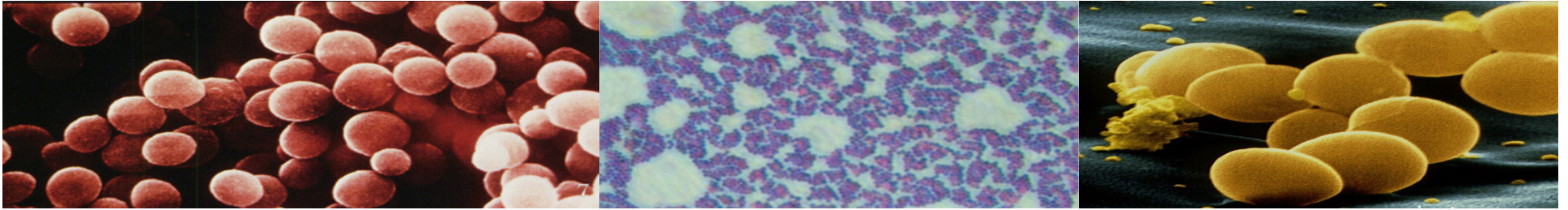
- **Bacteremia and Infective Endocarditis, Native Valve**
  - ✿ **Addition of gentamicin to vancomycin not recommended**
  - ✿ **Addition of rifampin to vancomycin not recommended**
  - ✿ **Clinical assessment to identify source and extent of infection with elimination and/or debridement of other sites of infection should be conducted**
  - ✿ **Additional blood cultures 2–4 days after initial positive cultures**





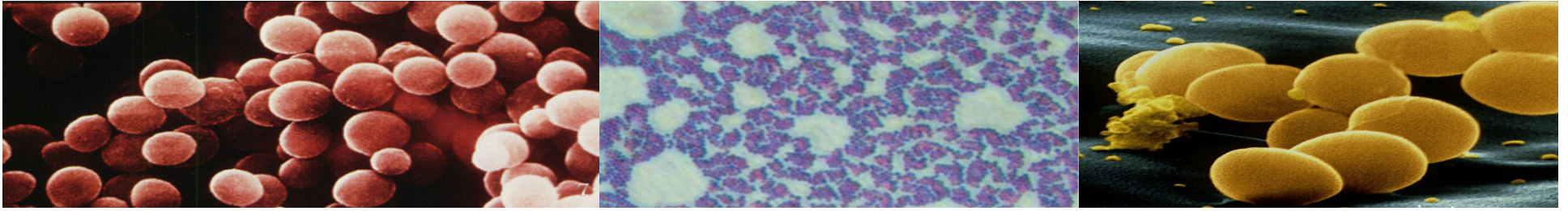
# Clinical Practice Guidelines

- **Bacteremia and Infective Endocarditis, Native Valve**
  - ✿ **Evaluation for valve replacement surgery is recommended**
    - **Large vegetation**
    - **Occurrence of  $\geq 1$  embolic event during the first 2 wks of therapy**
    - **Severe valvular insufficiency**
    - **Valvular perforation or dehiscence**
    - **Decompensated heart failure**
    - **Perivalvular or myocardial abscess**
    - **New heart block**
    - **Persistent fevers or bacteremia**



# Clinical Practice Guidelines

- **Infective Endocarditis, Prosthetic Valve**
  - ✿ **Vancomycin + Rifampin every 8 h for at least 6 weeks + Gentamicin every 8 h for 2 weeks**
  - ✿ **Early evaluation for valve replacement surgery**
- **Pediatric consideration**
  - ✿ **In children, Vancomycin every 6 h is recommended for the treatment of bacteremia and infective endocarditis**
  - ✿ **Duration of therapy 2 to 6 weeks**
    - **Depending on source, presence of endovascular infection, and metastatic foci of infection**
    - **Daptomycin 6–10 mg/kg/dose IV once daily may be an option**
    - **Clindamycin or Linezolid should not be used if there is concern for infective endocarditis or endovascular source of infection**
      - **May be considered in children whose bacteremia rapidly clears and not related to an endovascular focus**

