In spite of the availability of adequate antibiotics, Staphylococci continue to challenge the treating physicians. New disease entities, new emerging species, and the changing spectrum of antibiotic susceptibility are examples of such challenges. Early in this century and before the advent of antibiotics, Staphylococcus was a major cause of morbidity and mortality. With the discovery of penicillin, it was thought that an upper hand had been achieved; however, Staphylococcus aureus (S. aureus) escaped this threat by producing β-lactamase that renders them resistant to penicillin. This stimulated the research for an alternative antibiotic, penicillinase-resistant penicillin, namely, cloxacillin and others. Again Staphylococci start to have some resistance, methicillin-resistant Staphylococcus aureus (MRSA) which is now one of the major problems in health-care facilities. In addition, coagulase-negative Staphylococci are becoming important pathogens in many situations including neonates, immunocompromised host, and patient with implanted prosthetic devices.

Organism

Staphylococci are Gram-positive cocci that are catalase positive and non-spore forming. Staphylococcus genus includes a number of species that are classified to coagulase positive and coagulase negative according to production of a coagulation enzyme that aggregate sheep RBC. The coagulase-positive staphylococcus is Staphylococcus aureus. Staphylococcus aureus is the commonest cause of human infections. It produces a variety of diseases that could be severe or mild. When antibiotics were initially introduced in the 1940s, S. aureus was sensitive to penicillin, and then it quickly became resistant which led to the introduction of β-lactamase-resistant β lactam (methicillin, cloxacillin, and others). In the last 2 decades, methicillin-resistant S. aureus (MRSA) emerged as an important pathogen, initially in health-care settings, but recently it is becoming common in community-acquired infections. MRSA carry a chromosomally mediated gene that mediates resistance through alteration of penicillin-binding proteins (PBP). MRSA is one of the major problems in hospital-acquired infections, especially in hospitals with burn and intensive care units. Many epidemics due to MRSA have been reported in NICU, PICU, and burn units. MRSA is not more virulent than methicillin-sensitive S. aureus; however, it is difficult to treat because of its nature of being multiply resistant to many antibiotics including cephalosporins and aminoglycosides. They are usually susceptible to vancomycin, teicoplanin, linezolid, and daptomycin. Most of the hospital-associated MRSA strains are also resistant to other antibiotics like clindamycin, TMP/SMX, rifampin, and fluoroquinolones. Community-associated MRSA (CA-MRSA) are less resistant and it tends to be sensitive to clindamycin, cotrimoxazole, erythromycin, and tetracycline. However, attention should be paid that some of CA-MRSA is also multidrug resistant. When an MRSA is sensitive to clindamycin

The approach to treating patients with MRSA infection relies on a comprehensive surveillance for such organism in patients in the high-risk areas like burn unit and PICU. Patients who are colonized with MRSA but have no disease should be isolated in private rooms and barrier precaution are applied. Treatment of such patients has failed to eradicate colonization. If epidemics arise due to MRSA, a trial to eradicate infection by treating all colonized patients with TMP/SMX combined with rifampin or ciprofloxacin may be beneficial. Patients who develop diseases due to MRSA should be treated with vancomycin and if they have intravascular devices attempts to remove such devices is advisable. Application of mupirocin cream locally to the colonized areas has shown some success in eradicating infection.

There are almost 39 species of coagulase-negative Staphylococcus (CONS), the most important of which are S. epidermidis, S. heminis, S. hemolyticus, S. werner, S. lugodensis, and S. saprophyticus. Staphylococci are facultative, nonfastidious organisms which can be cultured in ordinary media like blood or chocolate agars. Both S. aureus and some species of CONS are normal commensal of human skin.
**Staphylococcus aureus**

*S. aureus* is a primary human pathogen that is a major cause of human disease. In the 1960s, it was the commonest cause of neonatal sepsis. Nowadays, it is the major cause of nosocomial and community-associated infections. *Staphylococcus aureus* causes a variety of illnesses which are divided into:

(a) Skin and soft tissue infections  
(b) Deep-seated infections  
(c) Bacteremia and sepsis

**Cutaneous Infections**

**Impetigo**

Ten to twenty percent of impetigo is caused by *S. aureus*. In another 10–20% of cases of impetigo, the causative agents are *S. aureus* and Group A *Streptococci* (GAS). The remainder is caused by GAS. Impetigo is a skin disease that starts as a macular erythematous lesion which changes soon to pustule that then form a honey-colored crust. Any part of the body surface can be involved and the patient may infect himself at multiple sites by self-inoculation of the organism through scratching. Other siblings in the family may be affected. *S. aureus* is the main cause of bullous impetigo. In recent years, spiderlike or herpeslike lesions may be the presentation of staphylococcal skin infections. This presentation is being attributed to a staphylococcus that produces Panton–Valentine leukocidin (PVL).

