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Of the many conditions seen by those caring for acutely ill infants and children, none can be so frightening, and yet rewarding to treat, as severe upper airway obstruction. The severe consequences of an incorrectly managed child mandate that these children be approached rapidly with a structured plan for securing and maintaining a patent airway.

—The Editor

Infectious Causes of Upper Airway Obstruction in Children

Authors: **Ronald M. Perkin, MD, MA, FAAP, FCCM**, Professor and Chairman, Department of Pediatrics, The Brody School of Medicine at East Carolina University, Greenville, NC; **James D. Swift, MD, FAAP,** Medical Director, Sunrise Children's Hospital, Las Vegas, NV.

Peer Reviewers: **James E. Colletti, MD,** Senior Associate Consultant, Department of Emergency Medicine, Department of Pediatrics, The Mayo Clinic, Rochester, MN; **Kenneth H. Butler, DO,** Associate Residency Director, Emergency Medicine Residency Program, University of Maryland School of Medicine, Baltimore.

Why Are Children at Greater Risk?

Children are particularly susceptible to conditions affecting the upper airway for two basic reasons: the small size of the conducting air passages and the dynamics of air flow. The narrowest portion of an infant or child's airway is the cricoid ring—about 3.5 mm in diameter in a newborn. In addition, the supportive tissues of the extrathoracic airway are more compliant in children and, therefore, are more liable to collapse with increased inspiratory effort. This leads to further airway narrowing, which increases resistance to airflow.

Laminar flow occurs along smooth straight tubes. Under these conditions, resistance to airflow is proportional to the length of the tube and inversely related to the fourth power of the radius; i.e., a narrow tube is much more resistant than a wide one.

If the radius of the airway was halved, it would require 32 times the pressure drop (and a significant increase in the work of breathing) to maintain the same airway flow.[1] Small degrees of obstruction, therefore, cause an increase in respiratory effort, decrease in volume exchanged, and increased transit times in either inspiration or expiration, depending on the level of obstruction. Extrathoracic airway obstruction is aggravated by the physiological collapse of the airways during inspiration, while intrathoracic obstruction is aggravated by airway compression during forced expiration.[2,3]

The resistance to flow through an airway also is related to two physical characteristics of gas: viscosity and density. In a smooth airway where the flow is laminar, gas viscosity determines flow. With an abrupt narrowing of an airway, as occurs in subglottic inflammation, the flow is turbulent and density is the property determining airflow.[1,2]

Another important characteristic of turbulent flow which differs from laminar flow is that the pressure gradient required to produce a given gas flow rate is proportional to the square of the gas flow rate. Since resistance to airflow is defined as pressure gradient divided by flow rate, resistance is not constant in turbulent flow as it is

in laminar flow, but rises in proportion to the flow rate. This is a crucial clinical point: When a child with acute airway obstruction becomes distressed or agitated, and increases gas flow, resistance to airflow increases. Put simply, the harder a child with acute airway obstruction tries to breathe, the harder it is for him or her to breathe.

Turbulent flow often is audible and invariably is present when obstruction to gas flow is a problem. The nature of the sound transmitted and its timing in the respiratory cycle further may assist in diagnosing the level of obstruction. In general, obstruction of the softer, boggy tissues of the oropharynx and nasopharynx are transmitted as snores, while vocalizations from the supraglottic area commonly are muffled. Obstruction at the vocal cord and subglottic level causes the classical dysphonic inspiratory stridor typical of viral croup.[3] Bronchotracheal obstruction causes a predominantly expiratory wheeze and a whistle.

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Editorial Group Head: Valerie Loner
Managing Editor: Allison Mechem
Marketing Manager: Schandale Kornegay

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Careful observation of the respiratory effort, nature of the retractions, and evaluation of timing and pitch of breath sounds may assist in assessing the severity and location of obstruction.

Viral Croup

Croup is a common respiratory illness in children. The illness commonly is manifested in young children by a hoarse voice; dry, barking cough; inspiratory stridor; and a variable amount of respiratory distress that develops over a brief period of time.

Definition and Terminology. The term "croup syndrome" refers to a group of diseases that varies in anatomic involvement and etiologic agents and includes laryngotracheitis, spasmodic croup, bacterial tracheitis, laryngotracheobronchitis, and laryngotracheobronchopneumonitis.[4-6]

Acute viral infection is the most common cause of croup, but bacterial and atypical agents also have been identified. It generally is accepted that acute laryngotracheitis and spasmodic croup are caused by viral agents alone, whereas both bacterial and viral agents may be responsible for causing disease further down the respiratory tract, such as laryngotracheobronchitis and laryngotracheobronchopneumonitis. Bacterial tracheitis, also known as membranous or bacterial croup, involves infection with bacteria such as *Staphylococcus aureus, Haemophilus influenzae*, and *Corynebacterium diphtheriae* and will be discussed later in this review.

Epidemiology. Croup accounts for about 15% of respiratory tract disease seen in pediatric practice.[4,5] Viral croup is primarily a disease of children between 1 and 6 years of age, with a mean age of 18 months. In the United States, its peak incidence is about 5 cases per 100 children during the second year of life. Although most cases occur during the late fall and winter, croup can manifest throughout the year.

Etiology. Parainfluenza viruses (types 1, 2, and 3) account for more than 65% of croup cases, with parainfluenza virus types 1 and 2 responsible for the majority of illnesses and outbreaks.[4-6]

Other viruses associated with this disease include influenza A and B, adenovirus, respiratory syncytial virus (RSV), and measles. The most severe laryngotracheitis has been noted in association with influenza A viral infections.[6]

Pathogenesis. As with most respiratory infections, viral infection in acute laryngotracheitis, laryngotracheobronchitis and laryngotracheobronchopneumonitis begins in the nasopharynx and spreads to the respiratory epithelium of the larynx and trachea. Diffuse inflammation, erythema, and edema develop in the tracheal walls, and the mobility of the vocal cords becomes impaired. The portion of the trachea below the larynx (subglottic trachea) is the narrowest part of a child's upper airway. This area is surrounded by firm cartilage, and any swelling in that region encroaches on the airway and can restrict airflow significantly. This airway narrowing leads to audible inspiratory stridor, and the vocal cord swelling results in a hoarse voice.

With disease progression, the tracheal lumen becomes further obstructed by fibrinous exudate and pseudomembranes. Histologic sections of the larynx and trachea reveal marked edema, with cellular infiltration of histiocytes, lymphocytes, plasma cells, and polymorphonuclear leukocytes.

Further extension of the disease from the trachea into the bronchi and alveoli results in laryngotracheobronchitis and laryngotracheobronchopneumonitis, respectively. However, the progressive obstructive disease at this level is usually the result of secondary bacterial involvement.[4]

In spasmodic croup, histology of the subglottic tissues shows noninflammatory edema. Accordingly, it is presumed that there is no direct viral involvement of the tracheal epithelium in this entity and that the obstruction is due to the sudden occurrence of noninflammatory edema within the submucosa of the subglottic trachea. Although there is an association with the same viruses that cause acute laryngotracheitis, the reason for this sudden edema is unknown. It has been suggested that spasmodic croup represents more of an allergic reaction to viral antigens than direct infection.

Clinical Presentation. *Acute Laryngotracheitis.* Acute laryngotracheitis typically starts with rhinorrhea, pharyngitis, a mild cough, and low-grade fever of a few days duration. However, after a short period, usually 12-48 hours, upper airway obstruction signs and symptoms are noted. The child develops a characteristic "barking" cough, hoarseness, and inspiratory stridor, with or without fever.

Physical examination reveals a child who has a hoarse voice, coryza, a normal or mildly inflamed pharynx, and a slightly increased respiratory rate. The speed of progression and degree of respiratory distress can vary substantially. Most cases are characterized by only the hoarseness and barky cough, with no other evidence of airway obstruction. These symptoms gradually normalize within 3-7 days. In other cases, an increasing severity of obstruction is evident and accompanied by increasing heart and respiratory rates, flaring of alar nasi and cyanosis with supra- and infraclavicular and sternal retractions. Affected children become restless and anxious with the development of progressive hypoxia and require close monitoring. The duration of illness in more severely affected children usually is 7-14 days. Children with previous airway surgeries, intubations or protracted newborn courses may have residual scar tissue which may predispose them to more severe croup and thus require a more careful assessment and conservative management strategy.

Spasmodic Croup. Spasmodic croup tends to occur at night in young children between 3 months and 3 years of age. Often, it is difficult at the onset to distinguish laryngotracheitis from spasmodic croup. The child may have cold symptoms and otherwise look well. Initially, the child awakens at night with sudden dyspnea, croupy cough, and inspiratory stridor. Fever is not present, and gentle reassurance and administration of moist air provide relief. The symptoms are the result of sudden subglottic edema, and the child can have repeat attacks on the same night and for the next three or four successive nights.[6] Spasmodic croup may be differentiated from laryngotracheitis with endoscopic examination. The laryngeal mucosa appears pale and boggy in spasmodic croup and erythematous and inflamed in acute laryngotracheitis.

Much has been written about differentiating spasmodic croup from viral croup, but this differentiation often is of limited usefulness for clinicians.[7,8]

Differential Diagnosis. The most frequent serious differential diagnostic problem has been distinguishing acute epiglottitis from acute laryngotracheitis. Ascertaining the child's immunization history is vital. Since the introduction of the *H. influenzae* type b vaccine in 1990 in the United States, cases of epiglottitis have declined markedly. However, because organisms other than *H. influenzae* occasionally can cause epiglottitis, this diagnosis cannot be forgotten.

In acute epiglottitis, the important differential points on clinical examination are lack of a croupy cough, drooling, toxic appearance, growing anxiety and apprehension, a sitting posture with the chin pushed forward and refusal to lie down. If the patient is completely stable and the posterior pharynx is examined, a cherry-red epiglottis would be present. In contrast, the child who has acute laryngotracheitis will have a barky cough, be comfortable supine, and be less apprehensive. On visual inspection, the epiglottis appears normal. Lateral neck and chest radiographs have been used to help make the diagnosis, but they usually are not recommended when epiglottitis is suspected because of the tenuous condition of these patients. When epiglottitis is suspected, the clinician must avoid agitating the patient, which could aggravate the child's already compromised respiratory state, and should have equipment for intubation readily available. Classic radiographs of a child who has laryngotracheitis show the characteristic "steeple sign," or airway narrowing in the subglottic area; in epiglottitis, these films classically demonstrate the "thumb sign" of the swollen epiglottis. Radiographs, if performed, should be used as an adjunct to help confirm the diagnosis; clinical correlation is key to the diagnosis.

Other diagnoses for a child presenting with acute upper airway obstruction include foreign body aspiration and angioneurotic edema. Acute angioneurotic edema usually presents with other evidence of swelling of the face and neck. Laryngeal diphtheria, although rare these days, should be considered. Important information in this regard is the immunization history, clinical evidence of pharyngeal involvement, greater degree of hoarseness, and relative slowness of disease progression. Other conditions to consider include retropharyngeal or peritonsillar abscess, subglottic stenosis, infectious mononucleosis, and bacterial tracheitis.

Diagnosis. Croup is diagnosed primarily on clinical grounds. Radiographs of the neck have been used to confirm the diagnosis of laryngotracheitis and exclude other causes of the croup syndrome.[6] The hallmark finding in croup is a tapered narrowing of the subglottic trachea (steeple or pencil sign) due to localized edema, as contrasted with the normally domed or shouldered configuration in the region.[9] The narrowing of the trachea should be visible on both frontal and lateral views because the edema is circumferential. Be aware of a potential false-positive steeple sign on frontal view due to a normal sloping of the subglottic trachea when the vocal cords are relaxed and, therefore, separated.[9] The lateral neck film may reveal overdistention (ballooning) of the hypopharynx during inspiration. The epiglottitis and the aryepiglottic folds appear normal.

However, these classic radiologic findings are present in only 50% of cases of viral croup, and many children who have croup will have normal findings on radiography. Furthermore, the steeple

Table 1. Clinical Scoring System for Assessing Children with Stridor

SIGN	0	1	2	3
Stridor	none	with agitation	mild at rest	severe at rest
Retraction	none	mild	moderate	severe
Air entry	normal	normal	decreased	severe decrease
Color	normal	normal	cyanotic with agitation	cyanotic with rest
Level of consciousness	normal	restless if disturbed	restless if undisturbed	lethargic

Total score: < 6 = mild severity; 7-8 = moderate severity; > 8 = severe.

Adapted from Rothrock SG, Perkin R. Stridor: A review, update, and current management recommendations. *Pediatr Emerg Med Rep* 1996;1:29-40.

sign frequently is present in radiographs obtained from children who do not have croup, depending upon the phase of respiration.[4]

Therefore, because radiologic findings do not correlate well with clinical findings, the diagnosis of croup should rest on clinical grounds and not upon radiologic findings.[6,10] The purpose of obtaining neck radiographs in a patient with suspected croup is not to document the diagnosis as much as it is to exclude other causes of upper airway obstruction that require intervention, such as a foreign body. These studies should be limited to children whose illnesses are atypical and whose respiratory status is stable.

