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155 Diphtheria and Other Corynebacterial Infections

The mechanism involves the replacement of the last d-alanine residue of peptidoglycan precursors with d-lactate (e.g., VanA and VanB) or d-serine (e.g., VanC), with consequent high- and low-level resistance, respectively. There is significant heterogeneity among isolates, but either substitution substantially decreases the affinity of vancomycin for the peptidoglycan; with the d-lactate substitution, the affinity for binding to the pentapeptide precur sor is decreased by ~1000-fold. Vancomycin-resistant organisms also produce enzymes that destroy the d-alanine-d-alanine ending precursors, ensuring that additional binding sites for vancomycin are not available. The genes encoding the machinery responsible for vancomycin resistance are located in the van operon and likely originated in soil bacteria. Several variants of the operon have been described, but VanA is the most common in clinical isolates in the United States, Latin America, and Europe, whereas VanB isolates are more fre quent in Australia. Two enterococcal species, E. gallinarum and E. casseliflavus, have intrinsic low-level resistance to vancomycin due to the presence of the VanC operon in the chromosome. High-level resistance to aminoglycosides (of which gentamicin and streptomycin are the only two tested by clinical laboratories) abolishes the synergism observed between cell wall–active agents and the aminoglycoside. This important phenotype is routinely sought by the clinical laboratory in isolates from serious infec tions (Tables 154-1 and 154-2). Genes encoding aminoglycosidemodifying enzymes are usually the cause of high-level resistance to these compounds and are widely disseminated among enterococci, decreasing the options for the treatment of severe enterococcal infections. Additionally, ribosomal methyltransferases, enzymes that methylate rRNA and, as a consequence, disrupt the binding site for aminoglycosides, also can lead to high-level resistance. Resistance to daptomycin has now been well documented in both E. faecalis and E. faecium. Daptomycin exerts its action by complexing with calcium and binding to phosphatidylglycerol in the bacterial membrane. After binding, daptomycin forms oligo mers, with recent data suggesting that it displaces enzymes impor tant for cell envelope synthesis (MurG and PlsX) and that it can form a complex with lipid II molecules critical for cell-wall synthe sis, among other effects on the membrane. Resistance to this antibi otic in enterococci arises via two main pathways. The first involves mutations in genes that coordinate the cell-wall and cell-

membrane stress response, most commonly a three-component system desig nated LiaFSR (for lipid II interfering antibiotics). These mutations lead to activation of the system, with increased expression of an extracellular protein known as LiaX capable of binding daptomycin and enhancing the signaling response. In clinical isolates, mutations in LiaFSR may lead to tolerance (loss of bactericidal activity)—usually in isolates with MICs near the daptomycin breakpoint (i.e., 3–4 mg/L). The second pathway involves changes in genes involved in phospholipid metabolism. It is thought that mutations priming the stress response system occur first, with the subsequent accrual of phospholipid changes leading to a fully resistant phenotype. Prior exposure to daptomycin has been identified as a risk factor for the emergence of daptomycin-resistant E. faecium in cancer patients. Resistance in the absence of exposure to the drug has also been well described, possibly due to the similarity of this antibiotic to antimicrobial peptides of the innate immune system. Thus, careful consideration of patient characteristics, bacterial phenotype, and daptomycin dose is warranted, and it is advisable to obtain infec tious diseases consultation in complicated VRE infections. The oxazolidinones (linezolid and tedizolid) act by binding to the ribosome and inhibiting the binding of aminoacyl-tRNAs, thus preventing protein synthesis. Resistance to this class of antibiotics is usually due to alterations of the binding site, either via mutations in the 23S rRNA genes or via the presence of an rRNA methylase. Since enterococci carry multiple copies of the gene encoding the 23S rRNA, prolonged exposure to oxazolidinones can select for increasing levels of resistance by favoring propagation of the resis tance allele via recombination. Changes in accessory ribosomal

proteins have also been associated with linezolid resistance and may act to mitigate the fitness defects of mutations in the rRNA. More concerning is the emergence of transferable resistance genes, which can readily move between enterococcal strains. Several of these genes were first recognized in bacterial isolates of animal origin, likely under the selective pressure of antibiotics such as florfenicol. The cfr (chloramphenicol-florfenicol resistance) gene encodes an rRNA methylase that modifies the 23S rRNA, leading to increases in the MIC of linezolid. Tedizolid tends to exhibit lower MICs in the presence of cfr; however, animal models suggest that some variants of the enzyme may compromise the activity of this drug. Two other transmissible resistance genes, optrA and poxtA, encode a ribosomal protection factor that has been implicated in linezolid resistance in enterococcal strains of human and animal origin. While still relatively rare to encounter in clinical practice, these determinants have been identified across the globe and could be an emerging source of resistance.