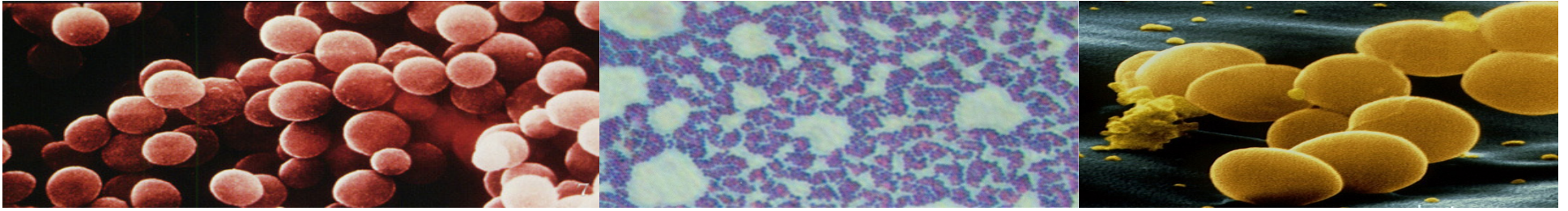


# Clinical Practice Guidelines

## ■ Pediatric consideration

- ✱ Data insufficient to support routine use of combination in children with bacteremia or infective endocarditis; decision to use combination individualized.
- ✱ Echocardiogram is recommended in children
  - Congenital heart disease
  - Bacteremia more than 2–3 days in duration
  - Other clinical findings suggestive of endocarditis

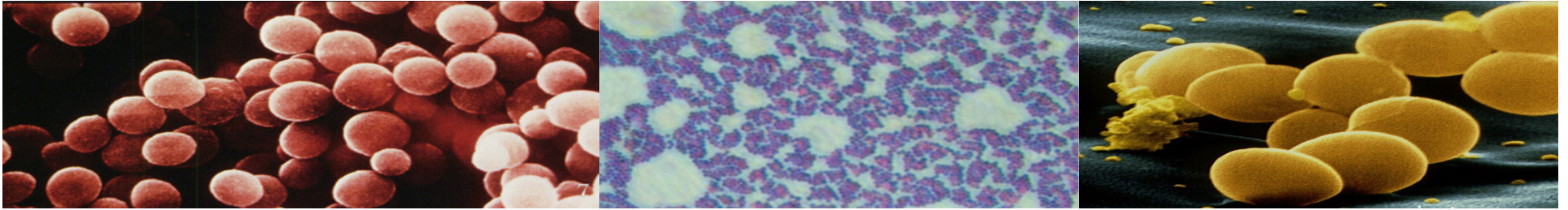




# Clinical Practice Guidelines

## What is the management of MRSA pneumonia?

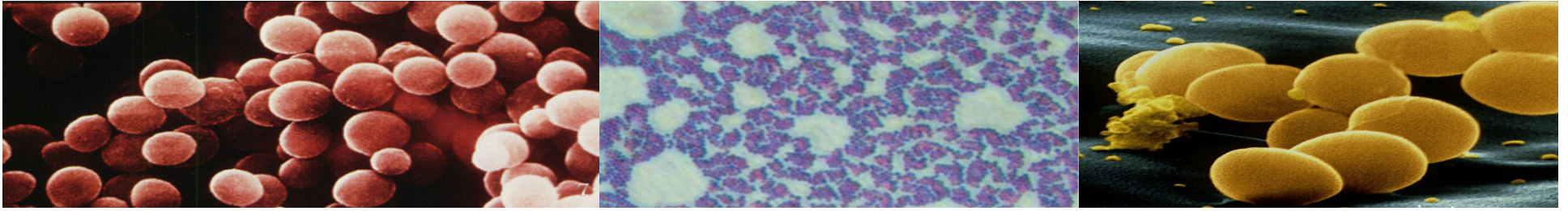
- Hospitalized patients with severe community-acquired pneumonia
  - ✿ Therapy for MRSA is recommended pending culture results
- Health care–associated MRSA (HA-MRSA) or CA-MRSA pneumonia
  - ✿ IV vancomycin
  - ✿ Linezolid
  - ✿ Clindamycin
  - ✿ If susceptible, recommended 7–21 days
- MRSA pneumonia complicated
  - ✿ Antimicrobial therapy against MRSA used in conjunction with drainage procedures



# Clinical Practice Guidelines

## ■ Pediatric considerations

- ✿ IV vancomycin is recommended
- ✿ If the patient is stable, Clindamycin 10–13 mg/kg/dose IV every 6–8 h used as empirical therapy
- ✿ Clindamycin resistance low
- ✿ Oral therapy
  - Linezolid 600 mg PO/IV twice daily for children  $\geq 12$  years
  - 10 mg/kg/dose every 8 h for children  $< 12$  years of age is alternative