Because laryngotracheitis is a disease of the upper airway, alveolar gas exchange usually is normal, and hypoxia and low oxygen saturation will be undetectable until a patient's condition is severe. Most children who have laryngotracheitis or spasmodic croup have normal findings on pulse oximetry. Serial observations remain the most accurate methods of monitoring a child who has acute laryngotracheitis. Pulse oximetry may be more useful in patients who have laryngotracheobronchitis or laryngotracheobronchopneumonitis, which involves the lower airway.

Most children who have spasmodic croup or acute laryngotracheitis do not require intubation or direct visualization of the airway. However, a child whose illness is severe, who has signs of epiglottitis, or whose condition fails to follow the benign course of viral croup, direct airway visualization may be necessary. There is general agreement that the patient in whom complete obstruction of the airway is imminent requires laryngoscopy and intubation in a well-controlled environment, preferably under a predesignated protocol with anesthesia and otolaryngology part of the response team.

Assessing Severity of Viral Croup. While most children with croup have mild symptoms that will not progress, a subset of children may develop progressive airway obstruction and respiratory failure.[3] Several clinical scoring systems have been proposed for assessing children with stridor.[3,11-13] Most of these "croup scores" are based on five clinical signs: level of consciousness, cyanosis, stridor, air entry and retractions. Each sign is given an arbitrary range of numerical values to represent the gradiations of severity of that sign. While the Westley Score[11] seems to be commonly used, no one particular scoring system has proven to be superior to any other. We suggest a modified Westley Score as provided in Table 1.

Croup scores are a relatively subjective measure of severity. Features suggesting a higher potential for respiratory failure have been identified, including age younger than 6 months, stridor at rest, cyanosis, decreased level of consciousness and hypercapnia.[3,14,15] One study found that clinicians were only 33% sensitive in identifying hypoxemia by physical examination in this population of children.[16] Hypoxemia generally indicates advanced disease and impending respiratory failure. Hypercapnia also has been found to be a predictor of clinical deterioration.[3,15]

Treatment. *Mist Treatment.* The mainstay of treatment for children who have croup is airway management. Since the 19th century, mist treatment has been used to treat croup symptoms. Cool mist is as effective as hot steam, and it avoids the risk of burns from hot water. Cool mist moistens airway secretions and soothes inflamed mucosa. Also, the humidity decreases the viscosity of tracheal mucus secretions.[4] Animal studies have shown that the mist may activate mechanoreceptors in the larynx that produce a reflex slowing of respiratory flow rate.[4] Young children best tolerate cool mist vapor delivered by aerosol while sitting on the parent's lap. Although cool mist is viewed as a safe and simple method to relieve croup symptoms, the humidity can intensify bronchospasm in children who have croup with wheezing due to laryngotracheobronchitis or pneumonitis. These children should have a trial cool mist that is discontinued if the wheezing continues or worsens.

There are only a few studies that have tested the efficacy of moist air in patients with croup and, unfortunately, none of them has documented a significant benefit.[6,7] Therefore, the use of humidified air for children with viral croup is a tradition without proven efficacy.[17,18]

Epinephrine. Often croup requires no other treatment beyond mist therapy, but occasionally pharmacotherapy also is necessary. Nebulized epinephrine has been used to treat severe croup symptoms for almost 30 years and has made tracheotomy for croup virtually nonexistent.[6,19] Prior to the use of nebulized epinephrine, hospitalization of patients with viral croup was associated with tracheotomy rates between 2.9 and 13% and mortality rates between 0.09 and 2.7%.[6]

Racemic epinephrine is a 1:1 mixture of the d- and l- isomers of epinephrine. The mechanism of action is believed to be stimulation of alpha-adrenergic receptors with subsequent constriction of capillary arterioles. This results in fluid resorption instead of capillary leakage from interstitial space and a consequent decrease in laryngeal mucosal edema.[6] Additional studies have

shown that equal doses of only the l-isomer of epinephrine have the same beneficial effects as the racemic form.[20]

Although nebulized epinephrine may have a dramatic effect on croup symptoms, decreasing inspiratory stridor and intercostal retractions, common adverse reactions to both the racemic and l-isomer forms, including tachycardia, hypertension, and myocardial infarction, may limit their desirability in certain populations, such as children with significant congenital heart disease.[6,21] In addition, the effect of the medication is brief (< 2 h), and as its activity diminishes, symptoms of croup can reappear (rebound phenomenon). Administration of nebulized epinephrine to children who had croup in the emergency department frequently led to hospital admission in the 1980s because of concern about the rebound phenomenon. Recent review and assessment of those recommendations suggest that it is safe to dismiss a child who has received nebulized epinephrine for croup from the emergency department after 3-4 hours of observation.[22-25] For safe discharge the child should meet the following conditions: no stridor at rest; normal air entry; normal color; normal level of consciousness; and received one dose of dexamethasone orally or intramuscularly (IM).

Nebulized epinephrine should be utilized in children who have evidence of respiratory distress, children who appear ill with symptoms consistent with croup, children with previous airway procedures and/or croup and stridor at rest. A dose of 0.25-0.75 mL of 2.25% racemic epinephrine solution in 2.5 mL of normal saline can be given via nebulizer as often as every 20 minutes. If racemic epinephrine is not available, a 5-mL mixture of l-isomer epinephrine (1:1,000) and saline may be used.

Corticosteroids. After decades of debate about the potential benefits of systemic corticosteroids in children who have laryngotracheitis, there is now ample evidence to support their use.[6,7] Clinical trials have demonstrated clear improvement in children who have viral laryngotracheitis treated with oral or parenteral steroids compared with those who received placebo. Clinical improvement, however, usually is not apparent until up to six hours after initiation of treatment.[4]

A review of the published literature during the past 10 years reveals a number of studies documenting the efficacy of corticosteroids in treating moderate, severe, and even mild presentations of croup. Additionally, two meta-analyses have been published—one in 1989 and another 1999.[26,27]

The majority of these studies are well-done trials (randomized, blinded, and placebo-controlled). They have differed in several respects: specific corticosteroids used, route of administration, dose of corticosteroids, and severity of croup. The most commonly used corticosteroids employed have been dexamethasone, given IM or orally, and budesonide administered by nebulization.

Beneficial effects of glucocorticoids evident from these studies include reductions in symptom severity (i.e., croup score); in the need for hospitalization after treatment in an emergency department; in the duration of hospitalization or time spent in an emergency department; in the necessity for admission to an intensive care unit; and in the need for further drug therapy (i.e., nebulized epinephrine). Recent commentaries, editorials, and review articles found in the literature all recommend corticosteroids for croup, even with mild presentations.[28,29]

No clinically significant adverse effects were reported in the majority of the studies described above, which is not surprising from the use of a single corticosteroid dose. In a study of nebulized dexamethasone, two neutropenic patients developed bacterial tracheitis, although it was unclear what role was played by dexamethasone.[30]

Dexamethasone has been evaluated the most extensively in published studies and has become the corticosteroid most often used in clinical practice. Dexamethasone is used because it has potent glucocorticoid (anti-inflammatory) activity as well as a long duration of action (> 48 hours). Earlier studies documented the beneficial effects of a single IM dose of 0.6 mg/kg (approximately equivalent to 4 mg/kg of prednisone in anti-inflammatory potency) in moderate to severe croup.[7,31] In the mid-1990s, studies using oral dexamethasone (single dose of 0.6 mg/kg) began appearing in the literature.[7,19,32] Oral administration of dexamethasone has the advantage of less distress of drug administration to the patient, who already is distressed, as compared to IM injection or nebulization with a face mask.[32]

Two studies further evaluated lower doses of dexamethasone, 0.15 mg/kg and 0.3 mg/kg. One study compared oral dexamethasone at doses of 0.25 mg/kg, 0.3 mg/kg, and 0.6 mg/kg in a randomized, double-blind manner, in the treatment of children hospitalized with croup.[33] All doses were equivalent in their clinical benefit of reducing croup scores, the need for nebulized epinephrine, and duration of hospitalization.

More recently published studies have evaluated dexamethasone in milder forms of croup, using lower doses, and given orally.[28,29] Geelhoed compared oral dexamethasone, 0.15 mg/kg, with placebo in a double-blind, randomized manner in 100 children with mild croup (croup score of 0.9/6; no stridor at rest).[28] The number of children who returned to medical care with continued croup was significantly lower ($P < 0.05$) in those receiving dexamethasone. The number of children admitted to a hospital, or the duration of croup symptoms did not differ significantly between the groups.[28]

Dexamethasone also has been evaluated in a nebulized route of administration.[30] This study was randomized, double-blind, and placebo-controlled, yet it included a relatively small number of patients and thus was somewhat limited in statistical power. These researchers found that dexamethasone, when given to children with moderate croup, resulted in improved croup symptoms at four hours, but it did not alter hospital admission rates four or 24 hours after treatment. The authors do not recommend using nebulized dexamethasone in the treatment of croup.

Budesonide is a potent synthetic corticosteroid that is commercially available as a metered-dose inhaler and as a nasal inhaler for the treatment of asthma and allergic disorders.[34] Trials evaluating budesonide for croup have compared it to placebo, nebulized epinephrine, and dexamethasone in patients with mild, moderate, and severe croup.[35-40]

Compared with placebo, budesonide reduced croup symptom severity and allowed earlier discharge from an emergency department.[35] Several studies have directly compared nebulized

Table 2. Management of Viral Croup

SEVERITY OF SYMPTOMS	INTERVENTION
Mild croup	• Oral dexamethasone (0.15-0.3 mg/kg) • Discharge to home
Moderate croup	• Nebulized racemic epinephrine or equivalent dose of l-epinephrine • Oral dexamethasone 0.3-0.6 mg/kg or nebulized budesonide 2 mg • Observation for 3-4 hours and discharge to home or admit to hospital ward
Severe croup	• Nebulized racemic or l-epinephrine • Dexamethasone 0.6 mg IM • Trial of heliox • Admit to intensive care unit

Adapted from Kaditis AG, Wald ER. Viral croup: Current diagnosis and treatment. *Pediatr Infect Dis J* 1998;17:827-834.

budesonide to dexamethasone (orally or IM) and generally have found them equally efficacious in reducing symptoms and duration of hospitalization. The beneficial action of nebulized budesonide occurs more rapidly.[36-38] One study, however, found IM dexamethasone superior to budesonide in reducing symptoms (croup score) five hours after treatment. Treatment with either drug resulted in fewer hospitalizations as compared to placebo.[39]

A recent, larger study compared three therapies, oral dexamethasone alone, nebulized budesonide alone, or their combination, in the treatment of mild-moderate croup.[40] Measures of croup score improvement, hospital admission rates, time spent in, or return visits to the emergency department were equal among all groups following treatment, and the authors concluded that oral dexamethasone should be the preferred treatment.

In conclusion, significant evidence now exists in the published literature to document the beneficial effects of corticosteroids in the treatment of croup, even in outpatients with milder presentations. *(See Table 2.)* Dexamethasone, given orally or IM, is effective, as is nebulized budesonide. Dexamethasone given orally may be the preferred treatment in most patients due to its ease of administration and low cost.[6,40,41] Although limited evidence indicates that oral doses of dexamethasone as low as 0.15 mg/kg are effective, further research is needed prior to acceptance of this regimen.

Helium-Oxygen Mixture. A mixture of helium and oxygen has been used to help manage children with severe viral croup.[42-45]

Although helium offers an additional tool in the treatment of various airway and pulmonary problems, it has no inherent therapeutic effect.[42] As such, it can be used only as a temporizing agent to allow time for therapeutic agents to work or for the natural resolution of the disease.

To be effective, helium must be administered in concentrations of 60-80%.[42] Helium concentrations less than 60% significantly blunt the density advantage.[43,44] A mixture of 80% helium and 20% oxygen is ideal, and premixed tanks can be obtained.

Epiglottitis

Epiglottitis is a very serious infection of the epiglottis and supraglottic structures that results in acute airway obstruction and, if not managed correctly, death may occur.[46-49] Since the development of the *H. influenzae* type B vaccine, this disease process has become unusual, but must be considered in a child with dyspnea and stridor. Although epiglottitis occurs mainly in children, it can occur at any age.[46-48]

Disease Mechanisms. Acute epiglottitis almost always is caused by *H. influenzae* type B (Hib), which can be cultured from direct epiglottic swabs or blood cultures. Other causative organisms are usually bacteria but occasionally viruses or Candida organisms.[46,52-54]

Direct invasion by Hib causes cellulitis with marked edema of the epiglottis, aryepiglottic folds, ventricular bands, and arytenoids. As edema increases, the epiglottis curls posteriorly and inferiorly. Infection of the supraglottic larynx may extend but does not usually reach the subglottis or the laryngeal lymphatic system. It is important to realize that in some cases the epiglottis itself may be only minimally involved but that the edema and inflammatory swelling of the uvula, aryepiglottic folds, false cords, and arytenoids causes equally severe obstruction. Supraglottitis is the more appropriate term to describe infection which involves all supraglottic structures.

