



Staphylococci

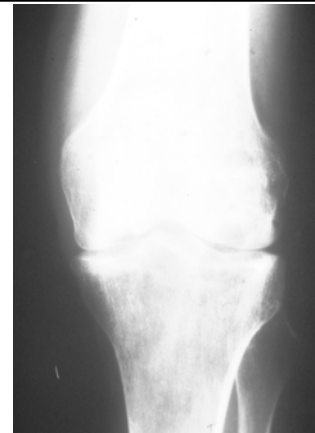
"Micrococcus, which, when limited in its extent and activity, causes acute suppurative inflammation (phlegmon), produces, when more extensive and intense in its action on the human system, the most virulent forms of septicæmia and pyæmia..."

Sir Alexander Ogston,
1882



What's to be Covered

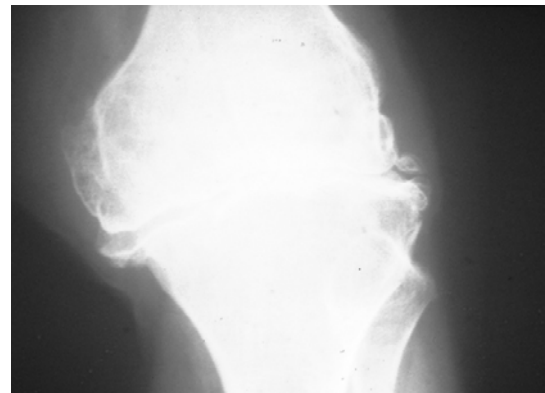
- Clinical Scenarios
- Microbiology of staphylococci
- Epidemiology of *S. aureus* infections
- Pathogenesis of *S. aureus* infections
 - Invasive disease
 - Toxin-mediated disease
- Recent events relevant to *S. aureus*
- Coagulase negative staphylococcal infections
- Treatment of *S. aureus* infections



Clinical Scenario #1

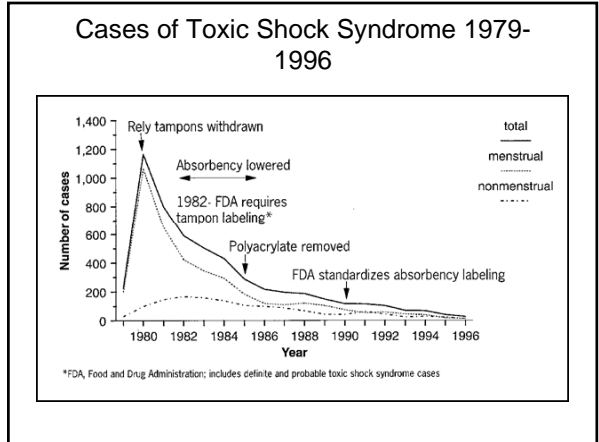
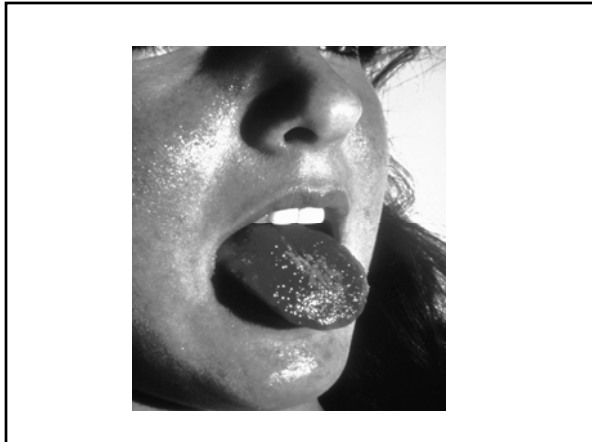
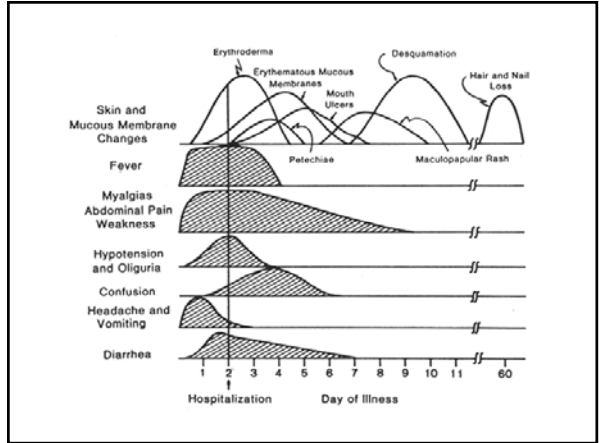
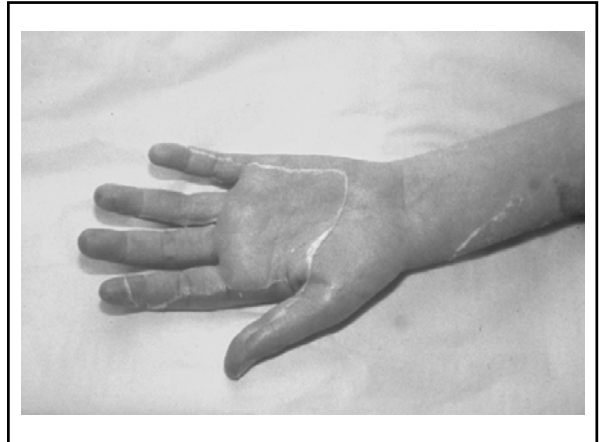
A 65 year old male with diabetes presents with a painful, swollen, warm mass at his hair line. Pus is easily expressible from the lesion. He tells you that this is the third such lesion he has had in the past 10 years.