**Illustrated Case**

A 13-month-old girl was admitted because of fever and skin lesions. The lesions were erythematous papule with necrotic center (spider-like lesions). It was thought to be herpetic lesion and she was given intravenous acyclovir. Twelve hours later she started to be hypotensive and was in respiratory distress. Chest radiography showed bilateral patchy consolidation and pleural effusion. She was transferred to intensive care unit and was started on vancomycin and ceftriaxone. She required ventilation and chest tube insertion. Pleural fluid was bloody. Blood and pleural fluid cultures grew methicillin-sensitive *S. aureus*. She required pleural decortication and her condition improved.

**Cellulitis**

Rarely, *S. aureus* may cause cellulitis especially in young children. However, GAS is the commonest cause of cellulitis. Treatment can be achieved by using penicillinase-resistant penicillin like cloxacillin.

**Folliculitis**

Folliculitis is a mild superficial skin infection that appears as small yellowish pimpls. They are self-limiting and can be treated by using a topical disinfectant.

**Furunculosis or Boils**

This is a staphylococcal infection of hair follicle. It starts as erythematous lesion which then becomes pus-containing vesicle. Treatment can be achieved by evacuation and topical antibiotics.

**Carbuncles**

Carbuncle is defined as infection of multiple hair follicles which usually coalesce and form large abscess with multiple draining sinuses. This type of infection is more common in patients who have phagocytic impairment either quantitatively or qualitatively. Local debridement and systemic cloxacillin are the therapies of choice.

**Tracheitis**

Although not common in children, it is a life-threatening condition that usually presents with high fever, toxic appearance, inspiratory stridor, drooling, and cough that is productive of tenacious sputum and retrosternal pain. In addition to *S. aureus*, GAS and other *Streptococci* are other causes. Tracheitis may arise without any preceding illness; however, it may complicate a preceding viral illness like varicella or influenza virus infections. Diagnosis can be achieved by obtaining sputum for culture. Intravenous therapy with an antibiotic agent that is effective against *S. aureus* and *Streptococci* should be instituted promptly. Cefuroxime or cloxacillin is appropriate. In patients with tracheostomy and thought to have tracheitis
Enterobacteriaceae like E. coli, Klebsiella pneumoniae and Enterocobacter as well as Pseudomonas may be involved as causative agents and this should be considered in the antibiotic coverage. In these cases, adding aminoglycoside or ceftazidime is recommended.

**Pneumonia**

In infants, S. aureus is one of the major causes of bacterial pneumonia and it is only preceded by S. pneumoniae and H. influenzae. However, H. influenzae is decreasing in frequency with the introduction of the conjugate Hib vaccine. Staphylococcal pneumonia is usually severe with complicating pleural effusions and empyema occurring in 30–50% of the cases. Diagnosis is achieved by positive blood culture, pleural fluid, or specimens obtained by bronchoscope. In addition to supportive therapy with oxygen and artificial ventilation if needed, intravenous antibiotics with cloxacillin or nafcillin should be used.

Chest tube drainage of pleural effusion may not be effective because of early loculations; therefore, the trend now is to use antibiotic therapy and observe the patient. If there is no response to this therapy within 7–10 days, then decortication may be needed after a trial of chest tube drainage.

**Bacteremia**

*S. aureus* is one of the major causes of nosocomial infections. Bacteremia is the third commonest cause of nosocomial infection in pediatric hospitals and the *S. aureus* is the commonest cause of nosocomial bacteremia. In addition, *S. aureus* can cause community-acquired bacteremia, but this is rare. Any patient with staphylococcal bacteremia should be investigated for an underlying focal infection like osteomyelitis, endocarditis, or deep abscess. Recently, fulminant sepsis that can be fatal is being reported.

