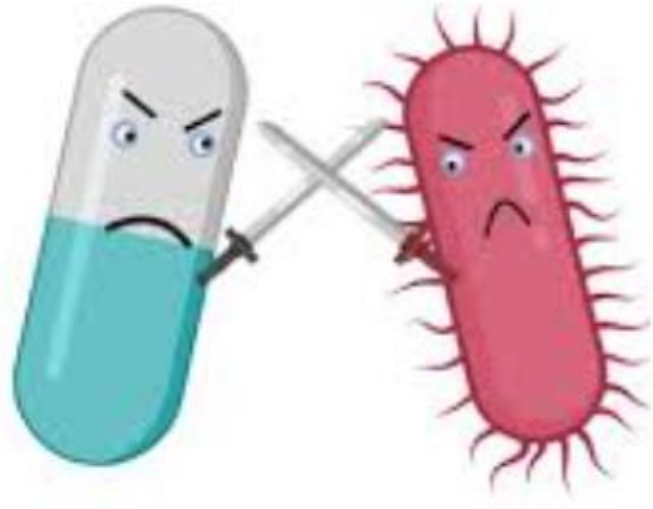
Antiobiotic Therapy for Staph, Strep, S pneumonia and Entrococcal Infections



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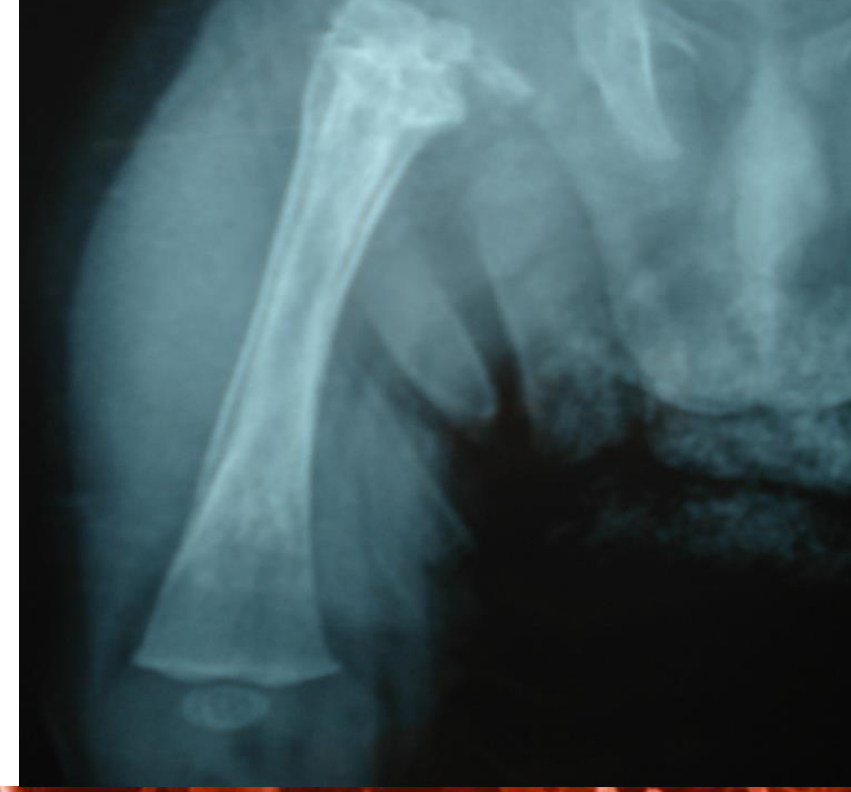
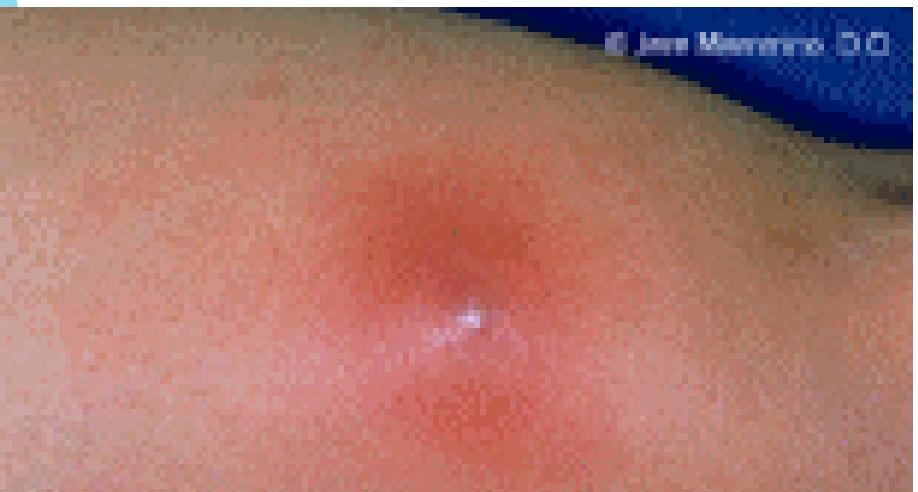
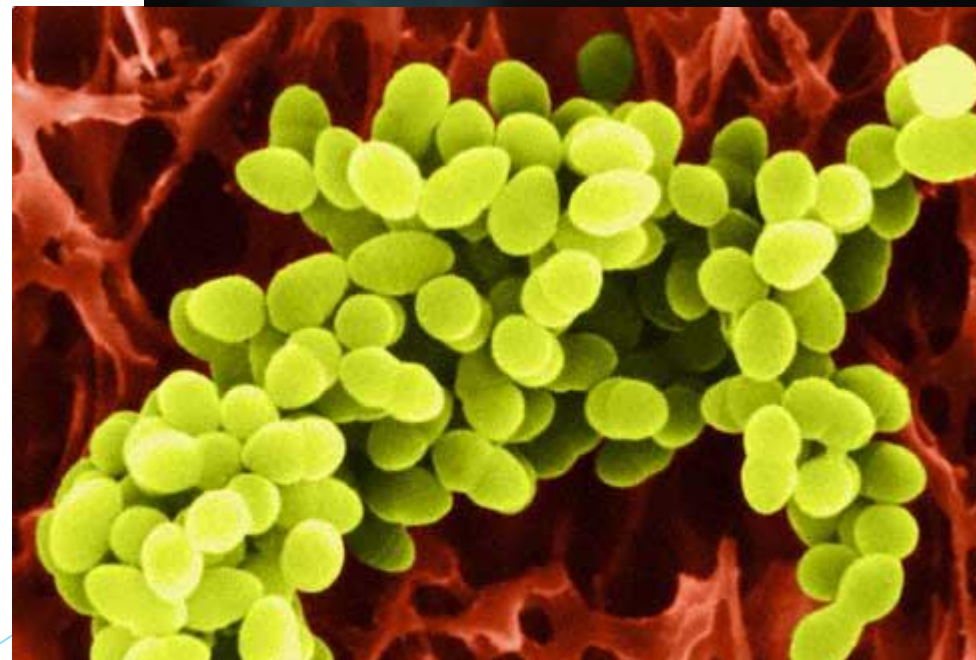
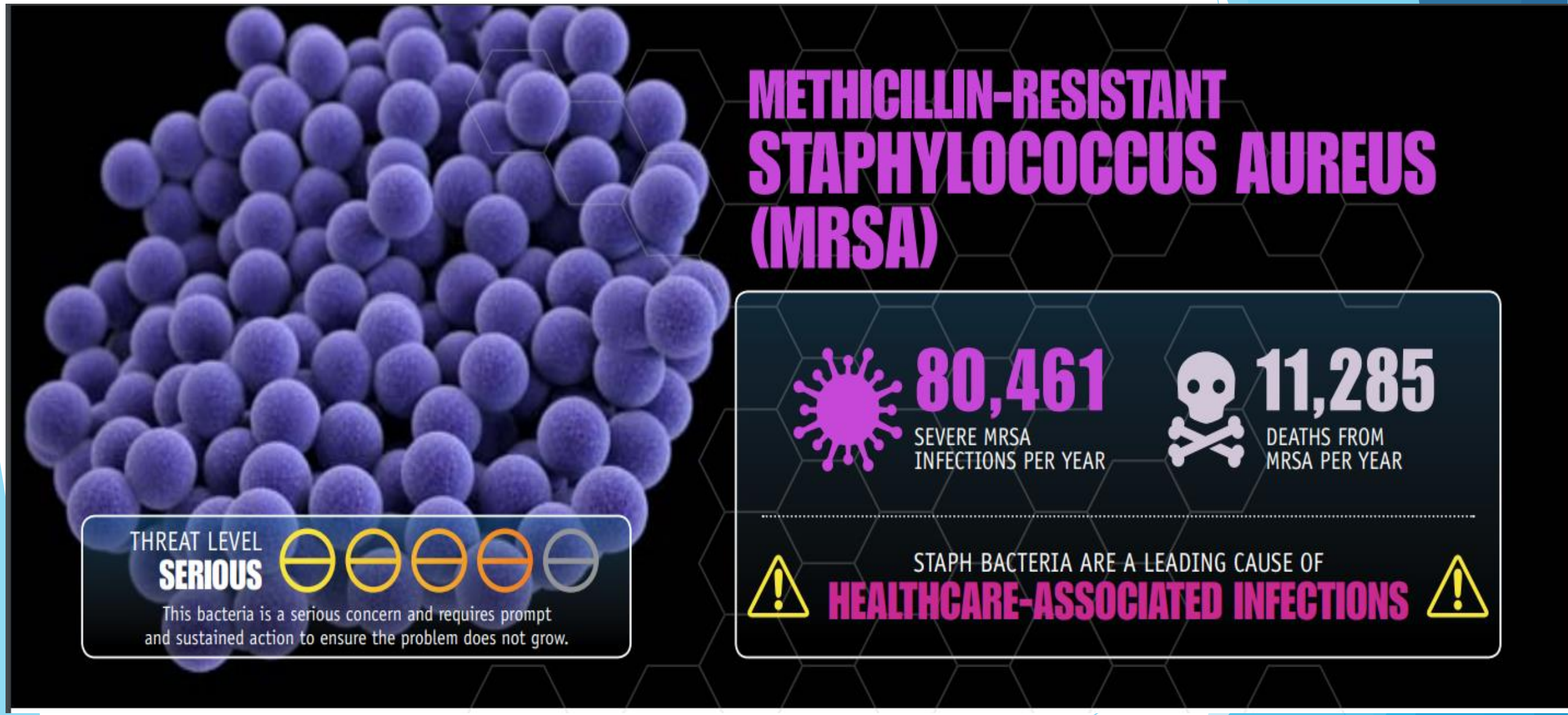
Disease Manifestations due to *Staphylococcus aureus*