Five days later he returns to you with fever and the onset of severe swelling and pain in his right knee. On examination you note that it is extremely warm and tender. Fluid is clearly present in the joint.



Clinical Scenario #2

A 25 year old female, previously in excellent health, presents with the sudden onset of fever, chills, sore throat and myalgias on the 4th day of her menstrual period. Two days later as the fever continues, she develops diarrhea, abdominal pain and becomes disoriented and drowsy. On exam she is hypotensive and has a generalized "sunburn" type rash.



Clinical Scenario #3

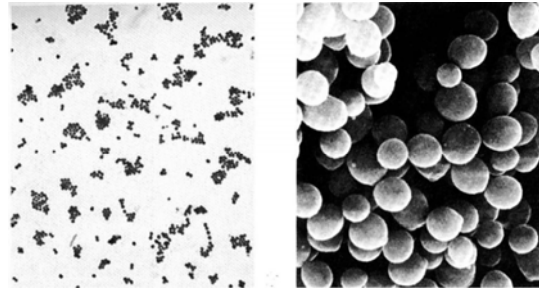
On Feb 3, 1975 196/344 passengers aboard a commercial aircraft developed the sudden onset of nausea, vomiting, abdominal cramps and diarrhea. An investigation incriminated ham as the vehicle of transmission. The attack rate was 86%.

The aircraft was forced to make an emergency landing. 142 passengers required hospitalization.