Clinical Manifestations. Epiglottitis is rare; most commonly occurring in children younger than age 5 years, with an annual incidence that varies from region to region. With the introduction of Hib vaccination, it virtually has disappeared.[55-59]

Up to half of patients have preceding upper respiratory tract symptoms. The onset of epiglottitis typically is abrupt, with duration of symptoms usually fewer than 24 hours and early toxicity.

Children may present with a very sore throat, difficulty swallowing because of pain, respiratory distress, drooling, a choking sensation, irritability, restlessness, and anxiety. The temperature is high, usually between 38.8° and 40°C (101.8°-104°F). Sighing respirations, mild stridor, retractions, and mild tachypnea may occur. Less common symptoms include cough, delirium, lethargy, hoarseness or aphonia, vomiting, chills, anorexia, cervical adenopathy, wheezing, and hypotonia.

The child naturally assumes a posture that maximizes the diameter of the obstructed airway: sitting and leaning forward with hyperextension of the neck and protrusion of the chin.

Previous publications have demonstrated a downward trend in the age at presentation in epiglottitis; up to 36% of all cases of epiglottitis occur in children younger than 2 years of age.[60-63] Analysis of these publications reveals that the history and presenting signs of infants younger than 2 years old are more variable, thus making distinction from other causes of acute upper airway obstruction more difficult. Signs and symptoms not routinely described in children with epiglottitis but often observed in infants with epiglottitis include the absence of fever, the presence of only low-grade fever, a history of antecedent urinary tract infection, a prominent "croupy" cough and a "non-toxic" appearance.[60-63]

Children with epiglottitis are at risk for total airway obstruction. The enlarged, inflamed supraglottic ring can progress to

respiratory obstruction with unexpected suddenness. The exact mechanism is not clear, and the early view that the swollen epiglottis collapses into the laryngeal inlet may be incorrect. Epiglottitis progresses to death in about 7% of children who do not have secured airways.[59] With accurate early recognition and elective intubation, the mortality rate should approach zero.

Complications are uncommon and may include exudative tonsillitis, cervical lymphadenitis, and otitis media. Evidence of pneumonia or atelectasis is sometimes seen on the chest radiograph. Meningitis, septic arthritis, and pericarditis occurring with epiglottitis are rare; routine lumbar puncture is unnecessary.

The diagnosis is often clear when a child has a classic presentation. However, it is sometimes difficult to differentiate epiglottitis from viral croup. The distinguishing features of epiglottitis include the absence of spontaneous cough and the presence of drooling and agitation. Toxicity, high fever, and sore throat also may occur with bacterial tracheitis, uvulitis, and retropharyngeal or parapharyngeal abscess. Nasopharyngeal diphtheria is rare now, but may mimic acute epiglottitis and is associated with serosanguinous discharge. Noninfectious causes mimicking epiglottitis include angioedema, a pharyngeal burn, and a foreign body that is in the valleculae or larynx or that penetrates the pharyngeal tissues.

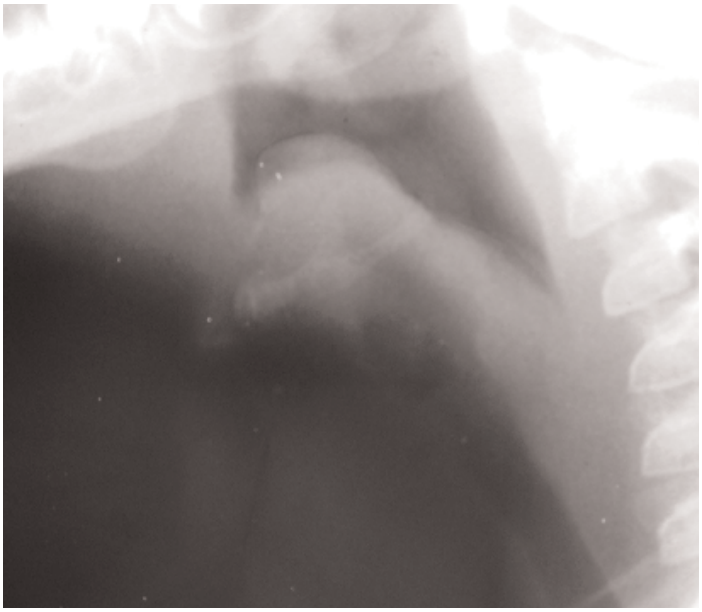
Chronic epiglottic enlargement may be seen with neck radiotherapy for cancer, granulomatous lymphangitis, or lymphangiectasis and infection with the human immunodeficiency virus. The chronicity of symptoms makes these conditions easily distinguishable from acute epiglottitis. Similarly, congenital anomalies of the airway and laryngeal papillomatosis usually are quite distinct by the presence of recurrent or persistent symptoms.

Diagnosis. Investigations should be left until the airway is secured. The diagnosis is confirmed under direct visualization.[46,64] Detection of the responsible organism is important for guiding antibiotic management. Direct culture of supraglottic tissues reveals the causative organism in the majority of patients. The blood culture is positive for Hib in about 70% of cases.

In atypical cases, where the patient is completely stable, lateral radiographic views of the soft tissues of the neck may be obtained with the patient's airway carefully monitored throughout the procedure. The best view of the anatomic structures of the upper airway is obtained with patient upright. In patients with epiglottitis, the hypopharynx is dilated, and the normal cervical lordosis may be replaced by a straight or kyphotic contour. The valleculae are narrowed and may be obliterated. There is marked enlargement of the epiglottis and thickening of the aryepiglottic folds. An obliquely imaged epiglottis may artifactually appear wide because both the left and right sides of the epiglottis are being imaged adjacent to each other. This should not be confused with a truly enlarged epiglottis. Epiglottitis is recognized on lateral neck film by the classic "thumb sign," which describes the rounded, thickened, edematous epiglottis, giving it the approximate shape and size of the dorsum of an adult's thumb. *(See Figure 1.)*[48]

Objective criteria have been used to diagnosis epiglottitis in children on lateral neck films. These include the measurement of the following ratios: the epiglottic width to the third cervical vertebral body width (EW/CSW) of greater than 0.5 and epiglottic width to epiglottic height (EW/EH) of greater than 0.6.[48]

Figure 1. Lateral Neck Radiograph in Child with Epiglottitis



The hypopharynx is dilated, there is marked enlargement of the epiglottis, and the aryepiglottic folds are thickened and convex superiorly.
(All radiographs in this issue are courtesy of Rajiv K. Sharma.)

Management. Because of the high risk of complete airway obstruction, great care must be should be taken in managing a child with suspected epiglottitis. Once a clinician suspects this diagnosis, the child should be constantly attended by an individual skilled in airway management. Delays of 2-3 hours have proved fatal. Every effort should be made to reduce the time needed to secure a patient's airway, preferably in the operating room under the direction of an airway management team (anesthesia and otolaryngology) and initiate antibiotic therapy. During the interval, unnecessary stress for the child should be prevented, the throat should not be examined, and radiographic confirmation usually is omitted.

The airways should be secured as early as possible after diagnosis. A large body of literature attests to the safety and efficacy of elective nasotracheal intubation, which is the treatment of choice. Optimally the child's airway should be secured by the most skilled individual available, usually an anesthesiologist with an ENT surgeon immediately accessible if the child requires a tracheotomy. A short period of airway maintenance is usually all that is required. A nasotracheal tube that is 0.5 mm smaller than that predicted by the patient's age is recommended. The criteria for extubation include being afebrile and swallowing comfortably. Repeat examination of the epiglottis and supraglottic structures by direct laryngoscopy or fiberoptic bronchoscopy is not normally necessary. Complications occurring after extubation may be laryngeal edema and subglottic granulations. Long-term complications of nasotracheal intubation are rare.

In about 10% of children with epiglottitis in whom there is severe airway obstruction, idiopathic pulmonary edema may occur before or after insertion of endotracheal tubes.[65] The hypo-

thetical mechanism is an increased pulmonary blood flow secondary to airway obstruction, causing markedly negative intrapleural pressure with increased venous return to the right side of the heart and decreased left ventricular output. These changes increase the pulmonary microvascular pressure and produce a role in altering vascular permeability, but it is not a necessary prerequisite. Continuous positive airway pressure in intubated patients may decrease the occurrence of pulmonary edema.

Until the results of sensitivity tests are known, the child should be treated with an intravenous antibiotic to cover the majority of possible isolates. Increasing numbers of *H. influenzae* produce β-lactamase (up to one-third in some communities); therefore, initial treatment is usually a second-generation cephalosporin such as cefuroxime or a third-generation cephalosporin such as cefotaxime or ceftriaxone. If the isolate is proved to be susceptible, ampicillin, a less expensive agent, may be substituted. If group A *S. pyogenes* is isolated form the airway, penicillin is the drug of choice. When *S. aureus* is isolated, a semisynthetic penicillinase-resistant penicillin or glycopeptide such as vancomycin should be used depending on sensitivity patterns. Erythromycin should be used for *C. diphtheriae*.

Although there have been some recommendations to use corticosteroids, no controlled data support their use; in fact, they may be hazardous because of the side effects.[5] Therapy with inhaled epinephrine has not proven beneficial.

Bacterial Tracheitis

Bacterial tracheitis usually presents as severe upper airway obstruction, most often in a child who has had viral croup for several days.[1] Alternative names are membranous laryngotracheobronchitis, pseudomembranous croup, and membranous croup.[5,66]

Disease Mechanisms. Direct bacterial infection of the tracheal mucosa is caused by a variety of organisms.[66-72] *S. aureus* is the most common bacteria reported. Influenza virus, parainfluenza virus, and enterovirus have been isolated in children with bacterial tracheitis, suggesting that bacterial invasion may occur in an airway already inflamed by viral infection.[72] Bacterial tracheitis is a recognized complication of measles.[70] In a review of tracheal cultures obtained from patients with bacterial tracheitis, 40% contained anaerobic organisms and 75% of the cultures contained more than one organism.[70] This suggests that, once injured (perhaps by an initial viral process), the tracheal mucosa becomes vulnerable to bacterial colonization, leading to opportunistic infection.[68]

The bacterial infection causes a diffuse inflammatory process of the larynx, trachea, and bronchi with mucopurulent exudate and semiadherent "membranes" within the trachea.[66] These membranes contain numerous neutrophils and cellular debris, and cause major obstruction.

Clinical Manifestations. Bacterial tracheitis most commonly occurs in children in the age group vulnerable to viral croup. The initial clinical features are similar to those of viral croup, but there is a high fever (usually greater than 38.5°C), the child appears toxic, and there is severe airway obstruction. About half of cases have clinical or radiographic evidence of pneumonia. A rare complication is toxic shock syndrome.[66]

The differential diagnosis includes severe laryngotracheobronchitis (viral croup), laryngeal or tracheal foreign body aspiration, and epiglottitis. Bacterial tracheitis has a longer duration, a more typical barking cough than epiglottitis, and no drooling. Diphtheria once was a serious consideration as the most common cause of "membranous croup," which produces severe airway obstruction because of adherent membranes that separate from the airway wall with difficulty, causing bleeding.

Diagnosis. A lateral neck radiograph shows subglottic narrowing and often reveals findings of radiopaque material in the airway lumen (pseudomembrane).[66,67,71] This may be confused with a foreign body.[9,67]

Endoscopy reveals thick mucopurulent material and sloughed epithelium.[66] The epithelium forms a sheetlike pseudomembrane that separates easily from the airway wall without hemorrhage and sometimes extends from the trachea to the major bronchi.

Bacterial cultures of tracheal secretions reveal the organism(s). The results from blood cultures usually are negative. White cell counts may be high or normal.

Management. In a child suspected of having bacterial tracheitis, management should occur in a pediatric intensive care unit. Intubation usually is needed to relieve the airway obstruction, which takes days to resolve.[66] Intermittent positive-pressure breathing is sometimes needed. Repeated suctioning is usually required because of the thick secretions and their tendency to form crusts, with intubation lasting 3-11 days. Meticulous care of the endotracheal tube, with adequate humidification and frequent suctioning, is imperative. Endotracheal tube plugging is a common complication. In extreme cases, reintubation with a fresh endotracheal tube and initiation of more aggressive pulmonary toilet is required. Sometimes, repeat endoscopic removal of the pseudomembrane is required. Occasionally, tracheotomy is needed if endotracheal tube management of secretions proves too difficult.

Nebulized epinephrine or corticosteroids do not relieve the acute airway obstruction. Intravenous antibiotics are vital, and should be directed initially against the four common pathogens until the results of tracheal cultures are known. The usual choice is oxacillin (150 mg/kg/day with four equal doses given every 6 hours) and a third-generation cephalosporin such as cefotaxime (150 mg/kg/day with four equal doses given every 6 hours) until the results of cultures and sensitivities are known.