**Illustrated Case**

An 8-year-old healthy boy brought to emergency room by his father after complaining of being tired and unable to walk for few hours. He was very well until around 15:00 same day of presentation; at which time he started to have generalized malaise and not feeling well and at around 19:00 he was unable to walk and therefore he was brought to ER. Upon arrival to ER, he was conscious and alert; however, he looks sick. His vital signs showed a temperature of 36.7°C, pulse rate 150 beats/min, respiratory rate 30/min, blood pressure 117/70, and pulse oximetry 98% in room air. He has normal chest and cardiovascular examination. His abdomen was soft. He has ice cold extremities with mottled skin and delayed capillary refill of around 6 s. He was judged to be in compensated shock likely of sepsis origin. Two boluses of intravenous normal saline at 20 ml/kg were given as well as a shot of ceftriaxone and vancomycin. His condition was worsening gradually with increasing work of breathing and desaturation. Arterial blood gas was done and showed pH 7.12, PCO2 52, PO2 28, HCO3 17, and base access 12.2 and therefore oxygen 5 L/min by face mask was given and he was continued on intravenous maintenance fluid. His initial laboratory workup revealed WBC 1,000/mm3, hemoglobin 95 g/L, platelet 41,000/mm3, CPK 9,315 U/L, lactic acid 12.9 mmol/L, CRP 330 mg/L, and d-dimer 2,279 mcg/L. By 23:45, he started to desaturate in spite of being on 10 L/min and therefore he was intubated and mechanically ventilated. His condition deteriorated farther with drop in blood pressure and increasing difficulty in ventilating him. Chest x-ray showed white out lungs suggestive of ARDS. He was started on dopamine, dobutamine, and norepinephrine but his blood pressure remained low and his heart rate started to drop and became asystolic and not responding to resuscitation. He died by 3:30 next morning. Two bottles of blood culture was positive for gram-positive cocci in clusters, which was identified as *S. aureus*; methicillin resistant based on MicroScan result which was confirmed by cefoxitin diffusion disk as well as positive PBP. Bacterial isolate underwent molecular characterization using multilocus sequence typing, staphylococcal cassette chromosome mec (SCCmec) typing, and PCR for the presence of the genes encoding Panton-Valentine leukocidin (PVL) and confirm a positive PVL.

**Endocarditis**

*S. aureus* is the second commonest cause of endocarditis; however, it is the commonest cause of endocarditis in patients with drug abuse.
Osteomyelitis and Septic Arthritis

*S. aureus* is the commonest cause of skeletal infection in all age groups. Although sicklemic patients have an increased susceptibility to *Salmonella* osteomyelitis, *S. aureus* is still common cause of osteoarticular infection.

Meningitis

*S. aureus* is a very rare cause of meningitis, but it is one of the major causes of brain abscess.

### Therapy of Staphylococcal Infections

#### Soft Tissue and Skin Infections

**Impetigo**

Most of the time, topical therapy is enough; however, if there is systemic manifestation, then an oral antibiotic with a drug that is effective against both *Staphylococcus aureus* and *Streptococcus pyogenes* is needed. Usually, a first-generation cephalosporin like cephalaxin is enough. However, if MRSA prevalence in the community is high, \( \geq 10\% \), then clindamycin is advised.

**Folliculitis**

Topical antibiotic is usually effective.

**Furunculosis, Carbuncles, and Abscesses**

If there is fluctuation and there are no systemic symptoms, then drainage is usually enough. If there is systemic manifestation like fever, then oral antibiotics like first-generation cephalosporin is added to the drainage.

**Cellulitis**

Cellulitis is usually associated with some systemic manifestations. Antibiotic therapy is needed. Because both streptococcus and staphylococcus can cause cellulitis, TMP/sulfisoxazole is not adequate. Other antibiotic like first-generation cephalosporin is recommended.

In community where community-associated methicillin-resistant *S. aureus* (CA-MRSA) prevalence is high \( (>10\%) \), clindamycin is advised. In some area, clindamycin resistance is high and in such areas other antibiotics like vancomycin, linezolid, and daptomycin can be used. It is always recommended that local susceptibility pattern of the CA-MRSA should be checked and antibiotics should be advised accordingly (Table 92.1).

### Deep-Seated Infection

When having deep-seated infection due to staphylococcal infection, some consideration should be taken into account:

1. Prevalence of CA-MRSA
2. Severe systemic manifestations
3. Comorbid conditions

As eluted to in the chapter about musculoskeletal infection, the recommended initial therapy is usually parenteral penicillinase-resistant penicillin like cloxacillin (Tables 92.2 and 92.3).

