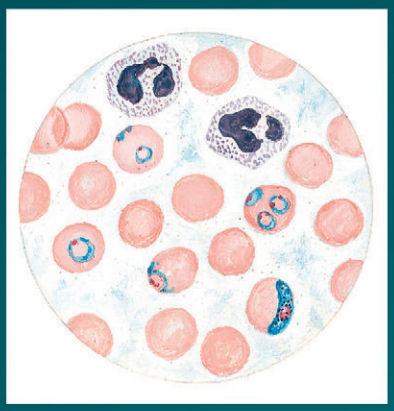

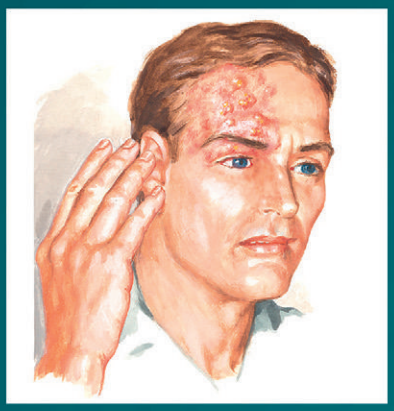

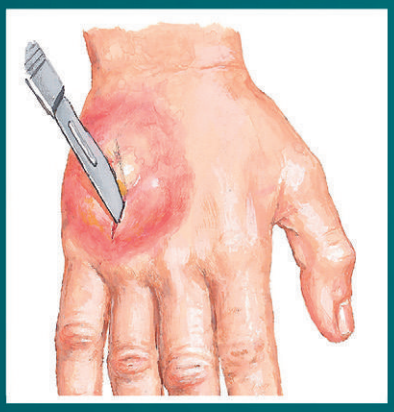

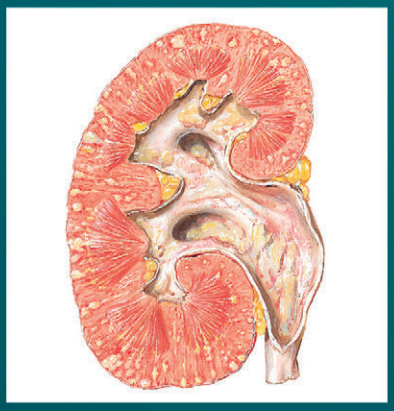

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NETTER'S INFECTIOUS DISEASES

2nd EDITION

F. Netter M.D.

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2nd EDITION

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ABOUT THE ARTISTS

Frank H. Netter, MD

Frank H. Netter was born in 1906, in New York City. He studied art at the Art Students League and the National Academy of Design before entering medical school at New York University, where he received his MD degree in 1931. During his student years, Dr. Netter's notebook sketches attracted the attention of the medical faculty and other physicians, allowing him to augment his income by illustrating articles and textbooks. He continued illustrating as a sideline after establishing a surgical practice in 1933, but he ultimately opted to give up his practice in favor of a full-time commitment to art. After service in the United States Army during World War II, Dr. Netter began his long collaboration with the CIBA Pharmaceutical Company (now Novartis Pharmaceuticals). This 45-year partnership resulted in the production of the extraordinary collection of medical art so familiar to physicians and other medical professionals worldwide.

In 2005, Elsevier, Inc. purchased the Netter Collection and all publications from Icon Learning Systems. There are now more than 50 publications featuring the art of Dr. Netter available through Elsevier, Inc.

Dr. Netter's works are among the finest examples of the use of illustration in the teaching of medical concepts. The 13-book *Netter Collection of Medical Illustrations*, which includes the greater part of the more than 20,000 paintings created by Dr. Netter, became and remains one of the most famous medical works ever published. *Netter's Atlas of Human Anatomy*, first published in 1989, presents the anatomical paintings from the Netter Collection. Now translated into 16 languages, it is the anatomy atlas of choice among medical and health professions students the world over.

The Netter illustrations are appreciated not only for their aesthetic qualities, but, more important, for their intellectual content. As Dr. Netter wrote in 1949, "…clarification of a subject is the aim and goal of illustration. No matter how beautifully painted, how delicately and subtly rendered a subject may be, it is of little value as a medical illustration if it does not serve to make clear some medical point." Dr. Netter's planning, conception, point of view, and approach are what inform his paintings and what makes them so intellectually valuable.

Frank H. Netter, MD, physician and artist, died in 1991.

Learn more about the physician-artist whose work has inspired the Netter Reference collection: https://netterimages.com/artist-frank-h-netter.html.

Carlos A.G. Machado, MD

Carlos Machado was chosen by Novartis to be Dr. Netter's successor. He continues to be the main artist who contributes to the Netter collection of medical illustrations.

Self-taught in medical illustration, cardiologist Carlos Machado has contributed meticulous updates to some of Dr. Netter's original plates and has created many paintings of his own in the style of Netter as an extension of the Netter collection. Dr. Machado's photorealistic expertise and his keen insight into the physician–patient relationship inform his vivid and unforgettable visual style. His dedication to researching each topic and subject he paints places him among the premier medical illustrators at work today.

Learn more about his background and see more of his art at: https://netterimages.com/artist-carlos-a-g-machado.html.

ABOUT THE EDITORS

Elaine C. Jong, MD, FIDSA, FASTMH, is Clinical Professor of Medicine Emeritus at the University of Washington School of Medicine (UWSOM) in Seattle, Washington. She was born in New York City, New York, graduated from Wellesley College with a bachelor of arts degree in biological sciences, and received her medical degree at the University of California-San Diego School of Medicine in La Jolla. After completing her internal medicine residency and a fellowship in Infectious Diseases at UWSOM, she joined the faculty in the Department of Medicine-Division of Allergy and Infectious Diseases and also served as an attending physician in the Division of Emergency Medicine. Engaging in basic research on the role of eosinophils in the host defense against schistosomiasis early in her career led to a lifelong interest in parasitic diseases, exotic infections, refugee and immigrant health, infections associated with international travel and outdoor activities, and vaccine-preventable diseases. Publications include more than 100 journal articles and book chapters and serving as editor or co-editor of more than a dozen books. At UW, Dr. Jong founded and directed courses and training clinics for the practice of refugee and immigrant medicine, and travel and tropical medicine. She served as the Director of the UW Student Health Center at the UW Hall Health Center and was the first Medical Director of the UW Campus Health Service, implementing programs for campus public health, occupational health, and employee health. Dr. Jong is a Fellow of the Infectious Diseases Society of America (IDSA) and a Fellow of the American Society of Tropical Medicine and Hygiene (ASTMH); she is a past President of the Clinical Group of the ASTMH and recently was awarded the Society's first Martin S. Wolfe Mentoring Award. Dr. Jong has served for many years as Chair of the International Medical Advisory Board for the International Association for Medical Assistance to Travellers (IAMAT).

