Thus, when the paranasal sinuses are imaged, either with plain radiographs, CT, or MRI in children or adults with uncomplicated URI, the majority of studies will be significantly abnormal with the same kind of findings that have been associated with bacterial infection of the sinuses. Because at the time of presentation with clinical symptoms patients are likely to have had a recent URI, abnormal imaging studies will be common. In accordance, an abnormal image cannot confirm the diagnosis of acute bacterial sinusitis and is not necessary to perform in patients with uncomplicated episodes of clinical sinusitis. In contrast, a normal image of the paranasal sinuses assures that any respiratory symptoms that are present are not the result of an infection of the sinuses.

In summary, the diagnosis of acute sinusitis should be made on clinical grounds in most patients. CT of the sinuses is useful for the evaluation of patients with intraorbital or intracranial complications of sinusitis, and for the evaluation of patients in whom sinus surgery is being considered to define the patient's anatomy. In addition, CT has an important role in the diagnosis and management of chronic rhinosinusitis.[89,103,104] MRI may have a role in the diagnosis of fungal sinusitis and is useful in the diagnosis of the intracranial complications of sinusitis.

THERAPY

Antimicrobial

Antibacterial agents are the primary therapy for acute bacterial sinusitis. In the past 40 years there have been numerous randomized, placebo-controlled trials of antimicrobials in patients with sinusitis. When evaluating the quality of such studies, it is imperative to consider the diagnostic criteria used to enter patients into the trial. If the diagnosis is made on clinical grounds but criteria for subject entry are too liberal, a large number of patients will be included who have viral URI rather than bacterial disease. This will bias the trial toward showing a lack of effectiveness of antibacterial agents.

There has been a recent trend in the literature to publish studies that mimic the "real-world" office setting in which the practitioner is making the diagnosis of sinusitis based on clinical criteria that are not stringent and without any kind of microbiologic confirmation. Table 62.6 summarizes randomized, placebo-controlled trials of antimicrobials in the treatment of sinusitis.[105–122] These trials have shown variable benefit to antibiotics over placebo. In one study, in which clinical criteria such as purulent nasal discharge for at least 2 days and pus visualized on rhinoscopy were required for entry, 40% of patients included in the study had normal radiographs, strongly suggesting that these patients did not have sinusitis.[112]

Further complicating the interpretation of antimicrobial efficacy studies is the fact that patients with sinusitis will have a high rate of spontaneous improvement within 2 weeks of presentation. Studies that included patients who had more severe or prolonged symptoms (i.e., >10 days) or those that used adjunctive diagnostic tests to confirm the diagnosis of sinusitis were more likely to show a benefit to antimicrobials versus placebo.[105,108,118,119,121] When patients enrolled in efficacy studies are followed closely over time, those who received antimicrobials show a more rapid improvement in symptoms compared with patients receiving placebo (Fig. 62.3). A recent trial of amoxicillin-clavulanate versus

TABLE 62.6 Randomized, Controlled Trials of Antibiotic Versus Placebo

STUDY	POPULATION	DIAGNOSTIC CRITERIA	ANTIBIOTIC	NO. (%) IMPROVED-ANTIBIOTIC	NO. (%) IMPROVED-PLACEBO	TIME AT FOLLOW-UP (DAYS)	MEASUREMENT OF SEVERITY	BENEFIT SHOWN TO ANTIBIOTICS?
Garbutt 2012[122]	Adults	Clinical	Amoxicillin	78/85(92)	80/85(94)	10	Yes	No
Wald 2009[121]	Children	Clinical	Amox/clav	18/28 (64)	9/28 (32)	14	Yes	Yes
Williamson 2007[111]	Adults	Clinical	Amoxicillin	71/100 (79)	71/107 (66)	10	No	No
Meltzer 2005[109]	>12 yr	Clinical	Amoxicillin/ steroids	NS	NS	≥15	No	+/–[a]
Merenstein 2005[110]	Adults	Clinical	Amoxicillin	32/167 (48)	25/168 (37)	14	No	+/–[b]
Kristo 2005[113]	children 4–10 yr	Ultrasound/ radiograph	Cefuroxime	22/35 (63)	21/37 (57)	14	No	No
Varonen 2003[114]	Adults	Clinical	Amoxicillin Penicillin Doxycycline	70/88 (80)	39/59 (66)	14	No	Yes
Bucher 2003[112]	Adults	Clinical[b]	Amox/clav	94/124 (76)	93/127 (74)	14	No	No
DeSutter 2002[115]	≥12 yr	Purulent rhinorrhea	Amoxicillin	59/170 (35)	47/164 (29)	7–10	No	+/–
Kaiser 2001[117]	Adults	Clinical + nasal culture	Azithromycin	29/40 (73)	17/37 (47)	7	No	Yes
Garbutt 2001[116]	1–18 yr	Clinical	Amoxicillin *or* amox/clav	83/103 (80)	43/55 (79)	14	No	No
Hansen 2000[118]	Adults	Clinical + ESR/CRP	Penicillin V	50/71 (71)	23/62 (37)	3–7	No	Yes
Haye 1998[119]	Adults	Clinical + radiograph	Azithromycin	50/86 (58)	26/83 (31)	10	No	Yes
Stalman1997[120]	Adults	Clinical	Doxycycline	84/198 (85)	78/94 (83)	10	No	No
vanBuchem 1996[107]	Adults	Radiograph	Amoxicillin	87/105 (83)	78/101 (77)	14	No	No
Lindbaek 1996[105]	Adults	Clinical/CT	Amoxicillin *or* penicillin V	71/83 (86)	25/44 (57)	10	Yes	Yes
Wald 1986[108]	Children	Clinical + radiograph	Amoxicillin Amox/clav	38/58 (65)	15/35 (43)	10	Yes	Yes
Rantanen 1973[106]	Adults	Clinical + radiograph	Doxycycline	24/33 (72)	36/44 (81)	14	No	No

[a]There was a benefit in some individual symptom scores but not in overall score.
[b]Median time to improvement day 8 in amoxicillin treated vs. day 12 placebo, $P = .005$.
Amox/clav, Amoxicillin plus clavulanate; *CRP,* C-reactive protein; *CT,* computed tomography; *ESR,* erythrocyte sedimentation rate; *NS,* not stated.

placebo in children, in which sinusitis was diagnosed based on careful clinical criteria in an office setting, demonstrated a cure or improvement in 64% of patients receiving antibiotic compared with 32% of those receiving placebo.[121]

Several meta-analyses of clinical trials of antimicrobials in sinusitis have been published. These analyses have consistently found a benefit for antimicrobials over placebo despite much heterogeneity in the diagnostic methods, exclusion criteria, and outcome measures found within the studies that were included (Table 62.7). Overall, antimicrobial agents reduce the rate of clinical failure by 25% to 30% within 7 to 14 days of initiating therapy.[123] In most studies evaluating the role of antimicrobials, the adverse event rate is higher in the antibiotic arm of the study. Diarrhea is the most common adverse event noted and is usually self-limited.

A recent Cochrane review deserves mentioning as an example of the difficulties in interpretation of results.[124] In this review 15 trials of antimicrobial versus placebo or no treatment in adults were analyzed.

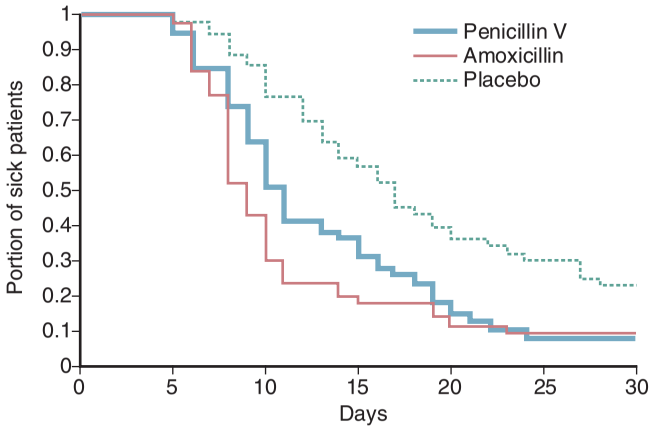

FIG. 62.3 Kaplan-meir curve of antimicrobials versus placebo. *(From Lindbaek M, Hjortdahl P, Johnsen UL. Randomised, double blind, placebo controlled trial of penicillin V and amoxicillin in treatment of acute sinus infections in adults.* BMJ. *1996;313:325–329.)*

TABLE 62.7 Meta-Analyses of Antibiotics Versus Placebo in the Treatment of Acute Rhinosinusitis

STUDY	NO. OF STUDIES	NO. OF PATIENTS	OR	95% CI	NNT
Lemiengre 2018[124]	15	3057	1.38	1.15–1.65	19
Falagas 2008[169]	17	2648	1.64[a]	1.35–2.0	
Young 2008[170]	9	2547	1.35[a]	1.15–1.59	8–15
Ahovuo 2008[171]	5	631	0.66[b]	0.44–0.98	
Rosenfeld 2007[172]	13	NS	NS	NS	7
Ip 2005[123]	39	15,739	0.69[b]	0.53–0.89	

[a]In these studies an OR >1 favored antibiotics.
[b]In these studies an OR <1 favored antibiotics.
CI, Confidence interval; *NNT,* number needed to treat; *NS,* not stated; *OR,* odds ratio.

The authors conclude that the benefit of antimicrobials was too modest, given the spontaneous resolution rate and risk of adverse events. However, the majority of studies in this metanalysis either used overly broad clinical criteria for eligibility or included imaging as criteria for the diagnosis of acute sinusitis. The antimicrobials studied were varied in class and dose. In addition, only one study was performed in the postpneumococcal immunization era.

Guidelines developed by various organizations in the United States have been published on the use of antimicrobials in sinusitis.[90,92,104,125,126] Guidelines published by the Infectious Disease Society of America (IDSA), the American Academy of Pediatrics (AAP) and the American Academy of Otolaryngology–Head and Neck Surgery Foundation (AAO-HNSF) (Table 62.8) recommend making the diagnosis of bacterial sinusitis on the basis of clinical criteria and treating acute sinusitis with antimicrobials.[90,92,126] Two guidelines offer watchful waiting as an option for the clinician. The AAP gives an option to observe for 3 days before starting treatment for nonsevere (onset with persistent symptoms) sinusitis in children, although the AAO-HNSF gives an option to observe up to 7 days and provide a safety-net prescription for all patients with uncomplicated bacterial sinusitis, regardless of severity of symptoms. The IDSA guidelines recommend that treatment be initiated as soon as the diagnosis of acute bacterial rhinosinusitis is made, and that amoxicillin-clavulanate be the first choice of antibiotic to be used. The AAP and AAO-HNSF guidelines recommend amoxicillin with or without potassium clavulanate as first-line therapy.

Patients who present with severe sinus disease or complications of sinusitis should be managed with parenteral antimicrobial therapy. Patients who have mild or moderately severe sinusitis may be treated with an oral antibiotic. Despite the heterogeneity of results in clinical studies, antimicrobial therapy in the treatment of acute sinusitis fits with our understanding of the pathogenesis of this infection. When there is an acute bacterial infection, effective agents exist that should provide levels of antimicrobial that will adequately treat the expected pathogens. Table 62.9 lists oral antibiotics used in the treatment of acute bacterial sinusitis. Antimicrobial therapy is directed at the three major pathogens of sinusitis: *S. pneumoniae, H. influenzae,* and *M. catarrhalis.* Choosing an appropriate antibiotic in patients with sinusitis is a balance between clinical efficacy, toxicity, and minimizing the emergence of resistant organisms. The current lack of up-to-date microbiologic data from studies of sinusitis or otitis media creates a conundrum in selecting the most appropriate antibiotic for the treatment of sinusitis. If the proportion of patients infected with *S. pneumoniae* that are nonsusceptible to penicillin are decreasing, as the most current data suggests, then standard-dose amoxicillin (45 mg/kg/day) rather than high-dose (80–90 mg/kg/day, maximum 4 g/day) may be used. However, if rates of isolation of β-lactamase–producing *H. influenzae* are increasing, then a β-lactamase–stable drug, such as amoxicillin-clavulanate or an advanced-generation cephalosporin, would be indicated.

For most adults and children amoxicillin with or without clavulanate remains an excellent first-line agent.[92,127–131] High-dose amoxicillin or amoxicillin-clavulanate should be used when the patient is at high risk for penicillin-nonsusceptible *S. pneumoniae* (≥10% nonsusceptible pneumococci, attendance at day care, age <2 years or >65 years, recent hospitalization, antibiotics in the past month). A recent controlled trial of high-dose amoxicillin-clavulanate versus standard-dose amoxicillin-clavulanate showed only modest benefit of the high-dose formulation.[132] In the child with a significant penicillin allergy, cefuroxime or cefpodoxime proxetil may be used and is preferred over cefdinir, which is

TABLE 62.8 Comparison of Two Major Guidelines for the Diagnosis and Treatment of Acute Bacterial Sinusitis

	DIAGNOSIS	TREAT	ANTIMICROBIAL OF CHOICE	AMOXICILLIN DOSE
IDSA[92]	Clinical	All patients	Amoxicillin/clavulanate	40–45 mg/kg/day 80–90 mg/kg/day or 2 g/day for high risk[a]
AAP[90]	Clinical	All severe patients Treat or wait 3 days for mild–moderate	Amoxicillin with or without clavulanate	40–45 mg/kg/day 80–90 mg/kg/day or 2 g/day for high risk[a]

[a]High risk: ≥10% nonsusceptible pneumococci, severe infection, attend day care, age <2 years or >65 years, recent hospitalization, antibiotics in the past month.
AAP, American Academy of Pediatrics; *IDSA,* Infectious Diseases Society of America.

TABLE 62.9 Oral Antimicrobial Agents for Acute Bacterial Sinusitis

ANTIMICROBIAL	ADULT DOSAGE	PEDIATRIC DOSAGE
Amoxicillin	500–875 mg q12h	40–80 mg/kg/day divided q12h
Amoxicillin/clavulanate[a]	875 *or* 2000 mg 12h	40–80 mg/kg/day divided q12h
Cefpodoxime proxetil	200 mg 12h	10 mg/kg/day divided 12h
Cefixime[b]	400 mg q12–24h	8 mg/kg/day divided q12–24h
Cefdinir	300 mg q12h *or* 600 mg q24h	14 mg/kg/day divided 12–24h
Azithromycin[c]	500 mg daily for 3 days	10 mg/kg daily for 3 days
Clarithromycin[c]	500 mg q12h for 14 days 1000 mg daily for 14 days	15 mg/kg/day divided q12h
Levofloxacin	500 mg daily	16–20 mg/kg/day divided every 12h[b]
Moxifloxacin	400 mg daily	400 mg daily for adolescents[b]

[a]Dosages specify amoxicillin component.
[b]Not US Food and Drug Administration approved for this indication.
[c]Macrolides not preferred because of poor activity against *Haemophilus influenzae*.

less potent. Alternative agents in adults include a respiratory fluoroquinolone, such as levofloxacin or moxifloxacin, or doxycycline.

The macrolides have become popular in the treatment of sinusitis due to their once-daily dosing and shorter courses. Despite recommendations against these agents, a study of prescribing habits in patients with sinusitis demonstrated that they are the second most commonly prescribed antibiotic after amoxicillin.[133] However, because of increasing resistance and the change in epidemiology of respiratory pathogens, their use cannot be endorsed. Neither azithromycin nor clarithromycin have adequate coverage for *H. influenzae;* furthermore, they are considered second-line therapy for *S. pneumoniae.*[104]

Patients treated with an antimicrobial may be expected to improve within 48 to 72 hours of starting therapy. If the patient fails to improve during this time frame, either the diagnosis of sinusitis should be suspect or a broader-spectrum agent should be used. Regimens in the child or adult failing therapy with high-dose amoxicillin-clavulanate should include a respiratory fluoroquinolone or cefixime in combination with linezolid.

The exact duration required for the treatment of sinusitis is unknown. Recommendations based on clinical observations have varied widely, from 10 to 28 days of treatment. A treatment course of 10 days is typical. Some guidelines suggest that therapy be continued for 7 days after the patient becomes free of signs and symptoms. The advantage of this strategy is that it results in a minimum of 10 days and avoids prolonged antimicrobial therapy in patients who are asymptomatic.[90] It is a particularly advantageous regimen when the patient responds more sluggishly to the antimicrobial regimen.

The efficacy of shorter courses of antimicrobials, particularly quinolones and macrolides, has been reported. For example, azithromycin given for 3 days was reported to be equivalent to 5 days, and 5 days of gatifloxacin was equivalent to 10 days.[123] Five-day courses of cefuroxime have also been compared with a 10-day course. Falagas and colleagues[134] performed a metanalysis of short course (3–7 days) versus long course (6–10 days) of antimicrobial treatment and found no difference between these groups. The diagnosis of sinusitis in these studies was based on radiographic findings, and thus many patients with uncomplicated URI may have been included, biasing the results against showing a difference.

ADJUNCTIVE TREATMENT

Corticosteroids

A number of nonantimicrobial therapies have been used to provide symptom relief to patients with sinusitis. The literature on adjunctive treatment of sinusitis has the same limitations as that of antimicrobial trials; many studies lack stringent definitions of sinusitis. In accordance, many of these studies include patients with uncomplicated viral URI, and the results must be interpreted cautiously. Intranasal corticosteroids have been studied with and without antimicrobials. Placebo-controlled trials of intranasal steroids have shown conflicting results.[109,135–139] Two recent meta-analyses of such studies demonstrated no difference between groups. Zalmanovici[139] found an overall resolution rate of symptoms of 73% in corticosteroid-treated patients versus 66% in placebo controls. Hayward's[140] analysis showed a 7% increase in improvement rate when patients were treated with intranasal corticosteroids compared with placebo. This modest benefit does not warrant endorsement when it adds substantially to the cost and complexity of treatment, although the AAO-HNS guidelines offer this as an option for symptomatic relief in adults.[126] In contrast, intranasal corticosteroids should be offered to those patients with chronic rhinosinusitis, particularly when there is a history of atopic nasal disease.

Antihistamines/Decongestants

Antihistamines have not been shown to be consistently effective in the symptomatic treatment of sinusitis. However, they do have a role in patients with underlying allergic disease. Topical and oral decongestants, which are α-adrenergic agonists, are used frequently as adjunctive therapy but have received little systematic study. Decongestants have a modest effect on decreasing nasal airway resistance. These agents may cause increased blood pressure, CNS stimulation, insomnia, or urinary retention. A recent review of the use of antihistamines and decongestants in children with sinusitis found a lack of well-controlled studies to determine the efficacy of these treatments.[141] Because of concern for adverse events, antihistamines and decongestants should not be used for symptomatic relief in children.[90,142]

Saline

Nasal saline spray, large-volume saline irrigation, and hypertonic saline have been popularized as a measure to reduce symptoms in patients with sinusitis. Such irrigations act by improving mucociliary function, decreasing mucosal edema, and mechanically reducing crusting and debris formation. This may serve to keep the osteomeatal complex clear and facilitate drainage. There is evidence in clinical trials that intranasal saline does provide a modest improvement primarily in adults with chronic symptoms. Large-volume irrigation is more effective than saline sprays. Because adverse events are minimal and mainly include slight nasal irritation, such measures are an option in providing symptomatic relief.[143–146] Data are limited for the effect of nasal saline for children with acute sinusitis but also support a modest benefit.[141,147–150]

Sinus Surgery

Surgical intervention in acute sinusitis may be indicated when there are intracranial or orbital complications or in the patient with severe acute infection refractory to antimicrobial therapy. Surgery is used frequently in patients with chronic sinusitis unresponsive to medical therapy.[90,104,151] Functional endoscopic sinus surgery is the most common procedure currently performed for this condition. In this procedure the emphasis is on restoring the normal anatomic and physiologic drainage of the sinuses through the osteomeatal complex. Diseased tissue, polyps, and bone within the ethmoid or frontal sinus cavities and sinus ostia is removed under endoscopic visualization. Recent attention has been focused on preserving the mucoperiosteum and normal structures as much as possible. Benefit from surgical intervention has been demonstrated primarily in uncontrolled trials in which improvement in both symptoms and quality of life have been noted.[152–155] Randomized, controlled trials have not demonstrated the advantage of functional endoscopic surgery compared with aggressive medical therapy.[156,157]

COMPLICATIONS

The complications of sinusitis result from the close proximity of the sinuses to critical structures of the skull and face, and may be divided into intracranial and extracranial manifestations. Intracranial complications include subdural empyema, epidural abscess, intraparenchymal brain abscess, meningitis, and venous sinus thrombosis. Intracranial

FIG. 62.4 (A) A child with orbital abscess as a complication of ethmoid sinusitis. Note the marked edema and proptosis. (B) Computed tomography scan of the orbit. White arrow demonstrated an orbital abscess. *(A courtesy Gary Williams, MD.)*

complications must be considered in any patient who presents with fever, altered mental status, seizures, or focal neurologic findings. Extracranial complications include orbital cellulitis, orbital abscess, and subperiosteal abscess.[158–161] The Pott puffy tumor is a subperiosteal abscess of the frontal bone that presents as a swelling over the forehead secondary to an underlying osteitis.[162] Orbital and intracranial complications are present together in up to 45% of complicated cases. The majority of complications of sinusitis are a consequence of infection of the frontal and ethmoid sinuses.[163] The pathogenesis of complications involves either direct extension from the sinus cavity or retrograde thrombophlebitis from the valveless venous network.[164]

Acute bacterial sinusitis is occasionally complicated by periorbital edema, particularly when the ethmoid sinuses are involved. These patients will have findings of discoloration and soft nontender edema of the upper and lower eyelids. The overlying skin may have a purple or reddish discoloration. This must be distinguished from signs of true orbital infection, such as orbital abscess or orbital cellulitis. Although these serious complications may also be associated with periorbital edema, accompanying proptosis or impairment of extraocular movements should alert the clinician to a true intraorbital infection (Fig. 62.4). A CT scan of the orbits and sinuses should be performed when an orbital infection is suspected. Immediate surgical intervention is indicated for many orbital and intracranial abscesses. However, small abscesses associated with sinusitis may be managed with a trial of antimicrobial therapy. If clinical improvement does not occur in 24 to 48 hours, then surgical drainage should be undertaken.

Anaerobic bacteria, viridans streptococci, gram-negative organisms, and *S. aureus* are frequently isolated from intracranial collections of purulent material.[164,165] The role of *Streptococcus anginosus* in the complications of sinusitis is being increasingly appreciated.[160] Empirical antibiotic therapy should include vancomycin, ceftriaxone, and metronidazole for intracranial infections. Orbital infections may be treated with ampicillin-sulbactam and vancomycin, or the combination of ceftriaxone plus clindamycin and vancomycin.

Complications of acute bacterial sinusitis are rare, and thus studies that show an impact of treatment of sinusitis on the prevention of complications are difficult to perform and interpret. A recent ecologic study of antimicrobial use in Sweden suggested there was no effect of antimicrobial use on the prevention of orbital or intracranial complications.[166] Often, the initial presentation of the child or adult with complications of acute sinus infection is with signs and symptoms of the complication.

PREVENTION

The prevention of rhinosinusitis is dependent on diagnosing and treating underlying conditions that predispose patients to recurrent or ongoing infection. Such conditions include allergic rhinitis, cystic fibrosis, gastroesophageal reflux disease, ciliary dyskinesia, or anatomic defects. These patients may present with multiple episodes of sinusitis or sinusitis recalcitrant to medical therapy. These conditions should be sought in the patient with recurrent sinus disease and treated aggressively. Attendance of a child in day care is a risk for recurrent URI and subsequent sinusitis. Children attending day care have twice the rate of URIs than those who do not attend day care.[167]

Vaccination has not played a major role in the prevention of acute sinusitis in children. Vaccination against influenza virus will prevent only one URI per year that may predispose the patient to an episode of acute bacterial sinusitis. Studies of the microbiology of the nasopharynx in adults and children have shown a reduction in the isolation of *S. pneumoniae* in the years since the pneumococcal conjugate vaccine has been in use.[43,168] A reduction in the actual incidence of sinusitis, however, has not been demonstrated after introduction of this vaccine.

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The complete reference list is available online at Expert Consult.

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63 Epiglottitis

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SHORT VIEW SUMMARY

Epidemiology and Etiology

- *Pediatric epiglottitis* is a localized, invasive *Haemophilus influenzae* type b infection of the supraglottic area, including the epiglottis, that can be associated with bacteremia (60%–98%); routine conjugate vaccination has largely eliminated this form of epiglottitis.
- *Adult epiglottitis* often involves more of the supraglottic structures (aryepiglottic folds, vallecula, tongue base) and is not associated with bacteremia (<15%); when a bacterial pathogen is identified, it is more likely to be *Streptococcus pneumoniae, Streptococcus pyogenes,* or *Neisseria meningitidis.*
- Before routine infant immunization with *H. influenzae* type b conjugate vaccines, 65% to 75% of all patients with epiglottitis were children 1 to 4 years of age; currently, 90% to 95% are adults.
- Incidence of adult epiglottitis in the United States and Europe is approximately 2 cases per 100,000 population.

Clinical Manifestations

- *Pediatric epiglottitis* is an abrupt illness in a febrile young child with a toxic appearance, dysphagia or sore throat, a muffled or hoarse voice, stridor, drooling, and often a distinctive posture—the "tripod position," comprising apprehension, sitting very still, preferring to lean forward with hyperextension of the neck, and protruding the chin. Cough is distinctly uncommon.
- In *adult epiglottitis,* 80% to 95% of patients have odynophagia and sore throat; only 20% to 40% have fever, drooling, or stridor.

Diagnosis

- Airway management should be promptly evaluated as soon as the diagnosis is considered. Laboratory and radiologic testing in a child with suspected epiglottitis should be performed only in a safe environment (i.e., in the operating room, emergency department, or intensive care unit, with an individual trained in pediatric airway intubation), because of the propensity to develop acute airway obstruction (although airway obstruction is much less common in adults).
- Peripheral leukocytosis is common but not universal. Lateral and anteroposterior neck radiographs show enlargement of the epiglottis (the "thumb sign," as opposed to the "pencil-point narrowing" of the airway in viral croup).
- Direct or indirect laryngoscopy and fiberoptic nasopharyngeal endoscopy are the definitive diagnostic tests.

Differential Diagnosis

- Stridor with toxicity and drooling but lack of cough favors epiglottitis; the presence of stridor, barking cough, and lack of drooling favors viral croup (laryngotracheobronchitis). Other conditions that mimic infectious epiglottitis include bacterial tracheitis, thermal epiglottitis (scald burn from smoke or hot beverages), possibly angioneurotic edema, retropharyngeal or peritonsillar abscesses, uvulitis, and diphtheria.

Therapy

- In *pediatric epiglottitis,* ideally the diagnosis is confirmed with visualization at the time the airway is secured by intubation, at which time laryngeal and blood cultures and complete blood cell counts may be obtained. Emergent tracheotomy or cricothyroidotomy is rarely required.
- In *adult epiglottitis,* in contrast to pediatric epiglottitis, patients generally tolerate direct visualization of the epiglottis for diagnosis. Hospitalization in an intensive care unit during the acute phase of the illness is suggested; however, in most adults (75%–80%) the infection is successfully managed without endotracheal intubation or tracheotomy.
- Empirical therapy for epiglottitis includes intravenous cefotaxime, ceftriaxone, or ampicillin-sulbactam to treat streptococci, pneumococci, *H. influenzae,* and meningococci. In areas with a high proportion of drug-resistant pneumococci, empirical therapy should be broadened.
- Therapy directed against *Staphylococcus aureus* should be considered if bacterial tracheitis cannot be excluded.

Prevention

- Chemoprophylaxis for household contacts of children with *H. influenzae* type b epiglottitis should be given in those households containing underimmunized or nonimmunized children younger than 4 years of age or immunocompromised children.
- Contacts of adults with epiglottitis are unlikely to require any prophylaxis, except in the rare instance of proven *H. influenzae* type b or meningococcal infection.

Acute epiglottitis (supraglottitis) is an invasive cellulitis of the epiglottis and its adjacent supraglottic structures (aryepiglottic folds, vallecula) that has the potential to cause abrupt, complete airway obstruction.