- Skin and soft tissue infections
- Impetigo
- Cellulite
- Osteomyelitis
- Pneumonia
- Endocarditis
- Septic phlebitis
- Catheter infections
- Surgical site infections
- Toxic shock syndrome
- Septicemia
- Septic arthritis

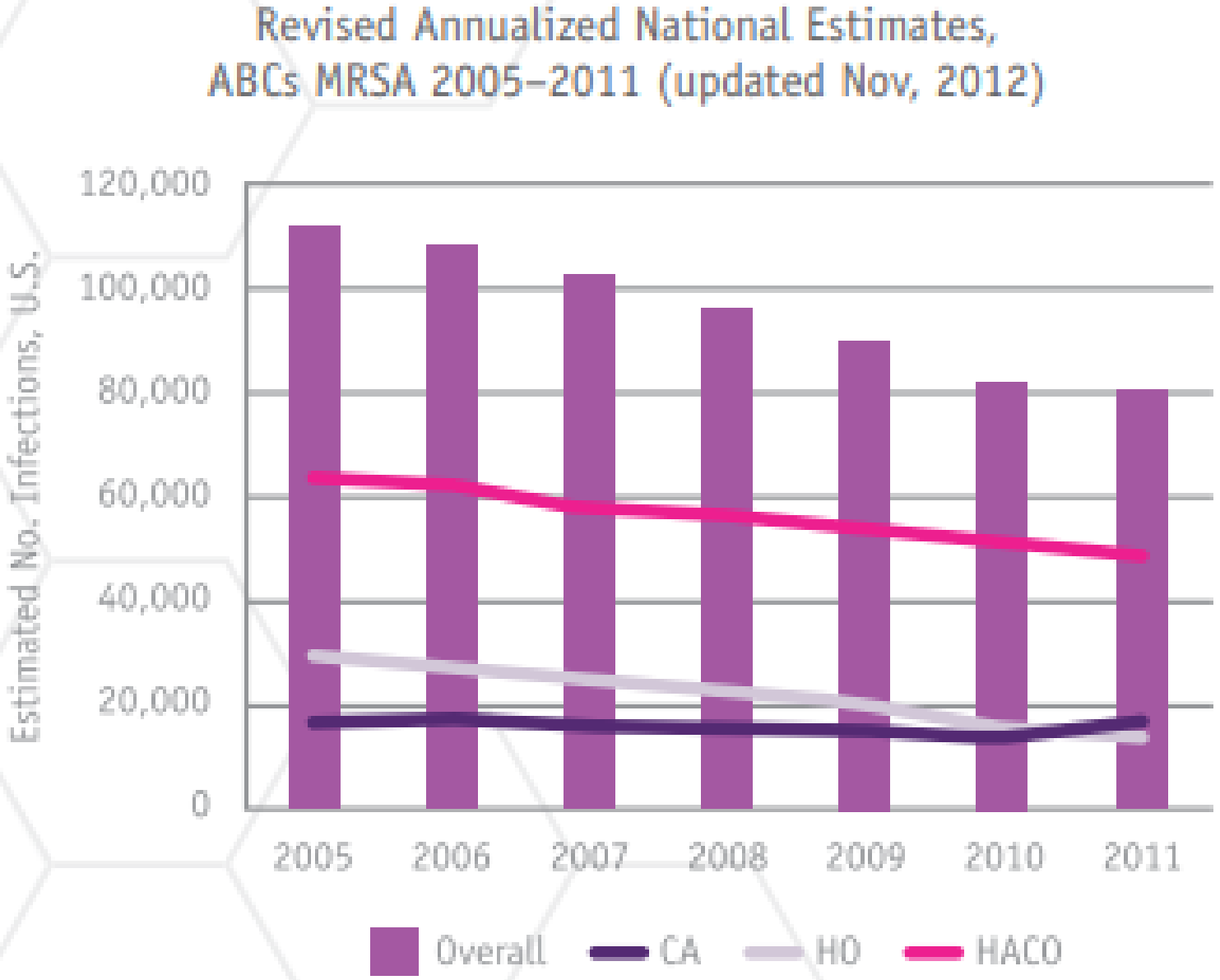




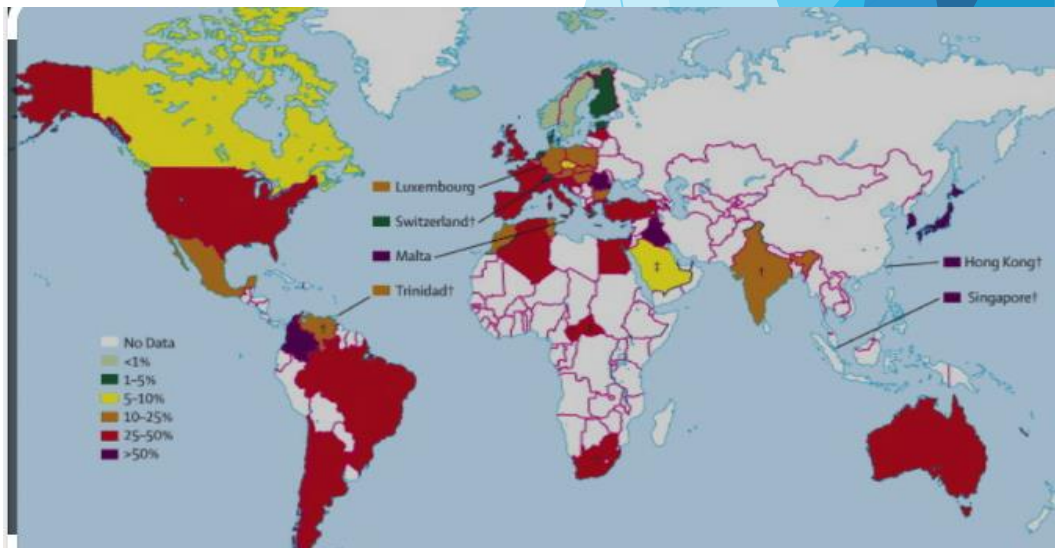



METHICILLIN-RESISTANT
STAPHYLOCOCCUS AUREUS
(MRSA)
80,461
SEVERE MRSA
INFECTIONS PER YEAR
11,285
DEATHS FROM
MRSA PER YEAR
THREAT LEVEL
SERIOUS
This bacteria is a serious concern and requires prompt
and sustained action to ensure the problem does not grow.
STAPH BACTERIA ARE A LEADING CAUSE OF
HEALTHCARE-ASSOCIATED INFECTIONS

Severe MRSA infections mostly occur during or soon after inpatient medical care.



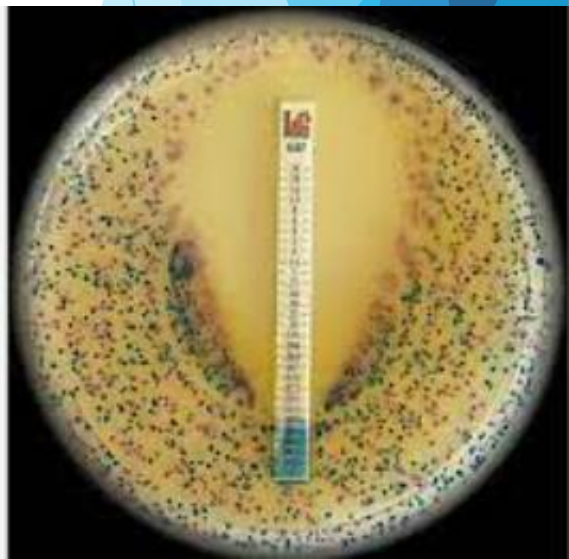
- MRSA has been endemic in most US hospitals since the 1980s and in 2016 accounted for approximately 40% of health care-associated *S aureus* bloodstream infections in pediatric inpatients.
- The incidence of invasive health care-associated MRSA infections has decreased in many communities since the mid-2000s.
- Studies show that about one in three (33%) people carry *S. aureus* bacteria in their nose, usually without any illness.
- About two in every 100 people carry MRSA. Although many people carry MRSA bacteria in their nose, most do not develop serious MRSA infections.
- The only way to know if MRSA is the cause of an infection is to perform a culture (a laboratory test) of the bacteria.
- People who carry MRSA but do not have signs of infection can spread the bacteria to others .



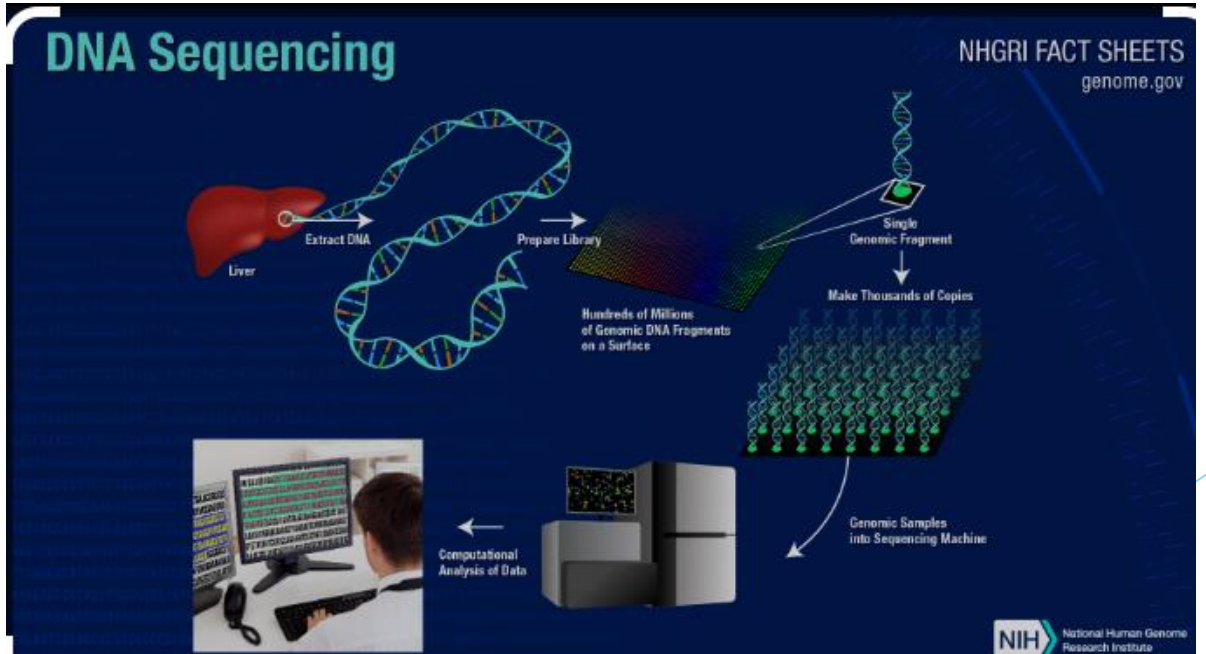
Risk factors for health care-associate MRSA infections

- hospitalization,
- surgery,
- dialysis,
- long-term care stay within the previous year,
- presence of an indwelling device,
- presence of wounds,
- history of prior MRSA infection or colonization.