Retropharyngeal Abscess

Retropharyngeal abscess (RPA) is a relatively uncommon infection of the space anterior to the prevertebral layer of the deep cervical fascia.[73-78] This infection is most common in children younger than 3 or 4 years, because of the rich concentration of lymph nodes in this space. These lymphatic chains begin to atrophy about the third or fourth year of life. Thus 50% of cases of RPA occur between 6 and 12 months of age, and the vast majority occur before age 6 years.[74,76,78] The symptoms of RPA can be similar to those of acute epiglottitis; however, children with acute epiglottitis usually appear more toxic and progress to respiratory distress much more rapidly than those with RPA. The unique abnormal physical finding in older children and adults with RPA,

which is an asymmetric bulge of the posterior pharyngeal wall when inflammation has progressed to phlegmon or frank abscess, may be difficult to appreciate in infants or toddlers.[73,74,77]

Retropharyngeal lymph node infection in children classically results from extension of oropharyngeal infections including pharyngitis, tonsillitis, and adenitis.[74,75] The infection progresses through three stages: cellulitis, phlegmon, and abscess. Probably only the last stage requires surgical drainage. Contrast-enhanced CT is invaluable in delineating the stage of inflammation, but boundaries (incomplete vs complete ring enhancement) between phlegmon and abscess stages may be blurred. Trauma, often caused by a fall while holding a pencil or stick in the mouth, and dental infections are the usual underlying causes of RPA in older children and adults.[73,74]

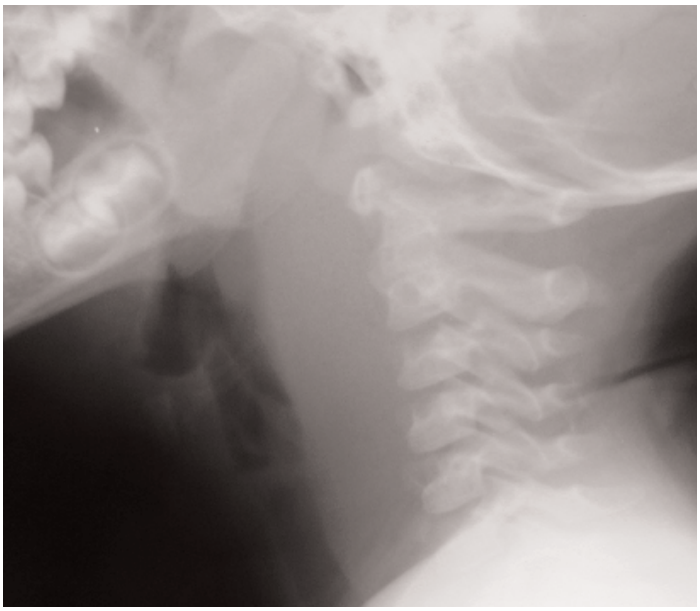
Most symptoms and signs of RPA are identical to those of acute epiglottitis. They include fever, irritability, oropharyngeal pain, unusual positioning of the head and neck, and odynophagia. As the infection progresses, there may be refusal to swallow solids or liquids including saliva, which leads to pooling in the oropharynx and overflow drooling. The most suggestive physical signs of both diseases are hyperextension of the neck, torticollis, muffled voice, stridor, and other signs of upper airway obstruction.[78] In several case series of patients with RPA, the classic physical sign of RPA, which is bulging of the posterior pharynx, was noted; however, this was present in fewer than 50% of infants.[78] The major causative organisms are *S. pyogenes, S. aureus*, and oropharyngeal anaerobic bacteria.[73,76]

The differential diagnosis includes acute epiglottitis, foreign body aspiration, vertebral osteomyelitis, hematoma (particularly in boys with hemophilia), and lymphoma.

Diagnostic studies commonly include roentgenograms of the cervical area and CT scans. To minimize false-positive results, a lateral view roentgenogram may be helpful when obtained with the patient in sitting position with the neck hyperextended and during inspiration, if possible. *(See Figure 2.)* Normal buckling of upper cervical prevertebral soft tissues that occurs during flexion or expiration can simulate a retropharyngeal mass.[78] A retropharyngeal space measured from the anterior aspect of the second cervical vertebral body to the soft tissues of the posterior pharyngeal wall greater than 7 mm (normal, 4-7 mm) or a retrotracheal space greater than 14 mm in a child (measured from the anterior/inferior aspect of C6 to the posterior pharyngeal wall) suggests a mass caused by phlegmon, pus, or blood.[3,73,75,78]

Another way to interpret abnormal thickening of the retropharyngeal soft tissue is the fact that in an infant or young child, the soft tissues between the posterior aspect of the aerated pharynx and the anterior aspect of the vertebral column should not exceed the anteroposterior diameter of the cervical bodies.[48] However, in infants, it is common to see "pseudothickening" of the retropharyngeal soft tissues when the lateral radiograph is taken without the neck being well extended. Supportive evidence that there is true widening of the retropharyngeal soft tissues includes apex anterior convexity of the retropharyngeal soft tissues. The only radiographic feature that can differentiate abscess from cellulitis is the identification of gas within the retropharyngeal soft tissues.[48]

Figure 2. Lateral Neck Radiograph in a Child with Retropharyngeal Abscess



Notice that the retropharyngeal space measured from the anterior aspect of the second cervical vertebral body to the soft tissue of the posterior pharyngeal wall exceeds 7 mm.

In suspicious cases, CT should be performed to define the extent of disease and help predict cases in which a drainable fluid collection is present.[3,48] On CT, a low-attenuation, well-defined area with an enhancing rim is suspicious for a drainable fluid collection.

Management of RPA depends on the maturity of the infection and the degree of airway compromise. Cellulitis or a phlegmon requires only targeted antibiotics active against common oral facultative and anaerobic bacteria.[74] Historically, the treatment of an abscess has been surgical drainage. However, several recent studies have shown that medical management alone can be curative for more than 50% of children with RPA (usually defined by CT).[73,77] Security of the airway is of paramount importance. All patients should have a secure intravenous catheter placed and be given nothing by mouth. If a patient is stable and the benefit of avoiding a surgery outweighs the risk of complications from RPA, a trial of intravenous antibiotics for 24-48 hours can be initiated. If there is no improvement, either clinically or as determined by imaging, then the decision may be made to perform surgical drainage.

Suppurative complications of RPA include rupture of the abscess with aspiration, asphyxiation, or pneumonia; empyema; and mediastinitis.[78] Vascular complications include thrombophlebitis of the internal jugular vein and erosion through the carotid artery sheath.[3,48,73]

Diphtheria

Pharyngeal diphtheria is now extremely rare in the United States. A single probable case was reported to the Centers for Disease Control and Prevention in 1998.[79] The disease occurs primarily among unimmunized or poorly immunized members of socioeconomically disadvantaged groups.[80] Of the 41 reported

respiratory diphtheria cases in the United States from 1980 to 1995, none of the patients had been adequately vaccinated, and the four children who died following severe illness had not received any diphtheria immunizations.[80] Appropriate vaccination protects against both severe disease and death.

The most notable physical finding is the grayish brown diphtheritic pseudomembrane, which may involve one or both tonsils or may extend widely to involve the nares, uvula, soft palate, pharynx, larynx, and tracheobronchial tree. Involvement of the latter structures can cause life-threatening respiratory obstruction. Removal of the membrane reveals a bleeding and edematous submucosa. Soft-tissue edema and prominent cervical and submental adenopathy may create a bull-neck appearance. The potent toxin elaborated by *Corynebacterium diphtheriae* may produce cardiac toxicity and neurotoxicity.[84] The diagnosis, which may be strongly suspected on epidemiologic and clinical grounds, should be confirmed by culture of the pseudomembrane in Loeffler's or tellurite selective medium. Pharyngeal diphtheria is treated with equine hyperimmune diphtheria antitoxin and penicillin or erythromycin.

Conclusion

The child's airway is vulnerable to obstruction secondary to its anatomy and small size. Although there are many potential causes of upper airway obstruction, a few diagnoses predominate. Common airway infections can progress to critical airway obstruction and hypoxia, causing organ damage or death.

Individuals caring for children must be prepared to diagnose and treat airway emergencies expeditiously. Appropriate management of acute upper airway obstruction tests the organization of emergency care systems. Successful management of airway emergencies in children requires a team approach, including the skills of the primary physician and the staff of the emergency department, radiology department, and operating room staff. Management of these cases can be anticipated, and protocols can be established.

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Physician CME Questions

41. Emergency room management of severe viral croup may include all of the following *except:*
    A. oxygen.
    B. racemic epinephrine.
    C. ribavirin.
    D. steroids.
    E. helium.

42. The most common infectious cause of laryngotracheitis is:
    A. influenza virus.
    B. mycoplasmae.
    C. adenovirus.
    D. parainfluenza virus.
    E. respiratory syncytial virus.

43. Which of the following findings would be most consistent with acute spasmodic croup?
    A. Cherry-red color and swelling of the epiglottis
    B. Diffuse erythema of the laryngeal mucosa
    C. Firmly adherent exudative membranes in the posterior pharyngeal and laryngeal areas
    D. Marked facial swelling associated with laryngeal edema
    E. Pale, boggy appearance of the laryngeal mucosa

44. A previously healthy 4-year-old girl is transported via ambulance because of a rapid onset of severe respiratory distress. In the emergency department, she appears toxic and very anxious. She is drooling and prefers to sit forward. The girl recently immigrated to this country and has had little health care. Of the following, these findings are most consistent with the diagnosis of:

A. acute angioneurotic edema.
B. bacterial tracheitis.
C. epiglottitis.
D. laryngotracheobronchitis.
E. retrophyaryngeal abscess.

45. Stridor correlates with upper airway obstruction and is associated with which of the following?
A. Viral croup
B. Retropharyngeal abscess
C. Epiglottitis
D. Recurrent respiratory papillomatosis
E. All of the above

46. Which one of the following statements is true regarding the management of viral laryngotracheitis (croup)?
A. Neck radiographs are essential for establishing the diagnosis and assessing the severity of illness.
B. Racemic epinephrine has a long duration of action and effectively decreases the length of illness.
C. Parenteral corticosteroids are indicated only for severe cases of croup.
D. Tracheotomy rarely is required.
E. In children with viral croup, plain radiographs of the chest are probably more useful than soft-tissue radiographs of the neck.

47. All the following statements regarding infectious causes of upper airway obstruction in children are true *except:*
A. Hospitalization in an ICU is mandatory for children with epiglottitis and bacterial tracheitis.
B. The patient with viral croup who receives racemic epinephrine to relieve symptoms in the emergency department must be hospitalized.
C. *S. aureus* is the most common bacteria reported in children with bacterial tracheitis.
D. Nebulized epinephrine or corticosteroids do not relieve acute upper airway obstruction in children with bacterial tracheitis.
E. Diseases that cause supraglottic obstruction have the potential to rapidly obstruct this part of the airway.

48. Which one of the following statements about retropharyngeal abscess (RPA) is true?
A. RPA is a rare but serious cause of subglottic airway obstruction.
B. The microbial agent mOst likely to cause an abscess is *Haemophilus influenzae* type b.
C. A retropharyngeal span wider than 7 mm anterior to the inferior border of the second cervical vertebral body is suggestive of RPA.
D. Racemic epinephrine and parenteral corticosteroids are useful treatments in children with RPA.
E. A retropharyngeal abscess is a type of peritonsillar abscess that occurs specifically in school-aged children.

49. Children with moderate to severe croup should be considered for dexamethasone therapy.
A. True
B. False

50. Because of the risk of airway obstruction, children with possible epiglottitis should have their airwayS closely monitored in the ED.
A. True
B. False

In Future Issues:

Meningitis

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PEDIATRIC Emergency Medicine Reports

The Practical Journal of Pediatric Emergency Medicine

Recurrent Respiratory Papillomatosis

Juvenile recurrent respiratory papillomatosis (also known as laryngeal papillomatosis), a condition with benign, wartlike tumors in the respiratory tract, may be associated with upper airway obstruction.[1] It occurs at all ages, with about half of all cases appearing in the pediatric age group. It is characterized by the growth of papillomatous lesions, particularly in the larynx, that have a high rate of recurrence after excision. Laryngeal papillomas are the most frequent masses to arise within the airway in older children, and morbidity can be severe.[2]

Disease Mechanisms. It is now recognized that human papillomavirus (HPV) causes most cases of recurrent respiratory papillomatosis.[3] The clinical presentation and course of the disease have not been definitively linked to a particular HPV type.

The replicating virus may cause overgrowth of squamous epithelial cells. The papillomata are multiple projections, each with a connective tissue stalk covered by well-differentiated stratified squamous epithelium. The tumors are benign but present obstructive problems because of their localization in the vocal cords or other sites. At presentation, papillomata usually are present on one or both vocal cords with the anterior commissure, supraglottis, or subglottis also commonly affected.[1,3]

Clinical Manifestations. Recurrent respiratory papillomatosis can occur at any age, with the youngest reported patient being 1 month of age.[4] In the pediatric age group, about half of patients have symptoms during the first year of life, although clinical recognition of the disease often is delayed. Patients usually come to medical attention late, with some degree of airway obstruction, including stridor, together with hoarseness or a weak cry.[3] Life-threatening upper airway obstruction may occur. Although the lesions usually are localized within the larynx, spread to other areas (pharynx, esophagus, trachea, and lung parenchyma) may occur and indicates a more pessimistic outlook.[2,3]

The most usual course of the disease is for the papilloma to continue to grow locally despite surgical removal and without significant spread. Over time, the majority of cases in children undergo spontaneous remission (analogous to skin warts). It traditionally was believed that the onset of puberty is associated with remission, although this view has been challenged.[1]

The condition is diagnosed by inspection of the larynx, either by indirect means such as fiberoptic laryngoscopy in an office or by more formal laryngoscopy and bronchoscopy when tissue biopsies can be taken.