EPIDEMIOLOGY AND ETIOLOGY

Although epiglottitis was reported in both children and adults in the first half of the 20th century, it became known as a classic pediatric infection by the 1970s.[1] It likely is the modern explanation for the illness known in the 18th century as "cynanche trachealis" (literally, "dog strangulation"), now thought to have been the cause of death of George Washington in 1799 (albeit complicated by iatrogenic bloodletting).[2,3]

Epiglottitis has most often been reported to exhibit a slight male predominance (roughly 60% of both children and adult cases occur in males) and a slight excess in cases during the spring and summer.[1,4–7]

Before routine infant immunization with *Haemophilus influenzae* type b conjugate vaccines began in 1990, 65% to 75% of reported cases of epiglottitis occurred in children 1 to 4 years of age (peak, 3 years of age).[1,6–10] Data from geographic areas in which routine *H. influenzae* type b conjugate vaccination is practiced show that 90% to 95% of all reported cases of epiglottitis now occur in adults and that the causative bacterial agent is often not found.[1,4,9,11–13] Thus, the remarkable change in the epidemiology of epiglottitis involves both an upward shift in the average age of patients and a shift in the likely microbiologic cause.

The virtual disappearance of classic pediatric epiglottitis is a direct consequence of the high protective efficacy of *H. influenzae* type b conjugate vaccines, along with the fact that pediatric epiglottitis was, almost uniquely (60%–98% of reported cases in various series), a bacteremic, invasive *H. influenzae* type b infection.[6–14] In the prevaccination era, population-based, age-adjusted estimates of the annual incidence of invasive *H. influenzae* type b infection (the majority of which was meningitis, but also epiglottitis, bacteremia, and bone, joint, and soft tissue infections) in the United States and Scandinavian countries

commonly ranged from 3 to 6 cases per 100,000 children from birth to 18 years of age.[5–13,15–19] The adjusted annual incidence rate for the population of children most at risk was even greater at 21 to 41 cases per 100,000 children from birth to 4 years of age.[15–19] Since the advent of routine conjugate immunization, there has been a 95% to 99% decline in pediatric epiglottitis incidence, such that current rates are 0.02 to 0.6 cases per 100,000 children from birth to 18 years of age.[11–19]

In contrast, in adults, the US and European annual incidence of epiglottitis has remained stable, at 1.8 to 2.0 cases per 100,000 adults, likely because adult epiglottitis tends to be associated with *H. influenzae* type b bacteremia in less than 10% of cases.[4,5,7,11–15] In general, no distinct pathogen is isolated; on occasion, other pathogens unrelated to *H. influenzae,* including *Streptococcus pneumoniae, Streptococcus pyogenes, Staphylococcus aureus,* or *Neisseria meningitidis,* are recovered from surface cultures of the epiglottis and rarely from blood cultures.[1,7,11–14,20–22] A few studies have reported mild increases in adult disease rates, both before and after conjugate pediatric vaccination, perhaps explained by better recognition of the syndrome.[4,14]

Unusual causes of epiglottitis include *Pseudomonas aeruginosa* and *Candida albicans,* especially in immunocompromised adults or in those with significant preceding antibiotic therapy that might allow opportunistic pathogen overgrowth. In addition, injury from consumption of very hot beverages or illicit substances such as inhaled crack cocaine can result in burns of the epiglottis ("thermal epiglottitis").[23–26]

The pathophysiology of epiglottitis is not completely understood. It is possible that local physical trauma or irritation from preceding viral infection predisposes the epiglottis to bacterial infection. The clinical observation that classic pediatric epiglottitis was far more likely than adult epiglottitis to lead to severe respiratory distress and respiratory arrest is often assumed to be explained by a "ball-valve" effect of the child's epiglottis, obstructing the anatomically smaller (with respect to the adult) airway. However, such an obstruction would not explain the success of bag-mask ventilation before intubation of these children. Instead, it seems more likely to be a consequence of pediatric airway physiology. Laminar airflow in the small bronchioles is governed by the Poiseuille equation, which can be expressed as stating that resistance to airflow is inversely proportional to the fourth power of the luminal radius; however, pharyngeal airflow is turbulent, which is less efficient.[27,28] Resistance to turbulent airflow is inversely proportional to the fifth power of the luminal radius. Thus, 1 mm of circumferential edema in the epiglottic region of a small child's airway might reduce its diameter from 4 mm to 2 mm; the cross-sectional area is decreased by 75%, and the resistance to turbulent flow is increased 32-fold. Yet, in an older child or young adult with an 8-mm airway, the same 1 mm of circumferential edema reduces the cross-sectional area by only approximately 44% and increases the resistance only about fivefold.[27,28]

CLINICAL MANIFESTATIONS

The classic presentation of pediatric epiglottitis was a preschool-aged child who acutely developed fever, irritability, and rapidly progressive respiratory distress with stridor.[1,6,7,13,29] These children frequently appeared toxic, were drooling oral secretions, and assumed a "tripod-like" or "sniffing" position, leaning forward in an upright position with hyperextension of the neck and protrusion of the chin, and perhaps bracing themselves with their hands on knees. Such children also exhibited a muffled, "hot potato" voice or hoarseness.[1,6,7,13,29] After the institution of routine *H. influenzae* type b conjugate vaccination, the typical age of children diagnosed with epiglottitis increased, as noted previously; in addition, a more indolent or subacute presentation of epiglottitis has been increasingly recognized in older children and adults. These older patients typically have a longer duration of symptoms before presentation, predominately complain of sore throat and odynophagia, exhibit less frequent respiratory distress at presentation, and do not have *H. influenzae* type b as the etiologic agent.[4–14,20–22,30,31]

Classic *H. influenzae* type b acute epiglottitis in children was a life-threatening illness, with a high incidence of airway compromise and bacteremia but curiously few metastatic sites of infection (i.e., it was rare to see concurrent meningitis, septic arthritis, or facial cellulitis, which were other well-known forms of pediatric invasive *H. influenzae* type b infections).[6,7] However, pneumonia or epiglottic abscesses have been reported.[6,7,30,31] In contrast, modern epiglottitis in adults is typically a nonbacteremic, somewhat less severe illness. Although most patients are in good health before onset of the disease, underlying conditions that compromise immunity may be a factor in some patients.[20–22] In addition, the morbidity and mortality of adult epiglottitis can be significant—5% to 38% of adults required mechanical ventilation and up to 6% died according to several reports from France, Israel, and Canada. In these series, surface cultures of the epiglottis were positive in approximately 20%, most often recovering *Streptococcus* spp. (including groups A, C, F, and *Streptococcus viridans*), *Haemophilus* spp., and gram-negative bacilli.[20–22] Laboratory tests in individuals with acute epiglottitis often reveal leukocytosis with a left shift.[5,7,13,15,31] Blood cultures yielded *H. influenzae* type b in 60% to 98% of children with classic epiglottitis, yet are positive for any pathogen in fewer than 10% of modern cases of epiglottitis in older children and adults.[5,7,20–22,32]

Lateral neck radiographs in patients with epiglottitis show an enlarged epiglottis ("thumb sign"), with ballooning of the hypopharynx and prevertebral soft tissue swelling.[33–37] Fig. 63.1A shows a schematic view of the normal epiglottis anatomy, with a bold line outlining the position of an edematous epiglottis, which easily could provoke greatly increased airway resistance. An endoscopic view of such an inflamed epiglottis is shown in Fig. 63.1B. Typical lateral neck radiographs of a child without (Fig. 63.1C) and with (Fig. 63.1D) epiglottitis contrast the appearance of the normal and "thumblike" swollen epiglottis. Fig. 63.2A is a lateral radiograph of the neck of a 65-year-old woman with a "thumb sign" of acute epiglottitis, and Fig. 63.2B is a computed tomography (CT) scan showing swelling and edema of the epiglottis.[35] Although the lateral neck radiograph thus can be very helpful in diagnosing epiglottitis, radiographs were not recommended to be performed in children with classic acute epiglottitis because of the risks in delay in securing the airway and the requirement for sending an ill and potentially unstable child to the radiology department (bedside neck radiographs were generally not sufficient for proper interpretation of the anatomic borders).[7]

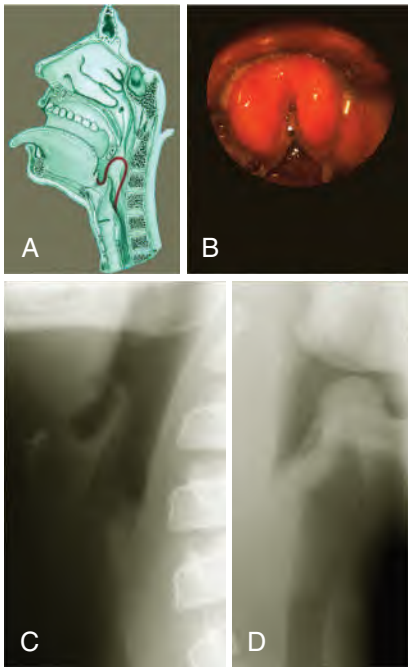

FIG. 63.1 Epiglottitis. Schematic (A) and endoscopic (B) views of swollen epiglottis. The typical lateral neck radiographs of a child without (C) and with (D) epiglottitis, demonstrating the "thumb sign" of the swollen epiglottis, are shown. *(From Hammer J. Acquired upper airway obstruction.* Paediatr Respir Rev. *2004;5:25–33.)*

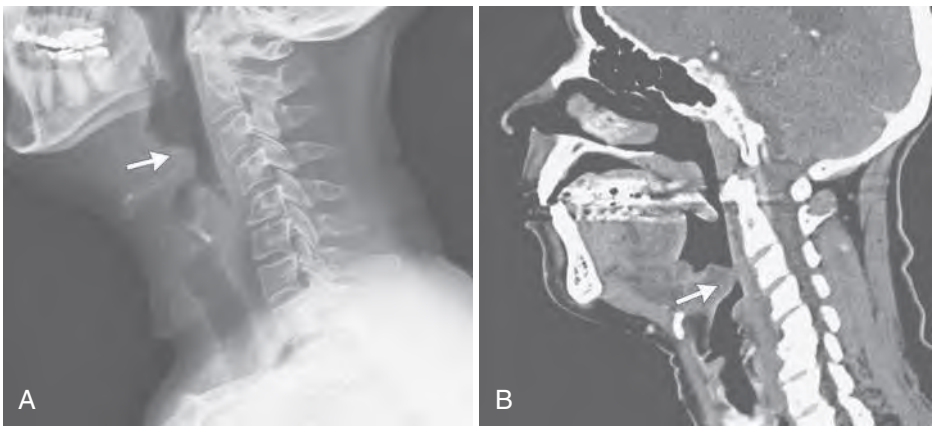

FIG. 63.2 Epiglottitis. Lateral neck radiograph of a 65-year-old woman with acute epiglottitis showing the "thumb sign" (A) and a computed tomography scan showing swelling and edema of the epiglottis (B). *(From Angirekula V, Multani A. Epiglottitis in an adult.* N Engl J Med. *2015;372:e20.)*

DIAGNOSIS

The diagnosis of epiglottitis is definitively established by visualization of an edematous, cherry-red epiglottis by direct or indirect laryngoscopy or by nasal fiberoptic endoscopy.[5–7,12,13,30] In children with classic epiglottitis, or in older children or adults with signs of respiratory distress, this examination should take place in a setting where the airway can be immediately secured—that is, in an intensive care unit or operating room—because airway obstruction may be sudden and precipitated by the examination.

As many as 29% of adults with epiglottitis have sought medical care previously for the same illness without the correct diagnosis being made.[5] Most were assigned a diagnosis of pharyngitis, without undergoing examination of the epiglottis. This emphasizes the need for a complete examination of the epiglottis in adults with severe sore throat or severe pharyngitis with odynophagia.[5] The epiglottis should be visualized directly, even if the radiograph is negative, in patients who are suspected to have epiglottitis. In adults, examination in the sitting-forward position, with a tongue depressor used to gently depress the tongue, may reveal the epiglottis without the need for direct or indirect laryngoscopy.

In subacute epiglottitis of the older child or adult, lateral neck radiographs should be obtained. CT of the neck is generally not required but may be useful for evaluation of epiglottic abscess. Cultures of the blood or epiglottis may be of use in defining a causative organism, although the yield of blood cultures in adult epiglottitis is poor and interpretation of pharyngeal cultures may be complicated by a high carrier rate of certain organisms in the upper respiratory tract.

DIFFERENTIAL DIAGNOSIS

Croup (viral laryngotracheobronchitis) is the most frequent and important diagnosis that mimics classic pediatric epiglottitis; the presentation is sometimes similar to epiglottitis, but the treatment of each syndrome is radically different. Although both illnesses can present as stridor, a toxic appearance is more common in epiglottitis. In a comparative analysis of 203 ill children with either epiglottitis or croup, the presence of drooling oral secretions was 79% sensitive and 94% specific for the diagnosis of epiglottitis; the absence of coughing was similarly predictive (98% sensitivity and 100% specificity).[29] Conversely, the presence of coughing and the absence of drooling heavily favored the diagnosis of croup.[29] Croup is frequently preceded by an upper respiratory tract infection, has a more gradual onset, involves somewhat younger children (median age of 18 months as opposed to median age of 34 months in epiglottitis),[29] and, in general, is a less febrile illness. However, differentiation of epiglottitis from croup is sometimes difficult unless the epiglottis is visualized.

Retropharyngeal abscess, peritonsillar abscess, and uvulitis (invasive bacterial infections generally caused by *S. pyogenes* or oropharyngeal microaerophilic or anaerobic bacteria, rather than *H. influenzae* type b) can mimic epiglottitis but can usually be differentiated by means of physical examination and radiographically. Bacterial tracheitis may be confused with epiglottitis, especially in a patient who has already had antibiotic therapy and may have staphylococcal overgrowth in the trachea; the appearance on laryngoscopy or intubation should clarify the diagnosis. Diphtheria can be differentiated from epiglottitis through the presence of a pseudomembrane in the respiratory tract and the presence of typical organisms on direct smear and culture of the membrane. Noninfectious diagnoses that mimic epiglottitis include angioneurotic edema and foreign-body aspiration; findings from the patient's history and physical examination should help differentiate these entities from epiglottitis.

THERAPY

Initial Management

Maintenance of an adequate airway should be the primary concern as soon as the diagnosis of epiglottitis at any age is even suspected, but especially in a young child. Children who are suspected of having acute epiglottitis should be handled as a medical emergency because of the potential for rapid deterioration to complete respiratory obstruction. Painful or anxiety-provoking procedures (including phlebotomy and lateral neck radiography) should be minimized until the airway is secured or the diagnosis has been excluded. Patients being transported between and even within medical facilities must be accompanied by personnel capable of securing the airway in case obstruction occurs. At the same time, bag-mask ventilation should not be forgotten if intubation or cricothyroidotomy is not possible, because the obstruction is usually not absolute.

Appropriate management of the child with classic pediatric epiglottitis requires the immediate insertion of an endotracheal tube; this procedure is both therapeutic and diagnostic, because visualization of the cherry-red epiglottis is made possible during intubation. Case series and widespread experiential data report that 70% to 100% of children with classic pediatric epiglottitis have undergone intubation for airway management, and generally a small number (<5%) have emergent tracheotomy or cricothyroidotomy.[6,7,15,30,32] However, older children with subacute non–*H. influenzae* type b epiglottitis might be able to be safely managed conservatively without immediate intubation; fewer data exist to guide this decision.

In contrast, it appears reasonably safe for the adult with epiglottitis to be managed without intubation but with careful observation in an intensive care unit with the capability to secure an artificial airway immediately on impending airway compromise (increasing stridor or dyspnea). Most case series of adult epiglottitis report intubation rates of 10% to 25%.[a]

At the same time, adults or older adolescents with epiglottitis accompanied by a rapid onset of symptoms, dyspnea, tachycardia, or tachypnea may benefit from early intubation.[12,13]

[a]References 4, 5, 7, 11–15, 20, 22.

Antibiotic Therapy

After the establishment of an airway, cultures should be obtained from blood and, if possible (i.e., immediately after intubation), the surface of the epiglottis, and empirical intravenous antibiotic therapy should be begun. Antibiotic therapy is directed at the most likely causative bacterial pathogens (*H. influenzae* type b, *S. pneumoniae* [including those with penicillin resistance], β-hemolytic streptococci, and possibly *S. aureus*), although with the recognition that an etiologic agent may not be recovered. This is best accomplished with the use of a third-generation cephalosporin such as ceftriaxone or cefotaxime or a β-lactamase inhibitor combination drug such as ampicillin-sulbactam; for immunocompromised individuals, piperacillin-tazobactam would offer increased coverage for gram-negative organisms while still including the more typical causes. Vancomycin should be added if high-grade penicillin-resistant pneumococci are prevalent in the area or if methicillin-resistant staphylococcal bacterial tracheitis is a diagnostic possibility. For individuals allergic to β-lactams, a combination of a fluoroquinolone (levofloxacin or moxifloxacin) and clindamycin is suggested. Trimethoprim-sulfamethoxazole and clindamycin in combination might also be considered for the β-lactam–allergic patient, depending on the local prevalence of resistance among pneumococci.

The decision to extubate is based on the patient's clinical condition, evidence of resolution on direct visualization of the epiglottis with a fiberoptic laryngoscope, and the presence of an increasing air leak around the endotracheal tube. Pediatric patients with acute epiglottitis usually improve approximately 48 hours after the initiation of appropriate antibiotic therapy. Depending on the patient's progress, the artificial airway can usually be removed within this period. Antibiotics should be continued for 7 to 10 days; in the past they were given intravenously, but it is likely that oral third-generation cephalosporins or respiratory fluoroquinolones, with or without clindamycin, could be used, depending on the individual patient's culture results, response, and status.

The role of nebulized epinephrine, corticosteroids, or other adjuncts to therapy is unknown; evidence of benefits from such interventions is lacking.[7,13,31]

PREVENTION

Household contacts of children with *H. influenzae* type b epiglottitis may require chemoprophylaxis if the household contains unvaccinated or incompletely vaccinated children younger than 4 years; for households without other young children, or if all children are fully immunized, chemoprophylaxis is not indicated.[38] The suggested chemoprophylaxis regimen for young children is rifampin (20 mg/kg/day administered orally once daily for 4 days, maximum daily dose of 600 mg). For pregnant women in whom rifampin use is contraindicated, intramuscular ceftriaxone is an alternative.[38] If a young underimmunized child is present in the household unit, prophylaxis is given to all household contacts, regardless of age or immunization status, to prevent "ping-pong" spread of carriage among individuals.[38] When the index child with invasive *H. influenzae* type b epiglottitis is treated with ceftriaxone or cefotaxime, colonization is successfully eliminated, such that the ill child does not require rifampin therapy. However, children who are treated with ampicillin-sulbactam or other agents will require "terminal prophylaxis" with rifampin at the end of their primary treatment, to prevent reintroduction of the organism into the household.[38] In general, chemoprophylaxis is no longer considered for school contacts of children with *H. influenzae* type b disease.

Contacts of older children and adults with epiglottitis do not require chemoprophylaxis at all, except in the rare case of documented meningococcal or *H. influenzae* type b epiglottitis, in which case rifampin, ceftriaxone, or ciprofloxacin would be used as appropriate.[38]

Primary prevention of *H. influenzae* type b and most pneumococcal serotypes causing pediatric infection is now afforded by routine conjugate vaccination.[38] Routine quadrivalent meningococcal vaccination of adolescents may also lessen the rare cases of meningococcal epiglottitis.[38]

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The complete reference list is available online at Expert Consult.

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64 Infections of the Oral Cavity, Neck, and Head

Anthony W. Chow

SHORT VIEW SUMMARY

Definition
- Infections of the oral cavity, neck, and head are diverse in etiology and clinical presentation.
- Although uncommon in the postantibiotic era, deep fascial space infections and vascular complications are potentially life threatening. These include Lemierre syndrome and Ludwig angina.
- A clear understanding of their interrelationships, anatomic routes of spread, and salient clinical features is critical to diagnosis and management.

Epidemiology
- Infections of the oral cavity are most commonly odontogenic in origin and include dental caries, periodontal disease, and deep fascial space infections.
- Nonodontogenic infections of the oral cavity include those of the oral mucosa, tonsils, epiglottis, supraepiglottic structures, and infections of the major salivary glands.
- Miscellaneous infections of the head and neck most commonly result from human or animal bites, irradiation, or surgical procedures but may also arise from suppurative adenitis, infected embryologic cysts, and suppurative thyroiditis.

Microbiology
- The microbiota associated with odontogenic infections generally reflect the indigenous oral microbiota and are typically polymicrobial, involving both strict anaerobes and facultative bacteria.
- Dental caries originate from "cariogenic" bacteria residing within the supragingival plaque or biofilm, whereas periodontal disease arises from "periodontopathic" bacteria residing within the subgingival plaque or biofilm.
- Important differences within these complex bacterial compositions support the concept of the "specific" plaque hypothesis of dental caries and periodontal disease.

Diagnosis
- Microbiologic investigation requires proper specimen collection, taking care to minimize contamination by resident commensal microbiota.
- Needle aspiration of loculated pus by an extraoral approach is desirable, and specimens should be transported immediately to the laboratory under anaerobic conditions.
- Tissue biopsy specimens should be routinely examined for histopathologic evidence of acute or chronic inflammation and infection.
- Immunofluorescence staining and rapid molecular diagnostic tools, such as DNA probes or polymerase chain reaction, are valuable for the detection of fastidious or noncultivable pathogens.
- Computed tomography (CT) with contrast is the most effective tool for localizing and evaluating the extent of deep space infections of the oral cavity, head, and neck.
- Magnetic resonance imaging with or without angiography is more sensitive than CT for assessing soft tissue and bone involvement, as well as vascular complications.
- Technetium bone scans in combination with gallium- or indium-labeled white blood cells may be useful for the diagnosis of acute or chronic osteomyelitis.

Therapy
- Surgical drainage of loculated infection and removal of necrotic tissue are the keys to management of deep fascial space infections of the oral cavity, head, and neck.
- Antimicrobial therapy is important in halting the local spread of infection and in preventing hematogenous dissemination.
- Choice of antimicrobial regimens is empirical, depending on the primary source (e.g., odontogenic or oropharyngeal vs. rhinogenic or otogenic), anticipated causative microorganisms, and immunity of the host (see Tables 64.2 and 64.3).

Prevention
- Oral hygiene and dental treatment to prevent caries and advanced periodontal disease
- Dietary counseling and use of topical fluorides and chlorhexidine oral rinses for patients at high risk for dental caries
- Behavioral modification of risk factors, such as tobacco smoking

Infections of the oral cavity are most commonly odontogenic in origin. Odontogenic orofacial infections include dental caries, pulpitis, periapical abscess, gingivitis, periodontal disease, and infections in the deep fascial spaces. Complications such as intracranial, retropharyngeal, or pleuropulmonary extension and hematogenous dissemination to heart valves, prosthetic devices, and other metastatic foci, although rare, clearly indicate the potentially serious nature of these infections. Nonodontogenic infections of the oral cavity include ulcerative mucositis, which complicates radiation and chemotherapy; noma (gangrenous stomatitis); and infection of the major salivary glands. Suppurative orofacial infections can also arise from the oronasopharynx, tonsils, middle ear and mastoids, and paranasal sinuses; these are discussed in Chapters 59, 61, and 62, respectively.

Infections of the neck and head in the adult most commonly result from human or animal bites, trauma, irradiation, and surgical procedures. In children cervical adenitis and thyroiditis caused by bacteria or viruses are more common. Rarely do embryologic cysts in the neck region become secondarily infected. These are considered separately from oral infections because they frequently involve different microbiota and necessitate alternative approaches to diagnosis and therapy.

MICROBIOLOGIC CONSIDERATIONS

The microbiota associated with odontogenic infections are complex and generally reflect the indigenous oral microbiota. Such infections are typically polymicrobial, and invasiveness is often influenced by synergistic interactions of multiple microbial species. Moreover, certain species or combinations may be more invasive or more resistant to therapy than others. Despite this complexity, there is strong evidence of a causative role of specific microorganisms in different forms of odontogenic infections.[1] Because the microbiota associated with these infections are typically polymicrobial, the components of these complex microbiota do not necessarily have equal pathogenic potential, and the numerically predominant cultivable microbiota may not be the most pathogenic. Furthermore, it may not be necessary to eradicate the complete microbiota for effective therapy. In addition, results of surveys with molecular tools such as culture-independent nucleic acid technologies indicate a level of diversity in the human subgingival microbiota that cannot be recognized by conventional culture techniques.[2] More than 1000 distinct bacterial species from the oral cavity have been identified.[3] In most instances the cultivable microbiota probably represent

less than 1% of the total extant population, as estimated by microscopy or other means.[4] Nevertheless, an appreciation of the indigenous oral microbiota and the host factors that may modify its composition, as well as knowledge of the most common microorganisms implicated in different odontogenic and nonodontogenic infections, should provide a more rational approach to the management of such infections arising from the oral cavity.

Unique Niches of the Indigenous Oral Microbiota

The oral cavity cannot be regarded as a single, uniform environment. Although representative species of microorganisms can be isolated from most areas of the mouth, certain sites, such as the tongue, tooth surface, gingival crevice, and saliva, are favored for colonization by specific organisms (Table 64.1).[5]

Quantitative studies indicate that obligate anaerobes constitute a large and important part of the residential oral microbiota. In the gingival crevice of healthy adults, for example, the total microscopic counts averaged 2.7×10^{11} microorganisms per gram of wet weight. The total cultivable anaerobic bacteria averaged 1.8×10^{11} microorganisms per gram, whereas facultative bacteria averaged 2.2×10^{10} microorganisms per gram, which is an eightfold difference. Overall, *Streptococcus, Finegoldia, Peptostreptococcus, Veillonella, Lactobacillus, Corynebacterium,* and *Actinomyces* account for greater than 80% of the total cultivable oral microbiota. Facultative gram-negative rods are uncommon in healthy adults but may be more prominent in seriously ill, hospitalized, and elderly patients. Unique ecologic niches have been observed.[5] For example, *Streptococcus sanguis, Streptococcus mutans,* and *Streptococcus mitis,* as well as *Actinomyces viscosus,* preferentially colonize the tooth surface. In contrast, *Streptococcus salivarius* and *Veillonella* spp. have a predilection for the tongue and buccal mucosa.[6] *Fusobacterium, Porphyromonas, Prevotella,* and anaerobic spirochetes appear concentrated in the gingival crevice.[6] The cultivable microbiota in the saliva most closely resemble those on the dorsum of the tongue. Factors that appear to govern these localization patterns include selective adherence characteristics of certain bacteria for various types of cells, local environmental conditions such as oxygen tension, oxidation-reduction potential (Eh) and pH, interbacterial coaggregation, and microbial inhibition.[7] Apart from anatomic considerations, numerous factors, such as age, pregnancy, diet and nutrition, eruption of deciduous dentition, oral hygiene, smoking habits, the presence of dental caries or periodontal disease, antimicrobial therapy, hospitalization, and genetic or racial factors, may influence the composition of the oral microbiota.[8]

Microbial Specificity in Odontogenic Infections

Of importance is that the normal commensal microbiota are closely adapted to their unique ecologic niches in the oral cavity within well-established structures known as *biofilms.* These highly organized microorganisms are encased in an extracellular matrix composed mainly of polysaccharides and exist in a relatively protected environment. Under normal "healthy" conditions, these commensal bacteria maintain an effective and nondestructive inflammatory barrier against potential pathogens.[9] Under pathologic conditions, however, this microbial homeostasis is disrupted, and the commensal microbiota shifts to a dysbiotic pathogenic form, which results in inflammation and tissue destruction.[10] Only certain microorganisms residing within dental plaques or biofilms are cariogenic or periodontopathic (i.e., the "specific" plaque hypothesis of dental caries and periodontal disease).[11] This microbial specificity demonstrated for different odontogenic infections probably reflects the acquisition of unique microbiota during the development of a supragingival dental plaque and its progression to a subgingival dental plaque. Plaques or biofilms that accumulate above the gingival margin are composed mainly of gram-positive facultative and microaerophilic cocci and rods; plaques or biofilms that accumulate below the gingival margin are composed mainly of gram-negative anaerobic rods and motile forms, including spirochetes (Fig. 64.1).[12] Microorganisms residing within the supragingival plaque are characterized by their ability to adhere to the tooth surface and by their saccharolytic activity. Microorganisms in the subgingival plaque are frequently asaccharolytic but proteolytic, and they need not be adherent.