Newer tetracycline agents, such as tigecycline, omadacycline, and eravacycline, retain activity in the presence of typical tetra cycline resistance determinants, including drug efflux pumps and ribosomal protection factors. However, resistance has been docu mented and appears to be related to changes in the S10 ribosomal protein, which is situated near the binding site for the drug. Acknowledgment The authors dedicate this chapter to the memory of Dr. Barbara Murray, a trailblazer in infectious diseases and a fearless leader. Dr. Murray was an exceptional scientist and an avid adventurer. She will be remembered as an everlasting mentor who touched many lives with her wisdom. Her indelible legacy will remain with us forever. CHAPTER 155 ■ ■FURTHER READING Berge A et al: The DENOVA score efficiently identifies patients with monomicrobial Enterococcus faecalis bacteremia where echocardiog raphy is not necessary. Infection 47:45, 2019. Contreras GA et al: Contemporary clinical and molecular epidemiol Diphtheria and Other Corynebacterial Infections ogy of vancomycin-resistant enterococcal bacteremia: A prospective

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Diphtheria and Other Corynebacterial Infections DIPHTHERIA Diphtheria is a nasopharyngeal and skin infection caused by Coryne bacterium diphtheriae. Toxigenic strains of C. diphtheriae produce a protein toxin that causes systemic toxicity, myocarditis, and polyneu ropathy. The toxin is associated with the formation of pseudomem branes in the pharynx during respiratory diphtheria. While toxigenic strains most frequently cause pharyngeal diphtheria, nontoxigenic strains commonly cause cutaneous disease.

■ ■ETIOLOGY C. diphtheriae is a gram-positive bacillus that is unencapsulated, nonmotile, and nonsporulating. The organism was first identified microscopically in 1883 by Klebs and a year later was isolated in pure culture by Löffler in Robert Koch’s laboratory. The bacteria have a characteristic club-shaped bacillary appearance and typically form clusters of parallel rays, or palisades, that are referred to as “Chinese characters.” The specific laboratory media recommended for the culti vation of C. diphtheriae rely upon tellurite, colistin, or nalidixic acid for the organism’s selective isolation from other autochthonous pharyngeal microbes. C. diphtheriae may be isolated from individuals with both nontoxigenic (tox–) and toxigenic (tox+) phenotypes. Uchida and Pap penheimer demonstrated that corynebacteriophage beta carries the structural gene tox, which encodes diphtheria toxin, and that a family of closely related corynebacteriophages are responsible for toxigenic conversion of tox– C. diphtheriae to the tox+ phenotype. Moreover, lysogenic conversion from a nontoxigenic to a toxigenic phenotype has been shown to occur in situ. Growth of toxigenic strains of C. diphthe riae under iron-limiting conditions leads to the optimal expression of diphtheria toxin and is believed to be a pathogenic mechanism dur ing human infection. Less commonly, diphtheria-like disease may be caused by Corynebacterium ulcerans and Corynebacterium pseudotu berculosis, which express the same toxin and are considered members of the C. diphtheriae group (discussed below).

■ ■EPIDEMIOLOGY While in many areas diphtheria has been controlled in recent years with effective vaccination, there have been sporadic outbreaks throughout the 1970s in the United States and the 1990s in Europe. Diphtheria is still common in parts of Africa, Asia, Latin America, and the Caribbean where mass immunization programs are not enforced. Large-scale epidemics of diphtheria have occurred in the post–Soviet Union independent states in the late 1990s and, more recently, in Nigeria and Yemen during 2022–2023. In temperate regions, respiratory diphtheria occurs year-round but is most com mon during winter months. PART 5 Infectious Diseases C. diphtheriae is transmitted via the aerosol route, usually during close contact with an infected person. Untreated individuals with respi ratory diphtheria are thought to be infectious for ~18.5 days and the R0 (basic reproduction number) is 1.7–4.3. There are no significant reser voirs other than humans. The mean incubation period for respiratory diphtheria is 1.4 days, but disease onset has occurred as late as 10 days after exposure. Prior to the vaccination era, most individuals over the age of 10 were immune to C. diphtheriae; infants were protected by maternal IgG antibodies but became susceptible after ~6 months of age. Thus, the disease primarily affected children and

nonimmune young adults. Cutaneous diphtheria is usually a secondary infection that fol lows a primary skin lesion due to trauma, allergy, or autoimmunity. Most often, these isolates lack the tox gene and thus do not express diphtheria toxin. In tropical latitudes, cutaneous diphtheria is more common than respiratory diphtheria. Toxin-producing diphtheria in symptomatic individuals, regardless of site (respiratory or cutaneous), is a reportable disease in the United States, while nontoxigenic disease is not. Nontoxigenic strains of C. diphtheriae have been associated with pharyngitis in Europe, causing outbreaks among men who have sex with men and persons who use illicit IV drugs. The development of diphtheria antitoxin in 1898 by von Behring and of the diphtheria toxoid vaccine in 1924 by Ramon led to the near elimination of diphtheria in Western countries. The annual incidence rate in the United States peaked in 1921, with 206,000 cases (191 cases per 100,000) and 15,520 deaths. In contrast, current U.S. rates are exceeding low, with only 14 cases reported from 1996–2018, with the last case of respiratory diphtheria occurring in 2003 in a returning trav eler from Haiti. Nevertheless, pockets of colonization persist in North America, and groups or individuals who resist vaccination remain at risk. Immunity to diphtheria induced by childhood vaccination gradu ally decreases in adulthood. An estimated 30% of men 60–69 years old have antitoxin titers below the protective level. In addition to older age