- Antimicrobial susceptibility testing should be performed for all *S aureus* specimens isolated from normally sterile sites.
- Laboratory practice includes routine screening (D-testing) to exclude inducible clindamycin resistance.
- Another phenomenon that has been described is heteroresistance to antibiotics, in which the heterogeneous or heterotypic strains appear susceptible by disk diffusion but contain resistant subpopulations that are only apparent when cultured with antibiotic-containing media.

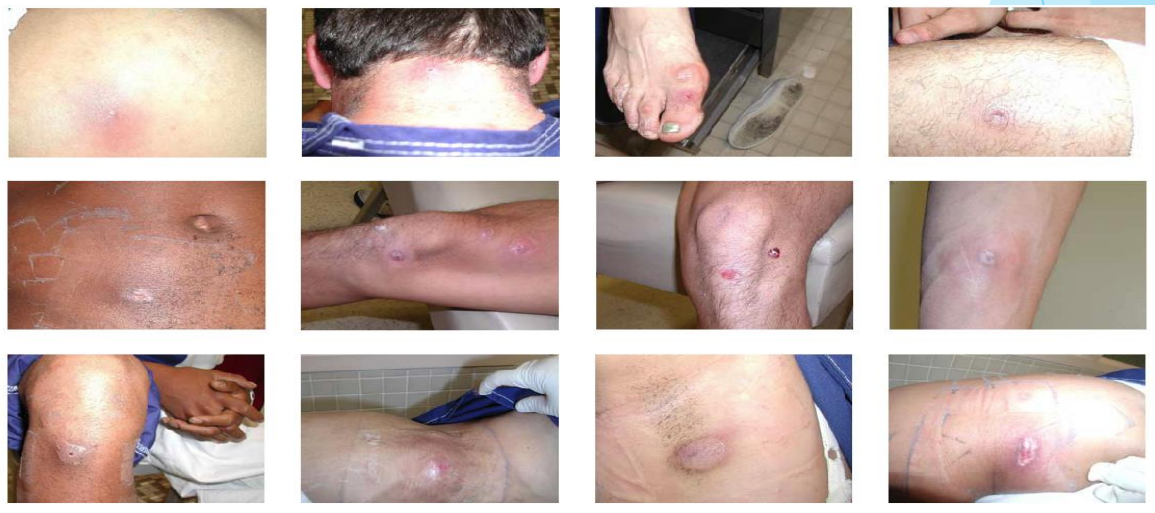


- *S aureus* strain genotyping, in conjunction with epidemiologic information, can facilitate identification of the source, extent, and mechanism of transmission in an outbreak.
- A number of molecular typing methods are available for *S aureus*, including pulsed-field gel electrophoresis, spa typing, and whole genome sequencing.



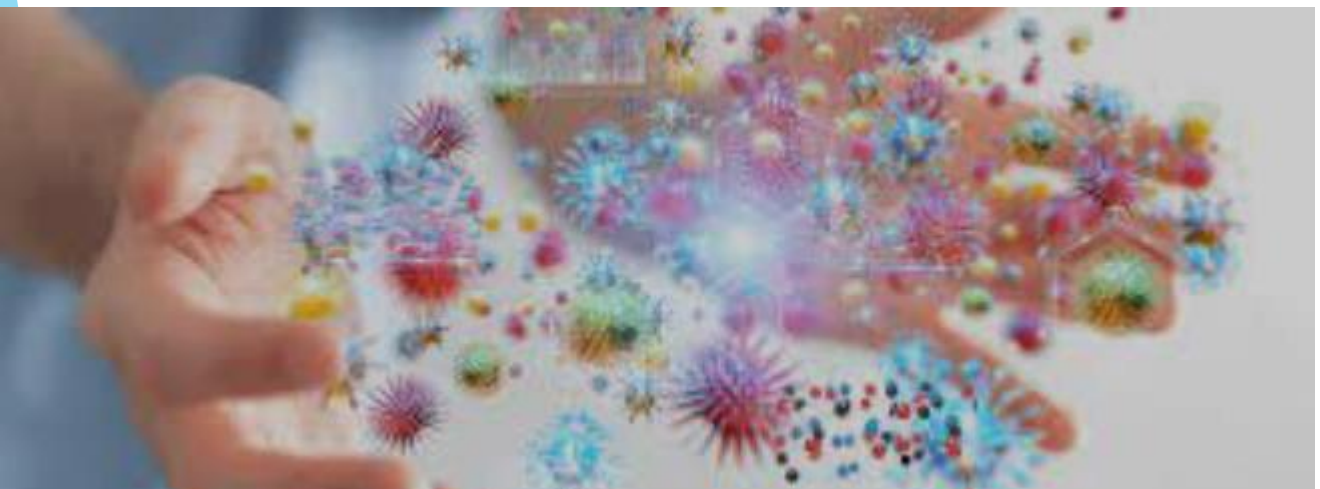
Skin and Soft Tissue Infection.

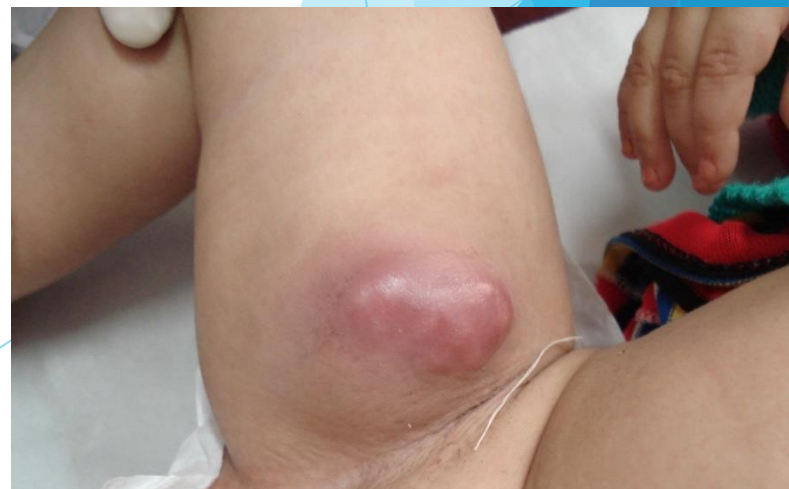
- Skin and soft tissue infections, such as diffuse impetigo or cellulitis attributable to methicillin-susceptible *S aureus* (MSSA), optimally are treated with oral penicillinase-resistant beta-lactam drugs, such as a first- or second-generation cephalosporin.
- For the penicillin-allergic patient and in cases in which MRSA is considered, trimethoprim-sulfamethoxazole, doxycycline, or clindamycin can be used if the isolate is susceptible.
- Topical mupirocin is recommended for localized impetigo.



Community-Associated MRSA

- These strains most commonly cause skin and soft tissue abscesses, although they can also cause more severe infections.
- Clinical infections are more common in settings where there is crowding; frequent skin-to-skin contact; sharing of personal items, such as towels and clothing; and poor personal hygiene and among those with nonintact skin including body piercings.
- Outbreaks have been reported among athletic teams, in correctional facilities, and in military training facilities.





- The most frequent manifestation of community-associated MRSA infection is skin and soft tissue infection, which can range from mild to severe.
- Drainage plus systemic oral therapy with either clindamycin or trimethoprim-sulfamethoxazole is associated with better outcomes.
- Applying mupirocin to the nares and bathing using chlorhexidine for 5 consecutive days for all family members have been associated with decreased recurrences.
- Studies in adults have reported success with a 7-day course of the combination of oral rifampin and doxycycline plus nasal mupirocin.

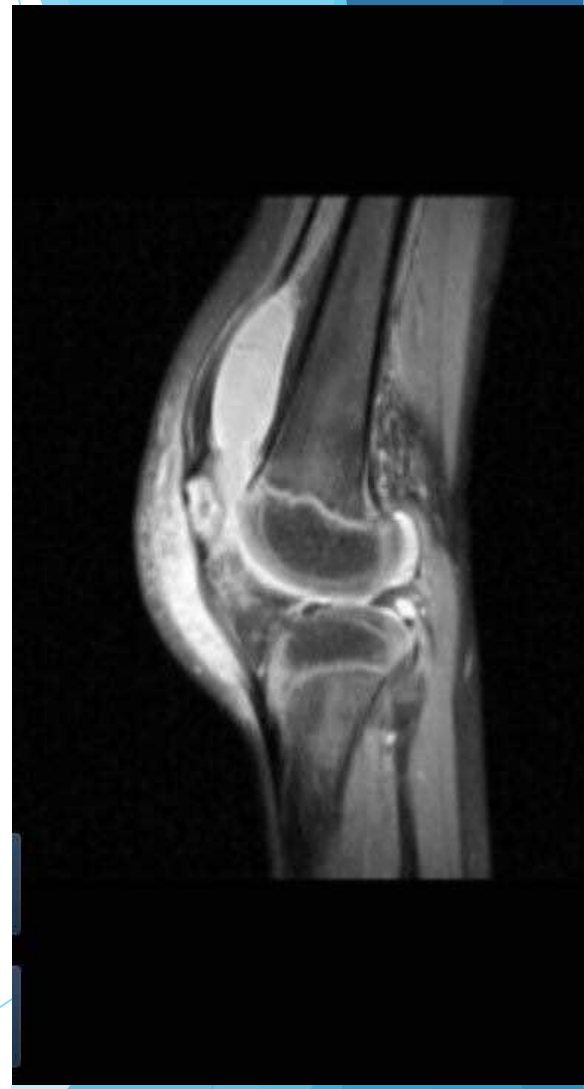
- Community-associated MRSA strains can also circulate in hospitals and cause health care-associated MRSA infections.
- Unlike health care-associated strains, community-associated MRSA strains are usually susceptible to a variety of non–beta-lactam antibiotics (eg, trimethoprim-sulfamethoxazole, clindamycin, tetracycline).