Important differences in bacterial compositions have been noted for dental caries, gingivitis, and different forms of periodontitis in comparison with cultures from healthy tissues.[11] An etiologic association of *S. mutans* in dental caries has been firmly established.[13] *S. mutans* is the only organism consistently isolated from all decayed dental fissures and is the only organism consistently found in greater numbers in carious teeth than in noncarious teeth. The infectious and transmissible nature of this organism in dental caries has been demonstrated in both experimental animals and in longitudinal studies in humans.[14]

Similarly, in gingivitis and periodontitis a unique and specific bacterial composition of the subgingival plaque has been identified.[15] In the

TABLE 64.1 Predominant Cultivable Bacteria From Various Sites of the Oral Cavity

TYPE	PREDOMINANT GENUS OR FAMILY	TOTAL VIABLE COUNT (mean %) Gingival Crevice	Dental Plaque	Tongue	Saliva
Facultative					
Gram-positive cocci	*Streptococcus* spp. *S. mutans* group *S. sanguis* *S. mitis* *S. salivarius* group	28.8 (0–30) (10–20) (10–30) (0–1)	28.2 (0–50) (40–60) (20–40) (0–1)	44.8 (0–1) (10–20) (10–30) (40–60)	46.2 (0–1) (10–30) (30–50) (40–60)
Gram-positive rods	*Lactobacillus*	15.3	23.8	13.0	11.8
Gram-negative cocci	*Moraxella*	0.4	0.4	3.4	1.2
Gram-negative rods	Enterobacteriaceae	1.2	ND	3.2	2.3
Anaerobic					
Gram-positive cocci	*Peptostreptococcus*	7.4	12.6	4.2	13.0
Gram-positive rods	*Actinomyces, Eubacterium, Leptotrichia*	20.2	18.4	8.2	4.8
Gram-negative cocci	*Veillonella*	10.7	6.4	16.0	15.9
Gram-negative rods	*Fusobacterium* *Prevotella* *Porphyromonas*	16.1 1.9 4.7	10.4 4.1 ND	8.2 0.7 0.2	4.8 0.3 ND

ND, Not detected.
Data modified from Hull MW, Chow AW. Indigenous microflora and innate immunity of the head and neck. Infect Dis Clin North Am. *2007;21:265–282.*

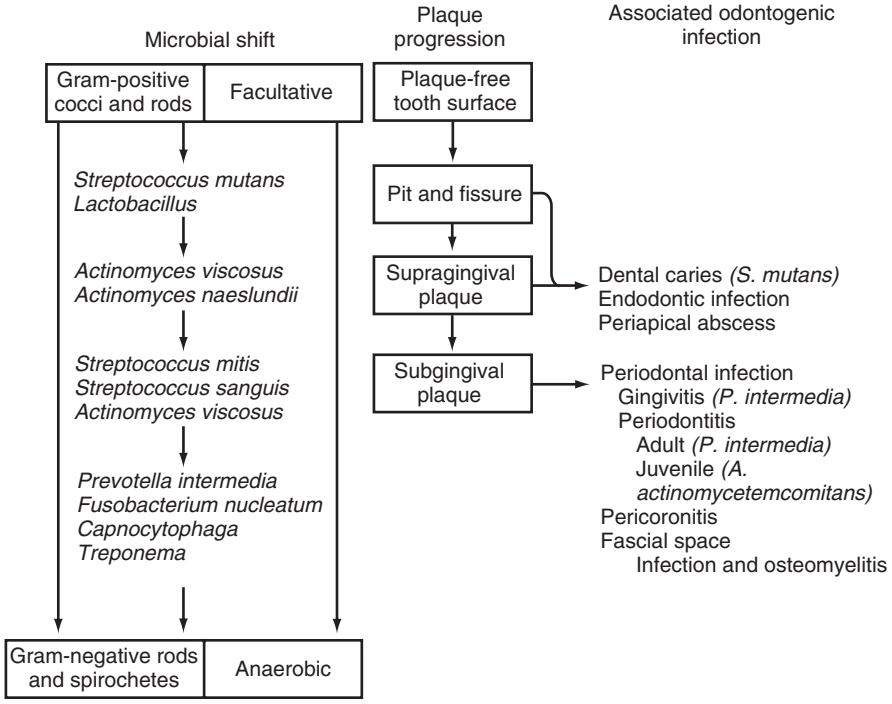

FIG. 64.1 Microbial specificity in odontogenic infections. A unifying hypothesis demonstrating a microbial shift from a plaque-free tooth surface and progression to supragingival and subgingival plaque organisms. *(Modified from Chow AW. Odontogenic infections. In: Schlossberg D, ed.* Infections of the Head and Neck. *New York: Springer; 1987:148.)*

healthy periodontium the microbiota is sparse and consists mainly of gram-positive organisms, such as *Streptococcus oralis, S. sanguis,* and *Actinomyces* spp. In the presence of gingivitis the predominant subgingival microbiota shift to a greater proportion of anaerobic gram-negative rods, and *Prevotella intermedia* (formerly *Bacteroides intermedius*), *Capnocytophaga* spp., *Finegoldia magna,* and *Peptostreptococcus* spp. are most commonly isolated. In adults with "established" periodontitis the microbiota further increases in complexity, with a preponderance of anaerobic gram-negative and motile organisms and spirochetes. *Porphyromonas gingivalis* (formerly *Bacteroides gingivalis), P. intermedia, Aggregatibacter actinomycetemcomitans, Tannerella forsythensis* (formerly *Bacteroides forsythus*), and *Treponema denticola* are most commonly isolated. In juvenile or "early-onset" periodontitis, a clinical variant seen primarily in adolescents, the subgingival plaque consists mainly of saccharolytic organisms, with *A. actinomycetemcomitans* and *Capnocytophaga* spp. as the most common identifiable species. *P. gingivalis* is rarely found in this condition.

In suppurative odontogenic infections, such as periapical abscesses or deep fascial space infections, polymicrobial microbiota are usually present; the predominant isolates are *Fusobacterium nucleatum,* pigmented *Bacteroides* spp., *Peptostreptococcus* spp., *Actinomyces* spp., and *Streptococcus* spp.[16] Except in patients with serious underlying illnesses, facultative gram-negative bacilli and *Staphylococcus aureus* are uncommonly isolated.

PATHOGENETIC MECHANISMS

The mechanisms by which pathogenic microorganisms in the oral cavity can cause disease are varied. To some extent these microbes must be able to adhere to mucosal or tooth surfaces; resist elimination by mechanical means, such as flushing by oral fluids; compete for space and nutrients with other resident microbiota; evade host defenses; and penetrate host tissues. The ability to attach to mucosal and tooth surfaces and form biofilms appears important for both commensal and pathogenic microbes within the dental plaque.[17,18] Commensal biofilms are health promoting and protect against a destructive host inflammatory response elicited by pathogenic biofilms.[9] Homeostasis of the plaque biofilm and its symbiotic relationship with the host is critical for oral health. Disequilibrium or dysbiosis within the plaque biofilms is the initiating event that leads to major oral diseases, such as dental caries and periodontal disease.[19,20]

Microorganisms that cause dental caries, such as *S. mutans* and *Streptococcus sobrinus,* reside within the supragingival plaque and are both acidogenic (able to produce acid) and aciduric (able to grow at low pH). They readily colonize the tooth surface shortly after tooth eruption but do not become cariogenic until they are exposed to dietary sucrose.[17] Fermentation of dietary sucrose by acidogenic plaque bacteria lowers the pH on the tooth surface, promoting demineralization and eventually tooth decay. *S. mutans* can also use sucrose to produce extracellular adhesive polymers, known as *glucans,* which enable *S. mutans* to stick avidly to the tooth surface, facilitating cariogenesis in the underlying structures.[21] In the healthy host at least three mechanisms protect the tooth from carious decay: (1) the cleaning action of the tongue and buccal membranes, which removes any food particles from the proximity of the tooth; (2) the buffering effect of saliva, which has a neutral pH that washes away bacterial acids and provides essential substrates for remineralization and repair of damaged tooth surfaces; and (3) the protective effect of an acellular bacteria-free coating of salivary origin on the tooth surface, known as the *acquired pellicle,* which acts as a surface barrier to most dietary and bacterial acids and other proteolytic substances. In the absence of tooth brushing and flossing, the acquired pellicle becomes rapidly colonized and is replaced by the bacterial plaque or biofilm. It is not surprising, therefore, that carious lesions occur most often in areas inaccessible to the self-cleaning mechanisms of the mouth and on the occlusal surfaces and sites that are protected from the reaches of the toothbrush.

Periodontal disease is caused mainly by selective periodontopathic microorganisms within the subgingival dental plaque, which penetrate the gingival epithelium, elicit an inflammatory host response, and ultimately cause destruction of the periodontium.[20,22] This tissue destruction results in apical migration of gingival tissues (gingival recession), loss of periodontal attachment, and an increase in the depth of the gingival crevice (periodontal pockets). Specific virulence factors, such as lipopolysaccharide and proteolytic enzymes, play a role in this destruction. For example, several oral microorganisms associated with periodontitis, including *A. actinomycetemcomitans,* produce a leukotoxin that destroys polymorphonuclear leukocytes and macrophages and is

believed to be a key virulence factor.[23] Host and environmental factors, such as smoking, malnutrition; underlying disease such as diabetes mellitus; and certain genetic factors may play an even bigger role.[24] In particular, patients with neutrophil defects, such as Chédiak-Higashi syndrome, agranulocytosis, and cyclic neutropenia, have a higher incidence of periodontal disease.[23] Other factors include various hormonal effects that may exacerbate disease activity during puberty, menstruation, and pregnancy. Two major predisposing factors are poor oral hygiene and increasing age.[25] In contrast to its role in dental caries, dietary carbohydrate intake does not appear to have a significant role in the pathogenesis of periodontal disease.

MUCOSAL IMMUNITY OF THE ORAL CAVITY

The oral cavity has three major host defenses against bacterial invasion: the oral mucosa as a physical barrier, nonspecific (innate) immunity, and adaptive (acquired) immunity (Fig. 64.2).[26] The oral mucosa consists of a layer of interconnected epithelial cells containing mainly keratinocytes resting on a basal membrane. The oral epithelium constantly undergoes cellular renewal and turnover. Microorganisms seeking to colonize mucosal surfaces must develop a strategy to counteract the constant turnover of the epithelial cell layer.

Keratinocytes also have an innate system for recognizing pathogenic microbes by the activation of Toll-like receptors (TLRs). TLRs function as pathogen-recognition receptors that interact with conserved domains on microorganisms (so-called pathogen-associated molecular patterns [PAMPs]).[27] Activation of TLRs results in a cascade of signaling pathways, ultimately leading to the upregulation of various proinflammatory (e.g., interleukin [IL]-1α, IL-6, IL-12, tumor necrosis factor-α [TNF-α]) and antiinflammatory (e.g., IL-10, transforming growth factor-β [TGF-β]) cytokines and chemokines (e.g., RANTES [regulated on activation, normal T-cell expressed and secreted], macrophage inflammatory protein-1 [MIP-1], IL-8), which are crucial for nonspecific defense in the oral cavity. Phagocytic cells such as leukocytes and macrophages are abundant in the lamina propria and serve as the first line of defense against pathogenic microbes. Keratinocytes also produce a variety of antimicrobial peptides, including histatins and β-defensins, which have broad antibacterial and antifungal properties. Human β-defensin (hBD)-1 is expressed constitutively in epithelial tissues, whereas hBD-2 and hBD-3 are expressed in response to bacterial stimuli or inflammation.

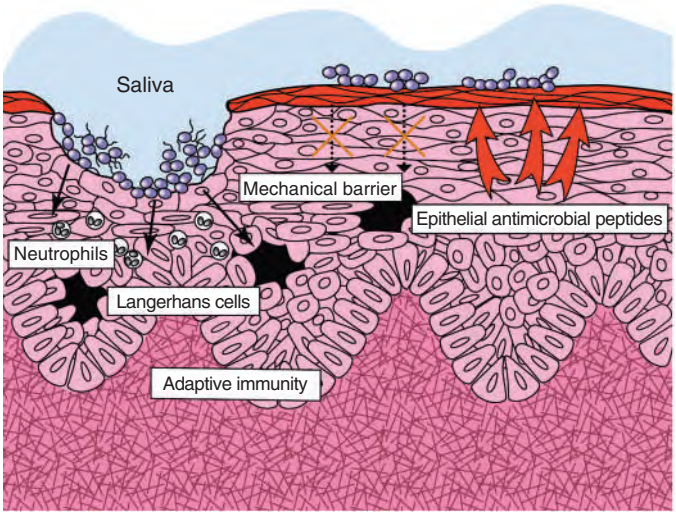

FIG. 64.2 Mucosal defenses against invading bacteria in the oral cavity. The oral mucosa has three types of antimicrobial defenses: physical barrier of the epithelial layer; nonspecific (innate) immunity derived from salivary constituents, neutrophils, and epithelial antimicrobial peptides; and adaptive immunity associated with mucosa-associated lymphatic tissues. *(Modified from Abiko Y, Saitoh M, Nishimura M, et al. Role of beta-defensins in oral epithelial health and disease.* Med Mol Morphol. *2007;40: 392–402.)*

Commensal and pathogenic bacteria have been found to use different signaling pathways in hBD-2 induction; this finding suggests that epithelial cells from different body sites may use common signaling mechanisms to distinguish between commensal and pathogenic bacteria.[28]

In addition, the lamina propria within the mucous membrane contains a full complement of immunocompetent cells that are responsible for adaptive immunity. These cells, which include lymphocytes, macrophages, dendritic cells, natural killer cells, and eosinophils, constitute a common mucosal immune system known as *mucosa-associated lymphoreticular tissue* (MALT). Dendritic cells within MALT (Langerhans cells) process foreign antigens for presentation to and activation of T cells, as well as differentiation of B cells into immunoglobulin-secreting plasma cells. The primary immunoglobulin secreted at these sites within salivary and other exocrine glands is secretory immunoglobulin A (sIgA), whose major function is bacterial agglutination, inhibition of bacterial adherence, toxin neutralization, and antigen exclusion at the mucosal surface.[29] IgA also downregulates the proinflammatory cytokine response by binding with the crystallizable fragment-α receptor (Fc-αR) on phagocytic cells. A number of oral microorganisms implicated in periodontitis, including *P. gingivalis, P. intermedia, Prevotella melaninogenica, Capnocytophaga* spp., *S. sanguis,* and *S. mitis,* are found to secrete IgA proteases.[30] It has been suggested that cleavage of IgA by microbial IgA proteases may impair local mucosal immunity of the host. It remains to be seen whether similar or other defects of host resistance can be identified in different forms of destructive odontogenic infections.

Finally, saliva also acts as an important source of antimicrobial activity against oral pathogens.[31] Mechanically, saliva serves to coat the teeth and contribute to the protective pellicle. In addition, it flushes the oral cavity, clearing away bacteria and their by-products, as well as food debris that may aid bacterial growth and colonization. The buffering capacity of saliva contributes to the maintenance of salivary pH. Numerous chemical constituents that inhibit bacterial growth, such as lysozyme, lactoferrin, defensins, and the peroxidase system, are found within the saliva.[32] Lysozyme is able to lyse bacteria by catalyzing breakdown of the bacterial cell wall in a manner akin to the action of penicillin. It is also active against gram-negative bacteria in the presence of complement and antibody, and it disrupts the lipopolysaccharide coat in the cell wall.[33] Lactoferrin sequesters iron from the environment, thus inhibiting the growth of various facultative and aerobic bacteria that are dependent on iron for metabolism. Salivary lactoperoxidase and myeloperoxidase are generated by polymorphonuclear leukocytes within the gingival crevices and have potent bactericidal properties. Lactoperoxidase generates a hypothiocyanite (HOSCN) molecule that is toxic to bacteria.[34]

ANATOMIC CONSIDERATIONS

Soft tissue infections of odontogenic origin tend to spread along planes of least resistance from the supporting structures of the affected tooth to various potential spaces in the vicinity. Accumulated pus, therefore, must generally perforate bone at the site where it is thinnest and weakest before it extends into the periapical areas or deeper fascial spaces. In the mandible this is usually in the region of the molar teeth on the lingual aspect and, more anteriorly, on the buccal aspect. In the maxilla the bone is weakest on the buccal aspect throughout and relatively thicker on the palatal aspect. If pus perforates through either the maxillary or the mandibular buccal plate, it does so intraorally if inside the attachment of the buccinator muscle to the maxilla or mandible and extraorally if outside this muscle attachment (Fig. 64.3A).[35] When a mandibular infection perforates lingually, it does so in the sublingual space if the apices of the involved teeth lie above the attachment of the mylohyoid muscle (e.g., mandibular incisor, canines, premolars, first molars) and in the submandibular space if the apices lie below the attachment of this muscle (e.g., second and third molars) (see Fig. 64.3B). Thus these local anatomic barriers of bone, muscle, and fascia predetermine the routes of spread, the extent, and the clinical manifestations of many orofacial infections of odontogenic origin. The clinically important "fascial spaces" most often involved are illustrated in Figs. 64.4 and 64.5. These are potential spaces between layers of fascia normally bound together by loose connective tissue. The breakdown of these

attachments by a spreading infective process results in a fascial space infection. These spaces intercommunicate with one another to varied degrees, and the potential pathways of extension from one space to another are illustrated in Fig. 64.6. A thorough understanding of the potential *anatomic routes* of infection not only provides valuable information on the nature and extent of infection but also suggests the optimal surgical approach for effective drainage.

CLINICAL MANIFESTATIONS AND MANAGEMENT

Orofacial Odontogenic Infections

Odontogenic infections originate in either the dental pulp or the periodontium (Fig. 64.7). The most common site is the dental pulp, and the most common infections are dentoalveolar. Deep fascial space infections are rare. Their clinical manifestations and management are briefly reviewed here. Antimicrobial therapy is further discussed later in the section "Therapeutic Considerations" (Tables 64.2 and 64.3).

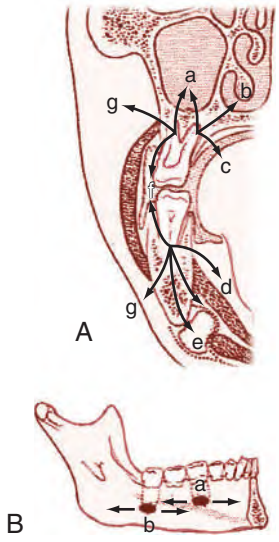

FIG. 64.3 Routes of spread of odontogenic orofacial infections along planes of least resistance. (A) Coronal section in the region of the first molar teeth: *a,* maxillary antrum; *b,* nasal cavity; *c,* palatal plate; *d,* sublingual space (above the mylohyoid muscle); *e,* submandibular space (below the mylohyoid muscle); *f,* intraoral manifestation with infection spreading through the buccal plates inside the attachment of the buccinator muscle; *g,* extraoral manifestation to buccal space with infection spreading through the buccal plates outside the attachment of the buccinator muscle. (B) Lingual aspect of the mandible: *a,* apices of the involved tooth above the mylohyoid muscle, with spread of infection to the sublingual space; *b,* apices of involved tooth below the mylohyoid muscle, with spread of infection into the submandibular space. *(From Chow AW, Roser SM, Brady FA. Orofacial odontogenic infections.* Ann Intern Med. *1978;88:392–402.)*

Dentoalveolar Infections

Pulpal infection most frequently results from carious exposure, rarely from physical or chemical injury. The carious process most frequently begins in pits and fissures on the occlusal surfaces of molars and premolars, in which food is likely to be retained. Interproximal sites and the gingival margin are the next most common areas where the carious process begins. Demineralization of the enamel results in discoloration, which is the first visible evidence of carious involvement. Destruction of the enamel and dentin and invasion of the pulp produce either localized or generalized pulpitis. If drainage from the pulp is obstructed, pulpal necrosis and rapid proliferation of endodontic microorganisms ensue and lead to invasion of the periapical areas (periapical abscess) and alveolar bone (acute alveolar abscess).

Clinically, the tooth is sensitive to percussion and to both heat and cold during early or reversible pulpitis, although the pain stops abruptly when the stimulus is withdrawn. During late or irreversible pulpitis, the tooth is exquisitely painful in response to a hot stimulus; the application of cold provides prompt relief. If drainage is established through the tooth before extension into the periapical region, chronic irritation from the necrotic pulp may result in periapical granuloma or cyst formation that may be relatively asymptomatic. Dental radiographs are particularly helpful for the detection of silent lesions, particularly those caused by interproximal caries, that are difficult to detect clinically.

The principles of treatment of dentoalveolar infections include prompt elimination of the infected pulp, deep periodontal scaling, or extraction of the affected tooth.[36] Dentoalveolar abscess should be surgically drained at the same time. Other supportive measures include hydration, a diet of soft foods, analgesics, and oral hygiene. Antibiotic therapy is indicated primarily if drainage cannot be adequately established or when infection has perforated the cortex and spread into surrounding soft tissue (see Table 64.2).

Gingivitis and Periodontal Infections

Periodontal disease is a general term that refers to all diseases involving the supporting structures of the teeth (periodontium), including the gingiva, periodontal ligament, alveolar bone, and cementum. In the early phase of periodontal disease, infection is confined to the gingiva (gingivitis). Later, the underlying supporting tissues are affected (periodontitis), ultimately leading to complete destruction of the periodontium and a permanent loss of teeth. Periodontal infections tend to localize in intraoral soft tissues and seldom spread into deeper structures of the face or neck.

Gingivitis

Acute and chronic inflammation of the gingiva is initiated by local irritation and microbial invasion associated with subgingival plaque. In *simple gingivitis,* there is a bluish-red discoloration, with swelling and thickening of the free gingival margin. A tendency for the gums to bleed after eating or toothbrushing may be one of the earliest findings. There is usually no pain, but a mild fetor oris may be noticed. In *acute necrotizing ulcerative gingivitis,* also known as *Vincent angina* or *trench*

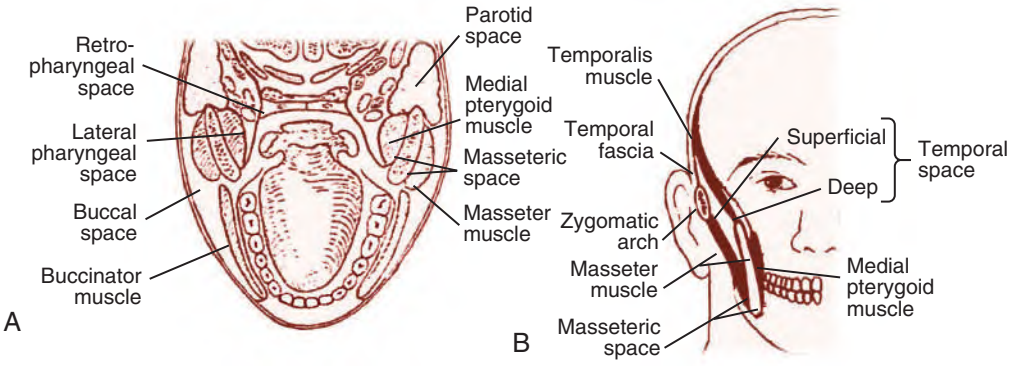

FIG. 64.4 Fascial spaces around the mouth and face. (A) Horizontal section at the level of the occlusal surface of the mandibular teeth. (B) Frontal view of the face. *(From Chow AW, Roser SM, Brady FA. Orofacial odontogenic infections.* Ann Intern Med. *1978;88:392–402.)*

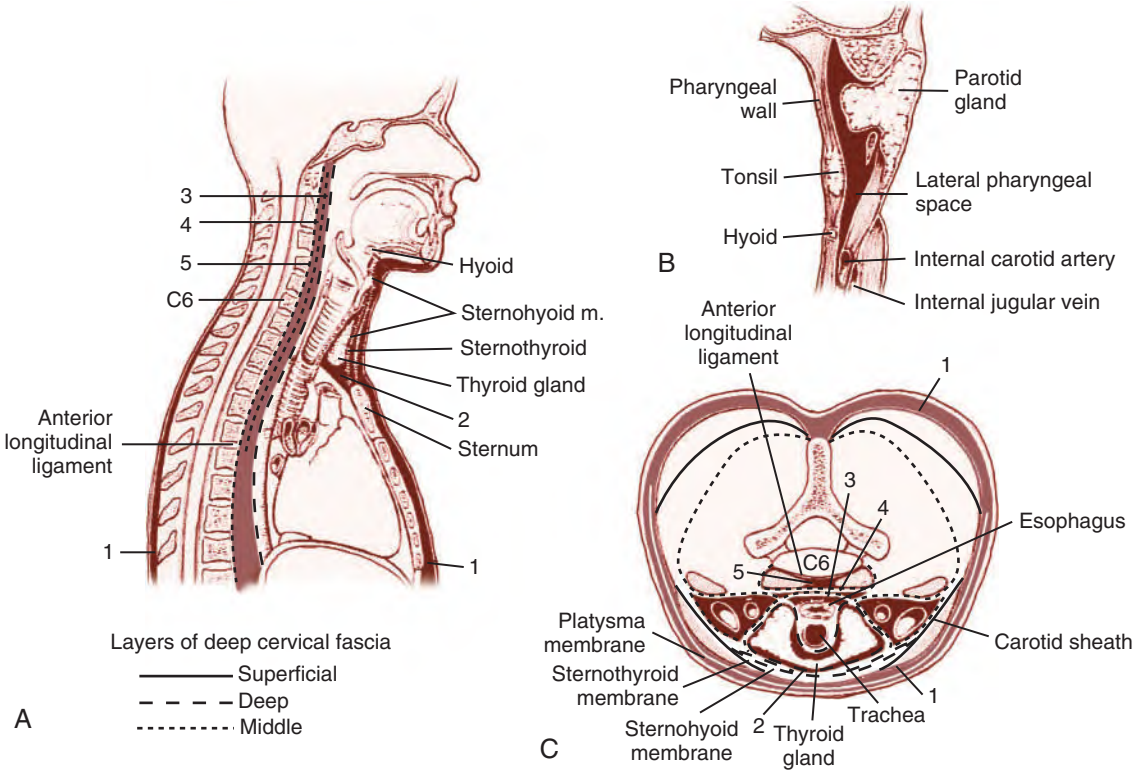

FIG. 64.5 Relation of lateral pharyngeal, retropharyngeal, and prevertebral spaces to the posterior and anterior layers of the deep cervical fascia. (A) Midsagittal section of the head and neck. (B) Coronal section in the suprahyoid region of the neck. (C) Cross section of the neck at the level of the thyroid isthmus. In all illustrations, *1*, superficial space; *2*, pretracheal space; *3*, retropharyngeal space; *4*, danger space; *5*, prevertebral space.

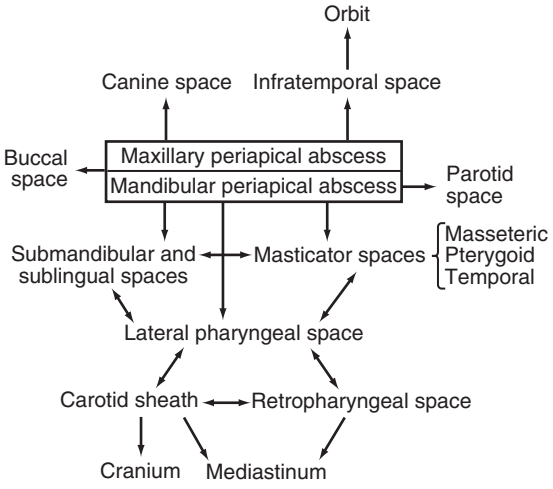

FIG. 64.6 Potential pathways of extension in deep fascial space infections.

mouth, the patient typically experiences a sudden onset of pain in the gingiva that interferes with normal mastication. Necrosis of the gingiva occurs mainly in the interdental papilla and results in a marginated, punched-out, and eroded appearance. A superficial grayish pseudomembrane is formed, and a characteristic halitosis with altered taste sensation is present. Fever, malaise, and regional lymphadenopathy are usually associated. Treatment includes local débridement and lavage with oxidizing agents, which usually alleviates pain within 24 hours. Antibiotic therapy with penicillin or metronidazole is indicated and is highly effective during the acute phase of infection.[37,38]

Periodontitis

Chronic inflammation of the periodontium is the major cause of tooth loss in adults. The destructive process proceeds insidiously, usually beginning in early adulthood. With inflammation, subgingival plaque is always present, and both supragingival and subgingival calculi are usually abundant. Unlike pulpal infection, in which drainage is frequently obstructed, periodontal infections drain freely, and affected patients experience little or no discomfort. Associated sensations include pressure and an itchy feeling in the gums and between the teeth, a bad taste in the mouth, sensitivity to hot and cold, and vague pains in the jaws. The gingiva is inflamed and discolored, bleeds readily, and appears as periodontal pockets around the affected teeth. Frank pus can be readily expressed by digital pressure, or it may exude freely from the pockets. As periodontitis advances, the supporting tissues are destroyed, ultimately leading to loosening and exfoliation of teeth. *Localized juvenile periodontitis* is a particularly destructive form of periodontitis seen in adolescents and is characterized by rapid vertical bone loss affecting the first molar and incisor teeth. Plaque is usually minimal, and calculus is absent. Excellent therapeutic results have been obtained with systemic tetracycline or metronidazole therapy combined with local periodontal treatment involving root débridement and surgical resection of inflamed periodontal tissues.[39] An effective plaque control program with scaling and root planing may be necessary for long-term management of the diseased periodontium.[40]

Periodontal Abscess

Periodontal abscesses may be focal or diffuse and manifest as red, fluctuant swelling of the gingiva, which is extremely tender to palpation. These abscesses are always in communication with a periodontal pocket from which pus can be readily expressed after probing. Treatment is surgical and aimed at drainage of loculated pus. After abscess resolution, endodontic or periodontal infections should continue to be treated by removal of necrotic infected pulpal tissues or by subgingival scaling and root planing. Apical surgery may sometimes be necessary to reach the apical part of the root for débridement.