Lancet 9/27/75

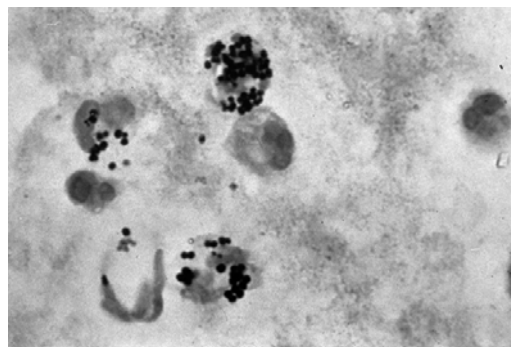
Laboratory Identification

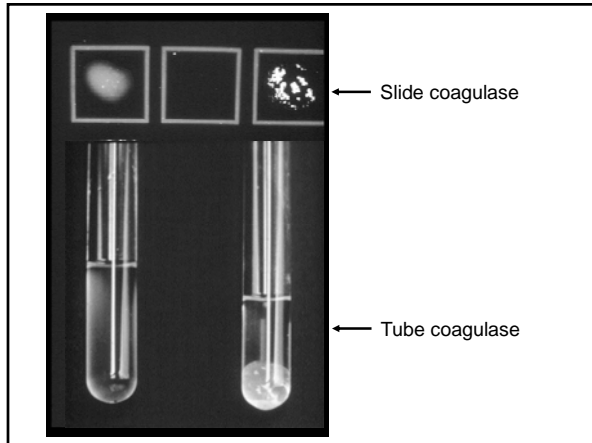
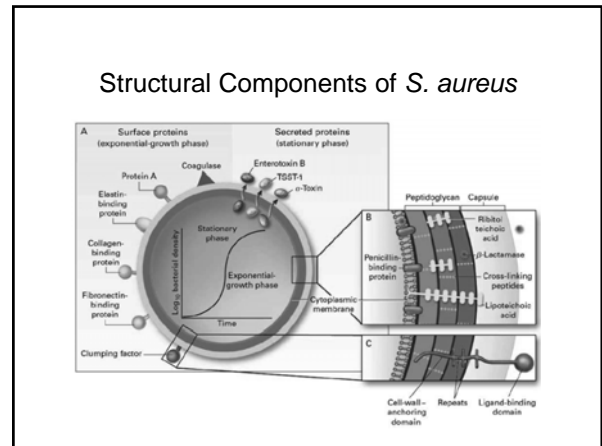
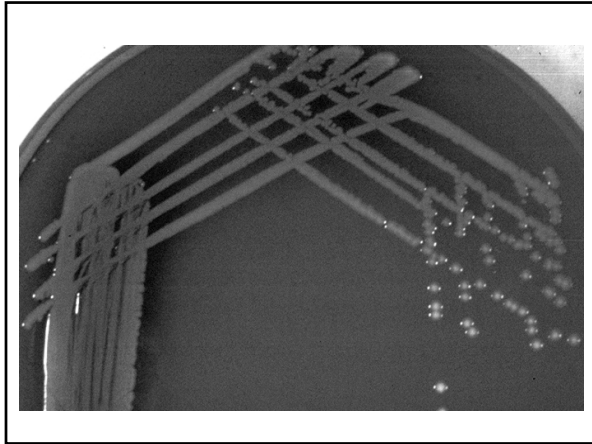
- Gram stain morphology
 - *staphyle* (Gk) bunch of grapes
- Form soft, round convex colonies on agar
 - *S. aureus* colonies tend to become golden
- All staphylococci are catalase positive
 - coagulase and mannitol tests used to distinguish between *S. aureus* and *S. epidermidis*



Description of the Staphylococci

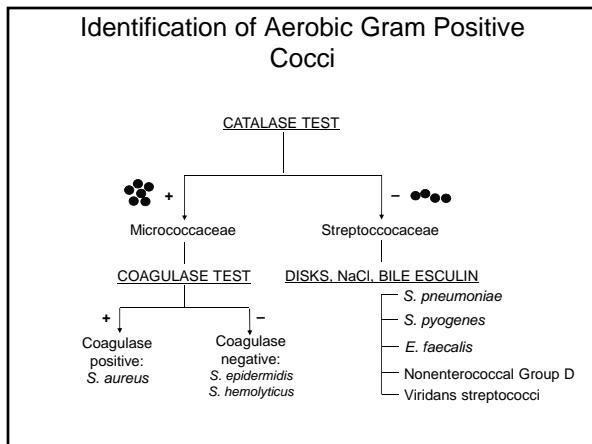
- Pyogenic Pathogens
- Members of the Micrococcaceae family
 - Includes *S. aureus*, *S. epidermidis* and *S. saprophyticus*
- Grouped as coagulase positive (*S. aureus*) or negative (the rest)
- Nonsporulating and nonmotile Gram positive cocci that grow in clusters
- Extremely hardy - survive a variety of environmental stresses





Secreted Products of *Staphylococcus aureus*

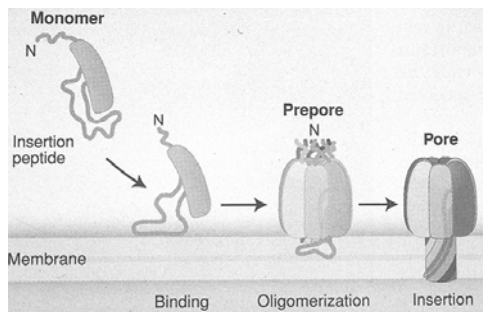
- Enzymes
 - Catalase - all staphylococci are catalase positive
 - $H_2O_2 \rightarrow H_2O$ and O_2
 - Coagulase converts fibrinogen \rightarrow fibrin
 - Hyaluronidases - hydrolyzes hyaluronic acids
 - Facilitates spread to adjoining tissues
 - Lipases - hydrolyze lipids (associated with abscesses, soft tissue infections)
 - Beta-lactamases - responsible for penicillin resistance



Secreted Products of *Staphylococcus aureus*

- Toxins
 - Superantigen Family - TSST-1, enterotoxins
 - Food poisoning, TSS
 - Exfoliative toxins serine proteases that are responsible for staphylococcal scalded skin syndrome
- Membrane damaging toxins
 - Leukocidin may be associated with soft tissue and necrotizing pulmonary infections
 - Alpha toxin cytotoxic to host cell membranes