Health care-associated MRSA strains are usually multidrug resistant and predictably are susceptible only to

- vancomycin,
- ceftaroline,
- linezolid,
- daptomycin

Invasive Staphylococcal Infections

- Empiric therapy for suspected invasive staphylococcal infection, including pneumonia, osteoarticular infection, visceral abscesses, and foreign body-associated infection with bacteremia, is vancomycin plus a semisynthetic beta lactam (eg, nafcillin, oxacillin).
- Subsequent therapy should be based on antimicrobial susceptibility results.
- Serious MSSA infections require intravenous therapy with an antistaphylococcal beta-lactam antimicrobial agent, such as nafcillin, oxacillin, or cefazolin.
- The addition of rifampin may be considered for those with invasive disease associated with an indwelling foreign body, especially if removal of the infected implant or device is not feasible.



- Vancomycin is not recommended for treatment of serious MSSA infections (including endocarditis), because it is weakly bactericidal.
- First- or second-generation cephalosporins (eg, cefazolin) or vancomycin are less effective than nafcillin or oxacillin for treatment of MSSA meningitis.
- Clindamycin is bacteriostatic and should not be used for treatment of primary bacteremia or endovascular infection.

- For MRSA pneumonia complicating influenza in children, vancomycin monotherapy in the first 24 hours of treatment was associated with higher mortality so vancomycin combined with a second antibiotic (clindamycin, linezolid, or ceftaroline) is recommended.
- Antibiotic therapy can be de-escalated to a single agent if there is clinical improvement and antibiotic susceptibility information to guide treatment

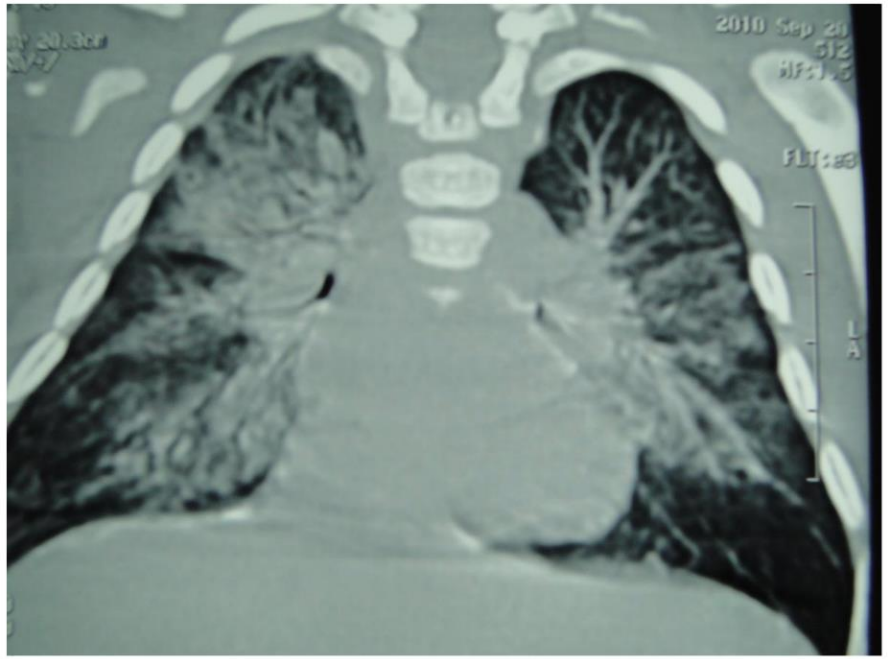


Table 3.54. Parenteral Antimicrobial Agent(s) for Treatment of Bacteremia and Other Serious *Staphylococcus aureus* Infections

Antimicrobial Agents		Comments
I. Initial empiric therapy (organism of unknown susceptibility)		
Drugs of choice:	Vancomycin (15 mg/kg, every 6 h) + nafcillin or oxacillin[a,b]	For life-threatening infections (ie, septicemia, endocarditis, CNS infection); ceftaroline or linezolid are alternatives, but there are limited efficacy data in children
	Vancomycin (15 mg/kg, every 6–8 h)[b]	For non–life-threatening infection without signs of sepsis (eg, skin infection, cellulitis, osteomyelitis, pyarthrosis) when rates of MRSA colonization and infection in the community are substantial; ceftaroline or linezolid are alternatives
	Clindamycin	For non–life-threatening infection without signs of sepsis when rates of MRSA colonization and infection in the community are substantial and prevalence of clindamycin resistance is <15%
II. Methicillin-susceptible *S aureus* (MSSA)		
Drugs of choice:	Nafcillin or oxacillin[c]	
	Cefazolin	
Alternatives:	Clindamycin	Only for patients with a serious penicillin allergy and clindamycin-susceptible strain
	Vancomycin[b]	Only for patients with a serious penicillin and cephalosporin allergy
	Ampicillin + sulbactam	For patients with polymicrobial infections caused by susceptible isolates
III. Methicillin-resistant *S aureus* (MRSA; oxacillin MIC, 4 µg/mL or greater)		
A. Health care-associated (multidrug resistant)		
Drugs of choice:	Vancomycin ± gentamicin[b,c]	

Table 3.54. Parenteral Antimicrobial Agent(s) for Treatment of Bacteremia and Other Serious *Staphylococcus aureus* Infections, continued

	Antimicrobial Agents	Comments
Alternatives: susceptibility testing results available before alternative drugs are used	Trimethoprim-sulfamethoxazole	
	Ceftaroline[d]	
	Linezolid[d]	
	Daptomycin[d,e]	
B. Community-associated (not multidrug resistant)		
Drugs of choice:	Vancomycin ± gentamicin[b,c]	For life-threatening infections or endovascular infections including those complicated by venous thrombosis
	Clindamycin (if strain susceptible)	For pneumonia,[a] septic arthritis, osteomyelitis, skin or soft tissue infections
	Trimethoprim-sulfamethoxazole	For skin or soft tissue infections
	Doxycycline (if strain susceptible)	
Alternative:	Vancomycin[b]	For serious infections
	Linezolid	For serious infections caused by clindamycin resistant isolates in patients with renal dysfunction or those intolerant of vancomycin
IV. Vancomycin-intermediately susceptible *S aureus* (VISA; MIC, 4 to 16 µg/mL)[d]		
Drugs of choice:	Optimal therapy is not known	Dependent on in vitro susceptibility test results
	Linezolid[d]	
	Ceftaroline[d]	
	Daptomycin[e]	
	Quinupristin-dalfopristin[d]	
	Tigecycline[d]	

CNS indicates central nervous system; MIC, minimum inhibitory concentration.

[a] For suspected MRSA pneumonia complicating influenza in critically ill children, add clindamycin, ceftaroline, or linezolid to vancomycin empiric treatment. Empiric selection of antibiotics is highly dependent on the local/regional susceptibility data.

[b] The area-under-the-curve to minimum inhibitory concentration (AUC/MIC) has been identified as the most appropriate pharmacokinetic/pharmacodynamic (PK/PD) target for vancomycin in adult patients with MRSA. Although there are limitations in prospective outcomes data in pediatric patients with serious MRSA infections, the most recent consensus guideline from the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, and the Society of Infectious Diseases Pharmacists recommends AUC guided therapeutic monitoring, preferably with Bayesian estimation, for all pediatric age groups receiving vancomycin.[f,g,h] This estimation accounts for developmental changes of vancomycin clearance from newborn to adolescent. Dosing in children should be designed to achieve an AUC of 400 to 600 µg-hour/L (assuming MIC of 1) and/or trough levels <15 µg/mL to minimize AKI risks. Bayesian estimation can be completed with 2 levels, with one level being recommended 1-2 hours after end of vancomycin infusion, and the second level being drawn 4 to 6 hours after end of infusion. Levels can be obtained as early as after the second dose. Software to assist with these calculations is available online and for purchase. It is recommended to avoid AUC >800 and troughs >15. Most children younger than 12 years will require higher doses to achieve optimal AUC/MIC compared with older children. Consultation with an infectious diseases specialist should be considered to determine which agent to use and duration of use.

[c] Gentamicin and rifampin for the first 2 weeks should be added for endocarditis of a prosthetic device. Addition of rifampin is recommended for other device-related infections (spinal instrumentation, prosthetic joint).

[d] Linezolid, ceftaroline, quinupristin-dalfopristin, and tigecycline are agents with activity *in vitro* and efficacy in adults with multidrug-resistant, gram-positive organisms, including *S aureus*. Because experience with these agents in children is limited, consultation with a specialist in infectious diseases should be considered before use. Further, tigecycline should not be used in children younger than 8 years if there are effective alternatives, because there may be reversible inhibition of bone growth and adverse effects on tooth development.

[e] Daptomycin is active in vitro against multidrug-resistant, gram-positive organisms, including *S aureus*. Daptomycin is approved by the US Food and Drug Administration only for treatment of complicated skin and skin structure infections and for *S aureus* bloodstream infections. Daptomycin is ineffective for treatment of pneumonia. Because experience with these agents in children is limited, consultation with a specialist in infectious diseases should be considered before use.

[f] Rybak MJ, Le J, Lodise TP, et al. Therapeutic monitoring of vancomycin for serious methicillin-resistant *Staphylococcus aureus* infections: a revised consensus guideline and review by the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, and the Society of Infectious Diseases Pharmacists. *Am J Health Syst Pharm*. Published online March 19, 2020. Available at: **https://doi.org/10.1093/ajhp/zxaa036**

Vancomycin-Intermediately Susceptible S aureus.