and lack of vaccination, risk factors for diphtheria outbreaks include alcoholism, low socioeconomic status, crowded living conditions, and Native American ethnic background. An outbreak of diphtheria in Seattle, Washington, between 1972 and 1982 comprised 1100 cases, most of which were cutaneous. During the 1990s in the states of the former Soviet Union, a much larger diphtheria epidemic included more than 140,000 cases and more than 4000 deaths; at its peak in 1995, more than 50,412 cases were reported. Clonally related toxigenic C. diphtheriae strains of the ET8 complex were associated with this outbreak. Beginning in 1998, this epidemic was controlled by mass vaccination programs, and between 2000 and 2009, the diphtheria incidence fell by >95%, with high-burden countries such as Latvia reporting fewer than 10 cases. Despite the World Health Organization (WHO) estimate that ~84% of the global population of children have been adequately vaccinated, 8638 diphtheria cases were reported globally in 2021, and many more cases are likely to have gone unreported. The recent coronavirus disease 2019 (COVID-19) pandemic, socioeconomic instability, migration, vaccine hesitancy, and other factors remain as threats to diphtheria control. For example, the WHO reported that the percentage of chil dren who received three doses of diphtheria, tetanus, and pertussis immunization fell by 5% (86% to 81%) during 2019–2021 due to health system strains from COVID-19. Additionally, multiple European nations have reported high rates of diphtheria (often cutaneous disease) among unvaccinated asylum seekers, with West Africa and Afghanistan as common source regions. ■ ■PATHOGENESIS AND IMMUNOLOGY Diphtheria toxin produced by tox+ strains of C. diphtheriae is the pri mary virulence factor in clinical disease. The toxin is synthesized in precursor form; is released as a 535-amino-acid, single-chain protein; and, in sensitive species (e.g., guinea pigs and humans, but not mice or rats), has a 50% lethal dose of ~100 ng/kg of body weight. The toxin is produced in the pseudomembranous lesion in the pharynx and is taken up in the bloodstream with subsequent distribution to all organs. Once bound to its cell surface receptor (a heparin-binding epidermal growth factor–like precursor), the toxin is internalized by receptor-mediated endocytosis and enters the cytosol from an acidified early endosomal compartment. In vitro, the toxin may be separated into two chains by digestion with serine proteases: the N-terminal A fragment and the C-terminal B fragment. Delivery of the A fragment into the eukaryotic cell cytosol results in irreversible inhibition of protein synthesis by NAD+-dependent ADP-ribosylation of elongation factor 2 and subse quent

cell death. In 1926, Ramon at the Institut Pasteur found that formalinization of diphtheria toxin resulted in the production of a nontoxic but highly immunogenic diphtheria toxoid. Subsequent studies showed that immunization with diphtheria toxoid elicited antibodies that neutral ized the toxin and prevented most disease manifestations. In the 1930s, mass immunization of children and susceptible adults with diphtheria toxoid commenced in the United States and Europe. Individuals with a diphtheria antitoxin titer of >0.01 U/mL are at low risk of disease. In populations where a majority of individuals have protective antitoxin titers, the carrier rate for toxigenic strains of C. diphtheriae decreases, and the overall risk of diphtheria among susceptible individuals is reduced. Nevertheless, individuals with non protective titers may contract diphtheria either through travel or expo sure to individuals who have recently returned from regions where the disease is endemic. Characteristic pathologic findings of diphtheria include mucosal ulcers with a pseudomembranous coating composed of an inner band of fibrin and a luminal band of neutrophils. Initially white and firmly adherent, in advanced diphtheria the pseudomembranes turn gray or even green or black as necrosis progresses. Mucosal ulcers result from toxin-induced necrosis of the epithelium accompanied by edema, hyperemia, and vascular congestion of the submucosal base. A sig nificant fibrinosuppurative exudate from the ulcer develops into the pseudomembrane. Ulcers and pseudomembranes in severe respiratory diphtheria may extend from the pharynx into medium-sized bronchial

airways. Expanding and sloughing membranes may result in fatal air way obstruction. APPROACH TO THE PATIENT Diphtheria Diphtheria, although rare in the United States and other developed countries, should be considered when a patient has severe pharyn gitis, particularly when there is difficulty swallowing, respiratory compromise, or signs of systemic disease (e.g., myocarditis or gen eralized weakness). The leading causes of pharyngitis are respira tory viruses (rhinoviruses, influenza viruses, parainfluenza viruses, coronaviruses, adenoviruses; ~25% of cases), group A streptococci (15–30%), group C streptococci (~5%), atypical bacteria such as Mycoplasma pneumoniae and Chlamydia pneumoniae (15–20% in some series), and other viruses such as herpes simplex virus (~4%) and Epstein-Barr virus (<1% in infectious mononucleosis). Less common causes are acute HIV infection, gonorrhea, fusobacte rial infection (e.g., Lemierre’s syndrome), thrush due to Candida albicans or other Candida species, and diphtheria. The presence of a pharyngeal pseudomembrane or an extensive exudate should prompt consideration of diphtheria (Fig. 155-1). ■ ■CLINICAL MANIFESTATIONS Respiratory Diphtheria The clinical diagnosis of diphtheria is based on the constellation of sore throat; adherent tonsillar, pha ryngeal, or nasal pseudomembranous lesions; and low-grade fever. In addition, diagnosis requires the isolation of C. diphtheriae or his topathologic isolation of compatible gram-positive organisms. The FIGURE 155-1 Respiratory diphtheria due to toxigenic C. diphtheriae producing exudative pharyngitis in a child displaying a pseudomembrane extending from the uvula to the pharyngeal wall. The characteristic white pseudomembrane is caused by diphtheria toxin–mediated necrosis of the respiratory epithelial layer, producing a fibrinous coagulative exudate. Submucosal edema adds to airway narrowing. The pharyngitis is acute in onset, and respiratory obstruction from the pseudomembrane may occur in severe cases. Inoculation of pseudomembrane fragments or submembranous swabs onto Löffler’s or tellurite selective medium reveals C. diphtheriae. (Photograph courtesy of the Centers for Disease Control and Prevention and Immunization Action Coalition, used by permission.)