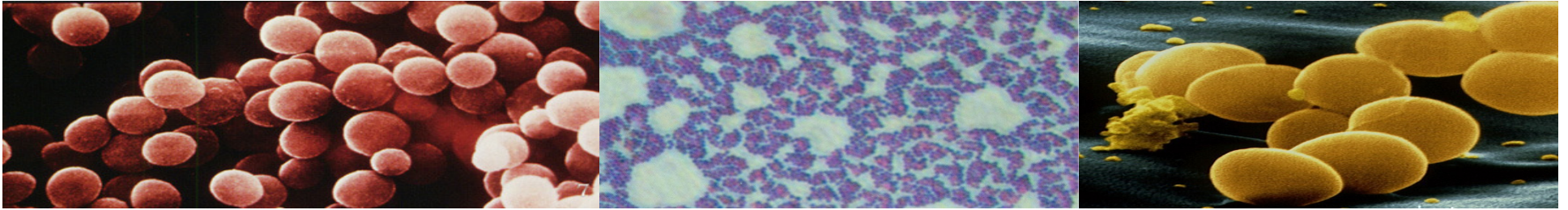
# Clinical Practice Guidelines

**What is the management of MRSA bone and joint infections?**

**■ Osteomyelitis**

- ✿ Surgical debridement and drainage mainstay of therapy**
- ✿ Optimal route of administration antibiotic therapy not established**
- ✿ Parenteral therapy followed by oral therapy**
  - Patient circumstances**





# Clinical Practice Guidelines

## ■ Osteomyelitis

### ✱ Antibiotics for parenteral administration

➤ Vancomycin

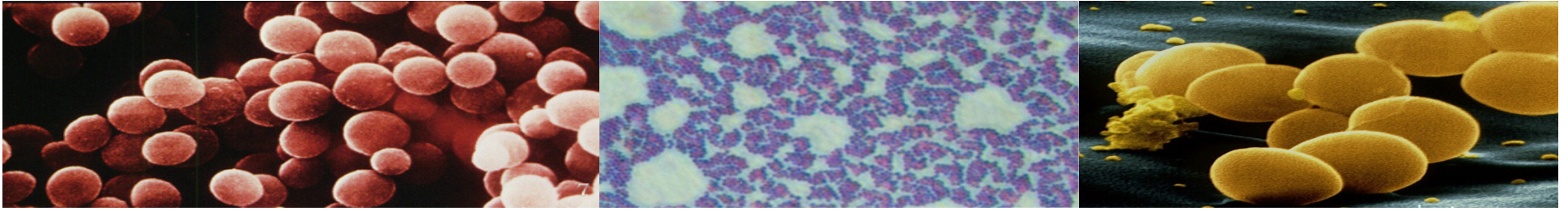
➤ Daptomycin 6 mg/kg/dose IV once daily

➤ Antibiotic options

■ TMP-SMX 4 mg/kg/dose twice daily combination with Rifampin 600 mg once daily

■ Linezolid 600 mg twice daily

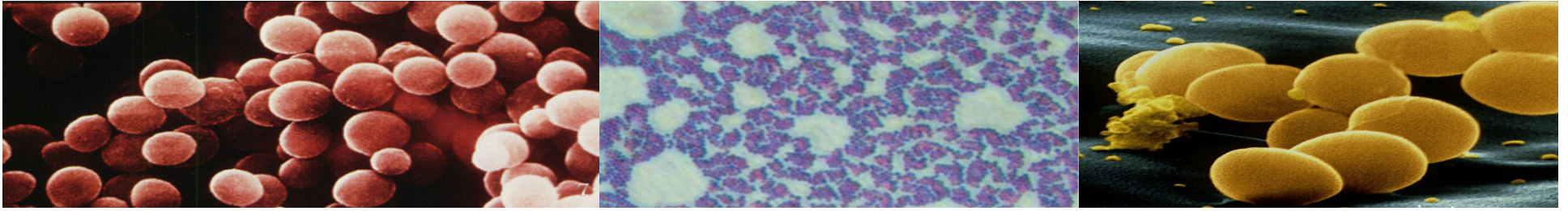
■ Clindamycin 600 mg every 8 h



# Clinical Practice Guidelines

## ■ Osteomyelitis

- ✿ Some experts recommend the addition of rifampin
- ✿ For patients with concurrent bacteremia, rifampin should be added after clearance of bacteremia.
- ✿ Optimal duration of therapy unknown
- ✿ Minimum 8-week course is recommended
- ✿ Some experts suggest an additional 1–3 months if debridement is not performed of oral rifampin-based combination therapy with TMP-SMX
- ✿ Magnetic resonance imaging (MRI)
- ✿ Erythrocyte sedimentation rate (ESR) and/or C-reactive protein (CRP) level may be helpful to guide response to therapy