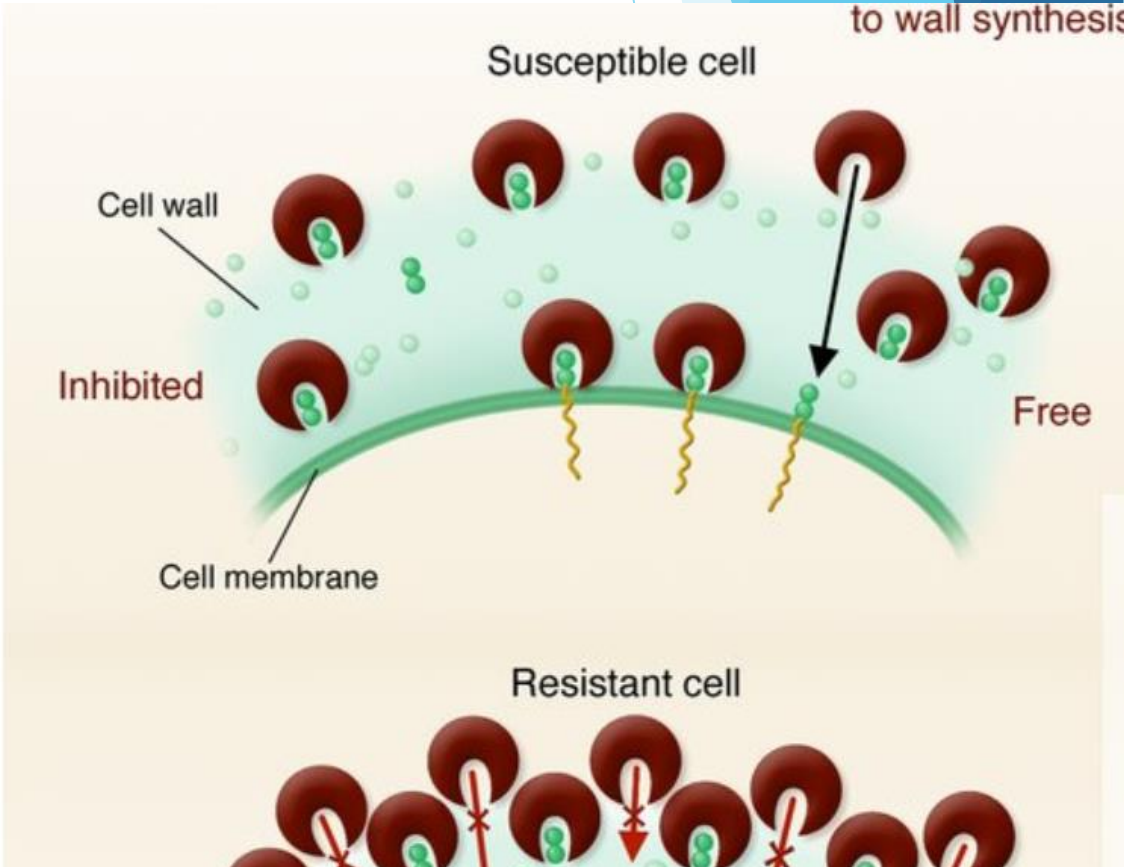
- Vancomycin-intermediately susceptible *S aureus* (VISA) strains (minimum inhibitory concentration [MIC], 4–8 μg/mL) have been isolated from people (historically, dialysis patients) who have received multiple courses of vancomycin.
- Strains of MRSA can be heterogeneous for vancomycin resistance
- Extensive vancomycin use allows VISA strains to develop during therapy.

VISA infection is rare in children

- For seriously ill patients with a history of recurrent MRSA infections or for patients failing vancomycin therapy in whom VISA strains are a consideration, initial therapy could include linezolid or trimethoprim-sulfamethoxazole, with or without gentamicin.

Vancomycin-Resistant S aureus

- Vancomycin-resistant *S aureus* (VRSA) infections (MIC >8 µg/mL) are very rare, and in all confirmed cases, reported patients had underlying medical conditions, a history of MRSA infections, and prolonged exposure to vancomycin.



IV. Vancomycin-intermediately susceptible *S aureus* (VISA; MIC, 4 to 16 µg/mL)[d]

Drugs of choice:	Optimal therapy is not known	Dependent on in vitro susceptibility test results
	Linezolid[d]	
	Ceftaroline[d]	
	Daptomycin[e]	
	Quinupristin-dalfopristin[d]	
	Tigecycline[d]	

Table 3.54. Parenteral Antimicrobial Agent(s) for Treatment of Bacteremia and Other Serious *Staphylococcus aureus* Infections, continued

	Antimicrobial Agents	Comments
Alternatives:	Vancomycin[b] + linezolid ± gentamicin	
	Vancomycin[b] + trimethoprim-sulfamethoxazole[c]	

Control measures recommended by the CDC have included;

- using proper methods to detect VISA,
- using appropriate infection- control measures,
- adopting measures to ensure appropriate vancomycin use.

Duration of therapy for serious MSSA or MRSA infections

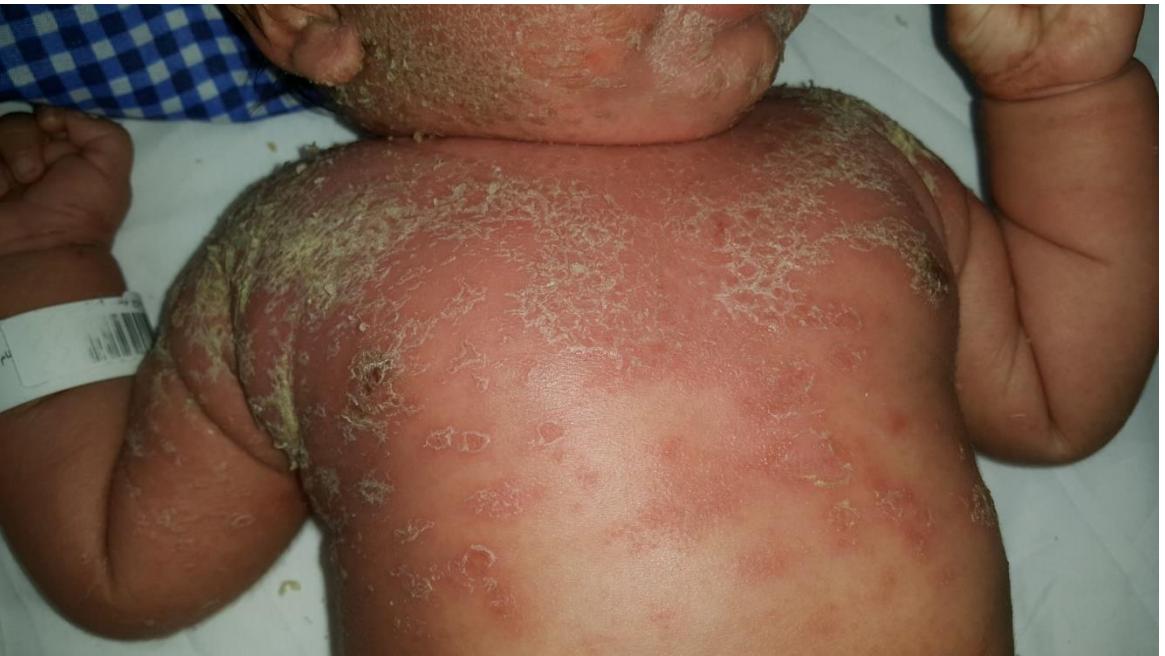
- It depends on the site and severity of infection but usually is 4 weeks or more for endocarditis, osteomyelitis, necrotizing pneumonia, or disseminated infection, assuming a documented clinical and microbiologic response
- In assessing whether modification of therapy is necessary, clinicians should consider whether the patient is improving clinically, should identify and drain sequestered foci of infection and remove foreign material (such as a central catheter) when possible.
- All guidelines recommends AUC guided therapeutic monitoring , preferably with Bayesian estimation, for all pediatric age groups receiving vancomycin.

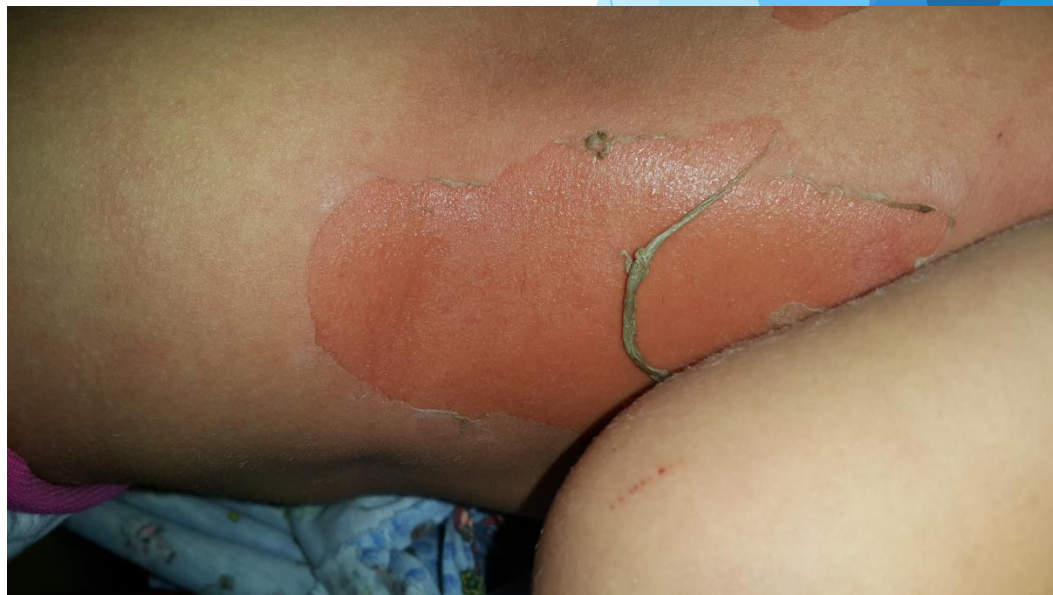
Management of S aureus Toxin-Mediated Diseases

- The principles of therapy for TSS include aggressive fluid management , source control , and anticipation and management of the commonly observed multiorgan complications of TSS.
- Initial antimicrobial therapy should include a parentally administered anti staphylococcal beta-lactam antimicrobial agent and a protein synthesis-inhibiting drug, such as clindamycin, at maximum dosages.
- Vancomycin should be added to the beta-lactam agent in regions where MRSA infections are common, although MRSA-associated TSS is rare in the United States.
- Empiric antibiotic therapy should be modified to targeted therapy once antibiotic susceptibilities are known.
- Administration of antimicrobial agents can be changed to the oral route once the patient is tolerating oral alimentation.
- Immune Globulin Intravenous (IGIV) can be considered in patients with severe staphylococcal TSS unresponsive to other therapeutic measures, because IGIV may neutralize circulating toxin.