Multiple endoscopies usually are required for further investigation and management, and flexible bronchoscopy is the method choice for surveillance. Although ultrasound examination of the airway correlates with laryngoscopic findings, it is seldom used in clinical practice.

Management. During the acute phase of management, the airway should be monitored and otolaryngology consulted for both diagnosis and therapeutic intervention. Recurrent respiratory papillomatosis is frustrating to treat because lesions often are recurrent and sometimes aggressive. The focus of management is to ensure a safe airway without causing irreversible long-term scarring, especially affecting the voice. Total removal of the disease is impossible in most cases because undeclared viral infection occurs in apparently normal adjacent areas and the degree of destruction necessary to clear the field would in most cases require too great a degree of tissue damage.

In particularly aggressive phases of the disease, total removal may require laryngoscopies with excision as often as twice a week. The frequency of the surgery is dictated entirely by how rapidly the papilloma regrows and is individualized for each patient. All patients can expect multiple endoscopies and surgical removal.

The most widely used surgical method for removing recurrent respiratory papilloma is use of the carbon dioxide laser, which acts as a very precise "knife," vaporizing the papilloma with minimal damage to the underlying larynx. However, it does not prevent regrowth any better than the older surgical methods, such as direct removal. In the hands of experienced endoscopists, there is a low to moderate incidence of laryngeal scarring. If possible, tracheotomy should be avoided because of the risk of seeding of the disease to the tracheotomy site.[3]

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PEDIATRIC Emergency Medicine Reports
The Practical Journal of Pediatric Emergency Medicine

Infectious Causes of Upper Airway Obstruction

Clinical Scoring System for Assessing Children with Stridor

SIGN	0	1	2	3
Stridor	none	with agitation	mild at rest	severe at rest
Retraction	none	mild	moderate	severe
Air entry	normal	normal	decreased	severe decrease
Color	normal	normal	cyanotic with agitation	cyanotic with rest
Level of consciousness	normal	restless if disturbed	restless if undisturbed	lethargic

Total score: < 6 = mild severity; 7-8 = moderate severity; > 8 = severe.

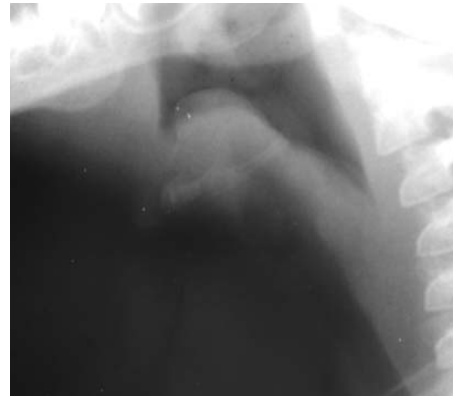
Adapted from Rothrock SG, Perkin R. Stridor: A review, update, and current management recommendations. *Pediatr Emerg Med Rep* 1996;1:29-40.

Management of Viral Croup

SEVERITY OF SYMPTOMS	INTERVENTION
Mild croup	• Oral dexamethasone (0.15-0.3 mg/kg) • Discharge to home
Moderate croup	• Nebulized racemic epinephrine or equivalent dose of l-epinephrine • Oral dexamethasone 0.3-0.6 mg/kg or nebulized budesonide 2 mg • Observation for 3-4 hours and discharge to home or admit to hospital ward
Severe croup	• Nebulized racemic or l-epinephrine • Dexamethasone 0.6 mg IM • Trial of heliox • Admit to intensive care unit

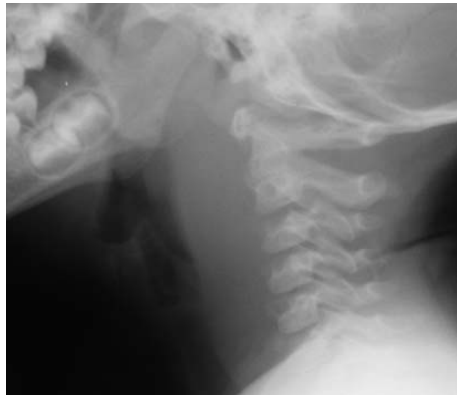
Adapted from Kaditis AG, Wald ER. Viral croup: Current diagnosis and treatment. *Pediatr Infect Dis J* 1998;17:827-834.

Lateral Neck Radiograph in Child with Epiglottitis



The hypopharynx is dilated, there is marked enlargement of the epiglottis, and the aryepiglottic folds are thickened and convex superiorly.
(Radiograph courtesy of Rajiv K. Sharma.)

Lateral Neck Radiograph in Child with Epiglottitis



Notice that the retropharyngeal space measured from the anterior aspect of the second cervical vertebral body to the soft tissue of the posterior pharyngeal wall exceeds 7 mm.
(Radiograph courtesy of Rajiv K. Sharma.)

Supplement to *Pediatric Emergency Medicine Reports*, November 2002: "Infectious Causes of Upper Airway Obstruction in Children." *Authors:* **Ronald M. Perkin, MD, MA, FAAP, FCCM**, Professor and Chairman, Department of Pediatrics, The Brody School of Medicine at East Carolina University, Greenville, NC; **James D. Swift, MD, FAAP,** Medical Director, Sunrise Children's Hospital, Las Vegas, NV.

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One Year Later: Emergency Department Response to Biological Terrorism

Part II: Smallpox, Viral Hemorrhagic Fevers, Tularemia, and Botulinum Toxins

Author: **Kevin Coonan, MD,** Department of Emergency Medicine, Madigan Army Medical Center, Fort Lewis, WA.

Peer Reviewer: **Steven Winograd, MD, FACEP,** Attending Physician, Department of Emergency Medicine, Jeannette District Memorial Hospital, Jeannette, PA; St. Clair Memorial Hospital; University of Pittsburgh Medical Center; Pittsburgh, PA,

The threat of bioterrorism continues to loom over the United States with emergency departments likely to be the front lines. In the second article of this two-part series, the author updates the emergency department (ED) physician on the current status of smallpox, viral hemmorhagic fevers, tularemia, and botulism as both disease entities and weapons of bioterrorism.

—The Editor

Smallpox

Clinical Features. Few diseases have rivaled smallpox as a cause of human suffering and death, with epidemics of smallpox surpassing other diseases such as plague, cholera, and yellow fever as instruments of morbidity and mortality.[1] It is ironic that the possibility of an outbreak is more feasible after this disease has not been seen in the last quarter-century and vaccination programs were halted in the wake of this accomplishment.[2-4] Known repositories of variola are limited to the two sites specified by the World Health Organization (WHO): the Centers for Disease Control and Prevention (CDC) in Atlanta and VECTOR in Novosibirsk, Russia. The former Soviet Union had created weapon forms of variola in ton quantities. While the stockpiles of smallpox reportedly were destroyed, the accounting of such is incomplete and the true disposition is uncertain.[5] In addition, other nations strongly are suspected of maintaining hidden stocks as part of clandestine biological weapons programs.[6,7]

Smallpox is extremely contagious. In one of the last outbreaks in Europe, a single index patient infected 11 others, who subsequently infected 175 others, resulting in 35 deaths. Due to the delay in clinical diagnosis, some 10,000 contacts of patients had to be quarantined and 20 million were vaccinated.[8] In conditions of low temperature and low humidity, aerosolized variola is very stable, and has resulted in widespread, hospital-based epidemics. The predominant method of transmission is by respiratory droplet requiring face-to-face (within 2 meters) contact, although patients with cough frequently generate infectious aerosols that may result in airborne spread. Infected bed linens and other fomites also have resulted in a small number of outbreaks. In previous epidemics it was common to see 10-20 secondary cases from each infected patient, eventually resulting in one-third of all contacts becoming infected.[9,10] Infectivity is maximal during the first week of rash, and is increased markedly in patients who manifest a cough.[6]

The case fatality rates are strain-dependent, with fewer than 1% in immunologically naïve patients infected with the variola minor strain, but 30% of unimmunized and 3% of vaccinated patients infected with variola major. Soviet scientists had developed strains with considerably higher virulence and transmissibility. This, coupled with the large inoculum expected from an intentional aerosol release, likely would result in much higher fatality rates.[11]

Following a 10- to 14-day incubation period, patients with smallpox present with acute onset of fever, prostration, malaise, myalgias, rigors, vomiting, backache, and cephalgia.[10] Patients appear toxic, and some fair-skinned patients will exhibit an erythematous exanthem. Acute delirium is seen in 15% of patients. After 2-3 days, the pathognomic rash begins as an enanthem on the oropharynx, and within 1-2 days develops on the face, forearms, and hands. It then spreads to the trunk and lower extremities. The lesions begin as macules and display synchronous development into deeply rooted papules. These lesions subsequently evolve into vesicles and tense, often umbilicated, pustules.[12] Approximately 8-9 days after eruption, the pustules involute and form scabs, eventually crusting on days 14-16. The crusting of the lesions is associated with resolution of fever. A week later, the crusts separate, leaving hypopigmented scars, particularly on the face.[6] Lesions may be so extensive as to appear confluent. Cough and bronchitis commonly are associated with infection, but pulmonary consolidation is unusual except in fatal cases. Secondary bacterial infections are rare. Monkeypox is identical in presentation, except that lymphadenopathy is more common and mortality is only 10-15%.[13]

Variola minor shows a similar progression of symptoms with less toxicity and often smaller lesions. Both show the typical progression starting with the face and lower arms, with fewer lesions on the abdomen, and with all lesions in adjacent anatomic areas at the same stage of development.[14] One-fifth of variola major resulted in atypical presentations. Modified smallpox often was seen in those with prior vaccination, with sparse, short-lived skin lesions and infrequent toxicity. Even those with recent immunization were susceptible to a brief upper respiratory infection after exposure. Flat-type smallpox has been reported in 2-5% of cases, with severe systemic toxicity associated with slow development of flat, soft, velvety skin lesions; it usually is fatal (95% in unvaccinated patients, 66% in vaccinated). Hemorrhagic smallpox, seen most often in pregnant women, shows a rapid progression, with development of mucosal bleeding, petechiae, and ecchymoses prior to death.[12,14] Asymptomatic infections likely are more common than previously appreciated, and virus may be recovered from the oropharynx of such individuals. The potential transmission from these asymptomatic carriers is not known, but probably is limited.[9,14]

Diagnosis. Historically, experienced clinicians in endemic areas reliably could diagnose smallpox based on clinical features. However, in nonendemic areas, variola minor frequently was confused with varicella. However, varicella lesions are more superficial, evolve in a variety of stages over a given anatomic region, spare the soles and palms, and are more prominent on the trunk.[8] Other exanthems and pustular dermatosis that were less frequently confused with smallpox lesions include erythema multiforme with bullae, contact dermatitis, and impetigo.[6,10]

Treatment. Treatment largely is supportive and symptomatic. Strict isolation to reduce secondary transmission is essential starting with onset of rash until all scabs have separated. Anyone exposed to a patient in this time period must be vaccinated and quarantined for 17 days.

Antiviral therapy historically has not been useful. Both cidofovir and ribavirin inhibit variola in vitro, and both had significant but lesser activity against monkeypox and vaccinia.[15] Cidofovir, currently licensed in the United States for treatment of cytomegalovirus (CMV) retinitis at a dose of 5 mg/kg, is protective in a mouse cowpox model at a 20-fold higher dose.[16] Cidofovir only is available as an intravenous formulation, and must be administered with concomitant hydration and probenecid to reduce the risk of nephrotoxicity.[17] There are no in vivo studies of ribavirin for poxvirus infections. Other proposed antiviral therapies are undergoing study.[18,19]

Vaccination is effective in preventing infection or attenuating disease. It is possible that EDs will assist in a public health disaster by providing vaccination, and it is certain that any vaccine-related complications would require ED intervention.