Pericoronitis

Pericoronitis is an acute localized infection associated with gum flaps overlying a partially erupted or impacted wisdom tooth. Food debris

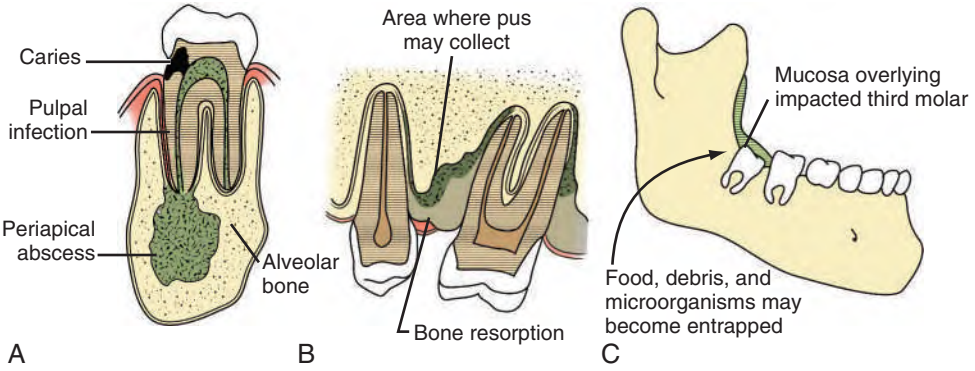

FIG. 64.7 Odontogenic infections. (A) Dental caries, pulpal infection, and periapical abscess. (B) Periodontal infection. (C) Pericoronal infection overlying impacted tooth. *(From Chow AW, Roser SM, Brady FA. Orofacial odontogenic infections.* Ann Intern Med. *1978;88:392–402.)*

TABLE 64.2 Antimicrobial Regimens for Various Odontogenic and Nonodontogenic Orofacial Infections

CLINICAL ENTITY	COMMON CAUSATIVE ORGANISMS	ANTIMICROBIAL REGIMENS
Odontogenic		
Supragingival dental plaque and dental caries prevention	*Streptococcus mutans,* other streptococci, *Actinomyces* spp.	Any one or combinations of the following topical applications: Fluoride-containing toothpaste or oral rinses (e.g., sodium fluoride 1.1% or stannous fluoride 0.4%) two or three times daily Fluoride-containing varnishes (e.g., sodium fluoride 5%) applied three or four times yearly Chlorhexidine 0.12% oral rinses three times daily, or varnishes applied once daily
Acute simple gingivitis	Streptococci, *Actinomyces* spp., oral spirochetes	Amoxicillin-clavulanate, 500 mg PO q8h (or ampicillin-sulbactam, 1.5–3 g IV q6–8h) *plus* metronidazole, 500 mg PO or IV q8h *or* Clindamycin, 450 mg PO q6–8h or 600 mg IV q6–8h
Acute necrotizing ulcerative gingivitis or Vincent angina	*Prevotella intermedia, Fusobacterium* spp., *Tannerella forsythensis, Treponema denticola*, other oral spirochetes	Metronidazole, 500 mg PO or IV q8h *or* Amoxicillin-clavulanate, 500 mg PO q8h *or* Ampicillin-sulbactam, 1.5–3 g IV q6h *or* Clindamycin, 450 mg PO q6h or 600 mg IV q6–8h
Early-onset, "aggressive," or "localized juvenile" periodontitis	*Aggregatibacter actinomycetemcomitans, Porphyromonas gingivalis, Treponema denticola, Prevotella intermedia*	Amoxicillin-clavulanate, 500 mg PO q8h (or ampicillin-sulbactam, 1.5–3 g IV q6–8h) *plus* metronidazole, 500 mg PO or IV q8h
Adult or "established" periodontitis	*Treponema denticola,* other oral spirochetes, black-pigmented *Bacteroides* spp. (*Porphyromonas gingivalis* and *Prevotella melaninogenica*), *Tannerella forsythensis*	Topical application of minocycline microspheres (Arestin) *or* Topical application of doxycycline hyclate periodontal extended-release liquid (Atridox)
Nonodontogenic		
Gangrenous stomatitis (noma)	*Fusobacterium nucleatum, Borrelia vincentii, Prevotella melaninogenica,* other oral anaerobes	Ampicillin-sulbactam, 1.5–3 g IV q6–8h *or* Amoxicillin-clavulanate, 500 mg PO q8h *or* Clindamycin, 450 mg PO q6–8h or 600 mg IV q6–8h Each *plus* metronidazole, 500 mg PO or IV q8h
Severe oral mucositis in immunocompromised hosts	Viridans and other streptococci, *Bacteroides* spp., *Peptostreptococcus* spp., and other oral anaerobes, facultative gram-negative bacilli	Topical chlorhexidine (0.12%) mouth rinses tid *plus one of the following:* Cefotaxime, 2 g IV q6h *or* Piperacillin-tazobactam, 3.375 g IV q6h *or* Imipenem, 500 mg IV q6h *or* Meropenem, 1 g IV q8h
Sialadenitis and suppurative parotitis	*Staphylococcus aureus*[a] *Streptococcus viridans* and other streptococci, *Bacteroides* spp., *Peptostreptococcus* spp., and other oral anaerobes	Nafcillin, 2 g IV q4h, or vancomycin, 1 g IV q12h *plus either* Metronidazole, 500 mg IV q6h *or* Clindamycin, 600 mg IV q6–8h

[a]For *Staphylococcus aureus* infections in which methicillin-resistant *S. aureus* is suspected, replace nafcillin with vancomycin, 1 g IV q12h; in immunosuppressed hosts, cefotaxime or ceftriaxone or imipenem, as described in the table, can be added.
IV, Intravenously; *MU,* million units; *PO,* orally; *tid,* three times a day.

TABLE 64.3 Initial Empirical Antimicrobial Regimens for Suppurative Infections of the Head and Neck

INFECTION	USUAL CAUSATIVE ORGANISMS	ANTIBIOTIC REGIMENS, NORMAL HOST[a]
Suppurative orofacial odontogenic infections, including Ludwig angina	*Streptococcus viridans* and other streptococci, *Peptostreptococcus* spp., *Bacteroides* spp., and other oral anaerobes	Amoxicillin-clavulanate, 500 mg PO q8h (or ampicillin-sulbactam, 1.5–3 g IV q6–8h) *plus* metronidazole, 500 mg PO or IV q8h *or* Clindamycin, 600 mg IV q6h *or* Cefoxitin, 1–2 g IV q6h
Lateral pharyngeal or retropharyngeal space infections		
Odontogenic	*S. viridans* and other streptococci, *Staphylococcus* spp., *Peptostreptococcus* spp., *Bacteroides* spp., and other oral anaerobes	Amoxicillin-clavulanate, 500 mg PO q8h (or ampicillin-sulbactam, 2 g IV q4h) *plus* metronidazole, 500 mg PO or IV q8h *or* Clindamycin, 600 mg IV q6h
Rhinogenic	*Streptococcus pneumoniae, Haemophilus influenzae, S. viridans* and other streptococci, *Bacteroides* spp., *Peptostreptococcus* spp., and other oral anaerobes	One of the following: (1) Ampicillin-sulbactam, 2 g IV q4h, *or* levofloxacin, 500 mg IV q24h, *or* ciprofloxacin, 750 mg IV q12h *plus* Metronidazole, 500 mg IV q6h, *or* clindamycin, 600 mg IV q6h *or* (2) Moxifloxacin, 400 mg IV q24h
Otogenic	Same as for rhinogenic space infections	Same as for rhinogenic space infections
Suppurative cervical adenitis and infected embryologic cysts	*Streptococcus pyogenes, Peptostreptococcus* spp., *Fusobacterium* spp., oral anaerobes	One of the following: (1) Ampicillin-sulbactam, 2 g IV q4h, *plus* metronidazole, 500 mg IV q6h *or* (2) Clindamycin, 600 mg IV q6h *or* (3) Cefoxitin, 1–2g IV q6h
Suppurative thyroiditis	*Staphylococcus aureus, Streptococcus pyogenes, S. pneumoniae, Haemophilus influenzae, S. viridans* and other streptococci, oral anaerobes	Nafcillin, 2 g IV q4–6h, or vancomycin, 1 g IV q12h *plus either* Metronidazole, 500 mg IV q6h *or* Clindamycin, 600 mg IV q6h
Cervicofacial actinomycosis	*Actinomyces israelii, Arachnia propionica, Aggregatibacter actinomycetemcomitans*	One of the following: (1) Penicillin G, 2–4 MU IV q4–6h *or* (2) Doxycycline, 200 mg PO or IV q12h *or* (3) Clindamycin, 450 mg PO q6h or 600 mg IV q6h
Human or animal bites	*S. pyogenes, S. aureus, Eikenella corrodens, Pasteurella multocida,* oral anaerobes	One of the following: (1) Ampicillin-sulbactam, 2 g IV q4h *or* (2) Amoxicillin-clavulanate, 500 mg PO q8h *or* (3) Moxifloxacin, 400 mg IV or PO q12h
Maxillofacial trauma, postsurgical wound infections	*S. aureus, S. pyogenes, Peptostreptococcus* spp., other oral anaerobes, *Pseudomonas aeruginosa, Enterobacteriaceae* spp.	Nafcillin, 2 g IV q4h, *or* vancomycin, 1 g IV q12h *plus one of the following*: (1) Piperacillin-tazobactam, 3.375 g IV q6h *or* (2) Imipenem-cilastatin, 500 mg IV q6h *or* (3) Meropenem, 1 g IV q8h *or* (4) Moxifloxacin, 400 mg IV or PO q24h *or* (5) Tigecycline, 100 mg IV, then 50 mg IV q12h
Suppurative jugular thrombophlebitis (Lemierre syndrome)	*Fusobacterium necrophorum;* same as for odontogenic space infections	Same as for odontogenic space infections
Suppurative cavernous sinus thrombosis	Same as for odontogenic, rhinogenic, or otogenic space infections	Same as for odontogenic, rhinogenic, or otogenic space infections
Mandibular osteomyelitis	Same as for odontogenic space infections	Clindamycin, 600 mg IV q6h *or* Moxifloxacin, 400 mg PO or IV q24h
Extension of osteomyelitis from prevertebral space infection	*S. aureus*[b] facultative gram-negative bacilli	Either nafcillin, 2 g IV q4h, or vancomycin, 1 g IV q12h *plus* *either* tobramycin, 1.7 mg/kg IV q8h, *or* ciprofloxacin, 400 mg IV q12h

[a]For immunocompromised hosts, consider replacing penicillin G with one of the following: cefotaxime, 2 g IV q4h; ceftriaxone, 1 g IV q12h; or cefepime, 2 g IV q12h. Other regimens to consider are piperacillin/tazobactam, 3.375 g IV q6h; imipenem, 500 mg IV q6h; meropenem, 1 g IV q8h; moxifloxacin, 400 mg IV q24h; or tigecycline, 100 mg IV, then 50 mg IV q12h.

[b]For *Staphylococcus aureus* infections in which methicillin-resistant *S. aureus* is suspected, replace nafcillin with vancomycin, 1 g IV q12h; in immunosuppressed hosts, cefotaxime or ceftriaxone or imipenem, as described in the table, can be added.

IV, Intravenously; *MU,* million units; *PO,* orally.

and microorganisms become entrapped under the affected gingival tissues. If drainage is interrupted by sudden swelling or trauma, infection extends along fascial planes of least resistance into adjacent soft tissues. The underlying alveolar bone is usually not involved. Clinically, the pericoronal tissues are erythematous and swollen. Digital pressure produces a small amount of exudate from under the infected flap. Because the masticator spaces are often involved, marked trismus secondary to irritation of the masseter or medial pterygoid muscle is a prominent presenting feature. Treatment of pericoronitis includes incision of the lesion and irrigation of the pericoronitis pouch with antiseptics. Systemic antibiotics may be necessary if cellulitis of fascial space infection occurs. Excision of the operculum or extraction of the involved tooth may also be considered.

Deep Fascial Space Infections

Infections of either odontogenic or oropharyngeal origin may extend to potential fascial spaces of the lower part of the head and upper portion of the neck. These "space infections" can be conveniently categorized as those around the face (masticator, buccal, canine, and parotid spaces); those in the suprahyoid region (submandibular, sublingual, and lateral pharyngeal spaces); and those involving the infrahyoid region or the total neck (retropharyngeal, danger, and pretracheal spaces) (see Figs. 64.4 and 64.5).[41]

Space Infections Around the Face

Masticator spaces. Masticator spaces consist of the masseteric, pterygoid, and temporal spaces, all of which are well differentiated but intercommunicate with each other, as well as with the buccal, submandibular, and lateral pharyngeal spaces (see Fig. 64.4). Infection of the masticator spaces begins most frequently around molar teeth, particularly the third molars (wisdom teeth). Clinically, the hallmarks of masticator space infection are trismus and pain in the area of the body or ramus of the mandible. Swelling may not be prominent, especially in the masseteric compartment, inasmuch as infection exists deep in large muscle masses, which obscures or prevents clinically apparent swelling. When present, swelling tends to be brawny and indurated, which could indicate cervicofacial actinomycosis or mandibular osteomyelitis. If infection extends internally, it can involve an area close to the lateral pharyngeal wall and result in dysphagia. A true lateral pharyngeal space infection, however, is accompanied by displacement of the lateral pharyngeal wall toward the midline, a finding not present in masticator space infections. Infection of the deep temporal space usually originates from involvement of the posterior maxillary molar teeth. Very little external swelling is observed early in the course of the infection; if present, it usually affects the preauricular region and an area over the zygomatic arch. As infection progresses, the cheek, eyelids, and whole side of the face may be involved.[42] Infection may extend directly into the orbit via the inferior orbital fissure and produce proptosis, optic neuritis, and abducens nerve palsy.

Buccal, canine, and parotid spaces. As noted previously, infections arising from mandibular or maxillary premolar and molar teeth tend to extend in a lateral or buccal direction. The relation of the root apices to the origins of the buccinator muscle determines whether infection exits intraorally into the buccal vestibule or extraorally into the buccal space (see Fig. 64.3). Infection of the buccal space is readily diagnosed because of marked cheek swelling with minimal trismus and systemic symptoms. Antibiotic therapy alone tends to resolve infection. Drainage, if required, is superficial and should be performed extraorally.

Involvement of the maxillary incisors and canines may result in a canine space infection, which manifests as dramatic swelling of the upper lip, canine fossa, and, frequently, the periorbital tissues. Pain is usually moderate, and systemic signs are minimal. On occasion, a purulent maxillary sinusitis may result from direct extension of infection into the adjoining antrum. Treatment consists of antibiotics and drainage, which can be accomplished intraorally.

Parotid space infection from an odontogenic cause generally represents secondary spread from a masseteric space infection in the area of the ramus of the mandible (see Fig. 64.4). Marked swelling of the angle of the jaw occurs without associated trismus. Pain may be intense and accompanied by high fever and chills. Because of its close relationship with the posterior aspect of the lateral pharyngeal space, a parotid space infection carries the potential risk of direct extension into the danger and visceral spaces and hence to the posterior mediastinum (see Fig. 64.5).

Suprahyoid Space Infections

Submandibular and sublingual spaces. These two spaces are separated by the mylohyoid muscle (see Fig. 64.3), and the submandibular space is further divided into the submaxillary and submental spaces. Infection in these spaces usually arises from the second and third mandibular molar teeth because their root apices lie inferior to the mylohyoid muscle. Swelling is typical, although much less trismus is present, in contradistinction to masseteric space infection, because the major muscles of mastication are usually not involved. Submandibular odontogenic infection should be distinguished from submandibular sialadenitis and lymphadenitis that arise from other causes. Therapy includes antibiotics, dental extraction, and extraoral surgical drainage.

Infection of the sublingual space generally arises from mandibular incisors because their root apices lie above the mylohyoid muscle. Clinically, this space infection manifests as a brawny, erythematous, tender swelling of the floor of the mouth that begins close to the mandible and spreads toward the midline or beyond. Some elevation of the tongue may be noted in late stages. Surgical drainage of the sublingual space should be performed intraorally by an incision through the mucosa parallel to the Wharton duct. If the submandibular space is also to be drained, both spaces can be reached through a submandibular approach.

Ludwig angina. The term *Ludwig angina* has been loosely applied to a heterogeneous array of infections involving the sublingual, submaxillary, and submandibular spaces.[43,44] However, for therapeutic and prognostic purposes, it is desirable to restrict this diagnosis to cases that conform to the following classic description: (1) The infection is always bilateral, (2) both the submandibular and sublingual spaces are involved, (3) the infection is a rapidly spreading indurated cellulitis without abscess formation or lymphatic involvement, and (4) the infection begins in the floor of the mouth. A dental source of infection has been found in 50% to 90% of reported cases. The second and third mandibular molars are most commonly involved because they have roots below the mylohyoid muscle. Clinically, affected patients have a brawny, boardlike swelling in the submandibular spaces that does not pit on pressure (Fig. 64.8). They usually hold their mouths open, and the floor is elevated,

FIG. 64.8 Early appearance of a patient with Ludwig angina with a brawny, boardlike swelling in the submandibular spaces. *(From Reynolds SC, Chow AW. Life-threatening infections of the peripharyngeal and deep fascial spaces of the head and neck.* Infect Dis Clin North Am. *2007;21:557–576.)*

which pushes the tongue to the roof of the mouth. Eating and swallowing are difficult, and respiration may be impaired by obstruction from the tongue. A rapid progression of the infection results in edema of the neck and glottis and may precipitate asphyxiation; therefore patients must be monitored and treated aggressively. Fever and systemic toxicity are usually present and may be severe. Treatment entails high doses of parenteral antibiotics, such as ampicillin-sulbactam or penicillin G plus metronidazole; airway monitoring; early intubation or tracheostomy when required; soft tissue decompression; and surgical drainage. Systemic antibiotics combined with aggressive surgical intervention have lowered the rate of mortality from Ludwig angina dramatically from greater than 50% in the preantibiotic era to 0% to 4% currently.[43]

Lateral pharyngeal space. The lateral pharyngeal space (also known as the parapharyngeal or pharyngomaxillary space) in the lateral aspect of the neck is shaped like an inverted cone, with its base at the skull and its apex at the hyoid bone (see Fig. 64.5). Its medial wall is contiguous with the carotid sheath, which contains several vital structures (including the internal carotid artery, the internal jugular vein, and the vagus nerve) and lies deep to the pharyngeal constrictor muscle. Infection of the lateral pharyngeal space may result from pharyngitis, tonsillitis, parotitis, otitis, or mastoiditis, as well as from odontogenic infection, especially if the masticator spaces are primarily involved. The source of infection is best investigated through computed tomography (CT) or magnetic resonance imaging (MRI). If the anterior compartment is infected, the patient exhibits fever, chills, marked pain, trismus, swelling below the angle of the mandible, dysphagia, and medial displacement of the lateral pharyngeal wall. The contiguous parotid gland is usually swollen. Dyspnea can occur, although it is not prominent. Posterior compartment infection is potentially life threatening because of the carotid sheath; it is characterized by septicemia with little pain or trismus. Swelling is usually internal and deep and can often be missed because it is behind the palatopharyngeal arch. Complications include respiratory obstruction from edema of the larynx, thrombosis of the internal jugular vein, and erosion of the internal carotid artery. Suppuration may advance rapidly to other spaces, particularly the retropharyngeal and danger spaces, thus reaching directly to the mediastinum inferiorly or the base of the skull superiorly (see Fig. 64.5). Because respiratory obstruction from laryngeal edema can occur suddenly, the patient must be closely observed, and prophylactic tracheostomy may be required. Treatment includes high doses of antibiotics and surgical drainage. It is usually prudent to wait for the infection to localize before drainage is attempted unless respiratory obstruction or hemorrhage necessitates early surgical intervention.

Infrahyoid Space Infections

Retropharygeal and danger spaces. The retropharyngeal space comprises the posterior part of the visceral compartment, in which the esophagus, trachea, and thyroid glands are enclosed by the middle layer of deep cervical fascia (see Fig. 64.5). It lies behind the hypopharynx and the esophagus and extends inferiorly into the superior mediastinum to about the level of T1 to T2. Posterior to this compartment lies the *danger space,* which descends directly into the posterior mediastinum to the level of the diaphragm. Infection of the retropharyngeal space may result from contiguous infection of the lateral pharyngeal space or from lymphatic spread of infection from more distant sites to involve the retropharyngeal lymph nodes. Dysphagia, dyspnea, nuchal rigidity, and esophageal regurgitation, as well as high fever and chills, may be present. Bulging of the posterior pharyngeal wall may be observed. Lateral soft tissue radiographs of the neck may reveal marked widening of the retropharyngeal space. Infection of the retropharyngeal space is potentially life-threatening, and prompt surgical drainage is required. Complications include hemorrhage and spontaneous rupture of retropharyngeal space contents (abscess) into the airway with asphyxiation, laryngeal spasm, bronchial erosion, and thrombosis of the jugular vein.

Pretracheal space. The pretracheal space comprises the anterior portion of the visceral compartment and completely surrounds the trachea. Infections reach this space most commonly through perforations of the anterior esophageal wall, occasionally through contiguous extension from a retropharyngeal space infection. The clinical presentation is characterized by severe dyspnea, but hoarseness may be the first complaint. Swallowing is difficult, and fluids may be regurgitated through the nose. A pretracheal space infection is always serious because of possible extension into the mediastinum, and prompt surgical drainage is crucial.

Complications of Odontogenic Infections

Complications of odontogenic infections can occur either by hematogenous spread or by direct extension. Transient bacteremia is common during or after various dental procedures, especially the extraction of infected teeth.[45] The temporal relationship between these procedures and subsequent bacterial endocarditis and cardiovascular prosthetic infections is well documented.[46] Reports of infected total hip replacements after dental procedures are of further concern.[45] Prophylactic antibiotic treatment during dental procedures, although frequently used, remains a controversial issue, especially in the absence of preexisting valvular heart disease.[47] Complications of odontogenic infections secondary to direct extension include mediastinal spread,[48] intracranial suppuration (especially cavernous sinus thrombosis),[49] suppurative jugular thrombophlebitis,[50] carotid artery erosion,[49] maxillary sinusitis,[51] and osteomyelitis.[52] Acute mediastinitis and intracranial suppuration secondary to odontogenic infections are relatively uncommon in the postantibiotic era.

Suppurative Jugular Thrombophlebitis (Lemierre Syndrome) and Carotid Artery Erosion

These complications of oropharyngeal or odontogenic infections are uncommon since the introduction of antibiotics. Extension of infection to the carotid sheath, which encloses both the internal jugular vein and the internal carotid artery, usually arises from the lateral pharyngeal space. Because the carotid sheath space in this area is relatively compact with little areolar connective tissue, there is little tendency to spread up and down this vascular sheath, with the exception of possible retrograde thrombophlebitis and intracranial extension. The major concern is protracted septicemia and erosion of the carotid artery or one of its branches.

The onset of suppurative jugular thrombophlebitis (also known as *Lemierre syndrome* or *postanginal sepsis*) is acute, with shaking chills, spiking fevers, and profound prostration.[50] However, symptoms of pharyngitis, which may be the initial presentation of infection, may be resolving before the onset of the septic syndrome. Localizing signs of pain and swelling at the angle of the jaw, tenderness and induration along the sternocleidomastoid muscle, and swelling of the lateral pharyngeal wall with dysphagia and neck rigidity are usually present. However, these findings may be subtle, and their clinical significance may not be fully recognized until postmortem examination. Dysphagia and dysphonia may also occur. Ipsilateral vocal cord paralysis or other neurologic signs representing lower cranial nerve involvement may be present. Systemic evidence of infection includes septic pulmonary emboli and metastatic abscesses to the brain, lungs, kidneys, and joints. Empyema may also occur. Contrast medium–enhanced CT may reveal the normal carotid artery and an enlarged jugular venous wall surrounding a more lucent intraluminal clot (Fig. 64.9). Thrombosis of the jugular vein can also be demonstrated by magnetic resonance angiography (MRA).[53] The organisms most frequently involved are *Fusobacterium necrophorum,* anaerobic streptococci, and *Bacteroides* (now including *Prevotella*) spp.[49] Most cases of suppurative jugular thrombophlebitis can be managed medically without the need for ligation or surgical resection of the infected vein. Prolonged courses of intravenous (IV) antibiotics (3–6 weeks) are required. Anticoagulants have sometimes been used in this setting, but their efficacy is unconfirmed.[49] Surgical ligation of the internal jugular vein, the only available therapeutic option before antibiotics were available, is now required only in the rare patient who fails to respond to antibiotic treatment alone.

Erosion of the carotid artery is a rare complication after odontogenic infection involving the carotid sheath. Infection may arise by spread from the lateral pharyngeal space, Ludwig angina, or suppuration of deep cervical lymph nodes.[54] The initial pathologic process is an arteritis caused by contiguous inflammation that eventually forms a false aneurysm. The patient is extremely ill with a fever of undetermined origin. Trismus is absent, and signs of local suppuration may be subtle

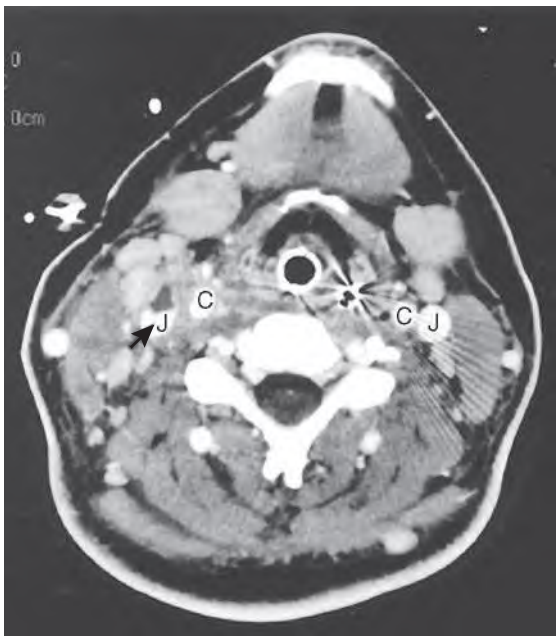

FIG. 64.9 Jugular venous thrombosis associated with a right peritonsillar abscess in a young adult. Contrast medium–enhanced axial computed tomographic scan showing a normal right common carotid *(C)* artery but an enlarged right internal jugular vein *(J) (arrow)* with a dense or enhancing wall that surrounds the more lucent intraluminal clot. *(From Chow AW. Head and neck infections. In: Baddour L, Gorbach SL, eds.* Therapy of Infectious Diseases. *Philadelphia: Saunders; 2003:37.)*

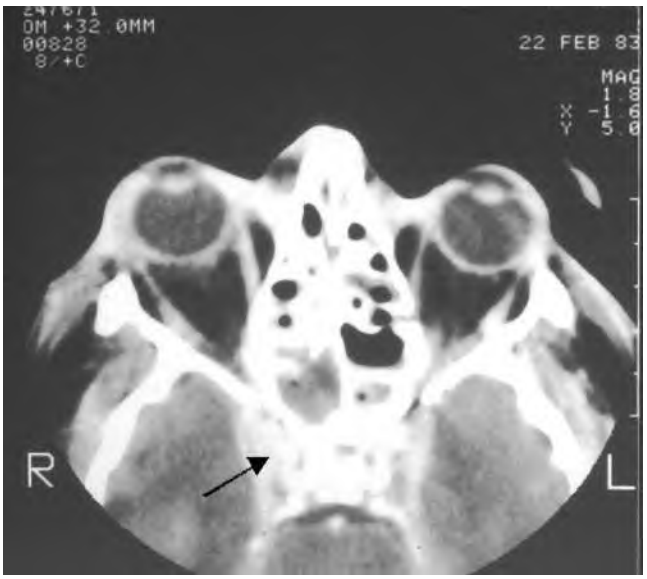

FIG. 64.10 Cavernous sinus thrombosis associated with pansinusitis in a young adult. Contrast medium–enhanced axial computed tomographic scan revealing opacification of the sphenoid and ethmoid sinuses and thrombus in the right cavernous sinus *(arrow). (From Chow AW. Life-threatening infections of the head, neck, and upper respiratory tract. In: Hall JB, Schmidt GA, Wood LH, eds.* Principles of Critical Care. *2nd ed. New York: McGraw-Hill; 1998:899.)*

because of the tight connective tissue around and within the carotid sheath. Rupture of the carotid artery may be heralded by recurrent minor hemorrhages from the nose, mouth, or ear ("herald bleeds"). This is followed by hematoma formation in the surrounding tissues of the neck, a protracted clinical course, and eventually shock caused by exsanguinations. Emergency ligation of the carotid artery may be necessary in cases of major hemorrhage, but the risk of stroke is significant. The mortality rate ranges from 20% to 40%, irrespective of treatment.[42]

Septic Cavernous Sinus Thrombosis

This dreaded complication is, fortunately, rare with the availability of antibiotics. Facial furuncles and purulent paranasal sinusitis were the major predisposing conditions. Infection of the maxillary teeth was the most common dental cause. Eagleton[55] described six criteria for the diagnosis of septic cavernous sinus thrombosis to help distinguish it from other less lethal infections, particularly those of the ethmoid sinus and the orbit: (1) a known site of infection; (2) evidence of bloodstream invasion; (3) early signs of venous obstruction in the retina, conjunctiva, and eyelid; (4) paresis of cranial nerves III, IV, and VI as a result of inflammatory edema; (5) abscess formation in neighboring soft tissue; and (6) evidence of meningeal irritation. Clinically, the onset is abrupt, with diplopia, photophobia, orbital edema, and progressive exophthalmos. Involvement of cranial nerves III, IV, V, and VI produces ophthalmoplegia, a midposition fixed pupil, loss of corneal reflex, and diminished sensation over the upper face. Obstruction of venous return from the retina results in papilledema, retinal hemorrhage, and visual loss. Contrast medium–enhanced CT (Fig. 64.10) and MRI are useful diagnostic tests, but MRA most reliably demonstrates the thrombosed cavernous sinus (see Chapter 93). Successful treatment requires early recognition, high-dose IV antibiotics, and surgical decompression of the underlying predisposing infection. Anticoagulation and steroid therapy are not indicated.[49] The mortality rate remains high, approximately 15% to 30%.[56]

Maxillary Sinusitis

In many people the roots of the maxillary molars lie proximal to the maxillary antrum. At times, congenital bony defects occur, with the root adjacent to the sinus membrane. In these cases sinusitis can result from direct extension of an odontogenic infection or from perforation of the sinus floor during extraction of a maxillary tooth.[51] The clinical manifestation of secondary sinus involvement is similar to that of primary sinus disease.