Alpha Toxin



Pathogenesis of *Staphylococcus aureus* Infections

- Colonization
- Infection
- Invasion - local vs. systemic
- Host Response

Epidemiology of *Staphylococcus aureus* Disease

- Humans are the primary reservoir of this organism
- Most infections, both community and hospital acquired, are the result of auto-inoculation
- Hospital infections may also result from person-person transmission
- Hospital outbreaks have been traced to single strains ("*staphylococcal cloud*") but this is the exception
- There are an increasing number of community-based infections occurring caused by methicillin-resistant staphylococci

S. aureus - The Commensal



- The anterior nares is the primary site of colonization
- Colonization occurs in 20-40% of "normals"
 - Toxin-mediated disease often occurs without infection
- Infections are increased in colonized subjects usually with the colonizing strain
 - Colonization increased in injection drug users, diabetics, HIV-infected
 - Elimination of carriage in high risk patients may reduce infection rates
 - Potential for selection of antimicrobial-resistant *S. aureus*

Diseases Caused by *Staphylococcus aureus*

- Skin and Soft tissue infections
- Bacteremia - sepsis, metastatic seeding
- Endocarditis
- Musculoskeletal infections
- Respiratory tract infections
- Toxin-related diseases
 - TSST-1, Scalded skin syndrome
 - Food poisoning

Infection

- Groups at increased risk: ↓ WBC, SA carriers, diabetics, injection drug users, dialysis patients
- Mechanical breaches of the skin or mucosal barrier
- Reduced inoculum in the presence of foreign material
- Primary host response is PMN infiltration → vascular thrombosis and tissue necrosis → abscess formation

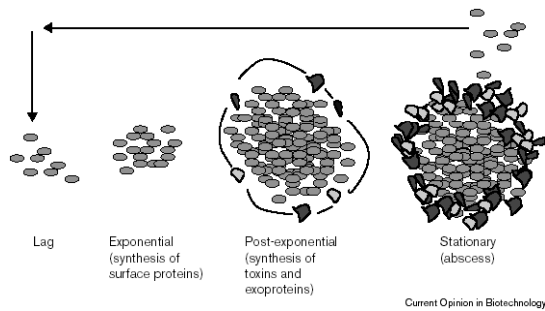
Invasion

- Elaboration of enzymes - lipase, coagulase, hyaluronidase, leukocidins, DNase which cause tissue damage
- Presence of different adhesins may facilitate seeding of different tissue sites
- Role of antibody in limiting infection is not well defined with exception of TSS

Staphylococcal Toxin Diseases

- Toxic shock syndrome
- Food poisoning
- Scalded skin syndrome

The Potential Role of Regulatory Genes in the Expression of *S. aureus* Virulence Determinants



Toxic Shock Syndrome Toxin 1 (TSST-1)

- *S. aureus* isolates from menstruation-associated TSS express toxin ($\geq 95\%$).
- In nonmenstrual isolates ~ 50% express TSST-1 Other enterotoxins also cause TSS in this setting.
- TSST-1 is a 22 kDa exotoxin. Its expression is subject to regulatory control.
- The TSST-1 gene (*tsf*) is on the chromosome and appears to be part of a mobile element.

Host Response to Infection

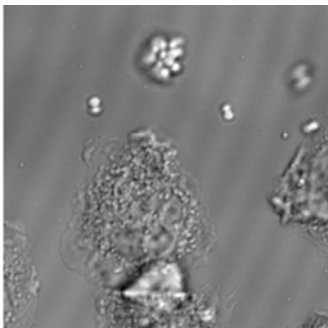
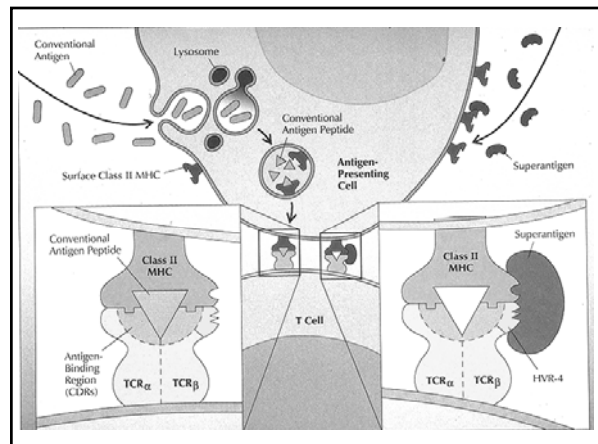
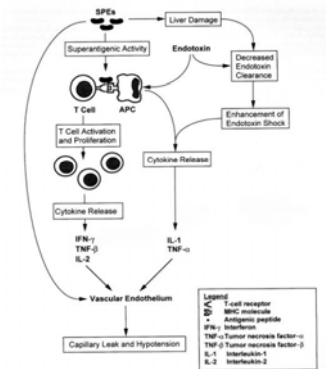