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Vaccination within five years prior to or within 2-3 days after natural exposure provides almost complete protection.[12] Revaccination is associated with prolonged immunity. To add a margin of safety, the WHO recommends revaccination if exposure occurs more than three years after vaccination. Vaccination 4-5 days after exposure attenuated natural disease and reduced death rates.[8]

Vaccinia immune globulin (VIG) has limited potential as a post-exposure prophylactic agent if given within a week of exposure in conjunction with vaccination.[10] It is given at a dose of 0.6 cc/kg, often requiring multiple intramuscular injections (as the volume for a typical adult is 42 cc), and can be repeated in 2-3 days if symptoms progress. Supplies are available through the CDC. It was derived for treatment of complications of vaccination, including eczema vaccinatum and some cases of progressive vaccinia. It also can be used in cases of severe generalized vaccinia. It is not effective in post-vaccination encephalitis, and is of no benefit in treatment of smallpox.[20]

Following successful dermal inoculation with the vaccine (referred to as a "take"), a papule forms after 4-5 days. This often intensely pruritic papule evolves over 2-3 days to an umbilicated vesicle or pustule, with surrounding erythema and induration peaking a week after initial appearance. Regional lymphadenopathy and mild systemic symptoms with fever are common. The pustule frequently ruptures prior to forming a scab, which separates with scarring two weeks later. The vaccination site must be covered with a non-occlusive dressing (e.g., a gauze pad) until the scab separates, and strict hand washing after contact with any drainage is essential to limit the inadvertent inoculation of additional sites or persons.[10,12,20] Occlusive dressings result in maceration and extensive local infection and should be avoided. Systemic antihistamines and non-narcotic analgesics often are useful for patient comfort. Common adverse effects which require only symptomatic treatment include nonspecific erythematous or urticarial eruptions, which may be confused with generalized vaccinia, as well as erythema multiforme.[20] Generalized vaccinia results in a vesicular eruption 7-9 days after vaccination, often accompanied by fever. The eruption usually is self-limited, requiring therapy only in immunocompromised patients.[10]

While most vaccinees experience mild morbidity that rarely interferes with activity, serious complications occur in 0.13% of primary vaccinations and an order of magnitude less often in revaccination.[21] The most common complication, accounting for over half of the serious adverse effects, is accidental inoculation of a site distant to the inoculation. Infection of the face, genitals, and rectum are common, but usually self-limited. More concerning are ocular infections, which account for one-fifth of accidental infections, which can result in corneal injury with permanent defects. One-fifth of accidental ocular infections occurred due to contact with a vaccinated person.[22] Ocular infection responds reasonably well to VIG and topical idoxuridine (one drop in affected eye q1h while awake, q2h while asleep).[10] However, if keratitis is established, there is an increased risk of corneal scarring with use of VIG, and its use is contraindicated.[20]

Eczema vaccinatum results in extensive or even generalized vaccinia infection in patients with eczema or other exfoliative skin disorders and, perhaps, burn victims. The disease usually is self-limited, but as many as one in 10 cases can be fatal.[10] It occurs independent of the current degree of eczema. Treatment with VIG is indicated and usually effective. If vaccination is essential, it can be done with concomitant administration of VIG.[20] VIG also is indicated in cases of vaccinia necrosum, a progressive vaccinia infection with extensive local destruction and metastatic lesions. Progressive vaccinia occurs only in patients with deficiencies in cell-mediated immunity and is fatal in three-quarters of cases.[10] Post-vaccination encephalitis complicates 12 per 1 million primary vaccinations, and two per 1 million revaccinations. VIG is ineffective and is not indicated.[20]

Routine contraindications to vaccination include immunosuppression, eczema, pregnancy, household contact with individuals with contraindications, or in children. Prior experience with vaccination showed very rare congenital infections, usually fatal, after primary vaccination of pregnant mothers. Prior to smallpox eradication, vaccination routinely was done in children, and in the face of exposure, this should not deter vaccination. In the face of a documented exposure to smallpox, it may be necessary to vaccinate even those with contraindications with concomitant VIG administration.[11,20]

Viral Hemorrhagic Fevers

Clinical Features. The viral hemorrhagic fevers (VHF) are prominent emerging infectious diseases. A variety of enveloped RNA-containing viruses are capable of causing severe illness marked by fever, shock, multi-organ failure, and hemorrhagic diathesis of varying severity. Recent outbreaks of Ebola hemorrhagic fever (EHF) in West Africa and Crimean-Congo hemorrhagic fever (CCHF) in Pakistan have highlighted the high mortality and potential for person-to-person transmission.[23] Increasing concern about the public health impact of VHF and potential to extend beyond traditional geographic boundaries is heightened by the potential for these highly infectious viruses to be used as terrorist weapons.[24,25] While technically difficult to produce in quantities similar to the former Soviet Union, small-scale production suitable for terrorist use can be accomplished in a typical two-car garage with minimal modifications.[26]

The filoviruses, Ebola and Marburg, have been responsible for severe explosive outbreaks and sporadic nosocomial cases. A well-documented, large outbreak occurred in Zaire in 1995, with 316 cases and an 80% fatality rate.[27-30] One-quarter of those infected in the Kikwit, Zaire, outbreak were health care workers.

The arenaviral hemorrhagic fevers are caused by Lassa fever virus, from Africa, and the Tacaribe complex of South American viruses: Machupo (Bolivian), Junin (Argentinean), Sabia (Brazilian), Guanarito (Venezuelan), and the recently described North American Whitewater Arroyo virus.[31-33] Human infection results from inhalation of infected rodent waste products, and may be transmitted person-to-person. Lassa fever is a substantial public health problem in West Africa, and accounts for one-quarter of febrile hospital admissions and deaths.[34]

CCHF has a wide endemic area, with sporadic tick-borne outbreaks and frequent hospital-centered outbreaks, marked by a

high incidence of fatal infections in health care providers.[33,35]

The filoviruses are associated with high-level viremia and widespread cytopathic effects without evidence of concomitant immunologic effect. Thrombocytopenia and lymphopenia with marked lymphoid depletion of bone marrow, spleen, liver, and peripheral lymph nodes only partially account for the immunosuppression.[36,37] While evidence of a consumptive coagulopathy occurs in the majority of patients, it is likely that direct viral destruction of endothelium and direct viral toxic effects are substantial contributors.[38,39] Hepatopathy without icterus usually is evident with elevations of aspartate aminotransferase (AST) greater than alanine aminotransferase (ALT).[40,41] Myocarditis and encephalitis appear common, but frequency depends on strain-specific features.[42] The virus survives in immunological privileged sites, such as the anterior chamber of the eye or the testes, which likely accounts for the delayed clinical features and protracted excretion of infectious virus in semen in survivors.[43-45] Similarly, the arenaviruses result in substantial thrombocytopenia, lymphopenia, and necrosis of liver, spleen, and adrenals without associated inflammatory response.[46]

All are highly infectious by aerosol in very low titers; perhaps as little as a single virion is infectious. All but yellow fever have been associated with person-to-person transmission and nosocomial epidemics. In the Kikwit Ebola outbreak, one-third of the physicians and one-tenth of the nurses contracted Ebola. The filoviruses are found in large amounts in and on skin. Physical contact with intact skin appears to be sufficient for transmission.[47] It appears, based on a small number of animal and epidemiological observations, that a minority of patients can generate infectious aerosols.[43,48-50] Argentine hemorrhagic fever (AHF) and Bolivian hemorrhagic fever (BHF) appear less transmissible, with occasional person-to-person spread, but may be secreted in semen after recovery, resulting in infection in intimate partners.[51] Guidelines for management of these patients are based on the infrequent generation of highly infectious aerosols, and call for strict respiratory and mucosal protection, negative airflow precautions, and isolation and decontamination of all bodily fluids.[24,35,52,53]

All agents of VHF present as a similar, non-specific febrile illness. Myalgias, malaise, prostration, and headache are nearly universal. Orthostatic symptoms and relative bradycardia appear common. The arenaviruses typically present with insidious onset. Common physical findings include evidence of diffuse capillary leak with hypovolemia, conjunctival injection, flushing, and petechia.[42,54-57]

Significant hemorrhage is present inconsistently and the absence of a bleeding diathesis should not dissuade the clinician from considering the possibility.[41] Minor bleeding—typically gingival, gastrointestinal, or oozing from vascular puncture sites—is seen in approximately 13% of AHF infections (Junin virus); 50% of VHF cases (Guanarito virus) and 40% of Ebola (Zaire strain) infections.[54,55]

Ebola typically presents with significant gastrointestinal (GI) symptoms, with non-bloody diarrhea present in more than 80% of patients and vomiting in 60%. Sore throat is a symptom in two-thirds of patients. Chest pain was a prominent feature in the Ebola-Sudan (EBO-S) outbreaks, but was not prominent in patients afflicted with Ebola-Zaire (EBO-Z) or Marburg disease.[58] A non-pruritic morbilliform or macular rash frequently is seen in fair-skinned individuals. The disease progresses in a biphasic manner with apparent recovery after the first week. A minority will have mild disease and continue to convalesce gradually over the next six weeks with frequent sequelae, while the majority will develop the hemorrhagic signs, tachypnea, hiccoughs, encephalopathy, normothermia, and oliguria that precede death.[59]

AHF, the most common and best characterized of the South American arenaviruses, typically presents 6-14 days after exposure, but the incubation period may range from four to 21 days. Onset is insidious, with fevers, chills, anorexia, myalgias, and malaise progressing over several days to prostration, tremor, cephalgia, abdominal pain, photophobia, and GI motility disturbance. Sore throat, nasal congestion, and cough are distinctly absent, and are helpful in limiting the differential diagnosis. Examination may reveal flushing of the face and upper torso with edema and hyperemia of the conjunctiva, gingiva, and oropharynx. Petechiae of the soft palate and axilla are common, along with small palatal vesicles and cervical lymphadenopathy. Patients often develop neurologic disease within a week of presentation, with a wide range of central nervous system (CNS) dysfunction, including ataxia, decreased deep tendon reflexes, and hyperesthesia. Three-quarters of patients will improve over the second week of illness, with the others manifesting bleeding, progression of CNS disease, shock, and secondary bacterial infections, particularly pneumonias. Convalescence is protracted, and up to 10% of antihemophilic factor A (AHF) patients treated with immune plasma developed a late onset self-limiting neurologic syndrome. Mortality ranges from 15-30%, with coma, severe bleeding, seizures, and oliguria portending poorer outcome. Treatment with immune plasma or ribavirin has reduced this to approximately 1%.[51,60]

Lassa fever differs only slightly in presentation from the South American arenaviruses, with less neurologic involvement, less prominent bleeding diathesis, and inconsistent thrombocytopenia or leukopenia.[61-63] Recovery typically takes 10 days. A minority develop edema, encephalopathy, tachypnea, hypotension, and bleeding manifestations portending a poor outcome.[64] Higher case fatality rates occur in pregnant women and fetal loss is universal.[65] Lymphopenia may be seen, but white blood cells may be unaffected or may reflect a neutrophilia, particularly in severe cases.[61,66] Disseminated intravascular coagulation (DIC) is not associated with Lassa fever. An elevated AST (> 150 U/L) is associated with worse prognosis and is an indication for initiation of ribavirin therapy.[34,67,68]

Most VHFs present with nondiagnostic features in a seriously ill-appearing patient with multiple organ involvement similar to other biowarfare (BW) agents and endemic diseases of the tropics. Misdiagnoses have been common. Similar presentations are shared by a variety of tropical viral agents, such as yellow fever, dengue, and the Hantaviruses responsible for hemorrhagic fever with renal syndrome, and Rift Valley fever, all of which have limited BW potential and can present with hemorrhagic manifesta-

tions. Other tropical diseases include malaria and leptospirosis, which have been seen in conjunction with Ebola outbreaks in the past, and may confound the diagnosis and treatment of both. Other diseases considered in the differential diagnosis include typhoid fever, borreliosis, septicemic plague, typhus, dysentery, acute African trypanosomiasis, fulminant meningococcemia, or other causes of sepsis with DIC.[33,69]

Diagnosis. Any evidence of a bleeding diathesis should result in isolation and aggressive diagnostic testing, to include attempts at viral isolation at one of the reference laboratories with biocontainment capabilities.[33,52,70] Lymphopenia and thrombocytopenia commonly are seen in all VHF syndromes and are ubiquitous in arenaviral disease, and a platelet count of fewer than 100,000 or WBC fewer than 4500 is 100% sensitive.[54] Almost all patients will have laboratory evidence of a consumptive coagulopathy, but rarely full-blown DIC may be present. Similarly, all patients with arenaviral disease display proteinuria, which also is common in the other VHFs.[71-73]

Laboratory diagnosis of VHF is difficult, and even routine blood tests (e.g., CBC and chemistries) pose severe hazards to laboratory workers. If VHF is in the differential, the laboratory must be warned, and physiochemical viral inactivation must be employed.[52,74,75]

Viral culture often is essential to establish the diagnosis. Most patients have intense viremia at presentation and viral cultures can yield a specific diagnosis in 3-10 days. This must only be attempted under BSL-4 conditions by experienced technicians. Samples should be sent to a reference laboratory *(See Insert)*, after contacting the laboratory to arrange shipping and packaging details.

Rapid diagnostic testing is available for all the VHF agents, and antigen detection tests show remarkable sensitivity in acute disease. These tests are available through the reference laboratory system, and some may be available at local level B or C laboratories, as they do not require biocontainment after specimen inactivation.