Osteomyelitis of the Jaws

The mandible is much more susceptible to osteomyelitis than is the maxilla, mainly because the cortical plates of the mandible are thin, and its medullary tissues have relatively poor vascular supply. In view of the large number of odontogenic infections and the intimate relationship of teeth to the medullary cavity, it is surprising that osteomyelitis of the jaws is not more frequent. When osteomyelitis occurs, there is usually a predisposing condition that affects host resistance, such as a compound fracture, previous irradiation, osteopetrosis, Paget disease, diabetes mellitus, or steroid therapy. Osteomyelitis after dental extraction in irradiated bone is termed *osteoradionecrosis.* Prior high-dose radiation from squamous cell carcinoma of the tongue or oral mucosa commonly precedes osteoradionecrosis. Chronic treatment with bisphosphonate in cancer patients, women with osteoporosis, or patients with Paget disease can lead to a condition known as bisphosphonate-related osteonecrosis of the jaw (BRONJ).[57] The precise mechanisms leading to BRONJ remain unclear but may be linked to drug-induced immune dysfunction associated with circulatory γδ (gamma-delta) T-cell depletion.[58,59] At the initiation of mandibular osteomyelitis, the intramedullary pressure markedly increases, which further compromises blood supply and leads to bone necrosis. Pus travels through the haversian and perforating canals, accumulates beneath the periosteum, and elevates it from the cortex. If pus continues to accumulate, the periosteum is eventually penetrated, and mucosal and cutaneous abscesses and fistulas may develop. As the inflammatory process becomes chronic, granulation tissue is formed. Spicules of necrotic and nonviable bone may become either totally isolated (sequestrum) or encased in a sheath of new bone (involucrum).

Severe mandibular pain is a common symptom and may be accompanied by damage to the mandibular nerve, which can result in anesthesia or hypoesthesia on the affected side. In protracted cases mandibular trismus may develop. A clinical variant is chronic sclerosing osteomyelitis associated with a proliferative periostitis.[60] This entity is more common in children and young adults after a periapical infection of the mandibular first molar. It is a nonsuppurative form of osteomyelitis characterized

by a localized, hard, nontender swelling over the mandible. On radiographs the newly formed periosteal bone looks like layers outside the cortex, with a characteristic "onion skin" appearance.[61] Actinomycosis and radiation necrosis are two common causes of this form of osteomyelitis of the jaws. Actinomycosis may be associated with obvious or occult dental disease, usually progresses slowly, and is manifested by rock-hard induration that can drain spontaneously through the skin. Prolonged antibiotic treatment is usually required (see Chapter 254).

Association With Cardiovascular Risk

An association between chronic odontogenic infection and cardiovascular disease has been described in a number of studies.[62] Of importance is that intensive periodontal treatment appears to result in improvement of endothelial function, as well as in oral health.[63] The mechanisms by which chronic periodontitis predisposes to coronary heart disease are not well understood, but an adverse effect of systemic inflammation on endothelial function may play a role. In addition to local infection, other factors may contribute to systemic inflammation, including intermittent bacteremia and release of bacterial endotoxins of oral origin into the bloodstream, an effect that can be induced by gentle chewing.[64]

Orofacial Nonodontogenic Infections

Nonodontogenic infections of the oral cavity are most frequently secondary to chemical, thermal, or traumatic injury. Virtually all infectious microorganisms, particularly sexually transmitted agents and childhood viral enanthems, can produce intraoral manifestations. Patients with cancer who develop mucositis from cytotoxic drugs and human immunodeficiency virus (HIV)-infected individuals are especially susceptible to acute and chronic opportunistic infections of the oral cavity, particularly candidiasis, aspergillosis, mucormycosis, herpetic gingivostomatitis, and mixed gram-negative infections.[65] In this section some of the conditions affecting primarily the oral mucosa and salivary glands, in which an infectious cause is either proved or suspected, are briefly discussed. Antimicrobial therapy is further reviewed in the section "Therapeutic Considerations" (see Tables 64.2 and 64.3).

Infections of the Oral Mucosa

Noma (Gangrenous Stomatitis)

Also known as cancrum oris, noma is an acute, fulminating, and gangrenous infection of the oral and facial tissues. It usually occurs in the presence of severe debilitation and malnutrition, and children are most often affected.[66] The earliest lesion is a small, painful, red spot or vesicle on the attached gingiva in the premolar or molar region of the mandible. A necrotic ulcer rapidly develops and undermines the deeper tissue. Painful cellulitis of the lips and cheeks is observed as the lesion extends outward in a conelike manner. Within a short period, sloughing of necrotic soft tissues occurs and exposes underlying bone, teeth, and deeper tissues.

Noma is thought to be an infectious disease, but its cause remains unknown. Fusospirochetal organisms, such as *Borrelia vincentii* and *F. nucleatum,* are consistently cultured from noma lesions.[67] *P. melaninogenica* may also be present. Biopsy specimens of tissue from the advancing lesion show a mat of predominantly gram-negative threadlike bacteria that cannot be positively identified. Thus this lesion bears a similarity to acute necrotizing ulcerative gingivitis in several respects but appears to be more focal and destructive, involving deeper tissues beyond the gingiva. Treatment of noma requires high doses of IV antibiotics (see Table 64.2). Every effort should be directed to correct the dehydration and underlying malnutrition and debility. Loose teeth and sequestra may be removed, but saucerization should be avoided. Healing is by secondary intention. Serious mutilation and facial deformity may necessitate subsequent cosmetic surgery.[68]

Aphthous Stomatitis

Aphthous ulcers are the most common causes of recurrent oral lesions and must be distinguished from other conditions, such as those caused by herpes simplex virus or coxsackievirus infections, agranulocytosis, and Behçet syndrome. The cause of recurrent aphthous ulcers remains uncertain, although a number of infectious agents, including viruses, have been implicated. Recent data suggest multiple etiologies, including vitamin deficiencies, oral microbiota derangements, autoimmune conditions, stress, and genetic polymorphisms to oxidant-antioxidant imbalances, among others.[69]

Three major clinical variants are recognized: (1) minor aphthous ulcers, (2) major aphthous ulcers, and (3) herpetiform aphthous ulcers. In their most characteristic form, minor aphthous ulcers appear as a number of small ulcers on the buccal and labial mucosa, the floor of the mouth, or the tongue. The palatal soft tissues are rarely involved. Moreover, the ulcers are concentrated in the anterior part of the oral cavity, whereas the pharynx and tonsillar fauces are rarely implicated. A prodromal stage usually occurs. The ulcers appear gray-yellow, often with a raised and erythematous margin, and are exquisitely painful. Lymph node enlargement is seen only with secondary bacterial infection. The course of ulceration varies from a few days to a little more than 2 weeks and is followed by spontaneous healing. Major aphthous ulcers are more protracted and last up to several months. All areas of the oral cavity, including the soft palate and tonsillar areas, may be involved. Long periods of remission may be followed by intervals of intense ulcer activity. Herpetiform aphthous ulcers are small and multiple and characteristically affect the lateral margins and tip of the tongue. The ulcers are gray, without a delineating erythematous border, and are extremely painful, which makes eating and speaking difficult. Despite its name, there is little clinical resemblance to an acute herpetic gingivostomatitis. Although intranuclear inclusions have been demonstrated in herpetiform aphthous ulcers, there is no evidence to suggest that these inclusions bear any relationship to the presence of viruses.

The treatment of aphthous ulcers is primarily symptomatic. Strict oral hygiene should be maintained, and the use of antiseptic mouthwashes may be helpful in temporarily reducing secondary infection. Local anesthetic lozenges or gels may be used as a last resort for brief periods of pain relief. Amlexanox, a topical immunomodulating agent, appears to provide symptomatic relief and shorten the duration of ulcers.[70] Topical or systemic steroids may be beneficial in selected people with extensive disease, but caution must be exercised in their administration.[71] Thalidomide (100–200 mg/day orally for 2–6 weeks) has been reported to be effective for the treatment of large aphthous lesions in patients with acquired immunodeficiency syndrome (AIDS).[72,72a]

Mucositis and Stomatitis in the Severely Immunocompromised Patient

Much of what is known about the management of oromucosal infections has been studied in patients with cancer being treated with radiotherapy, chemotherapy, and bone marrow transplantation.[73] Mucositis involving the nonkeratinized oral epithelium is a frequent complication after irradiation or during chemotherapy for acute leukemia. Other patients who develop oromucosal complications include those undergoing solid-organ transplantation, patients with AIDS, and those with autoimmune diseases associated with xerostomia and systemic immunosuppression. The underlying mechanism appears to be a breakdown of the mucosal epithelium that leads to mucositis and secondary bacterial or fungal infection, or reactivation of latent viral infection. Oral candidiasis, herpes simplex, varicella-zoster, and cytomegalovirus infections may occur concomitantly. Four stages of disease progression are described: (1) inflammatory or vascular phase, (2) epithelial phase, (3) ulcerative/bacteriologic phase, and (4) healing phase.[74] Ulceration and pseudomembrane formation are evident, usually between 4 and 7 days after the initiation of chemotherapy, and they commonly involve the buccal and labial mucosa, soft palate, oropharynx, floor of the mouth, and the ventral and lateral surfaces of the tongue (Fig. 64.11). The clinical manifestations may be quite variable. The lesions are often protracted in duration and may not be associated with an obvious inflammatory reaction. Pain or tenderness may be the only abnormal finding.

A number of strategies are currently recommended for the prevention of oral mucositis in specific patient populations.[75] These include cryotherapy (the placement of ice chips in the mouth during delivery of chemotherapy) in patients receiving bolus 5-fluorouracil (5-FU), and recombinant human keratinocyte growth factor-1 in patients undergoing autologous stem cell transplantation for hematologic malignancy. A systematic review of cryotherapy for the prevention of mucositis found strong evidence that it results in large reductions in the incidence of

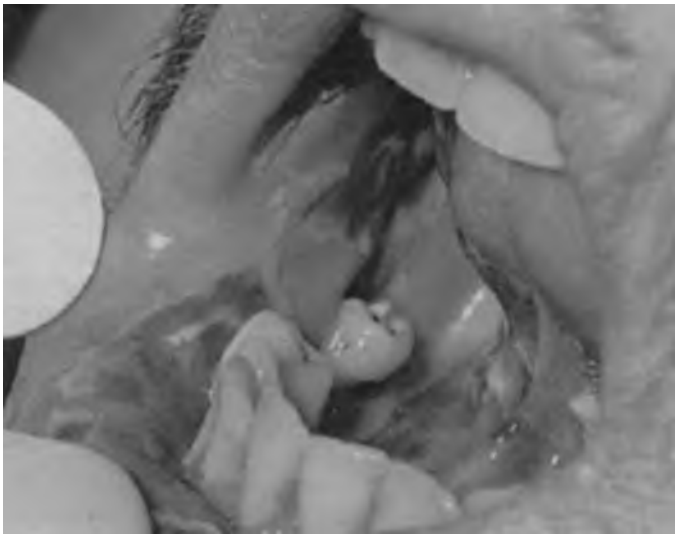

FIG. 64.11 Severe mucositis with marked erythema, loss of epithelial barrier, and extensive ulceration of the labial and buccal mucosa in a patient undergoing radiation therapy. *(From Epstein JB, Chow AW. Oral complications associated with immunosuppression and cancer therapies.* Infect Dis Clin North Am. *1999;13:901–923.)*

mucositis in patients receiving 5-FU.[76] Similarly, recombinant human keratinocyte growth factor-1 is effective in the prevention of oral mucositis in adults who are receiving radiotherapy to the head and neck with cisplatin or 5-FU, or those receiving chemotherapy alone for mixed solid and hematologic malignancies.[77] Topical antiseptic application with chlorhexidine has been shown to have a moderate effect on reducing both the frequency and duration of severe oral mucositis.[78] Because secondary infection is common but the etiologic agents cannot be readily predicted on clinical grounds alone, specific microbiologic diagnosis by culture, histopathologic examination, or molecular or antigen detection techniques may be necessary to guide appropriate antimicrobial treatment.

Frequent saline or bicarbonate rinses may reduce mucosal irritation, remove thickened secretions or debris, and increase moisture in the mouth. Ice chips, topical anesthetics or analgesic gels (e.g., benzydamine, viscous lidocaine), and cytoprotective coating agents (e.g., milk of magnesia or aluminum hydroxide gel) have provided symptomatic relief of painful oral lesions. Meticulous oral and dental hygiene, effective management of xerostomia, selective suppression of oropharyngeal microbial colonization, and early control of reactivation by latent viral infections appear to be key for prevention and reduction of the overall morbidity of oromucosal infections in severely immunocompromised patients.

Infections of the Salivary Gland

Sialadenitis, or infection of salivary tissue, is a relatively common disease. Sialolithiasis in elderly patients (particularly calculi in the Wharton duct) often leads to ductal obstruction and secondary infection. Other predisposing factors for ductal occlusion include dehydration, sialogogic drugs, general debility, and trauma.

Suppurative Parotitis

Acute bacterial parotitis is a specific clinical entity affecting primarily elderly, malnourished, dehydrated, or postoperative patients.[79,80] The onset of firm, erythematous swelling of the preauricular and postauricular areas is sudden and extends to the angle of the mandible. This is accompanied by exquisite local pain and tenderness. Systemic findings of high fevers, chills, and marked toxicity are generally present. Progression of the infection may lead to massive swelling of the neck, respiratory obstruction, septicemia, and osteomyelitis of the adjacent facial bones. Staphylococci have been the predominant isolates, and antibiotic therapy should include an antistaphylococcal agent (see Table 64.2). Enterobacteriaceae, other gram-negative bacilli, and anaerobes have also been reported to cause parotitis. Early surgical drainage and decompression of the gland are generally required because spontaneous drainage is uncommon.

Chronic Bacterial Parotitis

In this condition, parotitis is recurrent with intermittent acute exacerbations. Chronic, low-grade bacterial infection results in functional destruction of the salivary gland. Pus, when obtained directly from the gland, usually reveals the growth of staphylococci or mixed oral aerobes and anaerobes. Sialography during remission may reveal a sialectatic pattern of pooling of contrast medium that suggests multiple cystic cavities in place of the normal acinar pattern. Chronic parotitis may be confused with Sjögren syndrome, a noninfectious illness characterized by the triad of xerostomia, keratoconjunctivitis, and systemic autoimmune disease, such as rheumatoid arthritis, lupus erythematosus, scleroderma, periarteritis nodosa, and polymyositis. The presence of associated temporomandibular arthritis or arthralgia is strongly suggestive of Sjögren syndrome rather than chronic bacterial parotitis.

Therapy for chronic parotitis should initially be conservative and consists of systemic antibiotics and ductal saline or antibiotic irrigations. Parotidectomy may eventually be required for people with long-standing infection.[81]

Viral Parotitis

Mumps parotitis is characterized by the rapid, painful swelling of one or both parotid glands within 2 to 3 weeks after exposure to the mumps virus. A prodromal phase of preauricular pain, fever, chills, and headache may be present (see Chapter 157). Other viral causes of parotitis include influenza and enteroviruses, and virus cultures or serologic examinations may be required for distinguishing these from true mumps. Mumps parotitis usually resolves spontaneously in 5 to 10 days. Symptomatic relief of pain and fever is necessary, and prevention of dehydration and secondary bacterial infection is essential.

Miscellaneous Infections of the Neck and Head

Since the advent of antibiotics, dental causes have outnumbered oropharyngeal and tonsillar sources of deep neck infections. Peritonsillar abscess (quinsy) is discussed separately in Chapter 59. Other miscellaneous infections of the neck and head include suppurative cervical adenitis, infected embryologic cysts of the neck, suppurative thyroiditis, and those secondary to human and animal bites, irradiation, or surgical procedures of the head and neck. Their clinical manifestations and management are briefly reviewed here. Antimicrobial therapy is further discussed in the section "Therapeutic Considerations."

Suppurative Cervical Adenitis

The six groups of cervical lymph nodes (occipital, mastoid, parotid, facial, submandibular, and submental) form a collar at the junction of the head and neck. Within this collar near the base of the tongue lie the sublingual and retropharyngeal nodes. The anterior and lateral cervical nodes form a chain along the front and side of the neck, respectively. The lateral cervical chain serves as a common root for drainage. The final conduit from all lymphatic vessels in the head and neck is the large deep chain situated along the carotid sheath. Cervical adenitis that arises unilaterally is usually caused by pyogenic bacterial infections. Its anatomic location in relationship to major cervical landmarks provides the clinical clues to the primary source of infection. Bilateral acute cervical adenitis is generally suggestive of a nonspecific or viral cause, toxoplasmosis, or group A streptococcal infection. A more chronic or recurrent cervical adenitis is suggestive of typical or atypical mycobacteria, HIV infection, Epstein-Barr virus or cytomegalovirus mononucleosis, cat-scratch fever, actinomycosis, sarcoidosis, or lymphoproliferative and neoplastic disorders.

Infected Embryologic Cysts

Three distinct embryologic abnormalities can manifest with infection in the neck: (1) cystic hygroma or lymphangioma, (2) branchial cleft cysts, and (3) thyroglossal duct cysts.[80] Cystic hygroma is associated with a diffuse tumor mass, usually evident within the first 2 years of

life. It commonly involves the lower aspect of the neck, but it can appear anywhere in the cervical region. It is probably an abnormal development of lymphatic vessels from the jugular lymphatic sacs. Sudden enlargement by infection or hemorrhage into a lymphangioma may cause obstruction of the upper airways. Branchial cleft cysts can develop from the first, second (most common), or third branchial clefts. They usually manifest in childhood as fistulas or masses just posterior to the angle of the mandible along the anterior border of the sternocleidomastoid muscle. The mass can fluctuate in size, and enlargement can be associated with upper respiratory infection. Thyroglossal duct cysts originate from the foramen cecum of the tongue and descend through the body of the hyoid bone into the anterior portion of the neck. Any residual secretory lining may give rise to a thyroglossal duct cyst that is midline. It can cause respiratory obstruction or fistula formation if secondarily infected. Successful treatment of these congenital abnormalities during secondary bacterial infection requires broad-spectrum antibiotics, such as a penicillin or cephalosporin, in addition to clindamycin targeting the oral microbiota. Definitive surgical excision to prevent recurrence should be performed after complete resolution of the acute process.

Suppurative Thyroiditis

Although infections of the thyroid gland are rare, they are potentially life threatening. Such infections may arise by a variety of pathways, including hematogenous dissemination, direct spread from an adjacent deep fascial space infection, an infected thyroglossal fistula, or anterior perforation of the esophagus.[80] Preexisting diseases of the thyroid gland, such as a goiter or adenoma, are frequently present. Acute suppurative thyroiditis is characterized by fever, local pain, tenderness, warmth, erythema, and symptoms of dysphagia, dysphonia, hoarseness, or pharyngitis. The infection may involve a single lobe or both lobes, and fluctuance may not be apparent until late in the course. Subacute thyroiditis may produce similar local findings, but systemic manifestations are not as severe and tend to be more self-limiting. Laboratory investigation of thyroid infections should include ultrasonography, radionuclide scanning, and lateral radiography or computed tomographic scanning of the neck for evidence of peritracheal extension; thyroid function tests; and diagnostic needle aspiration for histopathologic and microbiologic diagnosis. *S. aureus, Streptococcus pyogenes*, and *Streptococcus pneumoniae* are most frequently isolated. Other isolated pathogens include *Haemophilus influenzae, Streptococcus viridans, Eikenella corrodens,* and *Bacteroides, Peptostreptococcus,* and *Actinomyces* spp. Successful treatment requires specific antimicrobial agents and appropriate surgical drainage.

Infections from Bites, Irradiation, and Surgical Wounds

Human and Animal Bites

Human and animal bite wounds to the head and neck are relatively common. Although they may look innocuous initially, serious complications can occur (see Chapter 315). For this reason, empirical antibiotic therapy is recommended when the bite wound involves the face, head, or neck. According to researchers who used adequate anaerobic culture techniques, indigenous oral microbiota rather than the skin microbiota may be the major source of bite wound infections.[82,83] Streptococci, *E. corrodens,* and *S. aureus* are the most prevalent facultative organisms, and *Bacteroides* and *Peptostreptococcus* spp. are the most common anaerobic isolates. Penicillin-resistant gram-negative rods are infrequently found. *E. corrodens* is unique in that it is susceptible to penicillin and ampicillin but resistant to oxacillin, methicillin, nafcillin, and clindamycin.[84] In animal bite wounds, *Pasteurella multocida* has been a common cause of infection.[85] It is susceptible to penicillin, cefoxitin, and fluoroquinolones but resistant to clindamycin and erythromycin. In view of these findings, penicillin, amoxicillin-clavulanate, or moxifloxacin is a reasonable antibiotic choice of initial therapy for either human or animal bite wounds (see Table 64.3).

Irradiation and Postsurgical Wounds

Malignancies of the head and neck are frequently treated with a combination of irradiation, chemotherapeutic agents, and surgical resection. Infectious complications are particularly common after such procedures.[86] Pharyngocutaneous fistulas, osteonecrosis of the mandible, or radionecrosis of the laryngeal cartilage may occur. *S. aureus* and *Pseudomonas aeruginosa* are pathogens commonly involved. Prolonged courses of IV antibiotics should be selected according to culture and sensitivity data, and frequent wound débridement and cleansing are indicated. Although some controversy still exists, immunocompromised patients undergoing oropharyngeal surgery for cancer should receive perioperative antibiotics because they are at particularly high risk for infection. A broad-spectrum antibiotic such as piperacillin-tazobactam or a carbapenem appears appropriate in this setting (see Table 64.3). Coverage of methicillin-resistant *S. aureus* (MRSA) may be prudent for known carriers.

DIAGNOSTIC APPROACHES

Microbiologic Investigation

A major challenge in the microbiologic investigation of oral infections is how to distinguish true pathogens from commensal microbiota. The mere presence of an organism is insufficient to assume that it is a cause of a polymicrobial endogenous infection. However, microorganisms with low virulence potential and usually considered harmless in a healthy host (e.g., coagulase-negative staphylococci, diphtheroids, enterococci) may nonetheless cause invasive disease in an immunocompromised patient. This possibility underscores the importance of proper specimen collection and the need to correlate laboratory data with clinical information. Aerobic and anaerobic cultures should always be obtained. Surface cultures obtained from mucosal sites are regularly contaminated by resident commensal microbiota and are generally not recommended. For closed-space infections, it is imperative that the normal resident oral microbiota be excluded during specimen collection so that the culture results can be interpreted appropriately. Needle aspiration of loculated pus by an extraoral approach is desirable, and specimens should be transported immediately to the laboratory under anaerobic conditions. For intraoral lesions, direct microscopic examination of stained smears often provides more useful information than do culture results from surface swabs. Gram and acid-fast stains for bacteria and potassium hydroxide preparations for fungi should be routinely performed. Tissue biopsy specimens should be routinely examined for histopathologic evidence of acute or chronic inflammation and infection. In chronic osteomyelitis soft tissue swelling and draining fistulas are frequently present. Aspirates from the adjacent soft tissue swellings may be valuable, but cultures from the sinus tracts may be misleading because these sinus tracts are often colonized by organisms that do not reflect what is actually occurring within the infected bone. Bone biopsies for histopathologic examination and culture are often necessary for a definitive diagnosis.

Immunofluorescence staining and DNA probes or polymerase chain reaction (PCR) are increasingly used to analyze pathogens that are fastidious or noncultivable.[87,88] The benzoyl-D,L-arginine naphthylamide (BANA) test is a useful tool for the diagnosis of anaerobic periodontal infections.[89] This test detects a trypsin-like enzyme (BANA) produced by various periodontopathic bacteria, including *P. gingivalis, T. denticola*, and *Tannerella forsythensis*. A positive BANA test result is correlated both qualitatively and quantitatively with the presence of these microorganisms and facilitates the diagnosis in the appropriate clinical setting.

Imaging Techniques for the Localization of Infection

Orthopantomography ("wingbite" radiography) may reveal the true extent of advanced periodontitis or the presence of periapical abscess. High-resolution ultrasonography is useful for assessing the parotid gland or calculi within the Stenson duct. Ultrasonography, radionuclide scanning, CT, and MRI are particularly useful for the localization of deep fascial space infections of the head and neck.[53] CT can both localize a process and define its extent, particularly invasion into the cranial vault, mediastinum, or the bone; therefore it is an invaluable tool for guiding needle aspiration or open drainage. A lateral radiograph of the neck may demonstrate compression or deviation of the tracheal air column or the presence of gas within necrotic soft tissues. The soft tissues of the posterior wall of the hypopharynx are approximately 5 mm deep, less than one-third the diameter of the fourth cervical vertebra

(C4). The retropharyngeal soft tissues should be approximately two-thirds the width of C4, and the retropharyngeal space slightly less.[53] CT can determine whether the soft tissue swelling or an abscess originated from the retropharyngeal space or the prevertebral space. The former suggests an odontogenic source, whereas the latter likely indicates hematogenous involvement of the cervical spine. Bone scanning with technetium, used in combination with gallium- or indium-labeled white blood cells, is particularly useful for the diagnosis of acute or chronic osteomyelitis. In acute osteomyelitis, both the bone scan and the gallium scan are likely to yield positive findings. In chronic osteomyelitis, the gallium or indium scans may yield negative findings, but the result of the technetium scan may be positive. MRI is more sensitive than CT and probably more accurate than bone scan in detecting bone involvement.[90] T2-weighted images may identify and localize areas of pus for drainage or aspiration. Gadolinium enhancement is important for accurately defining the soft tissue component. Finally, MRA is useful for imaging vascular lesions, such as jugular thrombophlebitis or cortical venous thrombosis.[49]

THERAPEUTIC CONSIDERATIONS

Dental Caries and Periodontitis

For both caries prevention and the treatment of periodontitis, the most important strategy is the effective control of the supragingival and subgingival biofilm or plaques through active promotion of and meticulous attention to oral hygiene. The diet should be scrutinized to eliminate or discourage frequent snacking on carbohydrate-rich foods or the intake of sugar-containing beverages. Various antiseptic and antimicrobial regimens are used for the prevention of dental caries and treatment of different clinical forms of periodontal disease (see Table 64.2). Fluoride-containing dentifrices and rinses (e.g., 1.1% sodium fluoride or 0.4% stannous fluoride) and dental flossing should be encouraged after each meal. Fluoride forms a complex with the apatite crystals in dentin by replacing the hydroxyl group, thereby lending strength to the entire structure. Further, fluoride promotes remineralization of the carious lesions and also exerts a bacteriostatic effect. Oral antimicrobial rinses with 0.12% chlorhexidine are also effective for the control of dental plaque bacteria that lead to caries.[91] Chlorhexidine acts as a cationic detergent that kills a wide range of bacteria and is retained on the oral surfaces for prolonged periods to prevent plaque advancement. A synergistic antibacterial effect has been demonstrated with the combination of chlorhexidine and fluoride, greater than that of either agent alone.[92] A disadvantage of chlorhexidine is that it has a bitter taste and stains the enamel and tongue. Prolonged application may also promote the emergence of resistant microorganisms. Among topical antibiotics, although both penicillin and tetracycline have cariostatic effects in animal models, only the topical application of vancomycin has been shown to reduce dental caries with some degree of success in humans.[93] None of these measures is routinely applied in clinical practice, but they are useful for the control of dental plaques in selected patients with rampant caries. With the development of improved restorative dental care and dental restorative materials, such as bonding and fluoride-releasing agents, the need for dental extractions has become much less frequent.