Image kindly provided by F. DeLeo



Mechanism of Action: Superantigens



MMWR Four Pediatric Deaths from Community-acquired Methicillin-Resistant *S. aureus* -- Minnesota and North Dakota, 1997-1999

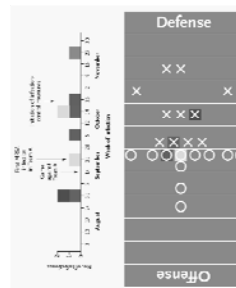
MRSA is an **emerging community pathogen** among patients without established risk factors for MRSA infection (e.g., recent hospitalization, recent surgery, residence in a long-term-care facility, or injecting-drug use).

MMWR 48:707, 1999

Staphylococcal Food Poisoning

- Enterotoxin mediated disease - does not require the presence of viable staphylococci
- Results from the ingestion of heat stable enterotoxin
- The enterotoxins stimulate the vagus nerve and the CNS vomiting center. They also increase peristalsis
- The active site is distinct from the site inducing Toxic Shock Syndrome

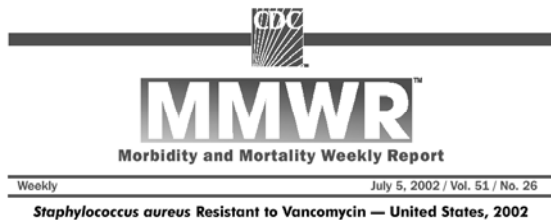
Outbreak of CA-MRSA Among Professional Football Players



- 8 MRSA infections in '03 among St. Louis Rams
- All occurred at turf abrasion sites
- Linebacker/linemen, high body mass index
- Nasal carriage not implicated
- Clonal outbreak - PVL + (USA 300)

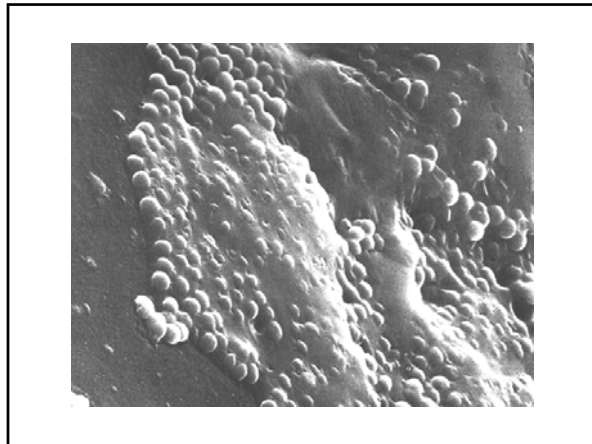
Kazakova et al., *NEJM*, 2005

Recent Events Relevant to *S. aureus*



Coagulase Negative Staphylococci

- Relatively avirulent bacteria
- Part of the normal skin flora
- *Staphylococcus epidermidis* is the most common pathogen among the coagulase negative species
- Unique niche for infections - prosthetic devices such as IV catheters, prosthetic heart valves
- Frequent contaminant in cultures



Treatment and Prevention of *Staphylococcus aureus* Infections

- Surgically drain abscesses, remove infected prosthetic material
- Treat with appropriate antibiotics
 - Problem of Methicillin-Resistant SA (MRSA) and more recently Vancomycin-Resistant SA (VRSA)
- Eliminate colonization in high risk individuals
- Several candidate vaccines and antibodies currently under investigation

What Should You Know?

- General microbiology of the pathogen
 - Gram stain morphology, classification, major biochemical tests for identification
- Epidemiology
 - Reservoirs, means of transmission, those at increased risk
- Pathogenesis of disease
 - Unique virulence determinants, 1st host response,
 - Pathogenetic mechanisms for different staphylococcal diseases
- Clinical presentations
 - Common scenarios for disease