However, in areas where CA-MRSA prevalence is high, other antibiotic is usually recommended like clindamycin if the clindamycin resistance is not high or vancomycin if clindamycin resistance is high.

| Disease           | No systemic signs | Systemic signs       |
|-------------------|-------------------|----------------------|
| Impetigo          | Topical therapy   |                      |
| Folliculitis      | Topical therapy   |                      |
| Furunculosis      | Drainage          | Add first-generation cephalosporin or clindamycin |
| Carbuncles        | Drainage          | Add first-generation cephalosporin or clindamycin |
| Abscess           | Drainage          | Add first-generation cephalosporin or clindamycin |
| Cellulitis        | First-generation cephalosporin or clindamycin |
In cases when severe systemic manifestations are present, a combination of cloxacillin and vancomycin is recommended until the susceptibility result is available. Bacteremia

Most of the staphylococcal bacteremia has a predisposing factor like musculoskeletal infections, implanted devices, or endocarditis. When bacteremia is isolated and no focal infection is identified, then a suitable parenteral antibiotic should be given for 10 days. In community where CA-MRSA is rare, cloxacillin or similar drugs can be used. In areas where CA-MRSA prevalence is high, the choice will be either clindamycin if clindamycin resistance is low or vancomycin if clindamycin resistance is high. Other agents like linezolid and daptomycin may be used.

When bacteremia is associated with a central line, then the duration should be expanded to 14 days besides that blood culture is cleared promptly and the central line is removed.

**Bacteremia associated with infective endocarditis requires a minimum of 4 weeks of parenteral therapy.**

Coagulase-Negative Staphylococci (CONS)

CONS have emerged as a major cause of nosocomial infections. There are more than 39 species, the most common of which are *S. epidermidis, S. hominis, S. hemolyticus, S. werneris, S. lugodensis*, and *S. saprophyticus*. Most of the infections due to CONS occur in patients who have underlying predisposing factors like those who are immunocompromised and those who have implanted prosthesis. Other susceptible patients are neonates who are born prematurely and being cared for in NICU with a number of invasive procedures.

Neonatal Infections

Many reports have shown that CONS are becoming the most common cause of nosocomial infection in NICU, especially among premature neonates. Many factors predispose premature neonates to CONS infections including...
prolonged hospitalization, intravascular devices, and TPN infusion. Varied presentations occur among infected neonates, the most common of which is bacteremia.

**Bacteremia**

Premature neonates are found to be more prone to bacteremia due to CONS. Some epidemiologic studies have shown that 10–25% of nosocomial neonatal bacteremia to be caused by CONS. The bacteremia due to CONS is usually indolent in its presentation with main manifestations including feeding intolerance, lethargy, apnea, bradycardia, decreased perfusion, hypotension, and temperature instability. Laboratory tests that frequently associate bacteremia include increased immature neutrophils, hyperglycemia, thrombocytopenia, and increased C-reactive protein. The major difficulty in diagnosing CONS bacteremia is the differentiation between true infection and contamination. However, in the presence of clinical signs, isolation of CONS indicates true infection.

**Central Line Infection**

Umbilical arterial catheter (UAC), umbilical vein catheter (UVC), or central lines can be colonized with CONS and become the cause of bacteremia. Polyvinyl catheters are more susceptible to be colonized than silastic catheter. TPN especially with intralipid infusion increases the susceptibility to infection. Diagnosis is by isolating CONS from blood that is drawn from the central line. Some quantitative estimates of the number of CONS colonies can help in differentiating colonization from infection. This can be done by semiquantitative method in which the intravascular tip of the catheter is rolled over the culture media.

If the number of colonies grown is more than 15 colonies then it indicates significant growth. If the line cannot be removed then comparing the colonies count of blood drawn from central line with that drawn from peripheral vein will give an idea of the source of infection. If the central count is more than peripheral one then this is likely to be central line infection. However, these methods are not standardized and cumbersome to do. Treatment requires removal of the central line and administration of appropriate antibiotics; however, in cases where removal of the line is not feasible, a trial of antibiotic therapy may result in cure although the failure rate is more common. The recommended therapy is vancomycin given through the central line for 10–14 days. Blood culture should be repeated in 24–48 h after starting the antibiotics. If the culture remained positive then central line should be removed.

**Pneumonia**

Reports of pneumonia caused by CONS have been increasing, especially congenital pneumonia and pneumonia in intubated neonates. Congenital pneumonia has been confirmed by isolating only CONS from placenta or from lung at autopsy.