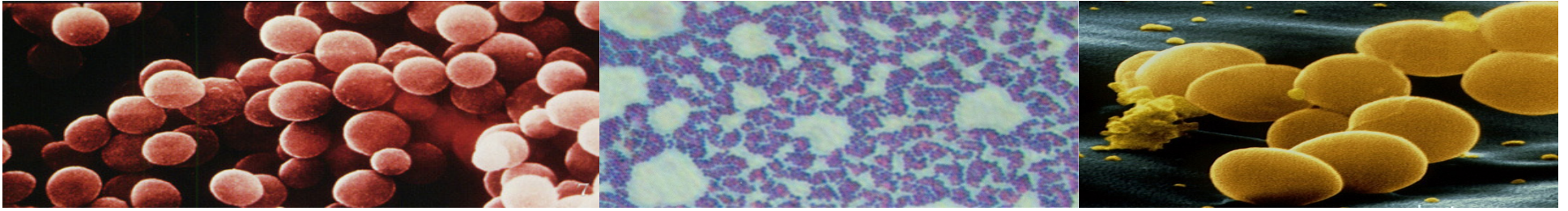
# Clinical Practice Guidelines

## ■ Septic Arthritis

- ✱ Drainage or debridement of the joint space
- ✱ Antibiotic choices for osteomyelitis
- ✱ 3–4-week course of therapy is suggested

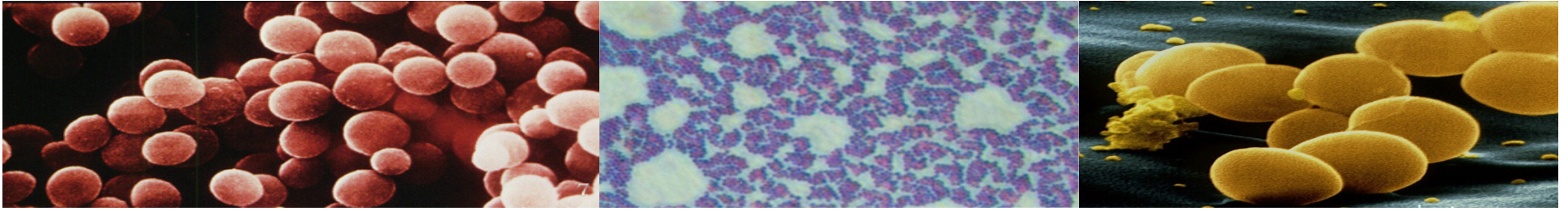
## ■ Device-related osteoarticular infections





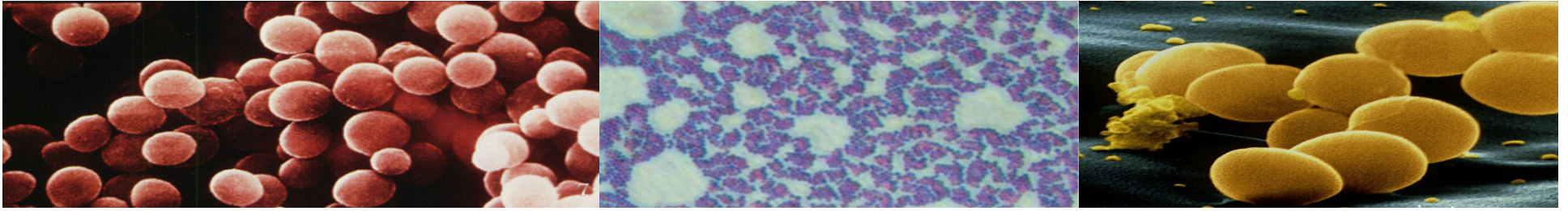
# Clinical Practice Guidelines

- **Early-onset (<2 months after surgery) or acute hematogenous prosthetic joint infections involving a stable implant with short duration ( $\leq 3$  weeks) of symptoms and debridement, initiate parenteral therapy plus rifampin for 2 weeks followed by rifampin plus a fluoroquinolone, TMP-SMX, a tetracycline or clindamycin for 3 or 6 months for hips and knees, respectively**
- **Prompt debridement with device removal whenever feasible is recommended**



## Clinical Practice Guidelines

- For early-onset spinal implant infections, initial parenteral therapy plus rifampin followed by prolonged oral therapy is recommended
- Long-term oral suppressive antibiotics if adequate surgical debridement is not possible should be given in conjunction with rifampin