Dennis L. Stevens, MD, PhD, has been Chief of the Infectious Diseases Section at the Veterans Affairs Medical Center in Boise, Idaho for 40 years and is currently Professor of Medicine at the University of Washington School of Medicine in Seattle. He is currently Program Director of a National Institutes of Health (NIH) Center of Excellence for Emerging and Re-emerging Pathogens in Boise, Idaho. Dr. Stevens obtained a Bachelor of Arts degree in microbiology from the University of Montana, a doctoral degree in microbiology from Montana State University, and a medical degree from the University of Utah. He completed an internal medicine residency at the University of Utah and performed his fellowship in infectious diseases at Brooke Army Medical Center. Dr. Stevens' major research interests have been the pathogenesis of serious infections caused by toxin-producing gram-positive pathogens including *Clostridium perfringens, Clostridium sordellii,* group A streptococcus, and methicillin-resistant *Staphylococcus aureus* (MRSA). Dr. Stevens recently received the IDSA Citation for his work on group A streptococcal infections and the William Altemeier Award from the Surgical Infections Society and was elected to membership in the Association of American Physicians. In 2018 he received the Veterans Affairs (VA) Infectious Disease Practitioners Lifetime Achievement Award. He has published more than 185 articles and 120 book chapters on serious invasive infections caused by gram-positive organisms and has been visiting professor at more than 70 national and 30 international institutions. He has been a member of the Centers for Disease Control and Prevention Working Group on Invasive Streptococcal Infections and a consultant to the World Health Organization, and he has been an invited participant to the National Institutes of Health Workforce on severe group A streptococcal infection. He has testified twice before the US Congress on the importance of basic science research in infectious diseases and on invasive group A streptococcal infections. Dr. Stevens is the current chairman of the IDSA's Guideline Committee for the Treatment of Skin and Skin Structure Infections.

ACKNOWLEDGMENTS

The invitation to edit a new book on infectious diseases was an honor and a challenge almost a decade ago when the two of us, colleagues in the Division of Allergy and Infectious Diseases at the University of Washington School of Medicine in Seattle, decided to combine our complementary academic interests and clinical experiences to create the first edition of *Netter's Infectious Diseases*. We both shared a deep admiration for the amazing medical artwork of the late Frank H. Netter, MD; as medical educators, our goal was to place the original Netter illustrations into the context of modern medical science, judiciously augmented by additional artwork and photographic images to create memorable moments of understanding and insight for medical students, trainees, and clinicians in practice, generalists and specialists alike. This remains our goal for the second edition: the content has been thoroughly reviewed, updated, and augmented; new contributing authors add fresh perspective to classic and emerging infectious diseases; and the addition of Clinical Vignettes to most chapters in this edition will further enhance the book as an educational resource and reference.

We acknowledge with gratitude the dedication and precious time contributed to this book by our Section Editors and Contributing Authors. As we reached out to our colleagues and friends, recognized subject experts in the broad field of infectious diseases (ID), to contribute chapters to the second edition, the Coronavirus Disease pandemic of 2019 (COVID-19) emerged midway into the book project timeline. The tidal wave of seriously ill patients stressed healthcare systems across the United States and around the world, and ID specialists in particular took on burdens of added responsibilities in response to the crisis. Despite all this, the contributing authors came through with their best; their chapters are readable, up-to-date, and unforgettable.

Production of this book in the Netter Medical Series of books is a concerted team effort, and we want to acknowledge and thank Marybeth Thiel, Content Strategist–Education Content, and Daniel Fitzgerald, Project Manager–Clinical Solutions, at Elsevier for their expert guidance, assistance, and collaboration—it was our pleasure to work with them. The encouragement of our families, especially our spouses, Dr. Britt Litchford and Dr. Amy E. Bryant, was essential to the completion of the book, and we thank them for understanding the toll on our family time.

A special thanks to the late Dr. Frank H. Netter for his artistic skills that incorporated anatomy, clinical signs, and pathogenesis into remarkable images that have improved patient care for over 5 decades. We would like to dedicate this book to those colleagues who are no longer with us but contributed greatly to modern infectious diseases: Merle Sande, Richard Root, William Kirby, Seymour Klebanoff, Walter Stamm, Alan Bisno, Robert Moellering, Sydney Finegold, and John Bartlett.

PREFACE

As longtime colleagues in the Division of Allergy and Infectious Diseases at the School of Medicine, University of Washington, Seattle, we were honored and challenged by the unique opportunity to create a new textbook of infectious diseases, with the goal of utilizing the beautiful medical artwork created by the late Dr. Frank H. Netter to teach and clarify important concepts in infectious diseases. Mindful of existing textbooks, such as Mandell's *Principles and Practice of Infectious Diseases*, that are considered authoritative as well as standards of excellence in the field, we set out to create a new resource with a strongly clinical orientation; the first edition of *Netter's Infectious Diseases* made its debut in 2012. This second edition continues our purpose: to provide healthcare providers, both generalists and specialists, with up-to-date clinical approaches to the broad spectrum of infectious diseases from the perspective of how these various infections may impact patients as individuals, members of communities, and as citizens of global society.

Reflecting the rapid accumulation of advances in the medical sciences, the infectious diseases specialty has many branches or subspecialties, and we were fortunate in recruiting outstanding Section Editors: Patrick W. Hickey (Vaccine-Preventable Diseases in Children and Adolescents), Thomas M. File, Jr. (Respiratory Tract Infections), E. Patchen Dellinger (Surgical Infections), Jeanne M. Marrazzo (Sexually Transmitted Infections), Vernon Ansdell (Parasitic Diseases), and M. Patricia Joyce (Emerging Infectious Diseases and Pandemics). We also participated as Section Editors: Skin and Soft-Tissue Infections (Dennis L. Stevens), Systemic Infections (Dennis L. Stevens), and Infections Associated With International Travel and Outdoor Activities (Elaine C. Jong).