Centers for Disease Control and Prevention (CDC) recognizes con firmed respiratory diphtheria (laboratory proven or epidemiologically linked to a culture-confirmed case) and probable respiratory diphtheria (clinically compatible but not laboratory proven or epidemiologically linked). Carriers are defined as individuals who have positive cultures for C. diphtheriae and who either are asymptomatic or have symptoms but lack pseudomembranes. Most patients seek medical care for sore throat and fever several days into the illness. Occasionally, weakness, dysphagia, headache, and voice change are the initial manifestations. Neck edema and difficulty breathing are evident in more advanced cases and carry a poor prognosis.

The systemic manifestations of diphtheria stem from the effects of diphtheria toxin and include weakness as a result of neurotoxicity and cardiac arrhythmias or congestive heart failure due to myocardi tis. Most commonly, the pseudomembranous lesion is located in the tonsillopharyngeal region. Less commonly, the lesions are located in the larynx, nares, and trachea or bronchial passages. Large pseudo membranes are associated with severe disease and a poor prognosis. A few patients develop massive swelling of the tonsils and present with “bull-neck” diphtheria, which results from edema of the sub mandibular and paratracheal region and is further characterized by foul breath, thick speech, and stridorous breathing. The diphtheritic pseudomembrane is gray or whitish and sharply demarcated. Unlike the exudative lesion associated with streptococcal pharyngitis, the pseudomembrane in diphtheria is tightly adherent to the underly ing tissues. Attempts to dislodge the membrane may cause bleeding. Hoarseness suggests laryngeal diphtheria, in which laryngoscopy may be diagnostically helpful. CHAPTER 155 Cutaneous Diphtheria This dermatosis is characterized by punched-out ulcerative lesions with necrotic sloughing or pseudo membrane formation (Fig. 155-2). The diagnosis requires cultivation of C. diphtheriae from lesions, which most commonly occur on the lower and upper extremities, head, and trunk. Diphtheria and Other Corynebacterial Infections Infections Due to Non-diphtheriae Corynebacterium Species and Nontoxigenic C. diphtheriae Non-diphtheriae species of Corynebacterium and related genera (discussed below) as well as non toxigenic strains of C. diphtheriae itself have been found in bloodstream and respiratory infections, often in individuals with immunosuppres sion or chronic respiratory disease. These organisms can cause disease manifestations and should not necessarily be dismissed as colonizers. Other Clinical Manifestations C. diphtheriae causes rare cases of endocarditis and septic arthritis, most often in patients with preexist ing risk factors, such as abnormal cardiac valves, injection drug use, or cirrhosis. FIGURE 155-2 Cutaneous diphtheria due to nontoxigenic C. diphtheriae on the lower extremity. (From the Centers for Disease Control and Prevention, Public Health Image Library [PHIL]. #1941.)

■ ■COMPLICATIONS Airway obstruction poses a significant early risk in patients presenting with advanced diphtheria and accounts for 60–65% of deaths typically in the first 1–2 weeks after symptom onset. Pseudomembranes may slough and obstruct the airway or may advance to the larynx or into the tracheobronchial tree. Children are particularly prone to obstruction because of their small airways.

Cardiomyopathy and polyneuropathy are late toxic manifestations of diphtheria arising 1 week or more after respiratory symptoms. Based on systematic reviews, toxic cardiomyopathy accounted for 20–25% of deaths and is typically associated with arrhythmias and dilated cardiomyopathy. Polyneuropathy is seen 3–5 weeks after the onset of diphtheria and has a slow indolent course but may account for 15% of deaths. Patients may develop severe and prolonged neurologic