# Clinical Practice Guidelines

## ■ Pediatric considerations

✿ For children with acute hematogenous MRSA osteomyelitis and septic arthritis, IV vancomycin recommended

➔ 3–4-week course for septic arthritis

➔ 4–6-week course for osteomyelitis

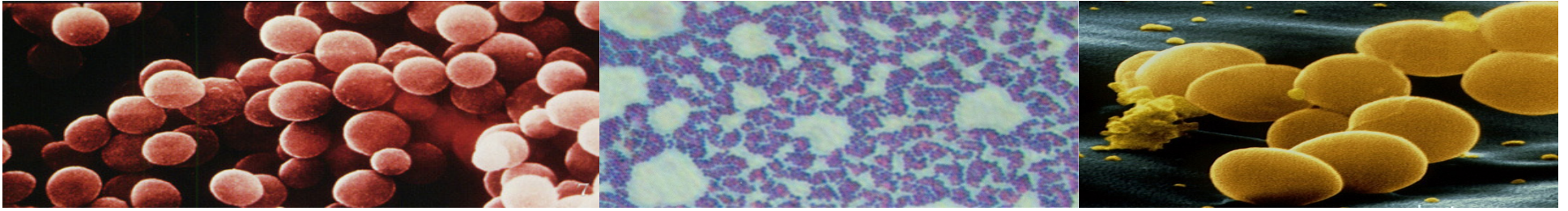
✿ Alternatives to vancomycin and clindamycin

➔ daptomycin 6 mg/kg/day IV once daily

➔ linezolid 600 mg PO/IV twice daily for children  $\geq 12$  years of age

➔ 10 mg/kg/dose every 8 h for children  $< 12$  years of age



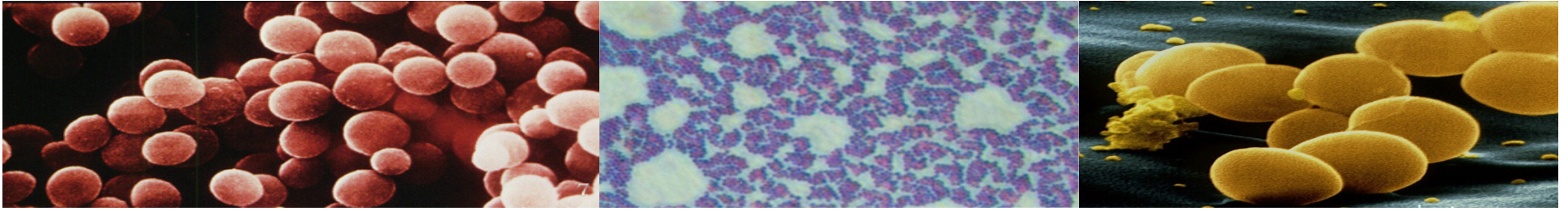


# Clinical Practice Guidelines

**What is the management of MRSA infections of the CNS?**

## **Meningitis**

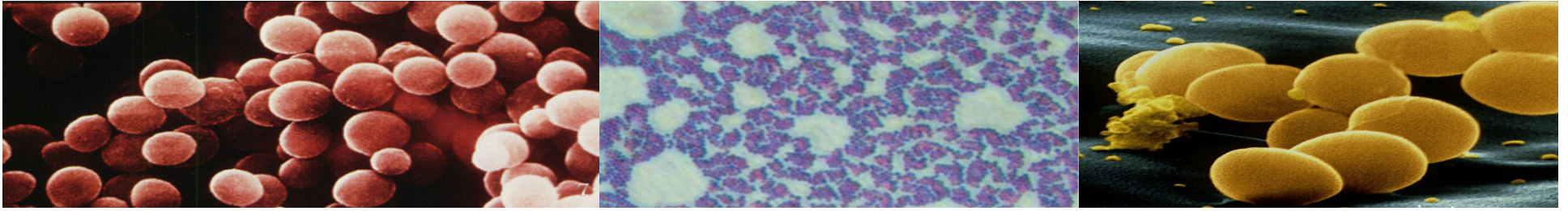
- ✿ **IV vancomycin**
- ✿ **For CNS shunt infection, shunt removal is recommended, and it should not be replaced until cerebrospinal fluid (CSF) cultures are repeatedly negative**



# Clinical Practice Guidelines

**Brain abscess, subdural empyema, spinal epidural abscess**

- **Neurosurgical evaluation for incision and drainage is recommended**
- **IV vancomycin for 4–6 weeks.**
- **Alternatives include the following:**
  - ✱ **Linezolid twice daily**
  - ✱ **TMP-SMX every 8–12 h**