SSSS (4S)

- SSSS in infants should be treated with a parenteral antistaphylococcal beta-lactam antimicrobial agent or clindamycin, depending on local susceptibility patterns and the severity of the disease.
- If MRSA is a consideration, vancomycin or clindamycin (depending on local susceptibility patterns) can be used.





CoNS

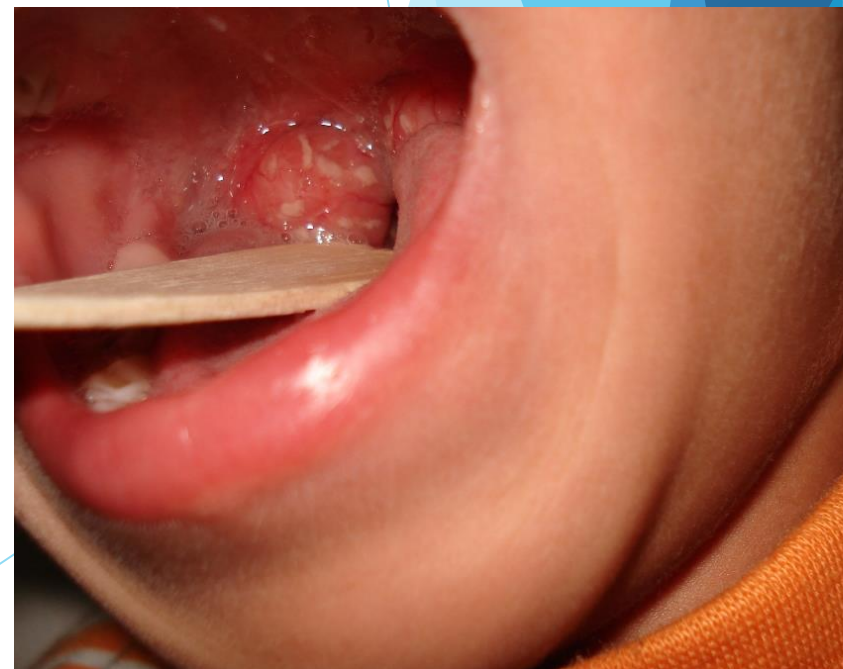
- More than 90% of health care-associated CoNS strains are methicillin resistant.
- Methicillin-resistant strains are resistant to all beta-lactam drugs, including cephalosporins (except ceftaroline), and usually several other drug classes.
- Intravenous vancomycin is recommended for treatment of serious infections caused by CoNS strains resistant to beta-lactam antimicrobial agents.
- Ceftaroline, daptomycin, and linezolid are alternative agents when vancomycin cannot be used.

Antimicrobial therapy of GAS infections

- *S pyogenes* is uniformly susceptible to all beta-lactam antibiotics (penicillins and cephalosporins); thus, susceptibility testing is needed only for non–beta-lactam agents, such as a macrolide or clindamycin, to which *S pyogenes* can be resistant.

Pharyngitis

- Penicillin V is the drug of choice for GAS pharyngitis.
- Prompt administration of penicillin shortens the clinical course, decreases risk of transmission and suppurative sequelae, and prevents ARF, even when administered up to 9 days after illness onset.
- Amoxicillin, orally as a single daily dose (50 mg/kg; maximum, 1000–1200 mg) for 10 days, is as effective as penicillin V.



- For patients who have a history of nonanaphylactic allergy to penicillin, a 10-day course of a narrow-spectrum (first-generation) oral cephalosporin (eg, cephalexin) is indicated.
- Patients with immediate (anaphylactic) or type I hypersensitivity to penicillin should receive oral clindamycin (20 mg/kg per day in 3 divided doses; maximum, 900 mg/day for 10 days) .
- Tetracyclines, sulfonamides, and fluoroquinolones should not be used for treating GAS pharyngitis.

- Children with recurrent GAS pharyngitis shortly after a full course of a recommended oral agent can be retreated with the same antimicrobial agent (if it is a beta-lactam), an alternative beta-lactam oral drug (such as cephalexin or amoxicillin-clavulanate), or an intramuscular dose of penicillin G benzathine.
- Susceptibility testing should be performed when considering a macrolide or clindamycin.

Table 3.60. Chemoprophylaxis for Recurrences of Acute Rheumatic Fever[a]

Drug	Dose	Route
Penicillin G benzathine	1.2 million U, every 4 wk[b]; 600 000 U, every 4 wk for patients weighing less than 27 kg (60 lb)	Intramuscular
OR		
Penicillin V	250 mg, twice a day	Oral
OR		
Sulfadiazine or sulfisoxazole	0.5 g, once a day for patients weighing 27 kg (60 lb) or less	Oral
	1.0 g, once a day for patients weighing greater than 27 kg (60 lb)	
For people who are allergic to penicillin and sulfonamide drugs		
Macrolide or azalide	Variable (see text)	Oral

Management of Toxin-Mediated Diseases

- Because *S pyogenes* and *S aureus* TSS are difficult to distinguish clinically, initial therapy should include an antistaphylococcal agent and a protein synthesis-inhibiting agent, such as clindamycin.

Antimicrobial therapy of serious GAS infections

Addition of clindamycin to penicillin is recommended for serious GAS infections, because :

- its antimicrobial activity is unaffected by inoculum size (does not have the eagle effect that occurs with beta-lactam antibiotics),
- has a long post antimicrobial effect, and
- inhibits bacterial protein synthesis, which results in suppression of synthesis of *S pyogenes* antiphagocytic M-protein and bacterial toxins.
- Clindamycin may be discontinued after a few days if there is adequate source control and clinical improvement.
- Clindamycin **should not be used alone** as initial antimicrobial therapy in life-threatening situations because of the potential for resistance.
- In 2017, 22% of invasive GAS case isolates from the Active Bacterial Core surveillance system in the United States were resistant to clindamycin.

Table 3.56. Management of Streptococcal Toxic Shock Syndrome Without Necrotizing Fasciitis

- Fluid management to maintain adequate venous return and cardiac filling pressures to prevent end-organ damage
- Anticipatory management of multisystem organ failure
- Parenteral antimicrobial therapy at maximum doses with the capacity to:
  - Kill organism with bactericidal cell wall inhibitor (eg, beta-lactamase–resistant antimicrobial agent)
  - Decrease enzyme, toxin, or cytokine production with protein synthesis inhibitor (eg, clindamycin)
- IGIV often is used as an adjunct, typically at 1 g/kg on day 1, followed by 0.5 g/kg on 1–2 subsequent days

Antimicrobial therapy of GBS infection

- Ampicillin plus an aminoglycoside is the initial empiric treatment of choice for a **newborn infant ≤7 days of age** with presumptive early-onset GBS infection;
- this reflects the need for coverage of other pathogens, such as *Escherichia coli*.
- In a critically ill neonate, particularly one with low birth weight, broader-spectrum empiric therapy should be considered when there is concern about non-GBS ampicillin-resistant infection.

- For empiric therapy of late-onset GBS disease in **infants 8 through 28 days of age** who are not critically ill and do not have evidence of meningitis, ampicillin plus either gentamicin or cefotaxime are recommended.
- If meningitis is suspected, ampicillin plus cefotaxime should be used; gentamicin should not be used if meningitis is suspected.
- For **infants 29 to 90 days of age**, ceftriaxone is recommended. If there is evidence of meningitis or critical illness, vancomycin should be added to expand empiric coverage.
- When GBS infection is identified definitively, penicillin G or ampicillin are recommended.

GBS Intrapartum Antibiotic Prophylaxis

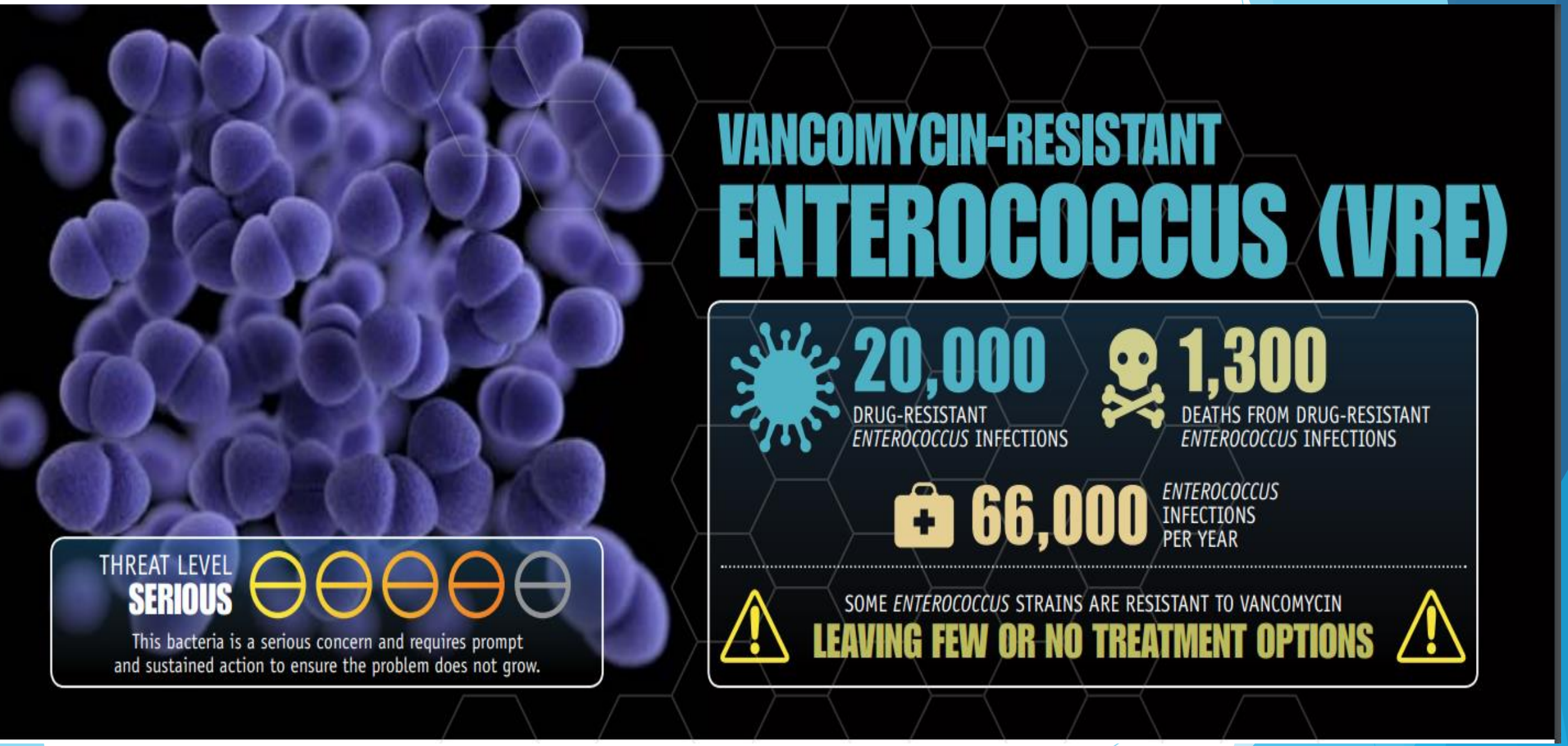
- Intravenous penicillin G (5 million U initially, then 2.5 to 3.0 million U, every 4 hours, until delivery) is the preferred agent for GBS IAP because of its efficacy and narrow spectrum of antimicrobial activity.
- Intravenous ampicillin (2 g initially, then 1 g every 4 hours until delivery) can be used as an alternative when penicillin is unavailable.
- Women who report penicillin allergies placing them at high risk for anaphylaxis should receive either intravenous clindamycin or vancomycin for IAP.