Acute simple gingivitis may be treated with (1) penicillin plus metronidazole, (2) clindamycin, or (3) ampicillin-sulbactam. Acute necrotizing ulcerative gingivitis responds well to metronidazole alone. Clindamycin, ampicillin-sulbactam, or amoxicillin-clavulanate is an alternative choice (see Table 64.2). Certain types of severe periodontitis are amenable to systemic antimicrobial therapy in conjunction with mechanical débridement (scaling and root planing).[39,94] This protocol has often obviated the need for radical surgical resection of periodontal tissues. In double-blind, randomized and prospective clinical studies of moderate-to-advanced periodontitis, systemic metronidazole (500 mg PO three times daily) plus amoxicillin (500 mg PO three times daily) for 7 days in conjunction with mechanical débridement of the root surfaces significantly improved clinical outcome compared with mechanical débridement alone at 1-year follow-up.[95] A topical antibiotic approach is also feasible. The US Food and Drug Administration has approved a powder containing minocycline microspheres (Arestin [Orapharma Inc., Bridgewater, NJ]), which releases controlled amounts of the antibiotics beneath the gum, for use in conjunction with scaling and root planing to reduce pocket depth in adults with "established" periodontitis.[96] Alternatively, topical application of an extended-release doxycycline hyclate liquid (Atridox; DenMat, Lompoc, CA) may also be beneficial.[97] In localized juvenile periodontitis systemic tetracycline therapy directed against *A. actinomycetemcomitans*, combined with local periodontal treatment, has yielded excellent results. Unfortunately, the administration of tetracycline to children younger than 9 years can cause staining of the permanent dentition and is not generally recommended. Furthermore, tetracycline resistance among periodontal pathogens has been increasingly recognized. Oral metronidazole plus amoxicillin is an alternative and the current regimen of choice.[95] The routine use of systemic antimicrobials prophylactically during oral or periodontal surgery in a healthy host is unwarranted because the risk of postoperative infections is low and overuse of antimicrobials leads to added cost and emergence of antimicrobial resistance.[98,99]

The need for definitive restoration or extraction of the infected tooth, the primary source of an odontogenic infection, is readily apparent. Deep periodontal scaling and endodontic treatment with root fillings are required in most instances. The key for the prevention and control of dental caries and advanced periodontitis is the active promotion of oral hygiene, including the following:

1. Rigorous brushing and dental flossing after each meal.
2. Dietary counseling to reduce the ingestion of carbohydrate-rich foods or beverages.
3. Use of topical fluorides and oral antimicrobial rinses, such as chlorhexidine, for patients at high risk for dental caries.
4. Behavioral modification of risk factors, such as tobacco smoking.
5. Overcoming the reluctance for regular visits to dental professionals.

Vaccines based on various immunogens derived from *S. mutans,* the principal bacterial agent associated with dental caries, have been explored, commercialization of an effective and safe vaccine for clinical application is unlikely in the near future.[100]

Suppurative Soft Tissue Infections

The most important therapeutic modality for pyogenic odontogenic or nonodontogenic orofacial infections is surgical drainage and the removal of necrotic tissue. Needle aspiration by the extraoral route can be particularly helpful for both microbiologic sampling and evacuation of pus. Effective surgical management requires a thorough understanding of the anatomic routes by which infection is most likely to spread. The neighboring potential fascial spaces should be carefully and systematically surveyed. For effective drainage, the incision site should be in the most dependent location. It is equally important that the timing for incision and drainage be optimum. Premature incision into an area of poorly localized cellulitis in an ill-conceived search for pus can disrupt the normal physiologic barrier and cause further spread of infection.

Antimicrobial therapy is important in halting the local spread of infection and in preventing hematogenous dissemination. The initial choice of specific antibiotics is based more on knowledge of the indigenous organisms that colonize the teeth, gums, and mucous membranes than on the results of culture and sensitivity testing.[101] Whereas endogenous oral pathogens were almost universally susceptible to penicillin in the past, this is no longer the case. β-Lactamase–producing anaerobic gram-negative bacteria in the oral cavity have been increasingly recognized.[102] They include pigmented *Prevotella* spp., *Porphyromonas* spp., and *Fusobacterium* spp. Failure of penicillin therapy for odontogenic infections caused by these microorganisms has been well documented.[101] Thus a combination of a β-lactam and β-lactamase inhibitor (e.g., ampicillin-sulbactam, amoxicillin-clavulanate) should be considered. Apart from penicillin, there are also increasing reports of in vitro resistance to metronidazole and azithromycin among *Fusobacterium* spp. and other anaerobic gram-negative bacteria isolated from odontogenic infections.[103] Their clinical significance at this time is unclear, however. Nevertheless, the emergence of resistance among oral bacteria is disconcerting and probably results from widespread and inappropriate use of broad-spectrum antibiotics. In accordance, in vitro susceptibility testing of suspected oral pathogens has become more

critical, particularly if the clinical response to initial empirical therapy is suboptimal.

The initial selection of antimicrobial agents should be guided by knowledge of the most likely causative organisms, their predicted antibacterial spectrum, and bioavailability in oral or parenteral formulations (see Tables 64.2 and 64.3). For normal hosts, metronidazole plus penicillin, combinations of β-lactam and β-lactamase inhibitors (e.g., ampicillin-sulbactam, amoxicillin-clavulanate), or clindamycin is generally the agent of choice. Cefoxitin, cefotetan, or moxifloxacin are alternative agents, although for each, the spectrum of anaerobic activity is limited. Erythromycin, other macrolides, and tetracycline are not recommended because of increasing resistance among some strains of streptococci and their lack of optimal anaerobic activity. Severely immunocompromised patients are at increased risk for unhalted and rapidly spreading infection, and coverage for nosocomial pathogens, including facultative gram-negative bacilli and MRSA, may be required. The antibiotic regimen must be broad spectrum, bactericidal, and appropriate in dose and schedule. Ciprofloxacin or a third- or fourth-generation cephalosporin (e.g., cefotaxime, ceftriaxone, ceftizoxime, cefepime), each in combination with metronidazole, is recommended. Monotherapy with an extended-spectrum penicillin β-lactamase inhibitor (i.e., ampicillin-sulbactam or piperacillin-tazobactam); a carbapenem (i.e., imipenem-cilastatin, meropenem, or doripenem); or tigecycline is an alternative choice.

Osteomyelitis

Treatment of osteomyelitis of the jaws is complicated by the presence of teeth and persistent exposure to the oral environment. Antibiotic therapy needs to be prolonged, often for weeks to months. Clindamycin and moxifloxacin have excellent bioavailability in bone tissue, and either is recommended. Adjuvant therapy with hyperbaric oxygen may prove beneficial in hastening the healing process, but its overall efficacy remains controversial. In one study of 33 patients with early chronic osteomyelitis of the jaw, 79% were free of symptoms 10 to 34 months after hyperbaric therapy combined with surgical débridement.[104] Osteoradionecrosis (ORN) refers to osteomyelitis occurring after dental extraction, usually from the mandible that was included in a radiation port. ORN responds poorly to antimicrobial therapy alone. Surgical removal of necrotic bone, closure of the mucosa over the socket, and prolonged antibiotic therapy may be required. In other forms of osteomyelitis surgical management, including sequestrectomy, saucerization, decortication, and closed-wound suction irrigation is also occasionally necessary. In a few advanced cases the entire segment of the infected jaw may have to be resected. For vertebral osteomyelitis with or without extension into the prevertebral space, the most common causative organism is *S. aureus,* followed by facultative gram-negative bacilli in at-risk patient populations such as those with a history of IV drug abuse. Coverage with nafcillin or vancomycin (if MRSA is suspected) plus ciprofloxacin is recommended.

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The complete reference list is available online at Expert Consult.

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C Pleuropulmonary and Bronchial Infections

65 Acute Bronchitis

Edward E. Walsh

SHORT VIEW SUMMARY

Definition
- Acute bronchitis is a self-limited syndrome characterized by acute cough with or without sputum but without signs of pneumonia.

Epidemiology
- Acute bronchitis occurs year-round and is caused by a large number of respiratory pathogens according to the typical epidemiology of each pathogen.

Microbiology
- Acute bronchitis is primarily caused by viral infections. Most common are rhinovirus, influenza viruses, respiratory syncytial virus, metapneumovirus, coronaviruses, and adenovirus. Fewer than 10% of cases are caused by *Mycoplasma pneumoniae, Chlamydia pneumoniae,* and *Bordetella pertussis.*

Diagnosis
- Diagnosis is primarily made by the clinical presentation in the absence of signs and symptoms of pneumonia.

Therapy
- Therapy is symptomatic because antibiotics are uncommonly required and unnecessary in the majority of cases.

Prevention
- Prevention is directed at specific pathogens when possible (e.g., influenza and pertussis vaccination).

Acute bronchitis refers to a clinical syndrome distinguished by a relatively brief, self-limited inflammatory process of large and midsized airways not associated with evidence of pneumonia on chest radiography. It is characterized by a dry or productive cough of less than 3 weeks' duration, is most prevalent in winter, and is primarily caused by viruses. This definition does not pertain to acute exacerbations of chronic bronchitis, a clinical syndrome also frequently associated with viral infection but in which bacteria play a more important role (see Chapter 67). It should also be distinguished from acute *bronchiolitis,* a clinical syndrome involving small airways most closely linked to respiratory syncytial virus (RSV) and human metapneumovirus (hMPV) infection in infants (see Chapters 158 and 159).

Acute cough is one of the most common reasons for physician visits in all age groups.[1] Incidence data may be imprecise because symptoms overlap considerably with those of the common cold, pneumonia, and asthma. Estimates from the National Health Interview Survey of US households have found that overall, 5% of persons annually report physician-diagnosed acute bronchitis, with highest rates during the winter months and in those younger than age 5 years.[2] Studies from the United Kingdom have reported similar rates of 54 cases per 1000 persons, ranging from 36 per 1000 in younger men to 225 per 1000 in those older than 85 years of age.[3,4]

MICROBIAL ETIOLOGY

Despite failing to uncover a specific pathogen in most case series, acute bronchitis is believed to be most commonly caused by a wide range of viruses (Table 65.1). Approximately 10% or less of cases are attributed to bacterial pathogens, principally *Mycoplasma pneumoniae, Chlamydia pneumoniae,* and *Bordetella pertussis.*[5] However, the recent increase in pertussis cases among adolescents and adults should be considered when evaluating illnesses. The relative proportion of cases caused by different pathogens varies according to age and the season studied but, importantly, is also influenced by the diagnostic methods used. Molecular tests, rather than standard culture, identify a greater number and wider range of viral pathogens, especially in adults, in whom many illnesses represent reinfection with common pediatric viruses (RSV, hMPV, parainfluenza viruses) often associated with low virus shedding in adults.[6,7] Influenza A and B viruses are most closely associated with winter outbreaks of acute bronchitis in both children and adults because of a high relative incidence of infection and the efficiency of influenza virus to infect and damage bronchiolar epithelial cells.[8,9] Although cough associated with most coronavirus and rhinovirus infections is commonly caused by postnasal congestion, these agents—including recently identified strains of human enterovirus D68, human rhinovirus C, and coronavirus—can infect the lower airway, causing acute bronchitis.[10,11,12,13,14] The higher temperature of lower airways was considered inhospitable to rhinovirus replication; however, recent evidence has convincingly documented virus presence in bronchiolar epithelial cells, although cytopathology is less than that with influenza virus infection.[14] Although found less frequently than other viruses in the general population, adenoviruses, including adenovirus types 4, 7, and 14, are important causes of bronchitis in military recruits.[15] Enteroviruses, primarily echovirus and coxsackievirus but also the newly emerged D68 strain, can cause acute bronchitis.[10] Simultaneous infection with two or more viruses occurs in 10% to 30% of cases, especially in small children, as is frequently the case with bocavirus infection. Worldwide, measles virus remains an important respiratory tract pathogen causing cough during the early prodromal phase; especially vulnerable are malnourished children in developing countries lacking resources for vaccination.[16] Although herpes simplex virus is commonly identified in respiratory secretions of patients with respiratory illness and is generally considered to be clinically insignificant, it has been associated on occasion with acute hemorrhagic tracheobronchitis in normal persons and has been described in critically ill intubated adults.[17] Human papillomavirus types 6 and 11 can produce symptoms of hoarseness, stridor, and chronic cough.[18]

TABLE 65.1 Viral and Bacterial Causes of Acute Bronchitis

PATHOGEN	SEASONALITY	COMMENTS
Influenza viruses	Winter	Local epidemics last 6–8 wk, during which clinical illness of cough and fever has high predictive value; laboratory diagnosis readily available; early neuraminidase inhibitor therapy effective
Rhinoviruses	Fall and spring	Most frequent cause of common cold syndrome; immunity is serotype specific
Coronaviruses	Winter to spring	Cause common cold syndrome; newer strains are difficult to culture and require RT-PCR for diagnosis
Adenoviruses	Year-round, winter epidemics	High attack rates in closed populations such as persons living in military barracks or college dormitories; serotype-specific immunity
Respiratory syncytial virus (RSV)	Late fall to early spring	Attack rates approach 75% in neonates, 3%–5% in adults; associated with wheezing in all age groups; rapid antigen test accurate in children but requires culture or RT-PCR to diagnose in adults
Human metapneumovirus (hMPV)	Winter to early spring	Associated with wheezing in adults and in infants; difficult to isolate in tissue culture and often requires RT-PCR
Parainfluenza viruses	Fall to winter	Similar to RSV and hMPV, parainfluenza viruses are primarily pediatric pathogens but can cause severe acute disease in some adults
Measles virus	Year-round	Can cause respiratory disease in malnourished children; illness causes transient immune suppression
Mycoplasma pneumoniae	Year-round, fall outbreaks	Long incubation period (10–21 days) results in staggered epidemic pattern in families; nonproductive persistent cough typical; diagnosed by IgM serology; treated with macrolide, quinolone, or tetracycline antibiotics
Chlamydia pneumoniae	Year-round	Associated with sinusitis; diagnosis by RT-PCR not readily available
Bordetella pertussis	Year-round	Severe illness in nonimmunized children; illness milder in partially immune adults but can be associated with prolonged cough; adults often reservoir for epidemics; early therapy with antibiotics can reduce spread

IgM, Immunoglobulin M; *RT-PCR,* reverse transcriptase–polymerase chain reaction.

Mycoplasma pneumoniae, C. pneumoniae, and *B. pertussis* are the bacteria most associated with acute bronchitis, implicated in perhaps 10% of cases.[3,5] Cough caused by these agents, especially *B. pertussis,* may persist in some cases for several months. Recently, *Bordetella holmesii* has been recognized as a cause of pertussis syndrome (see Chapter 230). In an acellular pertussis vaccine trial in adults, the incidence of pertussis was 0.7% in the placebo group.[19] However, the number of cases in adults has been increasing in recent years, attributed to incomplete vaccine uptake as well as failure of the vaccine to induce durable immunity.[20] This has resulted in a recommendation to provide a vaccine booster dose to adults and pregnant women (see Chapter 321). *Bordetella bronchiseptica,* a canine pathogen, can occasionally cause disease in humans, especially those who are immunocompromised.[21] Although *Streptococcus pneumoniae, Haemophilus influenzae,* and *Moraxella catarrhalis* can each be isolated from sputum in some patients with acute bronchitis, their pathogenic role in the illness is unclear since antibiotic therapy directed at these pathogens has not been shown to alter the clinical course. The recent presence of normal oropharynx colonizers, such as these pathogens, in the lower airways of normal healthy persons by use of bacterial 16S ribosomal DNA sequencing has altered the long-held concept that the lower airway is sterile.[22] Although many viruses enhance bacterial adherence to respiratory epithelial cells in vitro, the actual incidence of postviral bacterial infection in clinical situations has not been well defined.

PATHOGENESIS

The pathogenesis of acute bronchitis is the result of a combination of direct cytopathology of the pathogen and host immune response. Because cell tropism and pathogenic mechanisms vary for each of the viruses, it is not surprising that the location and extent of cytopathology in the airways also vary. Histopathologic changes in the airways during infection are best characterized for influenza virus.[23,24,25] In a recent autopsy series of 47 children with fatal influenza, submucosal congestion, hemorrhage, mononuclear cell infiltration, and epithelial necrosis were noted in 50% of cases.[24] Similar findings have been reported in adults, along with occlusion of airways by desquamated necrotic debris.[25] Respiratory syncytial virus has also been demonstrated to infect terminal bronchiolar lining cells with extensive debris occluding the lumen in infants, but similar data are lacking in adults.[26] Rhinovirus, which is primarily associated with upper respiratory common cold symptoms, produces patchy inflammation of bronchial epithelial cells up to 15 days after experimental challenge in adults.[14]

There is ample evidence that immune responses contribute significantly to disease pathogenesis in acute bronchitis. The innate immune response, characterized by virus-induced release of proinflammatory cytokines and chemokines by respiratory epithelial cells and immune cells, contributes to systemic and local symptoms. Early after infection with influenza virus or RSV, types I and III interferons, tumor necrosis factor, and interleukin-6 and interleukin-8 can be detected.[27] Interleukin-8 is a chemotactic factor for neutrophils, one of the earliest cells to migrate to the nasal mucosa. In experimental influenza virus infection, symptoms correlate temporally with the kinetics of cytokine secretion.[28] Cytokine induction by rhinovirus may also explain the important role that this virus plays in asthma episodes.[29] The immune response is thought likely to be responsible for the prolonged airway hyperreactivity that can be demonstrated for up to 6 weeks after influenza virus or RSV infection in normal adults.[30] Among the bacterial causes of acute bronchitis, *B. pertussis* is unique in that its expression of toxins may play a role in clinical symptoms, including the prolonged characteristic cough. However, a defined and specific pertussis "cough" toxin has not yet been identified.

CLINICAL MANIFESTATIONS

In most children and adults, acute bronchitis begins with signs and symptoms typical of the common cold syndrome. Nasal congestion, rhinitis, sore throat, malaise, and low-grade fever typical of the common respiratory viral pathogens are noted first, followed shortly by the onset of cough, which becomes the dominant sign in acute bronchitis. In mild cases the illness lasts only 7 to 10 days, whereas in others, cough may persist for up to 3 weeks or longer. Wheezing is not uncommon with acute bronchitis; in one study from the Netherlands, 37% of patients with acute bronchitis ultimately were diagnosed with asthma.[31] Disease severity and dominance of various symptoms may vary according to the specific pathogen. Fever is more common and higher with influenza virus or adenovirus infection, compared with rhinovirus or RSV infection at all ages. In contrast, RSV- or hMPV-infected persons are more likely to wheeze than influenza virus–infected patients.[7,32]

Various host factors such as age, underlying medical conditions, immune status, and environmental factors such as secondhand smoke exposure can influence clinical presentation and illness severity. Older patients and those with underlying cardiopulmonary conditions infected with influenza virus, RSV, or hMPV remain ill for an average of 16 to 17 days, in contrast to younger persons whose illness lasts an average

of 7 to 10 days.[7,32,33] In *M. pneumoniae* infection, cough can be particularly persistent and irritating, often with minimal phlegm, causing severe chest discomfort.

DIAGNOSIS

Acute bronchitis should be suspected in any person with an acute respiratory tract illness in which cough is the dominant complaint. Patient evaluation includes identification of underlying chronic obstructive pulmonary disease or asthma, and taking note of the season and the presence of influenza or other circulating viruses in the community. During community outbreaks of influenza, the presence of an acute illness with fever and cough can have a predictive value of 79% in young healthy persons.[34] Among hospitalized older persons with acute respiratory tract illness, similar clinical parameters increase the odds of influenza approximately threefold.[35] Exposure to environmental irritants should be sought, especially in the absence of typical upper respiratory tract symptoms. Travel history or exposure to ill family members or close contacts may provide useful information about the incubation period and thus the etiology. *Mycoplasma pneumoniae,* with an incubation period of 7 to 21 days, will progress slowly through the family in contrast to influenza, with its 2- to 4-day incubation period and close clustering of illnesses. Recent vaccination does not eliminate influenza from consideration, especially in older persons in whom protective efficacy is poor.[33,36] Prolonged cough longer than 4 weeks, with or without paroxysms or vomiting, should suggest *B. pertussis,* even among vaccinated adolescents and adults, because immunity is not durable.[19,20]

Physical examination should be attentive to signs of pneumonia, because a primary goal of evaluation is to discriminate acute bronchitis from pneumonia. A concern for clinicians is the occurrence of bacterial infection that can follow or occur concurrently with viral infection. This is best exemplified by the severe bacterial pneumonias that followed influenza infection during the 1918 H1N1 and 1957 H2N2 pandemics. Similarly, one report described bacteremic *S. pneumoniae* pneumonia in long-term care patients after antecedent parainfluenza virus infections.[37] Despite concerns about postviral bacterial pneumonia, several large studies have indicated that only approximately 7% of patients diagnosed with acute bronchitis will have radiographic evidence of pneumonia.[38] Combinations of signs and symptoms or overall clinical judgment is imprecise, with a sensitivity of only 23%.[39,40] One study has found that in the absence of any vital sign abnormality, radiographic evaluation could be safely omitted.[39] Standard laboratory tests, such as white blood cell count or inflammatory markers such as serum C-reactive protein, do not reliably discriminate viral from bacterial infection.[40] However, a serum procalcitonin level below 0.1 ng/mL may be a more reliable indicator of patients with a variety of acute respiratory syndromes, including acute bronchitis, that do not require antibiotic therapy.[41,42]

Ultimately, etiologic diagnosis requires laboratory confirmation. Identification of viral pathogens is most commonly performed using multiplex reverse transcriptase–polymerase chain reaction (RT-PCR) assays, especially useful in adults who may shed low levels of many of the most prevalent viruses (RSV, hMPV, coronaviruses, parainfluenza viruses).[6,7,33] Diagnosis of *M. pneumoniae* rests on demonstrating pathogen-specific immunoglobulin M in serum or with RT-PCR assay. *Bordetella pertussis* diagnosis can be made by serology, RT-PCR assay, or culture. *Chlamydia pneumoniae* is difficult to diagnose and requires RT-PCR assay or serology.

THERAPY

Therapy for patients with acute bronchitis is generally symptomatic, directed at relief of troublesome upper respiratory symptoms, cough, and wheezing. As noted, acute bronchitis and asthma can present with similar manifestations, and therapy directed toward bronchospasm may be required. Several approaches to controlling acute cough have included narcotic cough suppressants, expectorants, antihistamines, decongestants, and β_2-agonists.[43,44] Reviews of randomized controlled trials have not clearly concluded that they are beneficial. In a double-blind, placebo-controlled trial in experimental rhinovirus infection, the combination of ibuprofen (400 mg) plus chlorpheniramine (12 mg), administered every 12 hours for 4.5 days, reduced cough significantly, although the effect was optimal when combined with an intranasal antiviral compound (interferon-α).[45]

After their introduction after 1940, antibacterial agents were rapidly embraced for treatment of acute bronchitis; currently, 60% to 80% of patients receive antibiotics for this diagnosis.[46,47] However, empirical antibacterial therapy for acute bronchitis without regard for demonstrated pathogen-specific therapy has repeatedly been shown to provide no benefit for most patients.[48,49] A recently published meta-analysis of 17 randomized controlled trials in patients without chronic respiratory disease, but who had acute bronchitis, concluded that treatment with antibiotics failed to show a significant clinical benefit.[48] However, acute bronchitis remains one of the five most frequently cited rationales for excessive antibiotic use in outpatients. Acute bronchitis and other acute respiratory syndromes (otitis media, sinusitis, pharyngitis, upper respiratory tract infections) account for approximately 75% of ambulatory prescriptions in the United States.[1] Current guidelines, endorsed by a number of national societies—including the American College of Physicians, the Centers for Disease Control and Prevention, and the Infectious Diseases Society of America—do not recommend the routine use of antibiotics for uncomplicated acute bronchitis in otherwise normal persons.[50] Various strategies to reduce antibiotic use, including patient and physician education or delayed prescription filling, can reduce antibiotic use by approximately 50%.[51,52] Recent randomized controlled studies using levels of serum procalcitonin to guide therapy in acute respiratory infections, including acute bronchitis, have also demonstrated that antibiotic use can be partly reduced without adversely affecting outcome.[41,42] If a specific viral diagnosis can be confirmed using a rapid RT-PCR test, perhaps physicians would be more willing to forgo antibiotic treatment. Even patients with documented *M. pneumoniae* or *C. pneumoniae* infection may not benefit from specific therapy with macrolides or quinolones in the absence of pneumonia. In adults and adolescents, early therapy for infection with *B. pertussis* with macrolides or tetracyclines is indicated to prevent transmission, although the clinical findings early in infection are indistinguishable from viral causes of bronchitis.

It may be useful to seek a specific diagnosis of influenza during community outbreaks, because specific treatment with neuraminidase inhibitors active against influenza A and B strains can reduce the duration of illness when administered early in its course. In one study of adults with influenza, subsequent antibacterial use was 11% in zanamivir-treated patients compared with 17% in placebo-treated controls.[53] However, bacteriologic and radiologic confirmation of bacterial pneumonia was not sought in this study.

PREVENTION

Preventive measures to reduce transmission of agents known to cause acute bronchitis should be limited to standard respiratory and contact precautions when a specific etiology is unknown. Immunization against specific pathogens, such as influenza and pertussis, is of benefit and can reduce the incidence of symptomatic infection with these agents (see Chapter 321).

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The complete reference list is available online at Expert Consult.

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66 Acute Exacerbations of Chronic Obstructive Pulmonary Disease

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SHORT VIEW SUMMARY

Definitions
- Chronic obstructive pulmonary disease (COPD) is a chronic lung disease with irreversible airflow limitation with reduced forced expiratory volume in 1 second (FEV_1) and FEV_1/FVC ratio.
- An acute exacerbation is an acute increase of the patient's dyspnea, sputum volume, or sputum purulence. Each symptom contributes to the severity of the COPD exacerbation.

Epidemiology
- There is an increased risk for an acute exacerbation of COPD in winter months.
- Risk factors include cigarette smoking, environmental particulate matter, genetic predisposition, influenza, and other circulating viral infections that affect the respiratory tract.

Pathogenesis
- Intermittent progressive airway inflammation, remodeling, and loss of lung function occur.
- Ciliary dysfunction, excess mucous production, and impaired phagocytosis leading to bacterial colonization also occur.

Microbiology
- Airways of stable COPD patients are frequently colonized with *Streptococcus pneumoniae, Haemophilus influenzae,* and *Moraxella catarrhalis*; respiratory syncytial virus is the most frequent colonizing virus.
- Microaspiration in stable COPD introduces oral anaerobes such as *Prevotella* spp. and *Veillonella* spp. into the lower airway.
- During acute exacerbations, bacteria, viruses, or both may be isolated, with more gram-negative rods found with worsening lung function. "Atypical" bacteria are not frequently isolated. Acquisition of a new pathogen is associated with exacerbation.

Diagnosis
- Change in respiratory symptoms are the cornerstone of diagnosis, but procalcitonin may be useful in determining the need for antibiotics in acute exacerbations.

Treatment
- Increased bronchodilators (including long-acting β-agonists and long-acting muscarinic antagonists) are used for mild exacerbations, without antibiotics.
- Early empirical antibiotics and oral or intravenous steroids are administered for moderate-to-severe exacerbations.

Prevention
- Exposure to particular matter should be avoided, and patients should stop smoking.
- Influenza, pneumococcal, and pertussis vaccines are used for prevention.
- Prophylactic daily azithromycin may be considered in patients with advanced disease with a history of exacerbation and no cardiac risk factors.