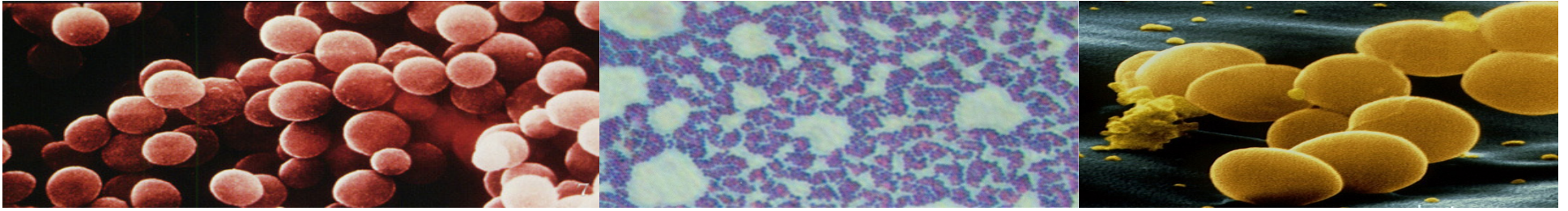


# Clinical Practice Guidelines

## Septic Thrombosis of Cavernous or Dural Venous Sinus

- Surgical evaluation for incision and drainage is recommended
- IV vancomycin for 4–6 weeks.
- Alternatives include the following:
  - ✱ Linezolid twice daily
  - ✱ TMP-SMX every 8–12 h





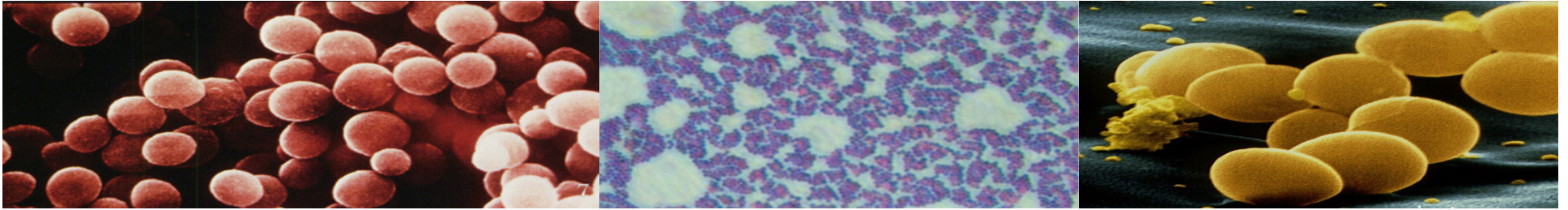
# Clinical Practice Guidelines

**What is the role of adjunctive therapies for the treatment of MRSA infections?**

- Not routinely recommended

**What are the recommendations for vancomycin dosing and monitoring?**

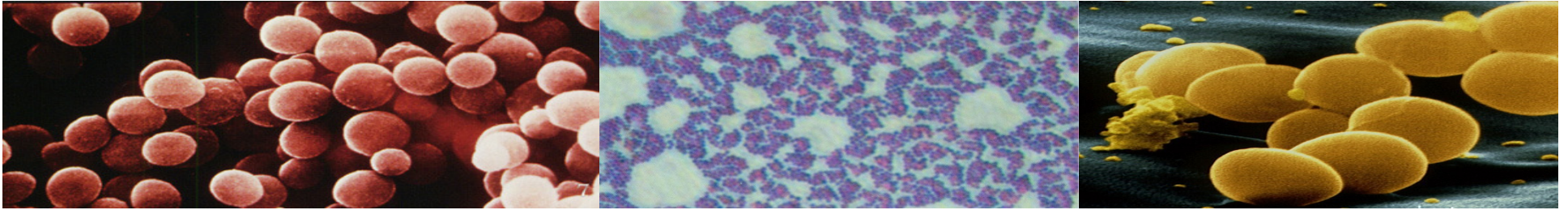
- Data are limited to guide vancomycin dosing in children. IV vancomycin 15 mg/kg/dose every 6 h is recommended in children with serious or invasive disease
- Trough concentrations considered in those with serious infections, such as bacteremia, infective endocarditis, osteomyelitis, meningitis, pneumonia, and severe SSTI (ie, necrotizing fasciitis)