A superb roster of talented contributing authors, recruited from our extended network of colleagues and friends, contributed their valuable time and expertise to writing concise, highly readable, and clinically relevant chapters. In each chapter, Dr. Netter's medical illustrations, in some cases revised to reflect new advances, are used to illustrate key points from the text, augmented by radiographic and photographic images, tables, and graphs. For some topics, there was creation of new and updated artwork by Carlos A. G. Machado, Tiffany S. DaVanzo, and Anita Impagliazzo, talented medical artists carrying on Dr. Netter's mission of using art as an educational icon.

Although our academic interests, clinical activities, and teaching commitments have kept us on different paths within our large Division in the past, we were drawn together to work on this book by our mutual admiration for the work of Dr. Frank H. Netter. His understanding of anatomy, physiology, pathogenesis, and clinical signs of disease are translated by his incredible artistic talent into visual images that are so powerful that they reduce complexities into simple concepts that remain embedded in our memories for decades. It is difficult to express the appreciation we have for how much his art contributed to our own enjoyment in medical education. We both had a strong desire to extend this experience to our peers, trainees, and students through the creation of a new up-to-date resource for learning about infectious diseases. We hope that we have succeeded in our goal and welcome your feedback, seeking further improvements for future editions.

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NETTER'S INFECTIOUS DISEASES

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SECTION I

Vaccine-Preventable Diseases in Children and Adolescents

Patrick W. Hickey

1

Introduction to Vaccine-Preventable Diseases in Children and Adolescents

Patrick W. Hickey

ABSTRACT

This section provides information about the vaccines currently recommended in the United States for routine immunization of children and adolescents, as well as the epidemiology and clinical manifestations of these diseases. This chapter provides an overview of how vaccine schedules are developed, the types of products used, and considerations related to safety and usage. Although overall vaccine coverage remains high in the United States and other industrialized nations and is expanding globally, sustaining access to and uptake of vaccines requires continued attention from policy makers and public health officials.

GEOGRAPHIC DISTRIBUTION AND EPIDEMIOLOGICAL TRENDS

Worldwide in 2018, the percentage of children immunized with three doses of diphtheria, tetanus, and pertussis (DTP) and oral polio vaccines, and a measles-containing vaccine exceeds 85%. Although vaccines have proven safe and cost-effective, saving $16.00 in healthcare costs, lost wages, and lost productivity due to illness and death for every dollar spent, many developing countries do not have adequate and consistent access to available or affordable vaccines, particularly for newer vaccine products, some of which have narrow geographic use, such as protein-conjugate pneumococcal, typhoid, and meningococcal vaccines, and Japanese encephalitis.

During the time period of 2016 to 2018, the immunization coverage rate in the United States at age 24 months with the full seven-vaccine series (4:3:1:3:3:1:4 series): four diphtheria toxoid and tetanus toxoid with acellular pertussis vaccine (DTaP); three polio; one measles, mumps, rubella vaccine (MMR); three (or four) *Haemophilus influenzae* type b vaccine [Hib]; three hepatitis B, one varicella, and four pneumococcal conjugate vaccines was only 68.5%. However, coverage rates exceeded 90% for polio, MMR, hepatitis B, and, varicella on an individual vaccine basis. Although only 1.3% of children had received no vaccines, vaccine coverage in the United States varies widely based on both geography and family demographics. Low vaccine coverage is associated with lack of private health insurance, poverty, and being of the Black or American Indian/Alaska Native race. Twenty states have MMR coverage less than 90%, with pockets in some communities significantly lower. In many of these localities, parental reluctance to vaccinate and acceptance by local governance of nonmedical exemptions to vaccine requirements are highly prevalent, putting them at risk for outbreaks of vaccine-preventable diseases, as represented by the more than 1200 measles cases that occurred nationwide in 2019. Vaccine hesitancy is an emerging problem for the United States and other industrialized nations that historically have had high coverage rates and had eliminated many of these diseases, only to see reemergence of the diseases with decreasing coverage. Engaging parents reluctant to vaccinate requires careful consideration of the underlying concerns and a thoughtful communication strategy, preferably from a trusted source.

GENERAL PRINCIPLES

Schedules

Synchronized immunization schedules for the United States are developed by the Advisory Committee on Immunization Practices (ACIP) of the Centers for Disease Control and Prevention (CDC), the American Academy of Pediatrics (AAP) Committee on Infectious Diseases (Red Book), and the American Academy of Family Practitioners (AAFP) and are posted annually in January. Two immunization schedules are posted for the pediatric age groups: one for children younger than 7 years of age and one for individuals 7 through 18 years of age. A separate schedule is available for immunizations for adults over the age of 18 years. The World Health Organization (WHO) Expanded Program on Immunization (EPI) publishes immunization schedules for all of the countries in the world.

Immunizations Received in Other Countries

Healthy individuals immunized in countries outside of the United States, now living in the United States should receive vaccines according to the recommended schedule for healthy infants, children, and adolescents. In general, only written documentation should be accepted as proof of previous vaccination. Written, dated, and appropriate records (e.g., correct age, dates, intervals, and number of doses) may be considered as valid, and immunizations may resume according to the US schedule. If vaccination status is uncertain, the options include vaccinating or performing serologic testing for antibodies against the selected vaccine antigen, if testing is available.

TYPES OF IMMUNIZATIONS

The two major types of immunizations are active and passive.

Passive Immunization

Passive immunization refers to receipt of preparations of preformed antibodies, usually as immune globulin (IG). IG may be a general formulation or hyperimmune IG developed with high concentrations of antibodies against a specific disease, such as hepatitis B immune globulin (HBIG).

Administration of IG may be useful for (1) prophylactic immunization for a host who is not able to make antibodies (e.g., an infant with congenital immunodeficiency), and (2) immediate preexposure or postexposure protection of individuals, especially when there is not sufficient time for the host to mount a protective antibody response (e.g., in acute exposure to hepatitis A in an immune compromised individual, or an infant too young to receive active immunization).

Active Immunization

With active immunization, a vaccine antigen is given to the host to elicit a protective immune response (e.g., antibodies and cellular immunity). The vaccine antigen may be composed of whole microorganisms, partial microorganisms, or a modified product (e.g., toxoid or purified component) of microorganisms. Whole organisms may be inactivated or live-attenuated. The elicited immune response usually mimics the response seen with natural infection, and ideally this occurs with no or minimal risks to the recipient.