abnormalities. The disorders typically occur in the mouth and neck, with lingual or facial numbness as well as dysphonia, dysphagia, and cranial nerve paresthe sias. More ominous signs include weakness of respiratory and abdomi nal muscles and paresis of the extremities. Sensory manifestations and sensory ataxia also are observed. Cranial nerve dysfunction typically precedes disturbances of the trunk and extremities because of proxim ity to the site of infection. Autonomic dysfunction also is associated with polyneuropathy and can lead to hypotension. Polyneuropathy is typically reversible in patients who survive the acute phase. Other complications of diphtheria include pneumonia, renal failure, encephalitis, cerebral infarction, pulmonary embolism, and serum sickness from antitoxin therapy. ■ ■DIAGNOSIS The diagnosis of diphtheria is based on clinical signs and symptoms plus laboratory confirmation. Respiratory diphtheria should be consid ered in patients with sore throat, pharyngeal exudates, and fever. Other symptoms may include hoarseness, stridor, or palatal paralysis. The presence of a pseudomembrane should prompt strong consideration of diphtheria. Once a clinical diagnosis of diphtheria is made, diphtheria antitoxin should be obtained and administered as rapidly as possible. PART 5 Infectious Diseases Laboratory diagnosis of diphtheria is based either on cultivation of C. diphtheriae or toxigenic C. ulcerans from the site of infection or on the demonstration of local lesions with characteristic histopathology. Corynebacterium pseudodiphtheriticum, a nontoxigenic organism, is a common component of the normal throat flora and does not pose a significant risk. Throat samples should be submitted to the laboratory for culture with the notation that diphtheria is being considered. This information should prompt cultivation on special selective medium and subsequent biochemical testing to differentiate C. diphtheriae from other nasopharyngeal commensal corynebacteria. All laboratory iso lates of toxigenic C. diphtheriae should be reported to the state health department. A diagnosis of cutaneous diphtheria requires laboratory confirma tion since the lesions are not characteristic and are indistinguishable from other dermatoses. Diphtheritic ulcers occasionally—but not consistently—have a punched-out appearance (Fig. 155-2). Patients in whom cutaneous diphtheria is identified should have the nasopharynx cultured for C. diphtheriae. The laboratory medium for cutaneous diphtheria specimens is the same as that used for respiratory diphthe ria: Löffler’s or Tinsdale’s selective medium in addition to nonselective medium such as blood agar. As has been mentioned, isolation of toxi genic strains of C. diphtheriae in symptomatic individuals is notifiable disease in the United States, regardless of the body site of origin. TREATMENT Diphtheria DIPHTHERIA ANTITOXIN Prompt administration of diphtheria antitoxin is critical in the management of respiratory diphtheria. Diphtheria antitoxin, a horse antiserum, is effective in reducing the extent of local disease as well as the risk of complications of myocarditis and neuropathy.

Rapid institution of antitoxin therapy is also associated with a sig nificant reduction in mortality risk. Because diphtheria antitoxin cannot neutralize cell-bound toxin, prompt initiation is impor tant. This product, which is no longer commercially available in the United States, can be obtained from the CDC Emergency Operations Center at 770-488-7100 (www.cdc.gov/diphtheria/hcp/dat/index.html) after first contacting the state health department. The current protocol for the use of diphtheria antitoxin involves a test dose to rule out immediate hypersensitivity. Patients who demonstrate hypersensitivity require desensitization before a full therapeutic dose of antitoxin is administered. Given that the world supply of equine anti–diphtheria toxin is limited, a human monoclonal antibody with the potential to provide a safer alternative to equine antitoxin therapy is being developed. ANTIMICROBIAL THERAPY Antibiotics are used in the management of diphtheria primarily to prevent transmission to susceptible contacts. Antibiotics also prevent further toxin production and may reduce the severity of local infection. Recommended treatment options for

patients with respiratory diphtheria are as follows: • Erythromycin, 500 mg IV q6h (for children: 40–50 mg/kg per day IV in two or four divided doses) until the patient can swal low comfortably; then 500 mg PO qid to complete a 14-day course • Procaine penicillin G, 600,000 U IM q12h (for children: 12,500– 25,000 U/kg IM q12h) until the patient can swallow comfortably; then oral penicillin V, 125–250 mg qid to complete a 14-day course A clinical study in Vietnam found that penicillin was associated with a more rapid resolution of fever and a lower rate of bacterial resistance than erythromycin; however, relapses were more com mon in the penicillin group. Erythromycin therapy targets protein synthesis and thus offers the presumed benefit of stopping toxin synthesis more quickly than a cell wall–active β-lactam agent. Alternative therapeutic agents for patients who are allergic to peni cillin or cannot take erythromycin include rifampin and clindamy cin. Other reasonable antibiotics are clarithromycin, azithromycin, linezolid, and vancomycin, although they have not been studied in comparison to the agents above. Eradication of C. diphtheriae should be documented after anti microbial therapy is complete. A repeat throat culture 2 weeks later is recommended. For patients in whom the organism is not eradi cated after a 14-day course of erythromycin or penicillin, an addi tional 10-day course followed by repeat culture is recommended. Drug-resistant strains of C. diphtheriae exist and are appearing at higher frequency; several reports have described multidrugresistant strains. Drug resistance should be considered when efforts at pathogen eradication fail. Cutaneous diphtheria should be treated as described above for respiratory disease. Individuals infected with toxigenic strains should receive antitoxin. It is important to treat the underlying cause of the dermatoses in addition to the superinfection with C. diphtheriae. Patients who recover from respiratory or cutaneous diphtheria should have antitoxin levels measured. If diphtheria antitoxin has been administered, this test should be performed 6 months later. Patients who recover from respiratory or cutaneous diphtheria should receive the appropriate vaccine to ensure the development of protective antibody titers. MANAGEMENT STRATEGIES Patients in whom diphtheria is suspected should be hospitalized in respiratory isolation rooms with close monitoring of cardiac and respiratory function. A cardiac workup is recommended to assess the possibility of myocarditis. In patients with extensive pseudomembranes, an anesthesiology or an ear, nose, and throat