# Clinical Practice Guidelines

## How should results of vancomycin susceptibility testing be used to guide therapy?

- For susceptible isolates, the patient's clinical response should determine the continued use of vancomycin, independent of the MIC
- If patient with clinical and microbiologic response to vancomycin, then it may be continued with close follow-up
- If patient with no clinical or microbiologic response to vancomycin despite adequate debridement and removal of other foci of infection, an alternative to vancomycin is recommended regardless of MIC
- For isolates resistant to vancomycin, an alternative to vancomycin should be used



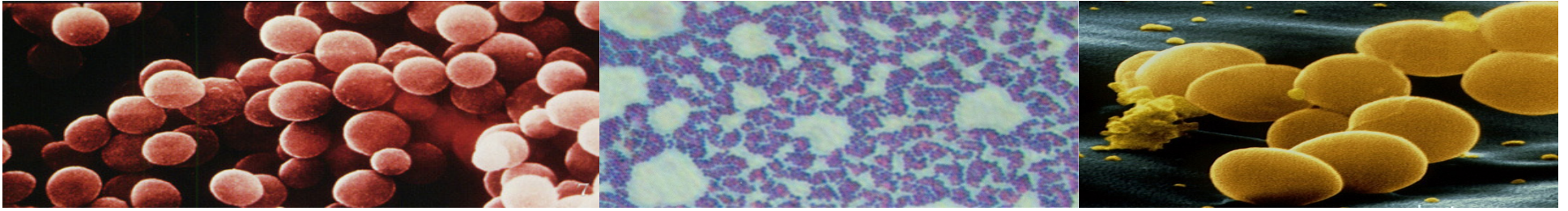
# Clinical Practice Guidelines

**What is the management of MRSA infections in neonates?**

## **Neonatal pustulosis**

- **For mild cases with localized disease, topical treatment with mupirocin may be adequate in full-term neonates and young infants**
- **For localized disease in a premature or very low-birthweight infant or more-extensive disease involving multiple sites in full-term infants, IV vancomycin or clindamycin is recommended, at least initially, until bacteremia is excluded**

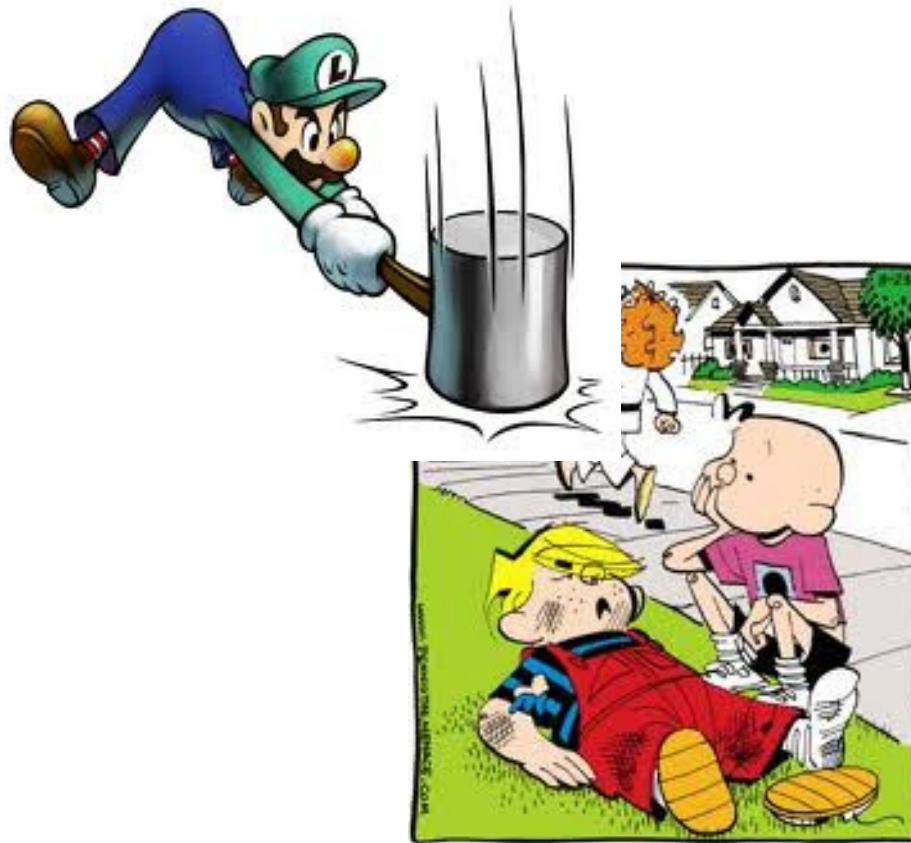
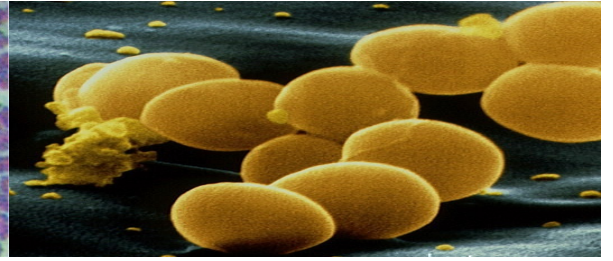
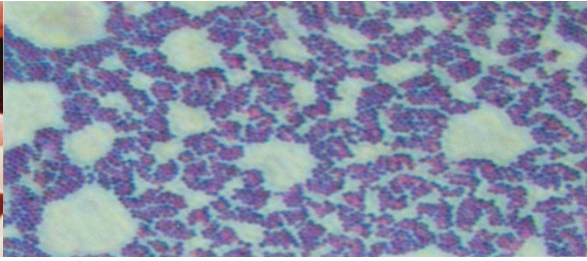
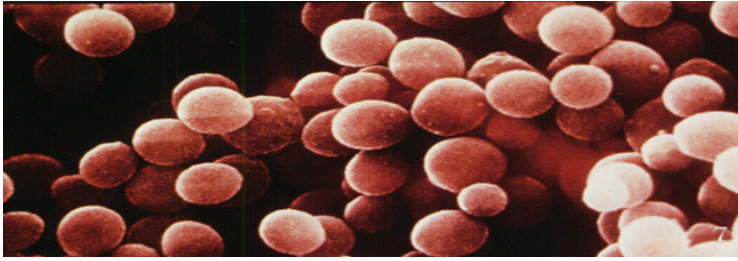