VACCINE RECIPIENTS

Healthy Pediatric Populations

In the United States, all licensed vaccines have undergone review by the US Food and Drug Administration (FDA) and have been proven safe and effective for the targeted population. Most of the routinely recommended pediatric vaccines are targeted for healthy children and adolescents (Fig. 1.1). Alternative schedules that are delayed or staggered have not been systematically studied for safety and efficacy and pose increased risk of disease acquisition.

Adolescents

Since 2005, several vaccines have become available for routine use in adolescents. These include tetanus toxoid with reduced-dose diphtheria toxoid and reduced-dose acellular pertussis vaccine (Tdap), human papillomavirus (HPV) vaccine, and meningococcal conjugate vaccines; all of these are discussed in detail in the chapters in this section. In addition, some existing vaccines for use in children, such as influenza and varicella vaccines, were given new recommendations for routine or "catch-up" indications in adolescents. The AAP has recommended a routine health visit at 11 to 12 years, and this visit can be used to ensure that the adolescent has received all recommended immunizations, as well as to afford the opportunity to provide anticipatory guidance for safe and healthy living for the teen years.

Immunocompromised Children

A growing number of children and adolescents have congenital or acquired immune dysfunction and should not receive immunizations as routinely recommended. Special accommodations may be needed for immunizing these individuals, such as adjusting the schedule or possibly not administering some agents. However, there are no indications for giving decreased or partial doses of vaccines. The plan for vaccination of an immunocompromised child should be determined by the nature and degree of the immunosuppression, weighing the risks and benefits of vaccination with those of exposure to natural infection. Efforts that support high rates of vaccine uptake among the general population are important to providing protective herd immunity for those with contraindications.

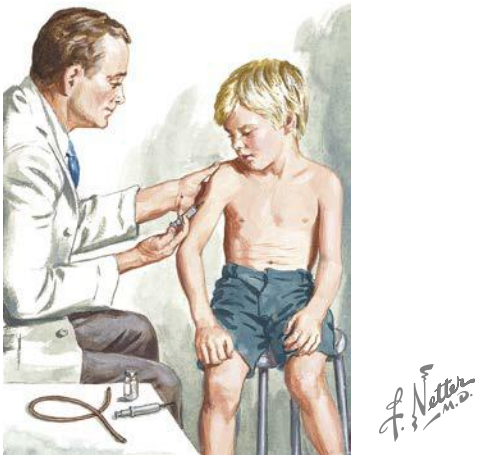

Fig. 1.1 Vaccination.

Preterm (<37 Weeks of Gestation) and Low–Birth-Weight (<2000 g) Infants

In general, medically stable premature and low–birth-weight infants may be immunized at the same dose, schedule, and postnatal age as full-term infants. One notable exception is the use of hepatitis B vaccine in infants who weigh less than 2000 g; details are provided in Chapter 15.

International Adoptees, Travelers, Immigrants, and Refugees

All routinely recommended vaccines should be up to date for age, as many families travel abroad without recognizing the possible exposures to vaccine-preventable diseases. In addition, traveling children and teens should receive vaccinations, as well as other preventative measures (e.g., malaria prophylaxis), targeted for their destination. There may be a need for an accelerated schedule—for example, early immunization with MMR and hepatitis A for infants 6 to 12 months of age traveling to endemic regions. Use of IG prophylaxis can be considered for some individuals susceptible to hepatitis A (e.g., infants under 6 months of age, short-notice travelers with chronic liver disease). Current recommendations for travelers are posted on the CDC website.

ADVERSE EVENTS AND VACCINE INFORMATION

Adverse Events

Safety information about vaccines for healthcare providers and laypersons is available from several reliable resources including the AAP, CDC, FDA, and WHO. A select list of internet resources for vaccine information is provided in Table 1.1. The vaccine manufacturer's package insert provides safety and tolerability data from the clinical trials for each specific vaccine. As with any medication, no vaccine is completely free of adverse effects (AEs), and the known AEs should be discussed with vaccinees (nonminors) and/or parents or legal guardians. Most AEs observed after routine immunizations are local injection-site reactions such as erythema, edema, and pain and systemic reactions such as fever or irritability. Although the majority of AEs are mild and self-limiting, some may be associated with transient impairment for the vaccinee, such as limited limb mobility because of pain. Serious AEs, which may lead to permanent disability or life-threatening illness, are rarely observed after routine pediatric vaccinations. The occurrence of an AE after immunization proves not that the vaccine is the cause of the event but that there is a temporal relationship. If a serious AE occurs after administration of a vaccine (especially within 30 days of receipt), a complete evaluation for all plausible causes, including the role of the vaccine antigen, should be performed. All serious AEs and clinically significant AEs should be reported to the Vaccine Adverse Event Reporting System (VAERS), which is maintained by the CDC and FDA. Reporting AEs is valuable because it helps identify events that are infrequent or unexpected and not observed in the prelicensure clinical trials.

Informing Vaccine Recipients and Parents

Vaccine recipients and parents or legal guardians should be informed about the risks and benefits of vaccination and about the natural disease that the vaccine is designed to prevent. The National Childhood

TABLE 1.1 Select Internet Resources for Vaccine Information

Resource	For Healthcare Providers	For Lay Persons
American Academy of Pediatrics (AAP)	https://www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/immunizations/Pages/Immunizations-home.aspx	https://www.healthychildren.org/english/safety-prevention/immunizations/
Centers for Disease Control and Prevention (CDC) and the Advisory Committee on Immunization Practices (ACIP)	https://www.cdc.gov/vaccines/hcp/ https://www.cdc.gov/vaccines/hcp/acip-recs/	https://www.cdc.gov/vaccines/parents/ https://www.cdc.gov/vaccines/vac-gen/
CDC travelers' health recommendations	https://wwwnc.cdc.gov/travel/yellowbook/2020/table-of-contents	https://wwwnc.cdc.gov/travel
CDC and AAP communication toolkits, messaging strategies	https://www.cdc.gov/vaccines/hcp/vis/ https://www.cdc.gov/vaccines/partners/childhood/index.html	https://www.healthychildren.org/english/safety-prevention/immunizations/
US Food and Drug Administration (FDA)	https://www.fda.gov/vaccines-blood-biologics/vaccines	https://www.fda.gov/vaccines-blood-biologics/resources-you-biologics/consumers-biologics
Vaccine Adverse Event Reporting System (VAERS)	https://vaers.hhs.gov/professionals	http://vaers.hhs.gov/
World Health Organization (WHO) Expanded Programme on Immunization	https://www.who.int/immunization/programmes_systems/supply_chain/benefits_of_immunization/en/	www.who.int/vaccine_safety/en

Vaccine Injury Act of 1986 requires that parents receive a Vaccine Information Statement (VIS) each time a child receives a vaccine covered under this legislation, regardless of the funding source used to purchase the vaccine. The VISs are available from the CDC at the National Immunization Program site. The vaccine manufacturer, lot number, date of administration, and that the VISs were provided should be documented.