Treatment. All VHF syndromes require barrier nursing and intensive supportive care, which has been shown to improve outcomes. Invasive procedures and IM injections should be avoided. No therapy available, including interferon, antibody preparations, or currently marketed antiviral drugs, is effective against the filoviruses.[76-79] Intensive efforts at developing new drugs have been promising.[80,81] Antibody preparations, chiefly in the form of serum or plasma from convalescent patients, reduces mortality of the South American arenaviruses, but is no longer available in the United States, and may be associated with late-onset neurological disease.[82-84] Uterine evacuation, in pregnant patients, improves survival in Lassa Fever and is indicated as fetal loss is ubiquitous.[65]

Ribavirin inhibits the arenaviruses, RVF, and CCHF.[79,85] Ribavirin is well tolerated with mild reversible hemolytic anemia as the only consistent adverse effect.[17,52,85] The initial dose is 30 mg/kg IV given over one-half hour in saline or 2 g orally. Intravenous ribavirin is available through the reference centers listed in the Insert. Survival benefit has been shown in large studies with the arenaviruses. Although experience with ribavirin in RVF and CCHF is limited, it is recommended.[68,79,83,86-90]

Tularemia

Clinical Features. Tularemia is a zoonotic infection that in many ways resembles brucellosis and plague. Sporadic outbreaks in the United States continue to occur, with frequent misdiagnosis.[91] While hospital microbiology laboratory acquired infections are common, person-to-person transmission has not been described.[92,93] Aerosolized *F. tularensis* is highly infectious, with 10-50 organisms required to establish infection in healthy adult humans.[94]

Tularemia's incubation period typically is 3-6 days, dependent on route and dose of inoculation, but may range from 1 to 21 days.[95,96] As many as six different clinical forms of tularemia have been described, depending on the site of local infection and degree of dissemination. Common presentations include local ulceration and lymphadenopathy (ulceroglandular), lymphadenitis (glandular), conjunctivitis with lymphadenopathy (oculoglandular), ulcerative or exudative pharyngitis, and pneumonia.[93,97] Ingestion of contaminated water commonly results in pharyngitis, abdominal pain, and fever. Regardless of the presenting form, systemic symptoms of asthenia, malaise, fatigue, myalgias, low back pain, headache, chills, and fever usually are seen.[92]

In approximately one-quarter of all cases, systemic dissemination may occur following one of the localized forms or in the absence of other signs, resulting in the typhoidal presentation.[94] Diagnostic considerations include typhoid fever, typhus, brucellosis, Legionella infection, Q fever, malaria, disseminated mycobacterial or fungal infections, rickettsiosis, endocarditis, primary HIV infection, toxic-shock syndrome, and other causes of sepsis. Mortality approaches 33% in typhoidal cases, in contrast to only 4% in ulceroglandular disease.[94,95]

Primary pulmonary tularemia, the chief form expected following aerosolization, presents with abrupt onset of high fevers, rigors, dyspnea, nonproductive cough, pleuritic chest pain, and diaphoresis. It may result in systemic disease without localizing pulmonary disease or progress to a fulminant, fatal pneumonia.[92] The pulmonary form is indistinguishable from other common causes of community-acquired, zoonotic, fungal, and tubercular pneumonia. A pulse-temperature discrepancy occurs in up to 42%.[95] Production of purulent sputum or hemoptysis are seen in a minority.[98,99] Pneumonia also may complicate dissemination from localized infection and present with a more indolent course, chronic fevers, cachexia, fatigue, and lymphatic suppuration. It is seen in 83% of typhoidal cases.[95]

Pulmonary findings are nonspecific, with rales and friction rubs most often described. Radiographic findings may mimic tuberculosis, with multiple granulomatous lesions, hilar adenopathy and effusions, or may present with typical pneumonic findings such as subsegmental or lobar consolidation.[100] The triad of oval opacities, hilar adenopathy, and pleural effusions are strongly suggestive of tularemia, but are seen only in a minority of cases.[99]

Exam may show evidence of simultaneous extrapulmonary inoculation, most typically pharyngitis. The ulcerative and exudative pharyngitis commonly is confused with infectious mononucleosis, adenoviral tonsillopharyngitis, or streptococcal pharyngitis. It may become membranous, similar in appearance to diphtheria.[101,102]

Localized infection resulting in ulceroglandular or oculoglandular tularemia remains the most common natural presentation. Localized disease may occur even with aerosol exposure.[92] The majority develop an abrupt fever, with variable complaints of chills, malaise, fatigue, cough, and headache. Fever, as well as the other systemic symptoms, may remit and recur for weeks to months.[93] Following cutaneous inoculation, patients develop a small, painful, papule which rapidly necroses and ulcerates. Lymphadenopathy may occur as an isolated finding, or may persist well beyond the acute febrile illness.[95] Ocular manifestations are analogous, with corneal or conjunctival ulcerations, conjunctivitis and anterior chamber inflammation, or even frank hypopyon.[103] Meningitis is an exceedingly rare manifestation.

The ulceroglandular form of tularemia may be mistaken for the cutaneous form of anthrax, sporotrichosis, and *Mycobacterium marinum*. However, the papule and ulcer of tularemia are painful with local adenitis, in sharp distinction to that of the more edematous anthrax, which has minimal discomfort.[99] Other considerations include pyogenic infections, cat-scratch disease, syphilis, chancroid, and herpetic whitlow.

In addition to the pathognomonic skin lesions, a wide range of disseminated dermatological manifestations has been described, and may occur in up to one-third of patients within the first two weeks of illness, including diffuse maculopapular and vesiculopapular eruptions, erythema multiforme, acneiform lesions, urticaria, and, most commonly, erythema nodosum.[14,104]

Diagnosis. Routine laboratory studies are nonspecific. Lymphocytosis occasionally is seen, but the lymphocyte count is most often within normal limits. Up to one in four may show microscopic pyuria, which may lead to misdiagnosis of pyelonephritis. Minimal transaminase and lactate dehydrogenase elevations reflect hepatic infection and infrequently patients may develop rhabdomyolysis with the associated elevation of creatine phosphokinase (CPK).[95]

Francisella tularensis is difficult and dangerous to cultivate in hospital microbiology laboratories.[105] The organism is not typically seen on Gram stain of clinical specimens, but may be cultured from blood, lymph node aspirate, pharyngeal swabs, sputum, and cutaneous or corneal ulcers. Modern automated blood culture systems detect *F. tularensis* in at least 60% of bacteremic cases, but misidentification is common.[106,107]

Due to the difficulties with culture, diagnosis typically is accomplished via serology.[108] Cross-reactivity to Brucella and Legionella is seen. Polymerase chain reaction (PCR) is emerging as a valuable tool, with rapid return of accurate results without the risk of laboratory acquired infection.[109-111] Additional diagnostic assistance can be obtained through the Division of Vector-Borne Infectious Disease, CDC, Ft. Collins, CO (dvbid@cdc.gov). *(See Insert.)*

Treatment. Untreated, most patients have a prolonged debilitating febrile illness lasting months. Antibiotic treatment may result in a rapid improvement, but a substantial number of patients have a suboptimal response, particularly if ineffective antibiotic therapy is used, therapy is abbreviated, or if there is a delay in initiation of treatment.[92,112] A Jarisch-Herxheimer-like reaction may be seen with initiation of antibiotic therapy. Streptomycin or gentamycin for 10-14 days is the standard treatment regimen, although longer or repeated courses may be required.[9,92,113,114] Streptomycin-resistant organisms were engineered and investigated by both the United States and Soviet programs.[92] Ceftriaxone has an unacceptably high treatment failure rate and should not be used.[115] Doxycycline and chloramphenicol have been used extensively, but have higher treatment failure and relapse rates than the aminoglycosides, particularly in those with immunocompromise or chronic systemic disease.[116,117] A minimum of 14 days of treatment is recommended.[92] The addition of chloramphenicol to an aminoglycoside is recommended in the rare cases of meningitis.[118] Fluoroquinolones, principally ciprofloxacin, have been used in a limited number of cases, appear to be very effective, and are a reasonable first-line alternative to the aminoglycosides.[49,116] A 10-day course is recommended.[92]

Limited studies in humans demonstrate that a two-week course of a tetracycline, but not a shorter course, is effective for post-exposure prophylaxis.[120] Ciprofloxacin (or other fluoroquinolone) also is recommended.[92]

Botulinum Toxins

Clinical Features. Botulinum toxins are the most toxic substance known, with an inhalational LD50 of 3 ng/kg, approximately 100,000 times as toxic as sarin.[121] In addition, it is easy to manufacture and is well absorbed via aerosol.[122] A gram of botulinum toxin potentially could kill 1 million people. The quantity of botulinum produced by Iraq would have been sufficient to kill three times the total living human population.[123]

Naturally occurring food-borne outbreaks of botulism remain public health emergencies. While each outbreak averages 2.5 patients, approximately half have only a single victim.[123] The three largest outbreaks involved a total of 121 patients, illustrating the potential for even accidental poisonings to generate mass casualties, with half presenting with clinical symptoms to an ED.[124] Due to the implications of on-going exposure, the delayed and often insidious onset, and possible geographic dissemination, a nation-wide surveillance system is in place through the CDC.[125]

Most cases present within 36-72 hours (range 6 hours to 8 days) with an afebrile symmetric descending flaccid paralysis with a clear sensorium.[126,127] Depending on dose and route, the presentation can range from a subtle motor weakness to acute profound flaccid paralysis with respiratory arrest. The initial GI symptoms associated with food-borne outbreaks are thought to be due to other microbial by-products and would not be seen if purified toxin was released.[123,125]

Presenting complaints include weakness, blurred vision, diplopia, dry mouth, and dysarthria.[124] Facial muscle weakness and diminished ocular motility mimicking cranial neuropathies may result in a diagnostic delay. Typically, the initial sign of progression is a loss of head control. While the sensorium remains clear, and sensory features are uncommon, acral paresthesias due to hyperventilation are well described. Patients may appear obtunded due to the hypotonia.[123] Deep tendon reflexes may be

preserved initially, but diminish with progression, in sharp contrast to Guillain-Barré syndrome and the descending Miller-Fisher variant.[129] Constipation and urinary retention are common.[130] Ptosis and upper extremity weakness may indicate progression to the point that respiratory compromise may require mechanical ventilation.[131] Respiratory failure may be prolonged, typically requiring 2-8 weeks of ventilatory support.[128] Without mechanical ventilation, fatality rates are approximately 60%; with contemporary ICU care, the rate is now 5-10%.[126]

Prompt clinical diagnosis is critical. Delays and misdiagnosis are common and are associated with worse outcomes.[132,133] Other clinical entities with similar presentations that would suggest the need to consider botulism include myasthenic crisis, cholinergic crisis, Guillain-Barré syndrome, basilar artery insufficiency, tick paralysis, Eaton-Lambert syndrome, and various drug and toxin intoxications.[124,134,135] Prominent symmetric bulbar motor and anti-muscarinic features strongly support botulism.

Routine laboratory and radiographic studies are usually normal or non-diagnostic. However, serum chemistries may reveal other diagnoses, such as abnormalities of calcium or potassium, an elevated CPK suggesting a myopathic process, an elevated CSF protein suggesting Guillain-Barré syndrome, evidence of stroke or mass on computed tomography of the brain or CSF evidence of CNS infection, especially tuberculous or fungal meningitis.[128,136]

Urgent consultation with a neurologist in equivocal cases may facilitate diagnosis, as electomyogram (EMG) findings are highly suggestive.[137] Early clinical botulism may respond to anticholinesterase therapy similar to myasthenia gravis.[128,136] Serum samples should be collected (4-6 vacutainer tubes; red or tiger top) prior to administration of antitoxin or cholinesterase inhibitors, as it interferes with the gold-standard mouse bioassay.[123] The mouse bioassay is very sensitive and specific, but is time consuming and is not widely available. New diagnostic modalities remain limited.[138,139] The more sensitive stool cultures and PCR, while helpful in food-borne outbreaks, would not be helpful if preformed toxin was released intentionally.[140]

Treatment. If significant oral exposure is suspected, activated charcoal may be effective at reducing absorption.[141] Any exposed or symptomatic patients should be treated with antitoxin, admitted and followed closely for respiratory failure.[9,142,143] In cases of mass casualty exposure, the decision to withhold administration of antitoxin until development of symptoms may be necessary. Patients who present late in the course with stable or improving symptoms do not require antitoxin.[123]

Patients who are not mechanically ventilated should be cared for in a reverse Trendelenburg position with sufficient head and neck support to prevent airway occlusion. Patients admitted will require frequent neurologic assessments with careful attention to ability to handle secretions and otherwise protect their airway. Pulmonary function testing may show a decrease in vital capacity and inspiratory force prior to onset of hypercarbia.[144] Clindamycin and aminoglycoside antibiotics should not be administered because they may precipitously worsen neuromuscular function.[145-149] Succinylcholine should be used with caution.[150] Aspiration or loss of a patent airway usually precedes hypoventilation. The need for mechanical ventilation ranges from 20% to 60% of cases.[123] Once respiratory compromise occurs, treatment is mechanical ventilation, which usually is sufficiently prolonged to mandate tracheostomy.[131] Efforts to stockpile ventilators for emergency use are ongoing.[151] Recovery is prolonged with frequent complications associated with protracted immobilization and tracheal intubation.

There is a single commercially available antitoxin, a trivalent (containing anti-A, anti-B, and anti-E activity) equine preparation made only by Connaught Laboratories. Small-scale production of other products is limited to Japan and two European suppliers.[125] Given early in the course, it arrests progression of neurologic disease, shortens duration of mechanical ventilation and reduces mortality.[142] In one series, administration within 12 hours of presentation reduced intubation rates from 85% to 57% and duration of mechanical ventilation from a median of 54 days to 11 days.[131] Patients with significant wheal and flare will require intensive desensitization over several hours. While it is usually well tolerated, up to 9% of recipients will manifest typical serum sickness or urticaria and 2% will have life-threatening reactions.[152] A single vial will neutralize several lethal doses and is sufficient for naturally occurring botulism.[153] Additional doses theoretically may be needed following exposure to large amounts of purified toxin.