consultation is recommended because of the possible need for tra cheostomy or intubation. In some settings, pseudomembranes can be removed surgically. Treatment with glucocorticoids has not been shown to reduce the risk of myocarditis or polyneuropathy. ■ ■PROGNOSIS A systematic review of over 20 reported outbreaks found the diph theria case fatality ratio among unvaccinated, untreated individuals to be 29%, with children under the age of 5 being at a 1.5-fold higher risk of mortality. Fatal pseudomembranous diphtheria typically occurs in patients with nonprotective antibody titers and in unimmunized patients. The pseudomembrane may actually increase in size from the time it is first noted. Risk factors for death include bullneck diphtheria; myocarditis with ventricular tachycardia; atrial fibrillation; complete heart block; an age of >60 years or <6 months; alcoholism; extensive pseudomembrane elongation; and laryngeal, tracheal, or bronchial involvement. Another important predictor of fatal outcome is the interval between the onset of local disease and the administration of antitoxin. Cutaneous diphtheria has a low mortality rate and is rarely associated with myocarditis or peripheral neuropathy. ■ ■PREVENTION Vaccination Diphtheria toxoid-based vaccine efficacy is estimated to be 87% in the prevention of symptomatic disease, and sustained campaigns for vaccination of children and adequate boosting vac cination of adults are responsible for the exceedingly low incidence of diphtheria in most developed nations. Diphtheria toxoid vaccine has typically been coadministered with tetanus vaccine (with or without

acellular pertussis). DTaP (full-level diphtheria toxoid, tetanus toxoid, and acellular pertussis vaccine) is currently recommended for children in five doses up to the age of 6 years; DTaP replaced the earlier wholecell pertussis vaccine DTP in 1997. Tdap is a tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine formulated for adolescents and adults and is the recommended booster for children 11–12 years old. Tdap is recommended for all adults if they have not received it previously regardless of the interval since the last dose of Td (tetanus and reduced-dose diphtheria toxoids, adsorbed). Tdap vaccination is a priority for health care workers, pregnant women, adults anticipating contact with infants, and adults not previously vaccinated for pertussis. Adults who have received acellular pertussis vaccine should continue to receive decennial Td booster vaccinations. In 2018, a hexavalent vaccine that combined diphtheria-tetanus tox oids, acellular pertussis adsorbed (DTaP), inactivated poliovirus (IPV), Haemophilus influenzae type b (Hib) conjugate, and recombinant hepatitis B (HepB) known as DTaP-IPV-Hib-HepB was approved by the U.S. Food and Drug Administration; this product may be used to replace the initial three childhood doses of DTaP (2, 4, and 6 months) or as part of a catch-up schedule in children under 5 years old. The vaccine schedule is detailed in Chap. 129. Prophylaxis Administration to Contacts Close contacts of diph theria patients should undergo throat culture to determine whether they are carriers. After samples for throat culture are obtained, antimicrobial prophylaxis should be considered for all contacts, even those whose cul tures are negative. The options are 7–10 days of oral erythromycin or one dose of IM benzathine penicillin G (1.2 million units for persons ≥6 years of age or 600,000 units for children <6 years of age). Contacts of diphtheria patients whose immunization status is uncertain should receive the appropriate diphtheria toxoid–containing vaccine. The Tdap vaccine (rather than Td) is now the booster vaccine of choice for adults who have not recently received an acellular pertus sis–containing vaccine. Carriers of C. diphtheriae in the community should be treated and vaccinated when identified. OTHER CORYNEBACTERIAL AND RHODOCOCCUS INFECTIONS Nondiphtherial corynebacteria, referred to as diphtheroids or coryne forms, are frequently considered colonizers or contaminants; how ever, they have been associated with invasive disease, particularly in

immunocompromised patients. Importantly, even though they are termed nondiphtherial corynebacteria, C. ulcerans and C. pseudotu berculosis may produce diphtheria toxin and therefore cause severe human illness. These organisms have been isolated from the blood stream, especially in association with catheter infection, endocarditis, prosthetic valve infection, meningitis, brain abscess, osteomyelitis, and peritonitis. Risk factors include indwelling intravenous or perito neal catheters and neurosurgical shunts. Patients infected with these organisms are often immunosuppressed or have significant medical comorbidities. The nondiphtherial coryneforms are a collection of bacteria that are taxonomically grouped together in the genus Cory nebacterium on the basis of their 16S rDNA signature nucleotides. Despite the shared rDNA signatures, these isolates are quite diverse. For example, their guanine-cytosine content ranges from 45 to 70%. Several nondiphtheroid corynebacteria, including Corynebacterium jeikeium and Corynebacterium urealyticum, are associated with resis tance to multiple antibiotics. Rhodococcus equi is associated with necrotizing pneumonia and granulomatous infection, particularly in immunocompromised individuals.