Particularly in an era when many adults have not seen or experienced the diseases for which childhood vaccination is offered, nor the morbidity and mortality they cause, there is a risk of hesitancy or refusal to vaccinate children. In situations where this occurs, it is important to both identify the source of this reluctance and then to have an informed discussion with parents that demonstrates both respect and prioritizing the child's welfare. Some caregivers will express religious reasons for vaccine refusal, although these situations are in fact quite rare among major religious faiths. Common misconceptions related to vaccines include such beliefs as, "natural immunity is better," "too many vaccines can overload the immune system," "vaccines are not effective anyway," "vaccines cause autoimmune diseases and/or autism," and "spreading out the vaccine series is safer." There is strong evidence to counter these false beliefs, and the AAP and CDC offer a number of resources (see Table 1.1) to help address these concerns with parents and caregivers. Parents should be informed of legal requirements for vaccination to access school and childcare services. Although some state laws allow for philosophical/nonmedical waivers to be provided, both the AAP and CDC discourage their provision. When a vaccine is refused, a "vaccine refusal" document should be signed by the caregiver.

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Diphtheria and Tetanus

Megan L. Donahue, Matthew D. Eberly

ABSTRACT

Diphtheria and tetanus are bacterial diseases mediated by extremely potent toxins. Diphtheria is a communicable infection of the upper respiratory tract, skin, and rarely other mucous membranes caused by *Corynebacterium diphtheriae,* whereas tetanus is a neurotoxin-mediated disease resulting from anaerobic wound infections caused by *Clostridium tetani.* These diseases can be life-threatening, and early recognition and intervention are essential for effective management. Immunization against both diseases is usually performed with combination vaccines containing diphtheria and tetanus toxoids, which induce toxin-neutralizing antibodies that are protective.

Diphtheria and tetanus are very different diseases in their clinical presentation. Nevertheless, the two diseases are commonly considered together because they share a common history, as well as key elements of pathogenesis and prevention. Potent toxins are central to the pathogenesis of diphtheria and tetanus. Diphtheria toxin (DipT) and tetanus neurotoxin (TeNT) were among the earliest recognized bacterial toxins, and early immunology was stimulated by the discovery of protective, toxin-neutralizing serum antibodies. The science of vaccination was promoted by the revelation that DipT and TeNT can be chemically treated to produce toxoids, namely, molecules that have lost toxicity but retain their ability to induce protective antibodies.

For both diseases the key to prevention is to maintain adequate concentrations of toxin-neutralizing antibodies. As a result of successful immunization programs, diphtheria and tetanus are now rare in the United States and in other developed nations. If diphtheria or tetanus is suspected, state and local health departments should be contacted for guidance because both diseases require treatment with specific antitoxin.

DIPHTHERIA

CLINICAL VIGNETTE

A 5-year-old child with a history of incomplete immunizations developed sore throat and low-grade fever a few days after returning from visiting family in rural India. She presented to an urgent care center, where rapid streptococcal testing was negative. She was diagnosed with viral pharyngitis and discharged home. Two days later, she complained of worsening sore throat and difficulty swallowing. She presented to an emergency department where examination revealed a thick, adherent, grayish membrane across the posterior oropharynx, involving the tonsillar pillars and uvula. Attempts to remove the membrane resulted in bleeding. She also had notable swelling of her anterior cervical lymph nodes. Based on her clinical presentation, immunization status, and recent travel history, a clinical diagnosis of diphtheria was made. A swab of the tonsillar exudate was sent for culture, and the Centers for Disease Control and Prevention (CDC) were contacted for release of diphtheria antitoxin (DAT). She was started on IV erythromycin while awaiting arrival of DAT from the CDC.

Geographic Distribution and Magnitude of Disease Burden

Corynebacterium diphtheriae is a species of aerobic, nonencapsulated, non–spore-forming, mostly nonmotile pleomorphic, gram-positive rods, and humans are the only natural host. Strains are found in four biotypes known as *gravis, intermedius, mitis,* and *belfanti;* all four types can cause human disease. Spread occurs through contact with respiratory secretions or infected skin lesions. The genes responsible for DipT production are carried on a chromosomally integrated bacteriophage. Strains of *C. diphtheriae* that do not carry the phage commonly colonize the human respiratory tract but cannot cause clinical diphtheria. Asymptomatic carriers of both toxigenic and nontoxigenic strains have been reported. Nontoxigenic strains are increasingly reported in several countries and have been associated with systemic disease in immunocompromised individuals. The bacteriophage can also be carried by *Corynebacterium ulcerans* or *Corynebacterium pseudotuberculosis,* and diphtheria-like illness has been observed in patients infected with *C. ulcerans.*

Before widespread vaccination, diphtheria was a leading cause of morbidity and mortality in the United States. In the prevaccine era, approximately 70% of diphtheria cases occurred in children younger than 15 years old. Disease was less common in infants younger than 6 months of age, presumably because of the protection provided by maternal antibodies acquired transplacentally. Asymptomatic infections were common. Clinical disease was less common in adults because most had immunity as a result of natural exposure. Immunity from exposure does not appear to be lifelong; however, immunity was maintained by frequent boosting through natural exposure.

In the United States, there were two cases of diphtheria reported between 2004 and 2017. Cases of cutaneous diphtheria continue to occur but are not reportable in the United States. However, respiratory diphtheria continues to cause disease globally in countries with poor routine vaccination coverage, with the annual number of reported diphtheria cases remaining largely unchanged for more than a decade. In the states of the former Soviet Union, a large outbreak of diphtheria involving 157,000 cases and 5000 deaths, primarily in adults, occurred from 1990 to 1998. This outbreak was found to be associated with declines in the public health infrastructure and vaccination coverage rates and demonstrated the importance of maintaining high immunization coverage in all populations. More recently, India has had the largest amount of reported cases annually, with 18,350 cases reported between 2011 and 2015. During this same time period, Southeast Asia accounted for 55% to 99% of all reported diphtheria cases, according to reports made to the World Health Organization (WHO). The majority of cases worldwide occur in adolescents and adults, likely due to increasing vaccination coverage in children and incomplete vaccination or waning immunity in adolescents and adults.