Antimicrobial therapy of Non-Group A or B Streptococcal Infection

- Diagnosis is established by culture of usually sterile body sites or abscesses with appropriate biochemical testing and serologic analysis for definitive identification.
- Genomic methods are being used increasingly, particularly for rapid identification of positive blood cultures.
- Antimicrobial susceptibility testing of isolates from usually sterile sites should be performed to guide treatment of infections.
-

- Penicillin G is the drug of choice for groups C and G streptococci.
- Other agents with good activity include ampicillin, third- and fourth-generation cephalosporins, vancomycin, and linezolid.
- The combination of gentamicin (when high level resistance is not present) with a beta-lactam antimicrobial agent (eg, penicillin or ampicillin) or vancomycin may enhance bactericidal activity needed for treatment of life-threatening infections (eg, endocarditis or meningitis).
- Many viridans streptococci remain susceptible to penicillin (minimum inhibitory concentration [MIC] ≤0.12 µg/mL).
- Infections caused by strains susceptible to penicillin, including endocarditis, can be treated with penicillin or ceftriaxone.

- Strains with an MIC >0.12 μg/mL and <0.5 μg/mL are considered relatively resistant to penicillin . In this situation, penicillin, ampicillin, or ceftriaxone for 4 weeks, combined for the first 2 weeks with gentamicin, is recommended for endocarditis treatment.
- Strains with a penicillin MIC ≥0.5 μg/mL are considered resistant.
- Nonpenicillin antimicrobial agents with good activity against viridans streptococci include cephalosporins (especially ceftriaxone), vancomycin, linezolid, and tigecycline, although pediatric experience with tigecycline is limited
- The combination of high-dose penicillin or vancomycin and an aminoglycoside can enhance bactericidal activity.


VANCOMYCIN-RESISTANT
ENTEROCOCCUS (VRE)
20,000
DRUG-RESISTANT
ENTEROCOCCUS INFECTIONS
1,300
DEATHS FROM DRUG-RESISTANT
ENTEROCOCCUS INFECTIONS
66,000
ENTEROCOCCUS
INFECTIONS
PER YEAR
SOME ENTEROCOCCUS STRAINS ARE RESISTANT TO VANCOMYCIN
LEAVING FEW OR NO TREATMENT OPTIONS
THREAT LEVEL
SERIOUS
This bacteria is a serious concern and requires prompt
and sustained action to ensure the problem does not grow.

	Percent of all *Enterococcus* healthcare-associated infections resistant to vancomycin	Estimated number of infections	Estimated number of deaths attributed
Vancomycin-resistant *Enterococcus faecium*	77%	10,000	650
Vancomycin-resistant *Enterococcus faecalis*	9%	3,100	200
Vancomycin-resistant *Enterococcus* (species not determined)	40%	6,900	450
Totals		20,000	1,300

Antimicrobial therapy of Enterococci infections

- The proportion of vancomycin-resistant enterococci (the vast majority of which are *E faecium*) among hospitalized patients can be as high as 30%.
- Molecular assays are available for direct detection of *vanA* and *vanB* genes (which confer vancomycin resistance) from rectal and blood specimens to identify vancomycin-resistant enterococci (VRE).
- Enterococci exhibit uniform resistance to cephalosporins (except ceftaroline and, where available, ceftobiprole), aztreonam, and antistaphylococcal penicillins.
- Most are intrinsically resistant to clindamycin and trimethoprim-sulfamethoxazole even if in vitro susceptibility indicates otherwise.
- The vast majority of *E faecalis* strains are susceptible to ampicillin (which can be extrapolated to amoxicillin, piperacillin-tazobactam, and imipenem, but not to penicillin).
- *E faecium* strains may be multidrug resistant.

Two types of vancomycin resistance are identified:

- intrinsic low-level resistance that occurs with *some strains* (these strains are ampicillin susceptible), and
- acquired resistance, which has been seen in *E faecium* and some *E faecalis strains*.

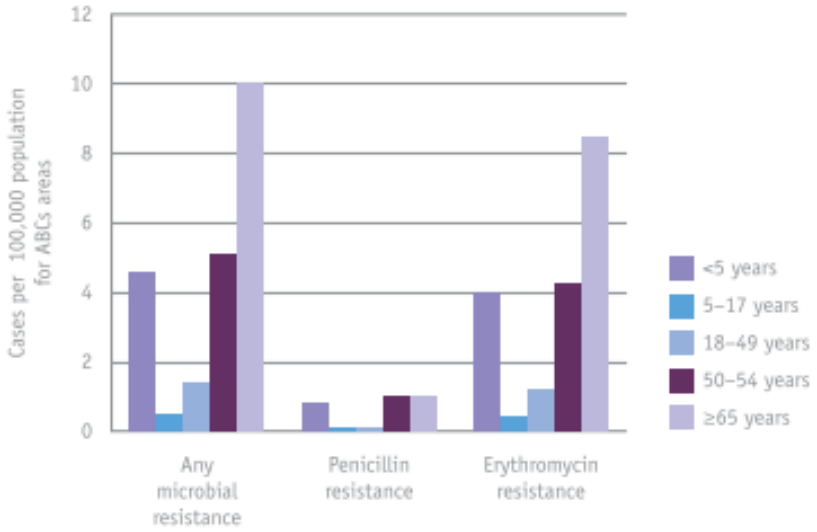
- Systemic enterococcal infections, such as endocarditis or meningitis, should be treated with penicillin or ampicillin (if the isolate is susceptible) combined with ceftriaxone or gentamicin ;
- vancomycin plus an aminoglycoside is suggested for patients unable to tolerate penicillins and who cannot be desensitized.
- Gentamicin should not be used if in vitro susceptibility testing demonstrates high-level resistance.
- In general, children with a central line-associated bloodstream infection caused by enterococci should have the device removed promptly.
- Combination therapy for treating central line-associated bloodstream infections generally is not needed

- Linezolid or daptomycin are options for treatment of other systemic infections caused by vancomycin-resistant *E faecium*.
- Isolates of VRE that are resistant to linezolid have been described, and resistance can develop during prolonged linezolid treatment
- Most vancomycin-resistant isolates of *E faecalis* and *E faecium* are daptomycin-susceptible.
- Daptomycin should not be used to treat pneumonia, as tissue concentrations are poor and daptomycin is inactivated by surfactants.
- Microbiologic and clinical cure has been reported in children infected with vancomycin-resistant *E faecium* who were treated with quinupristin-dalfopristin. This drug frequently causes phlebitis in peripheral intravenous lines, and pediatric dosing in children younger than 12 years is unclear.
- Tigecycline is approved for use in adults with complicated skin and skin structure infections caused by vancomycin-susceptible *E faecalis*. Tigecycline is bacteriostatic and experience with this drug in children is limited.
- There are case reports of successful use of daptomycin plus tigecycline for endocarditis and with intraventricular daptomycin for VRE ventriculitis.


DRUG-RESISTANT
STREPTOCOCCUS PNEUMONIAE
1,200,000
DRUG-RESISTANT INFECTIONS PER YEAR
19,000
EXCESS HOSPITALIZATIONS
7,000
DEATHS
$96,000,000
IN EXCESS MEDICAL COSTS PER YEAR
THREAT LEVEL
SERIOUS
This bacteria is a serious concern and requires prompt and sustained action to ensure the problem does not grow.

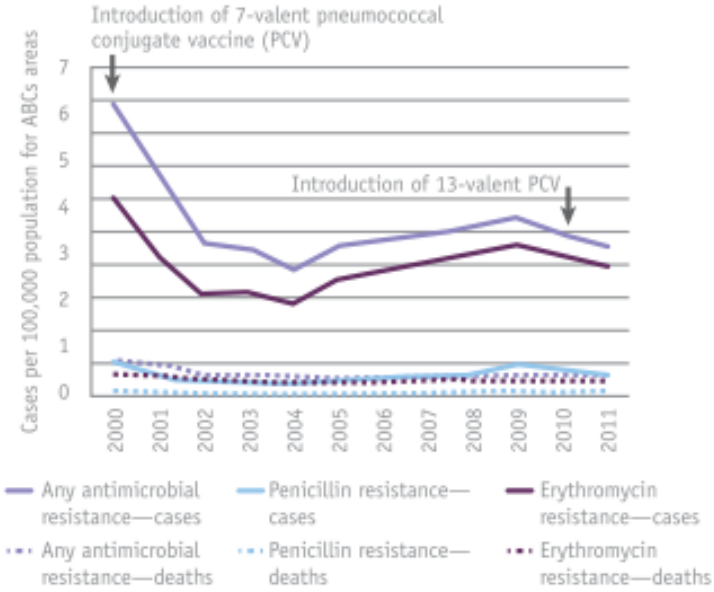
The very young and senior adults are most at risk for drug-resistant pneumococcal disease.