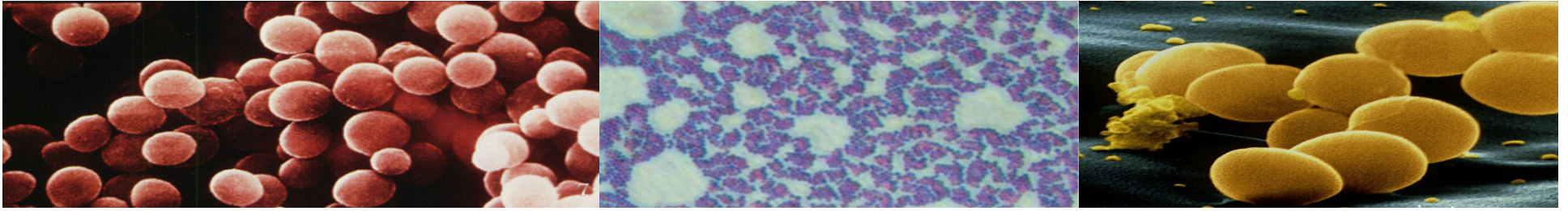
# Clinical Practice Guidelines

## Neonatal MRSA sepsis

- IV vancomycin is recommended
- Clindamycin and linezolid are alternatives for nonendovascular infections



"DID YOU HAFTA ASK HER TO DEMONSTRATE HOW SHE GOT HER BLACK BELT?"



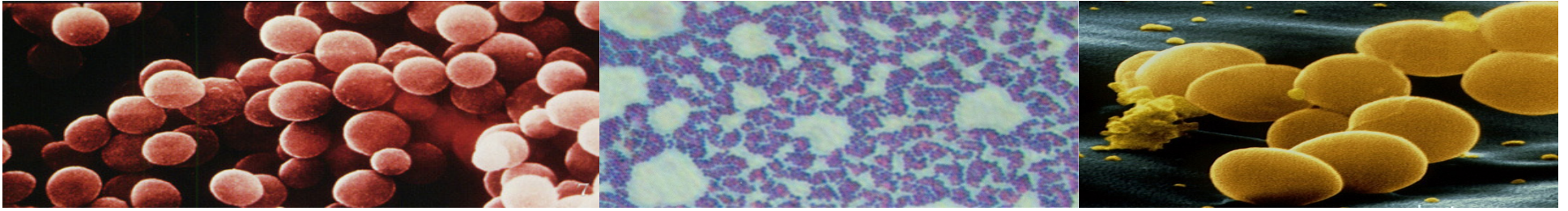
*We the physicians are the soul of  
preservation*

*We are a great source of strength*

*We can weather the storm*

*and face up to the  
challenge without  
compromise*





**THANK YOU!**