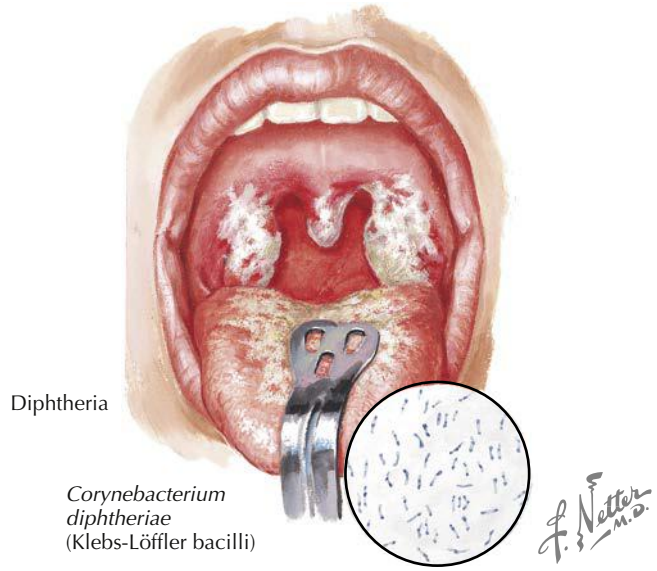

Fig. 2.1 Pseudomembrane (diphtheria).

Travelers to regions where diphtheria remains endemic due to inadequate vaccine coverage should ensure that they are up to date with diphtheria immunizations. Similarly, diphtheria should be considered in the differential diagnosis for symptomatic individuals coming from those regions.

Risk Factors

Increased risk is directly associated with inadequate serum concentrations of DipT-neutralizing antibodies. Notably, immunity from vaccine or natural disease does not appear to be lifelong. In the United States, coverage with diphtheria booster immunization decreases with age, and studies have suggested that 40% to 70% of adults older than 40 years of age are susceptible. In the United States and Canada, circulation of toxigenic strains is uncommon, except in some areas within the northern plains region. Although the opportunity exists for introduction of toxigenic strains into the general population, outbreaks are rare when high immunization rates in infants and children are maintained.

Clinical Features

The initial diagnosis is based on the observation of classic clinical features. Two main types of infection can occur: a benign, self-limited, and nonspecific skin infection, and a respiratory form that can manifest as a localized nasal infection or a more serious pharyngeal or laryngeal disease. The incubation period is usually 2 to 5 days but can range from 1 to 10 days. The respiratory disease begins gradually with nonspecific symptoms such as fatigue, sore throat, anorexia, and low-grade fever. Approximately 2 to 3 days after onset of symptoms, patients develop the classic pseudomembrane, which is an adherent grayish-white membrane which can cover the tonsils, posterior pharynx, uvula, and/or posterior tongue and will bleed with attempts to remove it (Fig. 2.1). As the disease progresses, patients may develop difficulty swallowing and a hoarse voice. In the most severe forms of respiratory diphtheria, extensive membrane formation and edema can result in airway obstruction; therefore patients should be monitored closely for respiratory compromise. Associated extensive cervical lymphadenopathy and soft-tissue swelling may cause the classic "bull-neck" appearance (Fig. 2.2). Absorption of DipT into the bloodstream can cause serious systemic complications, notably myocarditis with heart block and cranial and peripheral neuropathies.

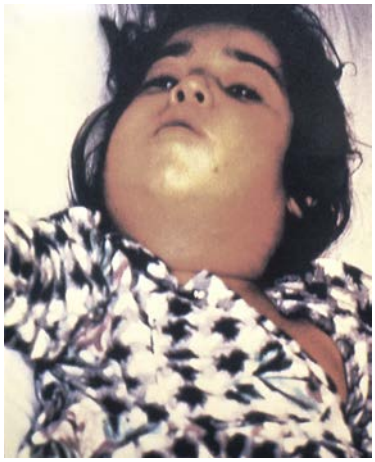

Fig. 2.2 Classic bull-neck appearance. (From Centers for Disease Control and Prevention, Public Health Image Library, 1995.)

Diagnosis

Diphtheria is initially a clinical diagnosis, and laboratory confirmation requires isolation of toxigenic strains of *C. diphtheriae* from the site of infection. Proper culture requires special collection techniques and growth media; few laboratories have maintained this capability. Therefore, in addition to discussion with the local laboratory, an experienced public health microbiology laboratory should be contacted for further guidance. For respiratory diphtheria, cultures should be obtained from the involved nasal or pharyngeal mucosa and should include both the pseudomembrane and the material beneath the membrane. Because there are asymptomatic carriers of nontoxigenic *C. diphtheriae,* confirmation also requires detection of DipT. The Elek immunoprecipitation assay is the traditional way to detect toxin production but is time consuming. The diphtheria toxin gene *(tox)* can be detected by polymerase chain reaction (PCR) testing, but actual production of toxin should be performed by the Elek test.

The differential diagnosis includes pharyngitis from more common causes, including bacterial pharyngitis caused by group A *Streptococcus* or *Arcanobacterium* and viral pharyngitis (e.g., caused by adenoviruses and enteroviruses); infectious mononucleosis from Epstein-Barr virus; and more unusual diseases such as acute necrotizing ulcerative gingivitis (Vincent angina) and severe oropharyngeal candidiasis.

Clinical Management

Respiratory diphtheria mandates prompt treatment with both antitoxin and antibiotics, supplemented with intensive supportive care. When diphtheria is suspected, treatment with equine DAT should begin before laboratory confirmation is obtained. No licensed product is available in the United States; however, DAT can be obtained from the CDC under an investigational new drug (IND) protocol. The local or state public health departments should be contacted for public health investigations. Antitoxin only neutralizes circulating DipT and has no effect on intracellularly bound toxin; therefore early use is required to minimize the severity of the disease. Because the antitoxin is made from horse serum, it carries the risk of hypersensitivity reactions or serum sickness, and patients should be tested for sensitivity before administration. Individuals with hypersensitivity should receive the antitoxin according to the desensitization procedure provided by the CDC protocol and only in settings equipped for treatment of anaphylaxis.