**Meningitis**

CONS rarely causes meningitis; however, a number of cases have been reported. Characteristically, meningitis occurs in premature babies who have intraventricular hemorrhage. Meningitis due to CONS is characterized by minimal or absent abnormalities in CSF cell count, protein, and glucose. It is presumed that CONS are of low virulence and thus elicit minimal inflammatory response in CSF.

**Enterocolitis**

Narcotizing enterocolitis (NEC) is not uncommon in premature babies. Although the disease has been characterized and its pathology is known, its cause remains enigmatic. Delta toxin produced by CONS has been claimed to be a factor that may precipitate NEC.

**Wound Infections**

Surgical wound infection and local skin infections may be caused by CONS. In NICU and PICU, CONS share with *S. aureus* the cause of such infections.

**Endocarditis**

Few cases of endocarditis have been reported in neonates who have UVC inserted in the right atrium. The endocarditis involves mainly the right side of the heart with the tricuspid valve being commonly involved. Such patients usually present with persistent bacteremia associated with thrombocytopenia.
Bacteremia

CONS has emerged as a major cause of nosocomial bacteremia in children’s hospitals. 20–30% of all nosocomial bacteremias are attributed to CONS.

CONS bacteremia is usually a disease of patients who have underlying predisposing factors, especially patients with malignancies or those who have undergone bone marrow transplant. Not all patients with CONS bacteremia have central lines or indwelling catheters. It is assumed that gastrointestinal tract may be the port of entry of CONS in the cases that have no indwelling catheters.

Urinary Tract Infection

*S. saprophyticus* is one of the principal causes of UTI in sexually active adolescent girls; however, it can cause UTI at any age group. *S. saprophyticus* has a specific adhesion that has higher affinity to attach to urogenital epithelium. Other CONS species can cause UTI. Because of their low virulence, even low colonies count may indicate a true infection rather than contaminant. Isolation of CONS species from urine in patients who are at risk of developing invasive disease may indicate the presence of bacteremia.

Endocarditis

Commonly arise following heart surgery especially during the first 3 months postsurgery. However, native valve endocarditis may be caused by CONS. In one study, 26% of native valve endocarditis was caused by CONS.

Infection of Intravascular Catheters and Related Devices

Central Venous Catheter

CONS is the major cause of central line–related bacteremia. CONS is also the major cause of other central line–related infections like exit site or tunnel infections. Diagnosis of central line–related bacteremia is difficult. The comparison of central and peripheral blood cultures may be useful with the presence of five- to tenfold higher colonies in blood drawn from central line indicating central line infection. However, not all laboratories perform quantitative cultures. If the line is removed then culturing the tip of the catheter by rolling it over a blood agar plate and then counting the colonies may give a clue to the source of infection. Count that are >15 colonies indicate that the central line is the likely cause of bacteremia.

Ventriculoperitoneal Shunt Infection

Ventriculoperitoneal (VP) shunt infection can occur in 3–40% of the cases. Most of the infections are caused by CONS and most of them occur in the first 2 months after insertion. Diagnosis of shunt infection depends on isolation of the organism from CSF obtained by shunt-tapping. The changes in the CSF parameters may be minimal, but the culture usually yields the organism. Clinical presentations of shunt infection are variable, but mostly present with signs of shunt malfunction and increased intracranial pressure including headache, vomiting, and fever. Some patients may have associated signs of peritonitis. Treatment of VP shunt infection has been controversial. The recommended treatment is shunt removal with systemic antibiotics administration. Alternatively, success has been achieved with externalizing the peritoneal end of the shunt and systemic antibiotics administration until the CSF culture is negative in 3 consecutive days then reimplantation of the shunt and continuation of systemic antibiotics for 10–14 days. Intraventricular administration of antibiotics has shown some contradictory results; however, most of the studies show no additional benefit of such therapy.

Peritonitis

CONS is the major cause of peritonitis in patients undergoing peritoneal dialysis. Affected patients usually present with symptoms and signs of peritonitis: fever, abdominal pain, and vomiting, as well as changes in the color of peritoneal dialysate. Most cases of the peritonitis are associated with peritoneal fluid white cell count of more than 100; however, some have reported peritonitis with lower cell count. Treatment can be achieved by administering appropriate antibiotics with the peritoneal dialysate for 10–14 days. Removal of the catheter is unnecessary unless the infection cannot be controlled by antibiotics.

Other Prosthetic Devices Infections

CONS has been reported as causing infections in almost any implanted devices including implanted lens, pacemaker, and joint and vascular grafts.
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