Cases of antibiotic-resistant invasive disease per 100,000 persons, by age group and resistance profile — Active Bacterial Core surveillance



Vaccination prevents spread of drug-resistant *S. pneumoniae* infections.

Cases and deaths per 100,000 population by resistance profile — ABCs areas, 2000–2011



In 2010, 13-valent pneumococcal conjugate vaccine (PCV13) replaced 7-valent pneumococcal conjugate vaccine (PCV7)

Susceptibility Testing of S pneumoniae

- All *S pneumoniae* isolates from normally sterile body fluids should be tested for antimicrobial susceptibility to determine the minimum inhibitory concentration (MIC) of penicillin, cefotaxime or ceftriaxone, and clindamycin.
- CSF isolates also should be tested for susceptibility to vancomycin, meropenem, and rifampin.
- If the patient has a nonmeningeal infection caused by an isolate that is nonsusceptible to penicillin, cefotaxime, and ceftriaxone, susceptibility testing to other agents such as clindamycin, erythromycin, trimethoprim-sulfamethoxazole, levofloxacin, linezolid, meropenem, and vancomycin should be performed.

Bacterial Meningitis Possibly or Proven to Be Caused by S pneumoniae.

- For children with bacterial meningitis possibly or known to be caused by *S pneumoniae*, vancomycin should be administered in addition to ceftriaxone because of the possibility of *S pneumoniae* resistant to penicillin and third-generation cephalosporins.
- Vancomycin should be stopped if susceptibility to third-generation cephalosporins is documented , if another organism not requiring vancomycin is identified, or if the CSF culture is negative.

- For children with serious proven hypersensitivity reactions to third- or fourth-generation cephalosporins, a pediatric infectious diseases specialist should be consulted for consideration of use of vancomycin plus either meropenem or rifampin.

A repeat lumbar puncture should be considered after 48 hours of therapy in the following circumstances:

- The organism is penicillin nonsusceptible by oxacillin disk or quantitative (MIC) testing, and results from cefotaxime and ceftriaxone quantitative susceptibility testing are not yet available or the isolate is cefotaxime and ceftriaxone nonsusceptible; or
- • The patient’s condition has not improved or has worsened; or
- • The child has received dexamethasone, which can interfere with the ability to interpret the clinical response, such as resolution of fever.

Table 3.63. Antimicrobial Therapy for Infants and Children With Meningitis Caused by *Streptococcus pneumoniae* on the Basis of Susceptibility Test Results

Susceptibility Test Results	Antimicrobial Management[a]
Susceptible to penicillin	Discontinue vancomycin **AND EITHER** Continue cefotaxime or ceftriaxone alone[b] **OR** Begin penicillin (and discontinue cephalosporin)
Nonsusceptible to penicillin (*intermediate* or *resistant*) **AND** *Susceptible* to cefotaxime and ceftriaxone	Discontinue vancomycin **AND** Continue cefotaxime or ceftriaxone
Nonsusceptible to penicillin (*intermediate* or *resistant*) **AND** *Nonsusceptible* to cefotaxime and ceftriaxone (*intermediate* or *resistant*) **AND** *Susceptible* to rifampin	Continue vancomycin and high-dose cefotaxime or ceftriaxone **AND** Rifampin may be added in selected circumstances (see text)

[a]Initial empiric therapy of nonallergic children older than 1 month of age with presumed bacterial meningitis should be vancomycin and cefotaxime or ceftriaxone. See Tables 4.2 (neonatal) and 4.3 (nonneonatal) in Tables of Antibacterial Drug Dosages, p 876, for dosages. Some experts recommend the maximum dosages.

[b]Some physicians may choose this alternative for convenience and cost savings but only in treatment of meningitis.

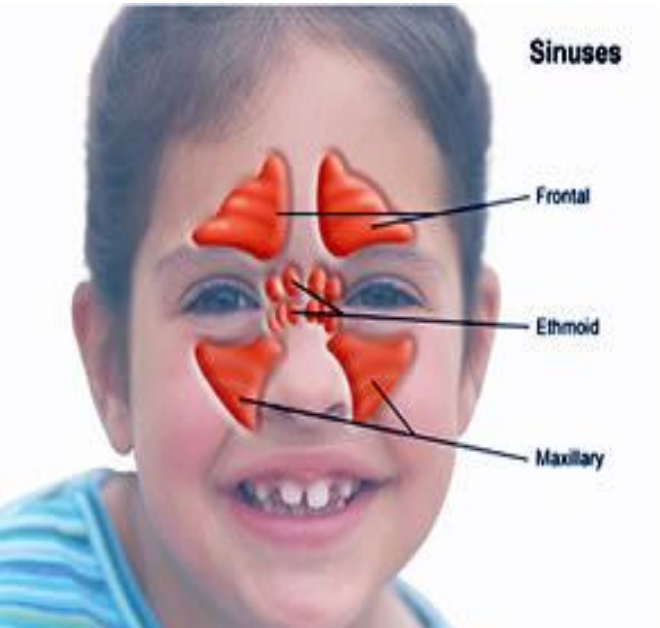
Non meningeal Invasive Pneumococcal Infections Requiring Hospitalization.

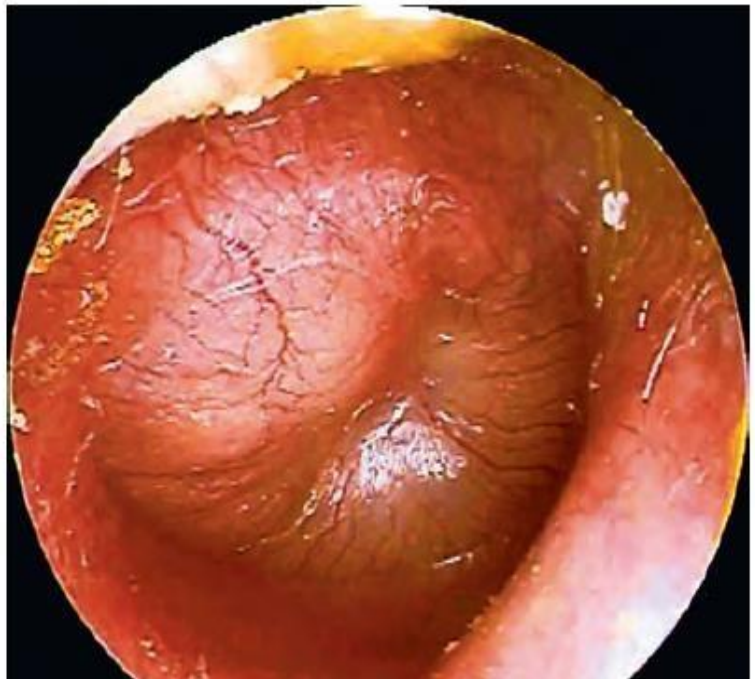
- For nonmeningeal invasive infections in previously healthy children who are not critically ill, antimicrobial agents currently used to treat infections with *S pneumoniae* and other potential pathogens should be initiated.
- For critically ill infants and children with invasive infections potentially attributable to *S pneumoniae*, vancomycin, in addition to empiric antimicrobial therapy (eg, ceftriaxone or others), can be considered.
- Such patients include those with presumed septic shock, severe pneumonia with empyema, or significant hypoxia or myopericardial involvement.
- If vancomycin is administered, it should be discontinued as soon as antimicrobial susceptibility test results demonstrate effective alternative agents.

- If the organism has in vitro resistance to penicillin, cefotaxime, and ceftriaxone therapy should be modified on the basis of clinical response, susceptibility to other antimicrobial agents, and results of follow-up cultures of blood and other infected body fluids.
- For children with severe hypersensitivity to beta-lactam antimicrobial agents (ie, penicillins and cephalosporins), initial management should include vancomycin or clindamycin, in addition to antimicrobial agents for other potential pathogens, as indicated.
- Vancomycin should not be continued if the organism is susceptible to other appropriate non–beta-lactam antimicrobial agents.

Acute Otitis Media and Sinusitis

- In acute suppurative otitis media (AOM), amoxicillin (80–90 mg/kg/day) is recommended for infants younger than 6 months, for those 6 through 23 months of age with bilateral disease, and for those older than 6 months with severe signs and symptoms.
- A watch-and-wait option can be considered for older children and those with non severe disease.





If the patient has failed initial antibacterial therapy

- Suitable alternative agents should be active against penicillin nonsusceptible pneumococci as well as beta-lactamase–producing *Haemophilus influenza* and *Moraxella catarrhalis*.
- Such agents include high-dose oral amoxicillin-clavulanate; oral cefdinir, cefpodoxime, or cefuroxime; or once-daily doses of intramuscular ceftriaxone for 3 consecutive days.
- Macrolide resistance among *S pneumoniae* is high, so clarithromycin and azithromycin are not considered appropriate alternatives for initial therapy.

- In type I (immediate, anaphylactic) reaction to a beta-lactam agent, treatment with clindamycin (if susceptibility is known) or levofloxacin is preferred.
- For patients with a history of non-type I allergic reaction to penicillin, agents such as cefdinir, cefuroxime, or cefpodoxime can be used orally.
- For multidrug-resistant strains of *S pneumoniae*, use of levofloxacin or other agents should be considered in consultation with an infectious diseases specialist and based on the specific susceptibility profile.

Pneumonia

- Oral amoxicillin at a dose of 45 mg/kg/day in 3 equally divided doses or 90 mg/kg/day in 2 divided portions is likely to be effective in ambulatory children with pneumonia caused by susceptible and relatively resistant pneumococci, respectively.
- Ampicillin is recommended for intravenous therapy of community acquired pneumonia.
- Cefotaxime or ceftriaxone is recommended for treatment of inpatients infected with pneumococci suspected or proven to be penicillin-resistant strains, for serious infections including empyema, or in those not fully immunized with PCV13.
- Vancomycin should be included in those with life-threatening infection.
- For patients with isolates resistant to penicillin (MICs of 4.0 μg/mL or higher) or significant allergy to betalactam antimicrobials, treatment with clindamycin (if susceptible) or levofloxacin should be considered, assuming that concurrent meningitis has been excluded