Antibiotics are also an important aspect of therapy, but they do not replace the use of antitoxin. Although antibiotics have no effect on

existing DipT, they will help to prevent further bacterial growth, slow toxin production, and decrease the risk of transmission. Antibiotic treatment consists of a 14-day course of either erythromycin (40 mg/kg/day; maximum 2 g/day given orally or by injection) or penicillin G (300,000 units IM every 12 hours for those weighing 10 kg or less; 600,000 units every 12 hours for those weighing more than 10 kg). Intravenous medications should be used initially but can be transitioned to oral medications as soon as the patient is able to tolerate oral therapy.

Supportive care involves careful respiratory and cardiac monitoring because patients are at risk for airway obstruction as well as arrhythmia and cardiac compromise from myocarditis. Droplet precautions should be maintained for patients with suspected respiratory diphtheria until completion of antibiotic regimens and until two cultures, separated by at least 24 hours, are negative. Contact precautions are recommended for individuals with cutaneous diphtheria, and lesions should be covered. Treatment should include antibiotics and routine management for skin ulcers; DAT is rarely needed. Active diphtheria infection may not induce protective immunity, and all patients should receive an appropriate vaccination series after resolution of the acute illness.

Immunization status should be assessed for all contacts of diphtheria cases, with full catch-up immunization recommended for incompletely immunized contacts. Swabs for diphtheria culture should be taken from all contacts, and a course of erythromycin or penicillin should be administered for 7 days.

Prognosis

Prognosis depends on the severity of the pharyngeal disease, the extent of respiratory compromise, the duration of disease before initiation of treatment, and the presence of myocarditis. Duration of illness depends on the severity of the disease and resulting complications and can range from a few days to several months. The overall case fatality rate of respiratory diphtheria is 5% to 10%, although it can be higher in children younger than 5 years and adults older than 40 years. Cutaneous diphtheria is rarely fatal.

TETANUS

Geographic Distribution and Magnitude of Disease Burden

Clostridium tetani is a gram-positive, spore-forming, strictly anaerobic bacterium that typically exhibits a terminal spore and can infect wounds. The spores are found in soil in nearly all areas of the world. Tetanus is typically associated with deep or penetrating wounds that create the anaerobic conditions that facilitate germination, growth of spores, and release of TeNT (often called *tetanospasmin*), the toxin responsible for the clinical manifestations of disease.

TeNT, one of the most toxic molecules known, achieves its toxicity through a series of complex steps that includes migration from the periphery to the central nervous system (Fig. 2.3). TeNT binds to neuronal cells at the site of infection and then is transported centrally, where it interferes with release of inhibitory neurotransmitters. Once the inhibitory control is lost, motor neurons undergo sustained excitation leading to the muscular stiffness and spasms characteristic of tetanus.

In the United States there is an average of 30 tetanus cases reported annually. Tetanus first became a reportable disease in 1947, and since then there has been more than a 95% reduction in cases, attributed in large part to immunization, as well as hygienic improvements in wound management and childbirth practices. Cases have been reported in all age groups; however, the incidence rates tend to increase with increasing age—for example, from 2001 to 2008, 30% of the cases reported to the CDC were in individuals older than 65 years of age, with less than 10% of cases reported in individuals less than 20 years of age. The case fatality rate over the same period was 13%; however, at least 75% of deaths occurred in individuals older than 65 years old.

Worldwide, a steady increase in tetanus toxoid vaccinations has been associated with a decline in cases and deaths. However, tetanus remains a problem in parts of the world with low immunization coverage, with maternal and neonatal tetanus responsible for the great majority of deaths. Maternal tetanus is associated with inadequate vaccination and unhygienic obstetric practices. Neonatal tetanus results from infection of the umbilical stump, particularly in infants born to mothers with inadequate immunization. Since 1989, the WHO has encouraged efforts to reduce maternal and neonatal tetanus (i.e., a reduction of neonatal tetanus incidence less than 1 case per 1000 live births per year in every district); however, as of July 2019, there are still 12 countries who have not achieved Maternal and Neonatal Tetanus Elimination (MNTE) status. In 2017, the WHO estimated that 30,848 newborns died from neonatal tetanus, an 85% reduction from the year 2000. Both maternal and neonatal tetanus are preventable via immunization of mothers, with neonatal protection resulting from transplacentally acquired TeNT-neutralizing antibodies.

Risk Factors

Mirroring the situation described earlier for diphtheria, higher risk is associated with inadequate concentrations of neutralizing antibodies, usually through a failure to stay up to date with recommended immunizations. Most cases of tetanus occur in individuals who lack TeNT-neutralizing antibodies and incur a wound that promotes the anaerobic growth of *C. tetani.* Conditions that encourage an anaerobic environment include deep puncture wounds, coinfection with other bacteria, devitalized tissue, or presence of a foreign body. Other risk factors include intravenous drug use and diabetes. Most nonneonatal cases occur after a penetrating injury; however, in approximately 30% of cases, the site of infection cannot be identified.

Clinical Features

Tetanus disease occurs in one of three clinical patterns: generalized (including neonatal), localized, or cephalic. The severity is influenced by the amount of toxin produced as well as the presence of preexisting, albeit not fully protective, concentrations of antibody. The incubation period from the time of inoculation is typically approximately 1 week but can be as rapid as 1 to 3 days or as long as many months. In general, rapid disease progression is associated with a more severe course. The most common and severe form of tetanus is generalized tetanus, accounting for 88% of tetanus cases in the United States. Generalized tetanus is characterized by diffuse tonic contraction of skeletal muscles as well as intermittent, painful muscular spasms (see Fig. 2.3). The disease typically begins with localized muscle spasms of the jaw known as trismus (lockjaw) or other cranial nerve involvement, which progress to include a stiff neck, opisthotonus (spasms and arching of the back), risus sardonicus (sustained muscle spasm of the face), a rigid abdomen, dysphagia, or apnea (caused by the contraction of the thoracic muscles and/or the glottal or pharyngeal muscles). Generalized tetanic spasms lead to a characteristic posture: clenching of the fists, arching of the back, flexion and abduction of the arms, and extension of the legs, often accompanied by apnea. Spasms can be exacerbated by noxious stimuli, including loud noises. Toxin damage to autonomic nerves also leads to autonomic instability, characterized early by irritability and restlessness, sweating, and tachycardia and later by labile blood pressures, cardiac arrhythmias, and fever.