■ ■MICROBIOLOGY AND LABORATORY DIAGNOSIS These organisms are non-acid-fast, catalase-positive, aerobic or fac ultatively anaerobic rods. Their colonial morphologies on blood agar vary widely; some species are small and α-hemolytic (similar to lac tobacilli), whereas others form large

white colonies (similar to yeasts). Many nondiphtherial coryneforms require special media, such as Löf fler’s, Tinsdale’s, or tellurite medium. These cultivation idiosyncrasies have led to a complex taxonomic categorization of the organisms. CHAPTER 155 ■ ■EPIDEMIOLOGY Humans are the natural reservoirs for several nondiphtherial coryne forms, including C. xerosis, C. pseudodiphtheriticum, C. striatum, C. minutissimum, C. jeikeium, C. urealyticum, and Arcanobacterium haemolyticum. Animal reservoirs including milk are responsible for carriage of C. ulcerans and C. pseudotuberculosis. Soil is the natural reservoir for R. equi. Diphtheria and Other Corynebacterial Infections ■ ■CLINICAL MANIFESTATIONS C. ulcerans This organism causes a diphtheria-like illness and pro duces both diphtheria toxin and a dermonecrotic toxin. The organism is a commensal in horses and cattle and has been isolated from cow’s milk. In contrast to diphtheria, this infection is considered a zoonosis, and cases have been traced to contact with animal carriers, including dogs and pigs. C. ulcerans causes exudative pharyngitis, primarily dur ing summer months, in rural areas, and among individuals exposed to animals. Treatment with antitoxin and antibiotics should be initiated when respiratory C. ulcerans is identified, and a contact investigation should be conducted (including throat cultures to determine the need for antimicrobial prophylaxis and, in unimmunized contacts, adminis tration of the appropriate diphtheria toxoid–containing vaccine). The organism grows on Löffler’s, Tinsdale’s, and tellurite agars as well as blood agar. In addition to exudative pharyngitis, cutaneous disease due to C. ulcerans has been reported. C. ulcerans is susceptible to a wide panel of antibiotics. Erythromycin and other macrolides appear to be the first-line agents. C. pseudotuberculosis Infection caused by C. pseudotuberculosis is an important animal pathogen (most notably of sheep) that rarely causes human disease. C. pseudotuberculosis causes suppurative granu lomatous lymphadenitis and an eosinophilic pneumonia syndrome among individuals who handle sheep; horses, cattle, goats, deer, and raw milk has also been implicated. Surgical excision of affected lymph nodes should be performed when feasible, and successful treatment with erythromycin or tetracycline has been reported. Some strains express diphtheria toxin and produce a diphtheria-like disease, which should be treated with antitoxin. C. jeikeium (Group JK) Originally described in American hospi tals, C. jeikeium infection was subsequently reported in Europe. After a 1976 survey of diseases caused by nondiphtherial corynebacteria,

CDC group JK emerged as an important opportunistic pathogen among neutropenic and HIV-infected patients. The organism has now been designated a separate species. C. jeikeium forms small, gray to white, glistening, nonhemolytic colonies on blood agar. It lacks urease and nitrate reductase and does not ferment most carbo hydrates. The predominant syndrome associated with C. jeikeium is sepsis, sometimes with associated pneumonia, endocarditis, menin gitis, osteomyelitis, or epidural abscess. Risk factors for C. jeikeium infection include hematologic malignancy, neutropenia from comor bid conditions, prolonged hospitalization, exposure to multiple anti biotics, and skin disruption. There is evidence that C. jeikeium is part of the inguinal, axillary, genital, and perirectal flora of hospitalized patients.

Broad-spectrum antimicrobial therapy appears to select for coloni zation. The organisms appear as gram-positive coccobacillary forms slightly resembling streptococci. C. jeikeium is resistant to the majority of antibiotic classes except oxazolidinones (e.g., linezolid) and glyco peptides (e.g., vancomycin). Effective therapy involves removal of the infectious source, whether a catheter, prosthetic joint, or prosthetic valve. Efforts have been made to prevent C. jeikeium infection with strict institution of infection control protocols for high-risk patients, particularly those in intensive

care units. C. urealyticum (Group D2) Identified as a urease-positive non diphtherial Corynebacterium in 1972, C. urealyticum is an opportunis tic pathogen causing sepsis and urinary tract infection. C. urealyticum appears to be the etiologic agent of a severe urinary tract syndrome known as alkaline-encrusted cystitis, a chronic inflammatory bladder infection associated with deposition of ammonium magnesium phos phate on the surface and walls of ulcerating lesions in the bladder. In addition, C. urealyticum has been associated with pneumonia, perito nitis, endocarditis, osteomyelitis, and wound infection. It is similar to C. jeikeium in its resistance to most antibiotics except oxazolidinones and glycopeptides. Vancomycin therapy has been used successfully in severe infections. PART 5 Infectious Diseases C. minutissimum (Erythrasma) Erythrasma is a cutaneous infection producing reddish-brown, macular, scaly, pruritic inter triginous patches. The dermatologic presentation under the Wood's lamp is of coral red fluorescence. C. minutissimum appears to be a common cause of erythrasma, although there is evidence for a polymicrobial etiology in certain settings. This microbe has also been associated with bacteremia in patients with hematologic malig nancy. Erythrasma responds to topical erythromycin, clarithromycin, clindamycin, or fusidic acid, although more severe infections may require oral macrolide therapy. Other Nondiphtherial Corynebacteria C. xerosis is a human commensal found in the conjunctiva, nasopharynx, and skin. This nontoxigenic organism is occasionally identified as a source of invasive infection in immunocompromised or postoperative patients and pros thetic joint recipients. C. amycolatum is a closely related species but tends to demonstrate more antibiotic resistance. C. striatum is found in the anterior nares, skin, face, and upper torso of healthy individu als. Also nontoxigenic, this organism has been associated with inva sive opportunistic infections in severely ill or immunocompromised patients. C. glucuronolyticum is a nonlipophilic species that causes male genitourinary tract infections such as prostatitis and urethritis. These infections may be successfully treated with a wide variety of antibacterial agents, including β-lactams, rifampin, aminoglycosides, or vancomycin; however, the organism appears to be resistant to fluoroquinolones, macrolides, and tetracyclines. C. imitans has been identified in eastern Europe as a nontoxigenic cause of pharyngitis. C. auris has been identified in children with otitis media; it is sus ceptible to fluoroquinolones, rifampin, tetracycline, and vancomycin but resistant to penicillin G and variably susceptible to macrolides. C. pseudodiphtheriticum is a nontoxigenic species that is part of the normal human flora. Human infections—particularly endocarditis of either prosthetic or natural valves and invasive pneumonia—have been reported only rarely. Although C. pseudodiphtheriticum may be