An investigational equine F(ab′)2 product with activity against toxin types A, B, C, D, E, and F has been developed and tested by the U.S. Army. It is available for clinical use under a compassionate use protocol.[154] Adjunctive therapy with guanidine or amino-pyridines is not effective.[155]

The trivalent equine antitoxin is stockpiled by the CDC in airports in New York, Chicago, Atlanta, Miami, Los Angeles, San Francisco, Seattle, and Honolulu. In addition, the state health departments of California and Alaska maintain their own stores. Additional stocks are held by the U.S. Army, and can be accessed by CDC officials. Canada maintains its own supply, but other members of the Pan American Health Organization are served by the CDC. This system allows most patients to be treated with antitoxin within 12 hours of contact with public health authorities.[125]

Any suspected case of botulism is a public health emergency. Local health departments work closely with the CDC's Food-borne and Diarrheal Disease Branch on a 24-hour-a-day basis. Emergency consultation, including diagnostic and treatment recommendations and provisions for antitoxin is available by calling (404) 639-2888.[125]

A formalin inactivated toxoid containing toxin types A, B, C, D, and E has been in use since the 1950s under an Investigational New Drug protocol to protect at-risk laboratory workers. It is safe and well tolerated, although the current product is rather painful on injection.

Although botulinum toxin has little potential for secondary aerosolization, aerosol release may require surface decontamination to avoid ingestion of persistent toxin.[121]

Use of Tetracyclines and Fluoroquinolones in Pregnant, Nursing, or Pediatric Patients

Although tetracyclines and fluoroquinolones usually are not used in children, nursing mothers, or pregnant women, their use for life-threatening infections is justified and recommended by the CDC, the Food and Drug Administration, the American Academy of Pediatrics, and the American College of Obstetricians and Gynecologists.[156-160] A growing body of literature on the safety of fluoroquinolones, particularly ciprofloxacin, suggests that risks are minimal and that clinicians should not hesitate to use them for serious infections.[161-169] Adverse effects of tetracyclines in pregnant women and in children are well described, but are acceptable in the face of life-threatening disease. In addition, doxycycline appears to be much safer than tetracycline, with no reports of untoward effects in children or in pregnancy.[170-173] Initiate therapy in children with ciprofloxacin (10-15 mg/kg/dose po q 12 hours not to exceed 1 g per day) or doxycycline (2.2 mg/kg/dose po BID not to exceed 100 mg po BID). If penicillin susceptibility is confirmed in a patient with anthrax, initiate or change to oral amoxicillin 80 mg/kg/day TID (maximum 500 mg/dose), or to trimethoprim sulfate if susceptible plague is isolated.[174]

Summary

Detection of a biological weapons attack hinges on a clinical suspicion, followed by laboratory investigations. Circumstances that should prompt immediate contact with surrounding EDs and urgent consultation with public health and law enforcement authorities include:

1) Any unusual temporal or spatial clustering of infectious diseases, especially if serious pulmonary symptoms or hemorrhagic diathesis are prominent or if stereotypical features are present;

2) Multiple, previously healthy patients with presentations of sepsis or fulminant pneumonia in otherwise healthy patients;

3) Clinical diagnosis or suspicion of smallpox;

4) Acute flaccid paralysis with prominent bulbar symptoms, suggesting botulism; and

5) Isolation of pathognomonic organisms; especially variola virus, agents of viral hemorrhagic fever, engineered or highly drug resistant *Bacillus anthracis, Yersinia pestis,* or isolation of genetically identical organisms from multiple regions.

There is little, if any, risk of contamination to health care workers following simple decontamination (removal of contaminated clothing and a soap and water shower). However, pneumonic plague, smallpox, and the viral hemorrhagic fevers present a substantial risk for secondary spread and explosive epidemics. Respiratory protection is required to care for these patients. Isolation or quarantine of cases and contacts is essential.

Viral cultures should be sent *only* to USAMRIID, CDC, or comparable facilities in other countries, via the local public health system.

Additional rapid and confirmatory diagnostic tests are available through the public health laboratory response network (NLRN).

Hospitals and EMS agencies should not participate in testing of environmental samples or materials suspected of harboring infectious agents. Any such concerns should be directed immediately to law enforcement agencies, which have the responsibility and expertise to address these issues.

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Physician CME Questions

To earn CME credit for this issue of Trauma Reports*, please refer to the enclosed Scantron form for directions on taking the test and submitting your answers.*

1. Which of the following is true regarding smallpox?
   A. The predominant method of transmission is by respiratory droplets.
   B. Smallpox is minimally contagious.
   C. Infectivity is not increased in patients with smallpox and a cough.
   D. Variola minor strains have the highest mortality rates.
   E. Variola minor lesions usually are larger than variola major.

2. Which of the following is/are true regarding the management of smallpox?
   A. Strict isolation is essential.
   B. Treatment largely is supportive.
   C. Anyone exposed to a patient with contagious smallpox should be vaccinated and quarantined for 17 days.
   D. Antiviral therapy historically has not been useful.
   E. All of the above

3. Which of the following is true regarding vaccination following exposure to a patient with contagious smallpox?
   A. An individual vaccinated 1 year ago requires a repeat dose of the vaccine.
   B. An exposed individual optimally should be vaccinated within 2-3 days of exposure.
   C. An individual vaccinated six years ago does not require a second dose of the vaccine.
   D. VIG is a highly effective post-exposure prophylactic agent.
   E. VIG is very effective against post-vaccination encephalitis.

4. Which of the following is a potentially serious complication associated with the smallpox vaccine?
   A. Urticarial eruptions
   B. Erythema multiforme
   C. Accidental inoculation of the eye
   D. Generalized vaccina in a non-immunocompromised host
   E. Mild systemic symptoms and regional lymphadenopathy

5. Which of the following is/are true regarding filoviruses?
   A. The filoviruses are associated with a high level of viremia.
   B. Thrombocytopenia and lymphopenia may occur.
   C. Hepatopathy without icterus may be present.
   D. Myocarditis is common.
   E. All of the above.

6. Which of the following is *not* typical for the presentation of a patient with a VHF infection?
   A. Severe tachycardia
   B. Myalgias
   C. Headache
   D. Orthostatic symptoms
   E. Hypovolemia

CME Objectives

Upon completing this program, the participants will be able to:

a.) Recognize or increase index of suspicion for diseases that may result from biological terrorism;

b.) Be educated about rapid stabilization, and the isolation of patients with exposure to or evidence of smallpox, viral hemorrhagic fevers, tularemia, and botulinum toxins;

c.) Understand various diagnostic and treatment modalities for diseases associated with biowarfare; and

d.) Understand both likely and rare complications that may occur.

7. Which of the following is true regarding AHF?
   A. It is an uncommon South American filovirus.
   B. Its onset typically is acute.
   C. Sore throat, nasal congestion, and cough typically are present.
   D. Patients often develop neurologic disease within a week of presentation.
   E. Treatment with immune plasma or ribavirin is ineffective.

8. Which of the following is true of management of a patient with VHF infection?
   A. Interferon decreases the duration of the illness.
   B. Antibody preparations reduce the infectivity of the patient.
   C. Ribavirin inhibits arenaviruses, RVF, and CCHF.
   D. Barrier nursing is not necessary.
   E. Invasive procedures and IM injections may be performed without caution.

9. Which of the following is/are associated with botulism?
   A. Weakness
   B. Blurred vision
   C. Dysarthria
   D. Facial muscle weakness
   E. All of the above

10. Which of the following is true regarding the diagnostic work-up of a patient with potential botulism?
   A. Routine laboratory studies are typically normal or non-diagnostic.
   B. CPK usually is elevated.
   C. CSF protein usually is high.
   D. CT scan of the brain may show diffuse edema.
   E. EMG findings typically are not helpful.

In Future Issues: **Rapid Sequence Intubation**

Summary of Major Agents

DISEASE	CLINICAL PRESENTATION	DIAGNOSTIC STUDIES	TREATMENT
Anthrax			
Inhalational	Nonspecific prodrome of fever, dyspnea, cough, retrosternal chest discomfort followed by respiratory failure and hemodynamic collapse. Mediastinal widening universal in late stage, pulmonary infiltrate seen in up to 25% and meningitis in 50%.	Blood culture and Gram stain, CSF Gram stain and culture, chest x-ray or CT, antigenemia by ELISA/PCR/CL	Ciprofloxacin (other fluoroquinolones likely effective, but largely untested; penicillin (amoxicillin acceptable); gentamycin or streptomycin. Add chloramphenicol if evidence of meningitis. Bodily fluids and secretions may generate spores if left in contact with air, and must be disinfected (e.g., soaked in bleach, incinerated, autoclaved). Aspiration of pustule may increase risk of bacteremia. Steroids effective for controlling edema, if required for airway impingement.
Cutaneous	Pruritic papule that progresses to pustule. Local edema and adenopathy common.	Gram stain and culture from under eschar	
Pneumonic plague	Fulminant pneumonia with hemoptysis, sepsis, and disseminated intravascular coagulation (DIC)	Sputum for Gram stain, culture, IFA	*Respiratory protection and droplet precautions (isolation room or cohort).* Avoid lactam antibiotics, if possible. Streptomycin or gentamycin with chloramphenicol for meningitis. Tetracyclines effective. Quinolones likely effective, but unproven. TMP/SMZ less effective.
Botulism	Bulbar neuropathy (diplopia, ptosis, dysarthria), mydriasis, xerostomia followed by descending paralysis with preserved cognition with respiratory failure in 12-72 hrs. Afebrile.	EMG helpful but not diagnostic; may see response to edrophonium, difficult to detect in serum.	Intubation for respiratory failure. If antitoxin is given, it will arrest progression, shorten requirement for mechanical ventilation, and reduce mortality.
Smallpox	Severe prostrating febrile illness with synchronous evolution of pustules, particularly on face and arms.	Pharyngeal swabs or scabs (BSL-4)	Cidofovir effective in mice. Vaccinia immune globulin 0.6 mL/kg IM within 72 hours of exposure in conjunction with Vaccinia vaccine. *Isolation essential to prevent dissemination.*
Pneumonic tularemia	Acute, nonspecific febrile illness with ulcerations, pharyngitis, and pneumonia	Blood, pharyngeal, or ulcer swabs for culture or PCR; serology	Gentamycin or streptomycin. Ciprofloxacin (other fluoroquinolones likely effective, but largely untested); doxycycline (or other tetracycline) less effective. Add chloramphenicol if evidence of meningitis.
Filovirus hemorrhagic fever	Severe disease, marked weight loss, prostration, late encephalopathy, and bleeding. Often see maculopapular rash. 25-90% case fatality.	Viral antigen in blood. Viral isolation	Supportive. *Isolation essential to prevent dissemination.*
Arenavirus hemorrhagic fever	Prostration, shock, bleeding, CNS disease (less common in Lassa fever). Thrombocytopenia, leukopenia, and proteinuria.	Viral antigen or IgM detection; viral isolation	Ribavirin. High titer plasma for AHF no longer readily available. Isolation advisable, at least droplet precautions.
Brucellosis	Protracted recurrent fever, depression, fatigue, myalgias, arthritis, endocarditis, meningitis, sacroiliitis, orchitis, and septic abortion. Cytopenias common.	Blood or bone marrow culture. PCR. Serology by ELISA, agglutination, or dipstick assay.	Prolonged treatment with doxycycline plus rifampin, streptomycin, or gentamycin. Fluoroquinolones plus rifampin, streptomycin, or gentamycin. TMP/SMZ less effective.
Q fever	Acute influenza-like illness, rare fulminant disease. High mortality due to endocarditis in predisposed patients. Liver function test (LFT) levations common.	Culture or animal inoculation (BSL-3) impractical. Serology widely available.	Macrolide, tetracycline, or fluoroquinolone for acute disease. Macrolide should be combined with rifampin if used for pneumonia. Doxycycline plus rifampin, chloroquine, or hydroxychloroquine if underlying valvular pathology.

Research and Reference Laboratories*

* **Initial contact and consultation, as well as specimen submission, is through state and local health departments. Phone numbers are available in the blue pages of the phone book or online listings at www.statepublichealth.org/directory.php or www.cdc.gov/other.htm or www.cdc.gov/ncidod/diseases/hanta/hps/noframes/statecon.htm.**

NAME	PHONE NUMBER	INTERNET
Centers for Disease Control and Prevention (CDC), Atlanta, GA	Tel: (770) 488-7100, (emergency response) (404) 639-1115 (special pathogens) or (404) 639-2888 (24 h)	www.bt.cdc.gov/ and www.cdc.gov/ncidod/dvbid/
Vector Borne Disease Laboratory, Fort Collins, CO	(970) 221-6400	
U.S. Army Medical Research Institute of Infectious Disease (USAMRIID), Fort Detrick, MD	(888)-872-7443	www.usamriid.army.mil