Chronic obstructive pulmonary disease (COPD) is characterized by airway inflammation and parenchymal destruction. Airflow obstruction produced by structural changes in the lung predisposes to acute declines in patient well-being associated with increasing dyspnea and sputum production; these are the essence of the diagnosis of acute exacerbation of chronic obstructive pulmonary disease (AECOPD). Smoking cessation and irritant avoidance are essential to reduce the risk of exacerbation. Currently, prevention of exacerbation with inhaled steroids and combination long-acting bronchodilators has become the cornerstone of management of patients at high risk for AECOPD. Once AECOPD is established, its management includes a combination of antibiotics and steroids.

EPIDEMIOLOGY

COPD, including emphysema and chronic bronchitis, has been the third leading cause of death since 2008 in the United States.[1] It will become the third leading cause of death in the world by 2020.[2,3] By 2030, 10% of the world's population will be expected to develop COPD. COPD prevalence has increased owing to increased longevity and long-term exposure to respiratory irritants such as tobacco smoke and, to a lesser extent, inhaled particulate matter (PM).[4] Smoking tobacco is the largest risk factor; 50% of smokers will develop COPD.[5–8] Consequently, COPD is an important driver of increased health care utilization, producing significant social and economic costs.[9–11] COPD affects predominately older individuals, with study cohorts having mean ages older than 60 years; however, presentation in young adulthood occurs in susceptible individuals.[12,13,14]

COPD is caused by multiple factors, including environmental exposures, infections, inflammation, and genetic predisposition. Newer conceptualization of COPD characterizes it as a syndrome that includes multiple different processes with distinct pathophysiologic derangements.[15–17] Tobacco smoking is the largest environmental risk factor in the United States. In other countries, occupational dust exposures, outdoor air pollution, and poor indoor air quality from burning biomass fuels also are major COPD risk factors.[18] Among immunocompetent adults, increased airway bacteria produce airway inflammation and accelerate airway obstruction.[19] Immunosuppression is an independent risk factor for COPD. Immunoglobulin A (IgA)-deficient individuals have repeated lower respiratory tract infections during childhood and poor adult lung function.[20] Human immunodeficiency virus (HIV) infection promotes chronic pulmonary inflammation and increased pulmonary matrix metalloprotease expression leading to smoking-related emphysema.[21,22] Even after effective antiretroviral therapy, patients with acquired immunodeficiency syndrome (AIDS) have an increased frequency of pulmonary infection and accelerated lung function decline.[23,24] Genetic susceptibility is another risk factor for development of COPD. Mutation of the α_1-antitrypsin gene leads to low serum antiprotease activity, causing a much higher risk of COPD in smokers and workers exposed to PM.[25] Homozygous α_1-antitrypsin deficiency (PI*ZZ) occurs in 1% to 4.5% of COPD patients, and the heterozygous form (PI*MZ), with less severe deficiency, occurs in 17.8% of COPD patients.[26] Ethnic origin is an important risk factor for COPD, raising the possibility of differential group-level genetic susceptibility

to lung injury.[27] For most individuals, predisposition to abnormal lung function is polygenic; more than 20 risk genes have been identified.[28,29] Poor socioeconomic status, chronic asthma, intrauterine growth retardation, poor nourishment, and history of pulmonary tuberculosis are other risk factors for COPD.[27,30–32]

Acute Exacerbation of Chronic Obstructive Pulmonary Disease

AECOPD produces significant morbidity and mortality. Frequent exacerbators may be defined as COPD patients who have two or more exacerbations per year and likely constitute a distinct subgroup within COPD with poor outcome.[33,34] Risk factors include viral and bacterial infections, change in environmental conditions such as smog, gastroesophageal reflux, lack of compliance with maintenance treatment, and severity of baseline disease.[33] Important to note, the best predictor for exacerbations is a past history of exacerbations.[35] AECOPD occurs approximately two times more frequently in winter than in summer, both in northern and southern latitudes. AECOPD is responsible for the greatest proportion of health care–related costs associated with COPD.[9–11] This chapter focuses on the impact of AECOPD on disease course, infectious etiologies of AECOPD, treatment of AECOPD, and AECOPD prevention, the central goal of current management strategies.

CLINICAL PRESENTATION

AECOPD manifests with progressive shortness of breath, cough, sputum production, reduced energy, and exercise limitation. These symptoms are associated with accelerated decline in lung function, which may continue despite smoking cessation. The dyspnea usually starts during exercise but can occur with minimal exertion or at rest as disease progresses. Cough and sputum production are usually intermittent and more pronounced in the morning. Other chronic pulmonary diseases with similar clinical presentation and acute exacerbations should be differentiated from COPD because treatment differs. Examples of these include asthma, cystic fibrosis, bronchiectasis, diffuse panbronchiolitis, and obliterative bronchiolitis. Worsening symptoms, increased sputum volume, and transition of sputum color from clear to green or yellow suggest AECOPD, which more commonly occurs during winter months.[36] The main differential diagnosis of exacerbations in patients with COPD includes pneumonia and congestive heart failure, both of which are common comorbidities in these patients.[5,8]

DIAGNOSIS

COPD is characterized by progressive airflow obstruction defined by reduction in forced expiratory volume in 1 second (FEV_1) and a postbronchodilator ratio of FEV_1/forced vital capacity (FVC) less than 70% on pulmonary function tests (PFTs). A highly affected subgroup of patients have characteristics of both COPD and asthma (asthma-COPD overlap) with partial bronchodilator reversibility of airflow obstruction.[37] Severity of stable COPD is based on pulmonary function (Table 66.1).[5,8]

TABLE 66.1 Spirometric General Classification of Chronic Obstructive Pulmonary Disease (COPD)

SEVERITY	FEV_1/FVC	FEV_1 % PREDICTED
GOLD 0: At risk Patients who: • smoke or have exposure to pollutants • have cough, sputum, or dyspnea • have family history of respiratory disease	>0.7	≥80
GOLD 1: Mild COPD	≤0.7	≥80
GOLD 2: Moderate COPD	≤0.7	50–79
GOLD 3: Severe COPD	≤0.7	30–49
GOLD 4: Very severe COPD	≤0.7	<30

FEV_1, Forced expiratory volume in 1 second; *FVC*, forced vital capacity; *GOLD*, Global Initiative for Chronic Obstructive Lung Disease criteria.

Acute Exacerbation of Chronic Obstructive Pulmonary Disease

Although there is no universal agreement on how to define or diagnose AECOPD, it is commonly defined as an acute event with worsening respiratory symptoms beyond normal day-to-day variation. The definition often requires increased rescue β-agonist inhaler use or addition of a long-acting muscarinic antagonist (LAMA) to control symptoms.[38,39] The differential diagnosis must include acute coronary syndrome, congestive heart failure, pulmonary embolism, and pneumonia.[8] One widely used scale to diagnose the presence and severity of AECOPD requires patients to have at least one of the following clinical presentations: upper respiratory infection symptoms within the prior 7 days, increased wheezing, fever without another identified cause, or an increase in heart rate or respiratory rate >20% from baseline. This scale then categorizes patients into three groups based on whether they have worsening dyspnea, increase in sputum purulence, increase in sputum volume, or a combination of these. A severe exacerbation meets all three criteria, a moderate exacerbation meets two, and a mild exacerbation meets only one criterion.[40] Although clinical presentation is the most important component in establishing the diagnosis of AECOPD, procalcitonin is a biomarker that may be useful in determining the need for antibiotics.[41] No biomarkers of systemic inflammation reproducibly predict future exacerbations.[42]

Risk factors associated with COPD exacerbations include having two or more COPD exacerbations in the previous year, reduced FEV_1, smoking, and nonadherence with O_2 therapy.[43,44] The risk of severe exacerbation depends on each patient's medical history, including baseline FEV_1, number of prior exacerbations, prior need for mechanical ventilation, and comorbidities. Although the vast majority of AECOPD can be managed in the outpatient setting, the presence of severe exacerbation should prompt consideration of hospital admission.[5,8] The clinical signs of risk for respiratory failure are the most important measure of the current exacerbation's severity. Tachypnea (especially with a respiratory rate above 25), tachycardia, inability to speak full sentences, and fatigue are indications for hospitalization. Oxygen saturation above 90% can be misleading because hypoxemia is frequently a late event in the progression to respiratory failure. In an acutely symptomatic patient, arterial blood gas measurement is more useful than oximetry because only the former can enable diagnosis of hypoventilation with hypercapnia. Use of accessory muscles with paradoxical breathing characterized by inward motion of the abdomen during inspiration indicates diaphragmatic fatigue and impending respiratory failure. Abdominal paradoxical breathing, progressive hypercapnia, or deteriorating mental status usually indicates the need for ventilatory support in an intensive care unit (ICU) with noninvasive or invasive positive pressure ventilation.[5,8]

Additional diagnostic tests include chest radiography to identify pulmonary infiltrates and electrocardiography to assess for cardiac ischemia and arrhythmias, particularly paroxysmal atrial tachycardia. The basic metabolic panel is helpful to assess severity of AECOPD. Elevated bicarbonate is a sign of chronic hypercapnia. Increased anion gap is a sign of anaerobic metabolism of the respiratory muscles, sepsis syndrome, or both. Hyponatremia sometimes occurs as a result of the syndrome of inappropriate antidiuretic hormone secretion. Hyperglycemia is a response to stress or systemic steroids, and renal insufficiency is a manifestation of reduced cardiac output in end-stage pulmonary hypertension. The presence of these derangements may warrant hospitalization.[5,8]

Radiology

Although chest radiography is an insensitive test to diagnose AECOPD, it is the usual first step in the evaluation of patients with progressive dyspnea and cough. It is essential for evaluation of alternative diagnoses such as pneumonia, congestive heart failure, lung cancer, or pulmonary fibrosis. However, computed tomography (CT) is more sensitive for defining alternate diagnoses, and quantitative CT allows estimation of the risk for exacerbation frequency and allows determination of indices of disease impact.[45] Pulmonary emboli can mimic AECOPD, and if they are suspected, a helical CT scan with contrast can reveal this alternate diagnosis.

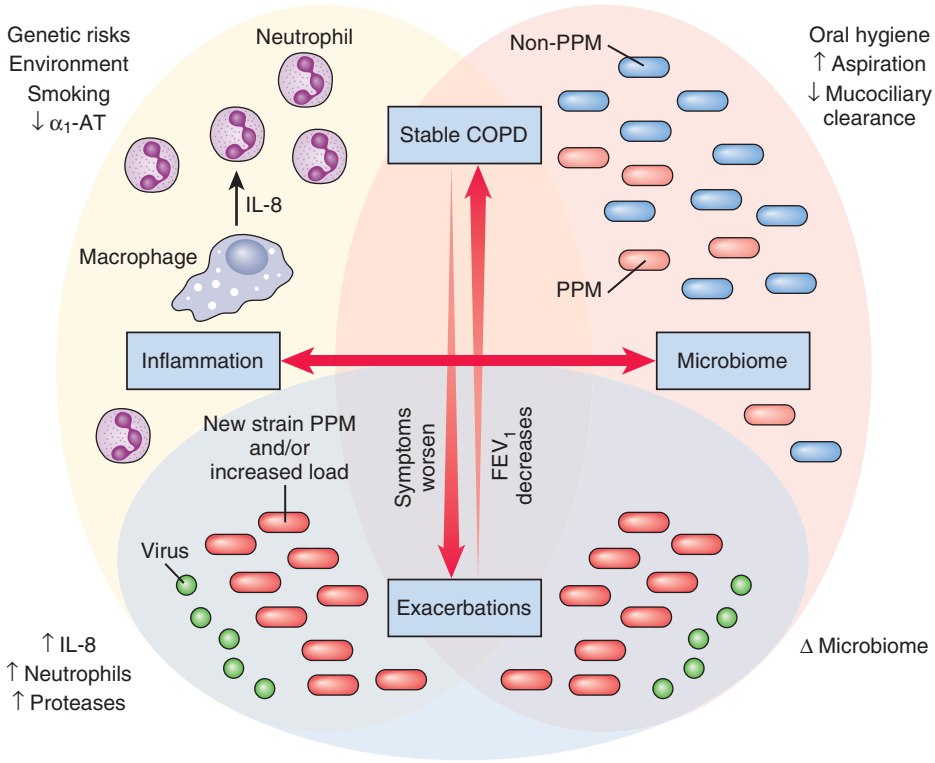


FIG. 66.1 Chronic obstructive pulmonary disease *(COPD)* pathophysiology. α_1-*AT,* α_1-Antitrypsin; *FEV_1,* forced expiratory volume in 1 second; *IL-8,* interleukin-8; *PPM,* potentially pathogenic microorganism.

PATHOPHYSIOLOGY

Impaired lung function in COPD is caused by destruction and remodeling of large and small airways due to chronic inflammation caused by complex interactions among the inhalants (dust or smoke), the lung microbiome, and the immune response in airway mucosa. Both inflammatory changes and lung function deterioration become more prominent with each exacerbation (Fig. 66.1). Early pathologic condition is produced by inflammation in bronchioles less than 2 mm in diameter followed by parenchymal remodeling.[46,47] In early stages, the central airway walls are infiltrated with $CD8^+$ lymphocytes producing bronchial wall thickening evidenced on chest CT.[48] Apoptosis and necrosis of epithelial and endothelial cells are also present, as are activated $CD4^+$ T cells.[49,50] As disease progresses, neutrophils become prominent and release neutrophil elastase, leading to parenchymal destruction.[51,52] Persistent airway injury also produces squamous metaplasia with loss of cilia function in affected bronchial segments. Disease of both the large and small airways contributes to airflow obstruction and ventilation heterogeneity.[53] Progressive disease is marked by increased airway mucin production.[54] Pulmonary hypertension due to loss of the pulmonary capillary bed can also develop in COPD. Chronic hypoxia produces vasoconstriction, which leads to fixed structural changes that worsen pulmonary hypertension.[55] As disease progresses, frequent exacerbations of COPD further contribute to increased lung inflammation and persistent loss of lung function.[56,57,58–60] The biology of exacerbations in COPD is heterogeneous and involves varying degrees of inflammation and microbial pathogenesis.[61]

Mucosal Inflammation

COPD patients have a 20-fold increase in alveolar macrophages (AMs) in alveoli, bronchioles, and small airways.[62,63] Because AMs are a major source of inflammatory cytokines and growth factors, recruitment of inflammatory cells into the lung accelerates the vicious inflammatory cycle produced by microaspiration. In spite of increased numbers, AMs have impaired phagocytosis, reducing their ability to clear bacteria from the lower airway, thereby causing further inflammation and oxidative stress.[64–67] Compared with smokers without COPD, those with COPD have higher levels of neutrophils, eosinophils, macrophages, B lymphocytes, and $CD4^+$ and $CD8^+$ T cells in biopsies of peripheral airways, highlighting the role of innate and adaptive immune responses in disease progression.[68] A proinflammatory subset of $CD4^+$ T cells, known as Th17 cells, are frequently found at the mucosal interface and are implicated in the pathogenesis of chronic inflammatory conditions, including COPD and asthma. Th17 cells secrete interleukin (IL)-17 and IL-22, which synergize on tissue parenchyma to elicit production of inflammatory cytokines and chemokines, often leading to the recruitment of neutrophils and other inflammatory cells. Levels of IL-17A and IL-22 are increased in the sputum of individuals with COPD,[69–71] and Th17 cells have been identified in bronchial biopsy specimens of patients with COPD.[72] IL-17 increases the expression of mucin-encoding genes (*MUC5AC* and *MUC5B*) in human airway epithelial cells.[73] A study has demonstrated that numbers of IL-17A- and IL-22-producing cells in bronchial submucosa are significantly increased in patients with stable COPD.[72] Neutrophils are then recruited and activated by nonresolving pulmonary inflammation, particularly during exacerbations. Neutrophil elastase and metalloproteinases lead to lung parenchyma destruction. Neutrophil elastase is also a potent mucous secretagogue leading to mucous gland hyperplasia.[74] Because neutrophils have a short tissue lifespan, the airway neutrophilia observed in COPD requires continuous neutrophil recruitment.[75] Smoking also impairs neutrophil phagocytic function.[76] Collectins, pentraxins, and complement also are deficient,[77] further impairing mucosal immunity and predisposing to lower respiratory tract infections. More recently, there has been increasing attention to the role of eosinophils in COPD. Eosinophilic airway inflammation occurs in approximately 15% to 40% of individuals with COPD.[78] Increased eosinophils are a risk factor for exacerbation after deescalation of inhaled corticosteroid therapy.[79] During exacerbations, there is an increase in the number of eosinophils in sputum.[80] Elevated eosinophils are associated with patients' responsiveness to corticosteroids during both acute exacerbations and stable disease.[79,81–83] High eosinophils may define a distinct host Th2-predominant endotype with asthma overlap that is more responsive to corticosteroids.[84] Investigations that have excluded patients with a history of asthma have shown that high blood

eosinophils do not predict steroid responsiveness.[85] The use of eosinophil levels in directing therapy requires further investigation.[86]

Pulmonary inflammation continues after smoking cessation, in part because of permanent structural damage, or proinflammatory epigenetic changes.[87,88] Bacterial colonization in the lower airways is also an important determinant of the degree of airway and systemic inflammation in stable COPD.[89] Inflammatory mediators "spill over," producing systemic inflammation with elevated levels of C-reactive protein (CRP) or fibrinogen or elevated leukocyte count, or a combination of these factors. Elevated CRP is most strongly associated with ischemic heart disease in smokers. Systemic comorbidities such as vascular disease are major risk factors for mortality during COPD exacerbations.[90,91] Systemic inflammation caused by COPD is also hypothesized to be associated with anemia, osteoporosis, depression, and metabolic syndrome.[92–94]

Microbes in Stable Chronic Obstructive Pulmonary Disease

Increased bacterial colonization of the lower airways in COPD occurs as a result of chronic microaspiration, impaired clearance of bacteria, and frequent COPD exacerbations.[95,96] Patients with COPD frequently have microaspiration owing to gastroesophageal reflux caused by incoordination between breathing and swallowing.[97–99] Impaired mucociliary clearance in smokers reduces the ability to clear oral microbes from the lower airways, exacerbating inflammation. This leads to chronic cough with progressive incoordination of breathing with swallowing. Inhaled medications may also carry oral bacteria into the lower airway. This vicious cycle could explain the association of poor oral health and increased airway bacterial load, COPD exacerbations, and reduced lung function.[100–104]

Viruses and bacteria in the lower airway perpetuate the inflammation in COPD, causing damage through a number of mechanisms.[19,105,106] They may be ciliotoxic, invade epithelial cells and cause apoptosis, increase mucin production, and/or degrade humoral immunity via secretion of IgA proteases.[107,108] Bacterial molecules such as endotoxins, membrane lipoproteins, peptidoglycan fragments, and lipoteichoic acid activate the innate immune response, exacerbating inflammation.[109] Patients with COPD whose airways are heavily colonized with bacteria have higher concentrations of inflammatory cytokines and neutrophils in respiratory secretions.[106] High bacterial burden in the lower airway is associated with accelerated FEV_1 decline, more comorbidity, more exacerbations, and worse symptoms during exacerbations.[23,110–113]

In stable COPD, the rates of positive routine bacterial cultures of sputum vary between 22% and 83%.[114–116] However, interpreting sputum culture is difficult because of upper airway contamination, which reduces specificity, and failure to grow fastidious bacteria from the complex lower airway microbiome, which reduces sensitivity. In stable COPD, non–potential pathogenic microorganisms (non-PPMs) are isolated much more frequently than potential pathogenic microorganisms (PPMs).[114] Non-PPMs are usually oropharyngeal microbes such as *Corynebacterium* spp., *Neisseria* spp., *Enterococcus* spp., coagulase-negative staphylococci, viridans-group streptococci, and fungi such as *Candida* spp.[114] The most commonly isolated PPMs are *Streptococcus pneumoniae, Haemophilus influenzae,* and *Moraxella catarrhalis.*[58,114,117] Culture-independent technologies that assay microbial nucleic acids and antigens often have found potential pathogens in culture-negative respiratory specimens.[118,119] For example, one-third of patients with stable COPD have *H. influenzae* within airway epithelial cells and AMs.[120] High-throughput sequencing of microbial 16S rRNA genes yields relatively unbiased estimates of the relative abundance of uncultivable and cultivable bacteria.[121,122] The lower airways of healthy individuals harbor low levels of oral bacteria such as *Prevotella* spp. and *Veillonella* spp.[123,124] Culture-independent techniques have challenged the dogma that the lower airway is normally sterile, and provide evidence that there are residential organisms, especially in individuals with already damaged lungs. Oral anaerobes likely modulate the pulmonary immune response in health and disease. Important to note, enrichment of the lower airway microbiota with oral bacteria anaerobes is associated with augmented lung inflammation characterized by a Th17 phenotype.[125] Through use of culture-independent techniques, a distinct lower airway microbiota, characterized by enrichment with Gammaproteobacteria (which includes *Haemophilus* and *Moraxella*) and the presence of upper airway taxa, has been found in advanced-stage COPD (Global Initiative for Chronic Obstructive Lung Disease [GOLD] score of 3 or 4).[121,122,126,127] Multiple mechanisms present in this disease may affect the microbial composition of the lower airways. Patients with COPD frequently have microaspiration due to gastroesophageal reflux,[97–99] in addition to impaired bacterial clearance.[95,96] This vicious cycle could explain the association of poor oral health and increased airway bacterial load, COPD exacerbations, and reduced lung function.[100–104,128] Investigations into possible mechanisms using mouse models have shown that lower airway dysbiosis can lead to increased Th17 inflammatory changes and COPD phenotype.[129,130]

Respiratory viruses are also frequently found in patients with stable COPD. With culture or polymerase chain reaction (PCR) techniques to assess sputum, the most commonly found respiratory virus is respiratory syncytial virus (RSV), found in up to 23.5% of patients with COPD, followed by non-RSV viruses, such as rhinovirus, coronavirus, and parainfluenza virus, in 16.2% of samples.[131] Increased inflammation has also been reported with adenovirus.[132] High-throughput complementary DNA (cDNA) sequencing can identify viral transcripts in an unbiased approach. A fuller understanding of the role of the virome in stable COPD and in AECOPD awaits resolution of the technical challenges of high-coverage RNA sequencing in lower respiratory tract samples.

Microbes in Acute Exacerbation of Chronic Obstructive Pulmonary Disease

Patients with acute exacerbations have accelerated loss of lung function, which emphasizes the importance of identifying the underlying causes of these episodes.[133] Two-thirds of patients with a COPD exacerbation have bacteria, viruses, or both cultured from lower airway secretions. Aerobic bacteria are isolated in one-half of patients, respiratory viruses are isolated in one-third, and bacterial-viral coinfection is present in one-quarter of patients with acute exacerbations.[58,134] The increased incidence of AECOPD during winter months may reflect the significant role that viruses play in the pathogenesis of AECOPD.

H. influenzae, S. pneumoniae, and *M. catarrhalis* are the bacterial pathogens most commonly isolated during COPD exacerbations. The same three also colonize stable COPD patients, and higher bacterial loads have been associated with AECOPD.[58,117,118,135–138] Acquisition of a new bacterial strain frequently precedes AECOPD.[106,119,135,138,139] The increase in total bacterial load during a COPD exacerbation is relatively small compared with the total bacterial load.[138] In this conceptual model, the humoral and cellular immune responses to the new bacterial or viral strain likely drive the increased inflammation that causes the COPD exacerbation. Newer culture-independent investigations evaluating longitudinal changes in sputum microbiota showed that AECOPD is associated with decreased microbial diversity and increased proportion of Proteobacteria.[140] Furthermore, changes in lung microbiota are associated with levels of IL-8 in sputum, a key neutrophil chemoattractive cytokine. Distinct microbial populations can be identified in sputum between subjects with exacerbations marked by positive bacterial culture or elevated eosinophils.

Individuals with greater degrees of functional impairment, recent antibiotic use, or systemic steroid therapy have higher rates of isolation of gram-negative bacteria such as *Pseudomonas aeruginosa, Stenotrophomonas maltophilia,* and members of the Enterobacteriaceae family from sputum.[141,142] Patients with an $FEV_1 > 35\%$ of predicted value and no systemic steroid or antibiotic use within the preceding 3 months have a low probability of Enterobacteriaceae or *P. aeruginosa* in sputum culture.[142] *H. influenzae* and *P. aeruginosa* are more common in patients with poorer lung function.[137] Polymicrobial exacerbations occur with advanced pulmonary dysfunction and severe exacerbations.[134,143]

The role of "atypical" bacterial pathogens such as *Mycoplasma pneumoniae, Chlamydia pneumoniae,* and *Legionella pneumophila* in exacerbation is poorly defined, but they are rarely found in AECOPD.[56,131,144] Variations in reported rates of atypical pathogens could be related to the technical or geographic differences among reports.[112,145] When serology or *M. pneumoniae* antigen detection has been used to indicate the presence of *M. pneumoniae* as a pathogen, PCR and culture

frequently do not confirm its presence.[131,146,147] Alternately, two reports from Italy and Greece indicate demonstration of *M. pneumoniae* in 7% to 9% of patients with AECOPD with use of serologic and PCR techniques.[148,149] Controversy also exists regarding the role of *C. pneumoniae* in COPD exacerbations. Several well-conducted studies detected no *C. pneumoniae* or *L. pneumophila*,[131,147] whereas others detected *C. pneumoniae* in 6% to 9% of patients with AECOPD.[112,148] Chronic colonization with *C. pneumoniae* occurred in one-third of patients and was associated with worse pulmonary function in one study.[112]

Rhinovirus is the virus frequently associated with AECOPD and is present approximately 20% to 34% of the time.[131,134,150] Coronavirus, parainfluenza virus, adenovirus, influenza virus, and human metapneumovirus also occur but are less prevalent.[143,150] Viruses can predispose to bacterial infection with higher bacterial burden, more sputum eosinophils, greater lung function impairment, and longer hospitalization.[134,143] It is likely that viruses and bacteria induce independent inflammatory pathways, accounting for more severe presentations and poorer outcome of patients with coinfection.

TREATMENT

Nonantimicrobial Treatment of Steady-State Chronic Obstructive Pulmonary Disease

Treatment of stable COPD should improve the patient's symptoms and functional status, reduce the risk of exacerbations, and slow the decline of lung function.[5,8] Smoking cessation and avoidance of environmental exposure are the most important interventions to prevent disease progression and should be encouraged at every medical visit. Multiple different behavioral and pharmacologic treatments should be explored, including varenicline, nicotine replacement, and bupropion.[151–154] Pneumococcal, influenza, and combined tetanus, diphtheria, and acellular pertussis (Tdap) vaccination is also recommended in every COPD patient.[5,155]

Nonantimicrobial Treatment of Acute Exacerbation of Chronic Obstructive Pulmonary Disease

Systemic corticosteroids (either oral or intravenous) and bronchodilators are the cornerstones of pharmacologic treatment of AECOPD. Short-acting bronchodilators are preferred because they allow titration of the dose required and because there is no clinical trial that has evaluated the use of long–acting bronchodilators during AECOPD. Although for sicker patients nebulized bronchodilators are routinely used in the hospital, data suggest that similar bronchodilator effects occur with metered-dose inhalers.[156] A 10- to 14-day course of systemic corticosteroids reduces treatment failure by 46% during both inpatient and outpatient management of COPD exacerbations.[157] Systemic corticosteroids are preferred during an exacerbation because they reduce recovery time, improve lung function, and increase arterial oxygenation.[158,159,160,161,162] Systemic steroids also reduce the rate of early relapse and length of hospital stay. Although there are no data to support a specific dose or route of administration for steroids, GOLD guidelines recommend 30 to 40 mg of oral prednisolone per day for 10 to 14 days.[5,162–164]

Antibiotic Treatment of Acute Exacerbation of Chronic Obstructive Pulmonary Disease

Rationale for Antibiotics

Early antibiotic treatment of AECOPD in both the outpatient and inpatient settings has become nearly routine in clinical practice even though the role of bacteria in many cases of AECOPD is uncertain. The choice of antibiotic has changed during the past several decades; in part reflecting the changing resistance patterns of infecting bacteria and the availability of newer antibiotics that are taken less frequently, have improved antimicrobial activity, are less toxic, and are heavily marketed to health care providers. Studies evaluating the effect of antibiotic treatment are mostly small and are difficult to compare because of heterogeneous patient populations, diverse outcome measures, and varied definitions of failure. In addition, many different antibiotics and treatment durations have been evaluated, reducing comparability among individual studies. Two meta-analyses and a Cochrane review concluded that antibiotics improve outcome in AECOPD in inpatients, especially those requiring ICU admission.[157,165,166] Among hospitalized patients, antibiotics reduced hospital mortality by 78%.[167–169] Antibiotics also led to improved peak expiratory flow rate by 22%.[170] The largest study to date evaluating antibiotic efficacy is a retrospective cohort of 84,621 inpatients from 413 acute-care centers in the United States.[171] Administration of antibiotics within the first 48 hours reduced the need for mechanical ventilation after 2 hospital days (1.07% vs. 1.80%), lowered rates of inpatient mortality (1.04% vs. 1.59%), reduced readmissions (7.91% vs. 8.79%), and produced fewer treatment failures (9.77% vs. 11.75%). However, there was a significantly higher rate of *Clostridioides difficile* (formerly *Clostridium difficile*) in patients who were treated with antibiotics (0.19% vs. 0.94%). The weight of evidence supports antibiotic use for hospitalized patients; particularly those admitted to the ICU.