isolated from the nasopharynx of patients with suspected diphtheria, it is part of the normal flora and does not produce diphtheria toxin. C. propinquum, a close relative of C. pseudodiphtheriticum, is part of CDC group D-1 and has been isolated from the human respiratory tract and blood. C. afermentans and subspecies belong to CDC group ANF-1; it is a rare human pathogen that has been isolated from human blood and abscesses. Rhodococcus Rhodococcus species are phylogenetically related to the corynebacteria. These gram-positive coccobacilli have been asso ciated with tuberculosis-like infections in humans with granulo matous pathology. While R. equi is best known, other near-relative species have been identified in human infections including R. fascians, R. erythropolis, R. rhodochrous, Gordonia bronchialis, G. sputi, G. terrae, and Tsukamurella paurometabola. R. equi has been recognized as a cause of pneumonia in horses since the 1920s and as a cause of related infections in cattle, sheep, and swine. It is found in soil as an environmental microbe. The organisms vary in length; appear as spherical to long, curved, clubbed rods; and produce large irregular mucoid colonies. R. equi cannot ferment carbohydrates or liquefy gelatin and is often acid fast. An intracellular pathogen of macrophages, R. equi can

cause granulomatous necrosis and caseation. This organism has most commonly been identified in pulmonary infection, but infections of brain, bone, and skin also have been reported. Most commonly, R. equi disease manifests as nodular and/or cavitary pneumonia of the upper lobe—a picture similar to that seen in tuberculosis or nocardiosis. Most patients are immunocompromised, often by HIV infection. Subcutaneous nodular lesions also have been identified. The involvement of R. equi should be considered when any patient presents with a tuberculosis-like syndrome. Infection due to R. equi has been treated successfully with antibiot ics that penetrate intracellularly, including macrolides, clindamycin, rifampin, and trimethoprim-sulfamethoxazole. β-Lactam antibiotics have not been useful. The organism is routinely susceptible to vanco mycin, which is considered the drug of choice. Arcanobacteria Arcanobacterium haemolyticum was identified as an agent of wound infections in U.S. soldiers in the South Pacific during World War II. It appears to be a human commensal of the nasopharynx and skin, but it is known to cause true pharyngitis as well as chronic skin ulcers. In contrast to the much more common pharyngitis caused by Streptococcus pyogenes, A. haemolyticum pharyngitis is associated with a scarlatiniform rash on the trunk and proximal extremities in about half of cases; this illness is occasionally confused with toxic shock syndrome. Because A. haemolyticum pharyngitis primarily affects teenagers, it has been postulated that the rash–pharyngitis syndrome may represent co-pathogenicity, synergy, or opportunistic second ary infection with Epstein-Barr virus. A. haemolyticum has also been reported as a cause of bacteremia, soft tissue infections, osteomyelitis, and cavitary pneumonia, predominantly in the setting of underlying diabetes mellitus. The organism is susceptible to most β-lactams, mac rolides, fluoroquinolones, clindamycin, vancomycin, and doxycycline. However, resistance to trimethoprim-sulfamethoxazole as well as tet racycline is common. ■ ■FURTHER READING Kim R, Reboli AC: Other coryneform bacteria and Rhodococcus, in Mandell, Douglas, and Bennett’s Principles and Practice of Infectious Diseases, 9th ed. JE Bennett et al (eds). Philadelphia, Elsevier, 2020, pp 2532–2542. Moore LS et al: Corynebacterium ulcerans cutaneous diphtheria. Lancet Infect Dis 15:1100, 2015. Saleeb PG: Corynebacterium diphtheriae (diphtheria), in Mandell, Douglas, and Bennett’s Principles and Practice of Infectious Diseases, 9th ed. JE Bennett et al(eds). Philadelphia, Elsevier, 2020, pp 2526–2531. Sharma NC et al: Diphtheria. Nat Rev Dis Primers 5:81, 2019. Truelove SA et al: Clinical and epidemiologic aspects of diphtheria: A systematic review and pooled analysis. Clin Infect Dis 71:89, 2020.

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