As opposed to relatively high-quality evidence supporting the use of antibiotics in the inpatient setting, there has been less convincing evidence to recommend antibiotics for outpatients. In the aforementioned Cochrane review, outcome was improved with antibiotic use when all outpatient studies were evaluated, but was not seen when the analysis was restricted to studies using currently available antibiotics.[40,166,172,173,174] However, a multicenter double-blind, placebo-controlled clinical trial of mild-to-moderate AECOPD documented that amoxicillin-clavulanate improves response to therapy within 9 to 11 days (74.1% vs. 59.9%) and increased the median time to the next exacerbation from 160 days in the placebo group to 233 days in those receiving antibiotics.[173] This study, the findings of which were published after the most recent meta-analysis,[166] suggests that antibiotics may be beneficial for some patients with mild-to-moderate AECOPD. Several other studies have demonstrated a delayed time to relapse or exacerbation with the use of antibiotics to treat AECOPD. In a retrospective cohort outpatient study of 270 patient visits (with relapse defined as a return visit within 14 days), antibiotics reduced the relapse rate to 19% (50/270) compared with 32% (29/92) among patients who did not receive antibiotics. Patients who received amoxicillin, however, had an even higher relapse rate of 54% (20/37) compared with those who did not receive antibiotics.[175] In another study, antibiotics added to oral corticosteroids increased the median time from second to third exacerbation from 189 days to 258 days and reduced mortality.[176] The limited effectiveness of antibiotics for less severe exacerbations may be a result of lower bacterial burden in this healthier group of patients. Doxycycline may not provide similar benefits. A very recent randomized, double-blind, placebo-controlled study comparing 7 days of doxycycline with placebo for outpatients receiving oral prednisolone among patients with GOLD stage 1 to 3 disease demonstrated neither a better initial response (87% in the doxycycline group vs. 83% in the placebo group) nor an increased time to second exacerbation (161 days vs. 138 days).[177] Determination of outpatients with mild-to-moderate AECOPD who would benefit from antibiotic treatment remains an area requiring further investigation.

There are few data comparing cost-effectiveness of using outpatient antibiotics versus withholding antibiotics. Ronaldson and colleagues have reported an observational study using the electronic medical records of AECOPD documented in the National Health Services database of the United Kingdom. The comparator groups were overall well matched, and >75% of patients had mild-to-moderate COPD. Use of antibiotics led to a decrease in costs, mainly driven by fewer hospitalizations, referrals to community respiratory teams, infections, and general practitioner visits.[178] This is an area that merits considerably more study given the potential problem of inducing greater levels of antibiotic resistance.

Whom to Treat

Given the large numbers of patients with COPD who develop AECOPD and the potential economic impact both in terms of antibiotic cost and toxicities of treatment, there has been much effort to identify patients who do not require antibiotics for AECOPD. Clinical investigations have used procalcitonin as a biomarker for bacterial infection in acute exacerbation in an attempt to limit unnecessary antibiotic use and reduce

the emergence of antibiotic resistance and *C. difficile* infection.[179–181] Whereas earlier studies included patients with AECOPD among the patient population with lower respiratory tract infections, several more recent studies have evaluated the effects of using procalcitonin measurement on patients hospitalized with the specific diagnosis of AECOPD. Corti and colleagues randomized patients to point-of-care procalcitonin testing or no testing; they used an algorithm that discouraged antibiotic use when the level was <0.25 ng/mL.[182] These investigators found significantly fewer days of antibiotic use among patients who were randomized to undergo procalcitonin testing. Wang and colleagues randomized patients with AECOPD who had a procalcitonin level <0.1 ng/mL to antibiotics versus no antibiotics and found no difference in outcome.[170] A meta-analysis demonstrated that procalcitonin-based protocols led to less initiation of antibiotics and less total exposure to antibiotics without a difference in multiple outcomes. However, the authors noted that the quality of the available evidence is low to moderate owing to the small study size and to methodologic issues.[183] A more recent population-based study evaluated the use of antibiotics over two time periods among hospitalized patients with AECOPD (505 US hospitals and 2,013,177 patients) in which procalcitonin testing was or was not incorporated. The authors found that there was a weak association toward less antibiotic use among hospitals that incorporated procalcitonin testing (performed 85% of the time on day 1 or 2 of hospitalization).[184] Procalcitonin testing was not associated with the duration of antibiotic treatment.[184] A study evaluating two institutions compared antibiotic use before and after introduction of procalcitonin testing and demonstrated that the use of this test was associated with a significantly decreased duration of antibiotic therapy (5.3 ± 3.2 days before vs. 3 ± 2.9 days after; $P = .01$). The number of patients receiving ≤1 day of therapy decreased from 43.8% to 14.5% in the after period, and there was no increase in readmission.[185] As procalcitonin is increasingly used in practice, its real-life impact on antibiotic usage and outcomes will need to be further studied.

The authors of the GOLD guidelines note that treatment with antibiotics is controversial but recommend antibiotic therapy for patients who have AECOPD who meet one of the following criteria: (1) have all three "cardinal" symptoms—increased dyspnea, increased sputum volume, and increased sputum purulence; (2) have two of the cardinal symptoms if increased purulence of sputum is one of the two symptoms; (3) have severe exacerbation that requires mechanical ventilation (invasive or noninvasive).[5]

In studies, patients who do not meet these criteria frequently have been prescribed antibiotics. Studies involving outpatients and inpatients have demonstrated that although approximately 80% of patients receive antibiotics, purulent sputum is found in only 39% to 64% of patients.[186–188] In a study from the United States, there was no correlation between the use of antibiotics and the presence of an indication for their use.[189] In a more recent study, 20% of patients who did not meet GOLD criteria for antibiotics received antibiotics before hospitalization, whereas approximately 20% who met criteria did not receive antibiotics.[190] A European COPD audit from 13 countries demonstrated that in 2010 and 2011, 38.6% of patients admitted to the hospital for a COPD exacerbation did not meet GOLD criteria for antibiotic use.[191] Although the use of bacterial cultures for treatment of AECOPD is debated, the use of purulence to define the need for antibiotics is based on several studies demonstrating a relationship between sputum color and/or neutrophils and positive bacterial cultures.[192–195] Sputum purulence has been an excellent guide for antibiotic use in several studies. In one, if sputum purulence was not present and antibiotics were withheld, therapy in only 2 of 32 patients failed.[195] In another study in which purulence was used to determine whether antibiotics would be prescribed, the therapeutic failure rate was 9% among those who had nonpurulent sputum and did not receive antibiotics versus 10% among those with purulent sputum who received antibiotics.[196] It is clear that many patients are prescribed antibiotics who do not need them, but the current state of knowledge does not clearly define the group who will be harmed more than they will be helped by a course of antibiotics. The GOLD recommendation for using antibiotics is based on symptoms, in particular sputum purulence, which remains the best guide to decide which patients with AECOPD require antibiotics.

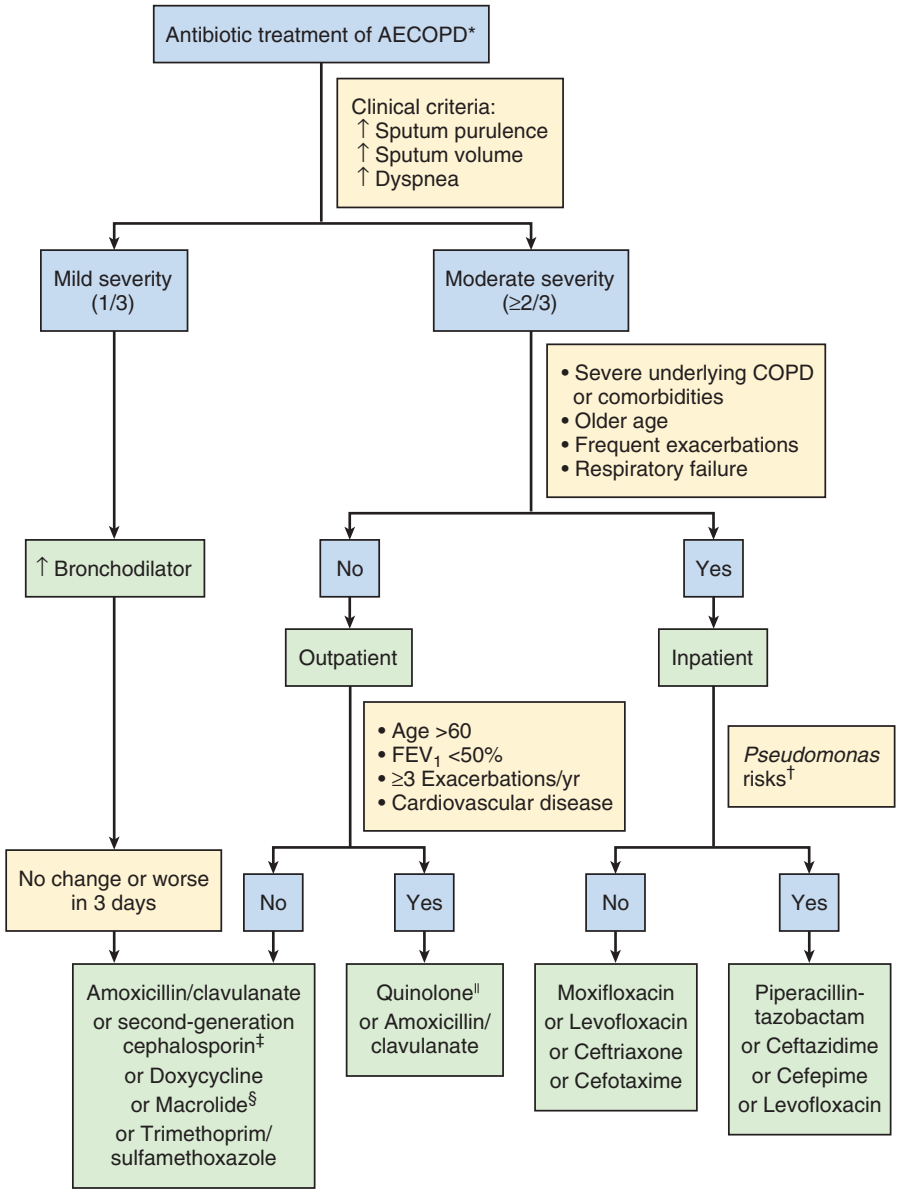
Choice of Antibiotic

Most recent comparative studies have used noninferiority designs to demonstrate equivalency between antibiotics. Among the more commonly studied antibiotics are macrolides (azithromycin and clarithromycin), second-generation cephalosporins (cefuroxime, cefpodoxime, cefdinir), penicillin or penicillinase inhibitors (ampicillin-clavulanate), quinolones (ciprofloxacin, levofloxacin, moxifloxacin, gemifloxacin), trimethoprim-sulfamethoxazole, and tetracyclines (doxycycline). Most of these trials have been performed in patients with acute exacerbation of chronic bronchitis. Several meta-analyses have been performed evaluating randomized controlled antibiotic comparison trials for treatment of AECOPD.[197–199] No agent or class is consistently superior in comparison to others in terms of clinical end points, although in any single study one agent may appear superior in terms of microbiologic eradication of one bacterium or overall microbiologic eradication.[197,200,201] There may be higher relapse rates when acute exacerbations are treated with amoxicillin compared with other antibiotics.[175] Increasing β-lactamase production by *S. pneumoniae, H. influenzae,* and *M. catarrhalis* challenges the use of amoxicillin or ampicillin as first-line empirical treatment of AECOPD.[202,203] An evaluation of 19,608 patients who were treated with either a quinolone antibiotic (13,469 patients) or macrolide antibiotic (6,139 patients) taken from a larger retrospective cohort study of hospitalized patients with AECOPD showed similar rates of treatment success, although less diarrhea occurred in the macrolide cohort.[204] Antimicrobial recommendations for the larger group of COPD patients with acute exacerbations are extrapolated from these data (Fig. 66.2).

Treatment is empirical, is based on risk factors for both antibiotic resistance and infection with Enterobacteriaceae or *P. aeruginosa,* and to some extent is dependent on the need for hospitalization (see Fig. 66.2). The specific choice of antibiotic should be made with an understanding of local bacterial resistance patterns, toxicity, allergies, drug interactions, and comorbidities. A sputum sample is not recommended routinely in either the GOLD guidelines or those of the American College of Physicians–American Society of Internal Medicine and the American College of Chest Physicians.[5,205] Sputum cultures and Gram stains are not reliable in terms of indicating the infecting pathogen. Furthermore, early sputum cultures do not seem to affect outcome with antibiotic treatment among inpatients.[171] An exception to this recommendation should be considered for patients in whom prior therapy has failed and patients at high risk for infection due to Enterobacteriaceae or *P. aeruginosa.*

Patients with AECOPD generally do not have significant systemic illness at presentation. By definition, chest radiographs do not demonstrate a new pulmonary infiltrate. However, because up to one-fifth of patients hospitalized for community-acquired pneumonia (CAP) have normal admission chest films but develop an infiltrate within 48 hours, providers may choose to dismiss a normal chest radiograph and prescribe antibiotics.[206] The combination of overlap between AECOPD and CAP along with antibiotic resistance leads to frequent use of broad-spectrum antibiotics in many hospitalized AECOPD patients.[189] If chest radiographs do not demonstrate an infiltrate at 48 hours, antibiotics can be tailored or stopped but still may be useful for AECOPD that meets other criteria.[207]

Despite increasing resistance to many of the older antibiotics, patients still respond to them clinically. Trimethoprim-sulfamethoxazole and ciprofloxacin were equally effective in a double-blind trial among patients with severe AECOPD requiring mechanical ventilation.[208] Surprisingly, bacterial susceptibility did not predict clinical success.[208] This may be due to the poor sensitivity and specificity of sputum samples in defining the bacteria that caused the AECOPD. Alternately, AECOPD may be driven by changes of a complex lower airway microbiome and not by a single microorganism. A shift in the lung microbiome could produce a flare of inflammation. Given the polymicrobial nature of the microbiome, organisms may not need to be effectively treated to reduce inflammation. In the near future, unbiased culture-independent techniques will more accurately describe the lung microbiome in COPD. A better understanding of microbiome changes preceding AECOPD and alterations produced by antibiotics will improve our understanding of the antibiotic response.



*If antibiotics used within past 3 months, use antibiotics from different class.
†*Pseudomonas* risk factors: >4 episodes antibiotics in past year, hospitalization within past 90 days, prior culture for *Pseudomonas*, FEV_1 <50% predicted.
‡cefpodoxime, cefuroxime, cefdinir.
§azithromycin, clarithromycin.
‖levofloxacin, moxifloxacin, gemifloxacin.

FIG. 66.2 Flowchart for antibiotic treatment decision in chronic obstructive pulmonary disease *(COPD)* exacerbation. *AECOPD,* Acute exacerbations of chronic obstructive pulmonary disease; *FEV_1,* forced expiratory volume in 1 second.

Although nebulized antibiotics have been used for the treatment and prevention of exacerbations in cystic fibrosis and bronchiectasis, there are limited published reports evaluating the efficacy of inhalational antibiotics for the treatment of AECOPD. One study of only 13 patients published in 2008 demonstrated that twice-daily nebulized tobramycin for 2 weeks decreased proinflammatory markers and resulted in a 42% decrease in COPD exacerbations compared with the 6 months before nebulizer use.[209] In a more recent study, 36 patients who were infected with *P. aeruginosa* were followed for 5 years on nebulized colistin. The authors reported a decrease in hospitalizations and duration of hospitalization but no decrease in exacerbation for patients not requiring admission.[210] Such therapy is enticing because if successful, it might limit adverse reactions caused by systemic levels of antibiotics. However, prolonged use of nebulized therapy may lead to microbial resistance. Nebulized amoxicillin-clavulanate for patients with COPD also has been shown to achieve adequate sputum concentrations and to have a good safety profile.[211] Larger, randomized, controlled efficacy studies in COPD patients are warranted.

Duration of Antibiotic Treatment

Outpatient studies have compared duration of therapy in acute exacerbations of chronic bronchitis. A regimen of 5 days of therapy with a quinolone, second-generation cephalosporin, or macrolide is as efficacious as and is associated with fewer adverse reactions than 7 days of antimicrobial therapy.[212–215] The GOLD guidelines currently recommend 5 to 7 days of therapy. Although there are no comparable inpatient trials, durations of therapy have varied between 7 and 14 days; 10 days of treatment have been used in studies of hospitalized AECOPD patients.[168,208] Eight days of therapy, which is currently recommended for ventilator-associated pneumonia, may suffice even in critically ill patients.[216] If tolerated, oral therapy is as effective as intravenous antibiotics.[168]

Treatment of Viral Infection

Patients with COPD would be considered at high risk for severe influenza infection and should be offered neuraminidase inhibitors such as oseltamivir or zanamivir when they develop an influenza-like illness during influenza season, even in the setting of a negative rapid virus detection study result.[217] Nonimmunized people with COPD who have had close family contact with a person with influenza should receive chemoprophylaxis with a neuraminidase inhibitor.[217]

Although numerous viruses other than influenza virus have been associated with AECOPD as noted earlier, there are no treatment options for these viruses currently. Inhaled ribavirin has been used therapeutically in infants and in patients with transplant infections with severe RSV infection, but reports from studies using this agent in patients with COPD are not available. As diagnostic and therapeutic modalities improve, specific antiviral therapy may become part of the armamentarium to decrease the duration of a COPD exacerbation.

PREVENTIONS OF ACUTE EXACERBATIONS OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

The goal of therapy is to avoid acute exacerbations because these are associated with accelerated declines in lung function.[133] β_2-Agonists (long-acting β_2-agonists [LABAs]) and anticholinergic bronchodilators (LAMAs) frequently combined in a single inhaler are effective in reducing exacerbations.[85] Oral phosphodiesterase inhibitors also reduce the frequency of acute exacerbations (Table 66.2).[5,218] These drugs relax airway smooth muscle, producing bronchodilation with improved lung function. They also have antiinflammatory activity, although the clinical significance of this is not clear.[219] Anticholinergic mediations also reduce sputum production in patients with chronic bronchitis. Corticosteroids in steady-state COPD are restricted to adjunctive therapy complementing long-acting bronchodilators in more severe cases of COPD and may be most effective in patients with characteristics of both COPD and asthma.[220] Inhaled corticosteroids do not reduce mortality but do reduce COPD exacerbations,[221] decrease inflammation, and stabilize lung function in moderate and severe COPD.[222] Unfortunately, inhaled corticosteroids increase the risk for pneumonia, which must be balanced with the benefit of less frequent exacerbations.[221,223] Other drugs such as nonselective and selective phosphodiesterase inhibitors (e.g., theophylline and roflumilast, respectively) may also be considered in cases of severe COPD with frequent exacerbations that are not adequately controlled with long-acting bronchodilators.[224,225]

Antibiotic Prophylaxis in Steady-State Chronic Obstructive Pulmonary Disease

Because bacterial colonization of lower airways plays a significant role in AECOPD, prophylactic use of antibiotics has been investigated. Successful use of prolonged, continuous oxytetracycline in a small number of patients was attempted in Britain as early as the mid-1950s.[226] The effectiveness of prophylaxis with oxytetracycline was not corroborated in later studies.[227,228] More recently, erythromycin, clarithromycin, and

TABLE 66.2 Modified GOLD Treatment Recommendations According to Stable State Patient Group Category

PATIENT GROUP	FIRST CHOICE	SECOND CHOICE	ALTERNATIVE CHOICE
Pharmacologic Treatment Options			
A	SABA prn	LABA or LAMA	Theophylline
Symptoms low	or	or	
Exacerbation: 0 or 1 (not leading to hospital admission)	SAMA prn	SABA and SAMA	
B	LABA	LAMA and LABA	SABA and/or SAMA
Symptoms high	or		Theophylline
Exacerbation: 0 or 1 (not leading to hospital admission)	LAMA		
C	LAMA	LABA and ICS	PDE4 inhibitor
Symptoms low	or LAMA and LABA		SABA and/or SAMA
Exacerbation: ≥2 or ≥1 leading to hospital admission			Theophylline
D	LAMA and LABA	ICS and LAMA	Carbocysteine
Symptoms high	or LAMA and LABA and ICS	or ICS and LABA and LAMA	Roflumilast
Exacerbation: ≥2 or ≥1 leading to hospital admission		or ICS and LABA and PDE-4 inhibitor or LAMA and LABA or LAMA and PDE-4 inhibitor	Theophylline Azithromycin
PATIENT GROUP	**ESSENTIAL**	**RECOMMENDED**	
Nonpharmacologic Treatment Options			
A	Smoking cessation	Physical activity Influenza and pneumococcal vaccination; Tdap	
B–D	Smoking cessation Pulmonary rehabilitation	Physical activity Influenza and pneumococcal vaccination; Tdap	

Symptoms low = mMRC 0–1 or CAT <10. Symptoms high = mMRC ≥2 or CAT ≥10.
CAT, COPD Assessment Test; *GOLD,* Global Initiative for Chronic Obstructive Lung Disease criteria; *mMRC,* modified British Medical Research Council questionnaire; *ICS,* inhaled corticosteroid; *LABA,* long-acting β_2-adrenergic agonist; *LAMA,* long-acting muscarinic antagonist; *PDE-4,* phosphodiesterase type 4; *SABA,* short-acting β_2-adrenergic agonist; *SAMA,* short-acting muscarinic antagonist; *Tdap,* combined tetanus, diphtheria, and acellular pertussis vaccine.
Modified from Vogelmeier CD, Criner GJ, Martinez FJ, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive lung disease 2017 report: GOLD Executive Summary. Eur Respir J. *2017;49:1750214.*

azithromycin have been the most widely studied prophylactic agents. Observational and placebo-controlled trials suggested that long-term macrolide prophylaxis is effective in reducing exacerbations and hospitalizations.[229–232] Macrolide use for 3 months has not resulted in significantly decreased rates of hospitalization or exacerbations of COPD.[233–235] A large-scale randomized, placebo-controlled study of azithromycin 250 mg daily for 1 year reduced AECOPD from 1.82 exacerbations per patient-year in the placebo group to 1.48 exacerbations per patient-year in the azithromycin group. Antibiotic treatment also extended time to first exacerbation from 174 to 266 days and improved quality of life.[232] The azithromycin group, however, had more hearing loss.[232] Among patients who became colonized, macrolide resistance occurred in 81% of the treated group versus 41% of the placebo control. Important to note, this trial excluded patients with cardiovascular risks including a resting heart rate >100 beats/min, prolonged QT (QTc) interval, or medications that increase the QTc interval. Therefore the potential for adverse cardiac reactions reported with macrolides was minimized in this study. There is still controversy about the increased risk for cardiovascular events reported with azithromycin use.[236,237] In addition, intermittent short courses of macrolides produced a fourfold increase in *S. pneumoniae* within 6 months.[238] The mechanisms that reduce exacerbation go beyond their antibacterial effect. These drugs are directly antiinflammatory, decreasing proinflammatory cytokine production, adhesion molecules, and reactive oxygen species.[239,240] In addition, macrolide administration in early emphysema leads to changes in microbiota and decreased levels of inflammatory cytokines in lower airways.[241] Important to note, the net antiinflammatory effect seemed to be mediated more by bacterial stress-induced metabolites than by direct macrolide effects on the host. Long-term macrolides have also been studied in cystic fibrosis and bronchiectasis, where they have led to fewer exacerbations of disease and stabilization of lung function.[242,243] For patients with low cardiovascular risk and frequent exacerbation in spite of adequate routine therapy, macrolides should be considered (see Table 66.2).[244] Intermittent (thrice-weekly) and daily azithromycin appear to provide similar benefits.[245] However, more widespread use of macrolides in less severe COPD cases is not currently recommended.

Another strategy to prevent AECOPD is intermittent antibiotic therapy. Moxifloxacin 400 mg for 5 days every 8 weeks for a total of six courses reduced the odds of exacerbation by 20% in the intention-to-treat analysis of the enrolled COPD patients and by 45% among patients with baseline purulent sputum. The authors reported no increased resistance to moxifloxacin among cultured bacteria but did find more gastrointestinal problems (4.7% with moxifloxacin vs. 0.7% with placebo).[246] Further research is needed to confirm that the benefits of this approach outweigh the risks of resistance and *C. difficile* colitis before this strategy gains widespread use.

Vaccination

The influenza, pneumococcus, and Tdap vaccines are recommended for patients with COPD. Influenza vaccination is recommended annually for persons with COPD by both the Centers for Disease Control and Prevention (CDC) and the Advisory Committee on Immunization Practices (ACIP).[5,8,155,247,248] The pneumococcal polysaccharide vaccine 23 (PPSV23) and the pneumococcal conjugate vaccine 13 (PCV13) are both recommended for patients older than 65 years and the PPSV23 is recommended for those younger than 65 with COPD and other comorbidities.

A systematic review of the literature evaluating influenza vaccine, including observational studies and randomized controlled trials in patients with COPD, concluded that the vaccine is immunogenic in patients with COPD and had no significant adverse reactions. Six of the seven studies evaluating effectiveness of the influenza vaccine revealed that seasonal influenza vaccine decreased the frequency of AECOPD, hospitalizations, outpatient visits, and all-cause and respiratory mortality.[249] Two other studies reported since the systematic literature review confirmed these findings.[250,251] It is of note that the efficacy or effectiveness of the influenza vaccine will be affected by the match between the circulating strains and the vaccine strains.

Pneumococcal vaccine is also recommended for all persons with COPD.[5,8,155] Pneumococcus is a common colonizing organism in addition to being a pathogen in this population. Some observational studies have demonstrated a decrease in pneumococcal bacteremia in the elderly and in hospitalization for pneumonia and mortality among elderly patients with chronic lung disease.[252,253] Others have not been able to corroborate these findings.[254] Based on a meta-analysis including 12 studies, there was a significant reduction in the likelihood of developing CAP but not specifically pneumococcal pneumonia, and a decrease in the likelihood of COPD exacerbation.[255] However, there was neither a decrease in all-cause mortality or cardiorespiratory mortality nor in the likelihood of all-cause or cardiorespiratory hospitalization. Studies evaluating the recent guidelines for sequencing the PPSV23 and the PCV13 vaccines in the COPD population are warranted.[256]

Several studies have reported that there is an additive effect when both the influenza vaccine and pneumococcal vaccine are used among patients with COPD. There was a significant reduction in hospitalization (63%) and in mortality (81%) when both vaccines were administered compared with no vaccine.[257] Two more recent cohort studies from Japan demonstrated better outcomes when both influenza vaccine and pneumococcal vaccine were administered compared with influenza vaccine alone.[258,259]

Given the relatively low rates of vaccination for influenza among patients with COPD in 2012 (48.5%) and pneumococcus among patients older than 65 years in 2016,[260] identifying barriers to vaccination among patients with COPD and evaluating interventions are critical to improve vaccination rates.

Although there have been no studies regarding efficacy of Tdap among patients with COPD, *Bordetella pertussis* has been reported to occur in a significant portion of patients with AECOPD when serologic diagnosis was used in Switzerland.[261] However, all cultures and PCR assay results for *Bordetella* spp. were negative in this study. Therefore it is not certain how to interpret the serologic data. Tdap is recommended by the CDC and ACIP for all adults ages 19 to 64 years, and it is reasonable that all patients with COPD receive this vaccine, particularly in light of the recent surge in cases of pertussis reported among adults.[155]

High rates of herpes zoster infection, due to either immune alterations or frequent steroid use, have been reported in patients with COPD.[260,262] In the population-based study by Yang and colleagues, the adjusted hazard ratio was 1.68 for COPD patients not taking steroids compared with the general population.[262] The hazard ratio increased to 2.09 for COPD patients taking inhaled corticosteroids, and was highest for those on oral steroids (adjusted hazard ratio of 3.00). This study evaluated only patients older than age 50 years, and it is not clear what the risk is for those diagnosed with COPD at a younger age. Zoster vaccine should be administered to patients with COPD per current ACIP guidelines.

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The complete reference list is available online at Expert Consult.

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