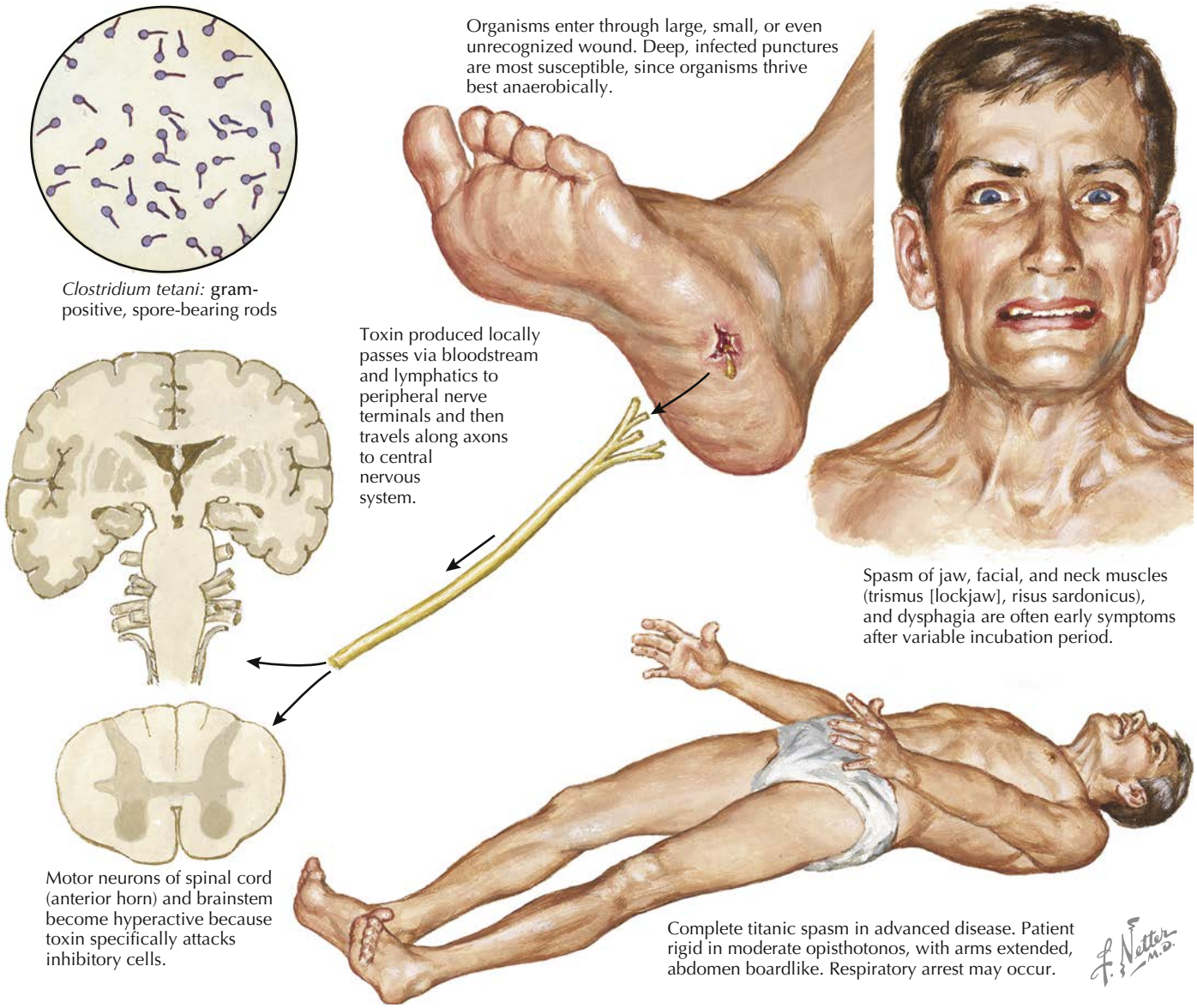

Fig. 2.3 Generalized tetanus.

Neonatal tetanus is a subset of generalized tetanus. Disease onset is very rapid and generally occurs within the first 2 weeks of life. Symptoms are similar to those of generalized tetanus, including diffuse rigidity, muscle spasms, and trismus, leading to complications of apnea and the inability to suck. In addition, seizures have been observed in infants with tetanus.

Localized tetanus is a rare clinical pattern characterized by muscle contraction in a single extremity or body region, accounting for 12% of tetanus cases in the United States. Cephalic tetanus is similar but involves only the cranial nerves, most commonly the facial nerve. It may be associated with otitis media or head lesions and may result in cranial nerve palsies. Many cases of both localized and cephalic tetanus progress to generalized tetanus and may represent an early stage of the disease.

Diagnosis

Tetanus is diagnosed solely on clinical grounds. Tetanus should be considered in the differential diagnosis of muscle spasms, particularly in patients with a history of an antecedent injury and inadequate immune status. The differential diagnosis includes drug-induced dystonias, dental infections, neuroleptic malignant syndrome, strychnine poisoning, and stiff person syndrome.

Clinical Management and Drug Treatment

Effective treatment of tetanus requires a multipronged approach, including neutralization of circulating toxin, reduction in toxin production, medical control of muscle spasms, management of autonomic instability, aggressive supportive care, and immunization. Neutralization of unbound, circulating antibody is achieved by the use of human tetanus immune globulin (TIG), a commercially available product licensed by the US Food and Drug Administration (FDA). TIG is administered intramuscularly as a one-time dose. The optimal therapeutic dose has not been established but experts recommend 500 international units. Prompt administration helps to minimize disease severity. If TIG is not available, human intravenous immune globulin (IVIG) can be used at a dose of 200 to 400 mg/kg; however, the FDA has not approved IVIG for this use. Aggressive wound debridement, as well as antibiotic treatment with

metronidazole (30 mg/kg/day divided every 6 hours), can reduce further TeNT production. Penicillin G (100,000 unit/kg/day given in 4- to 6-hour intervals) is an alternative treatment. Antibiotic treatment should continue for 7 to 10 days. Muscle spasms, in addition to being intensely painful, can be life-threatening when they lead to apnea. Limiting stimulation can minimize the frequency of spasms. Additional management includes the use of sedatives such as benzodiazepines or, in severe, refractory cases, neuromuscular blockade. Autonomic instability is often managed with magnesium sulfate, morphine, or beta-blockade. Supportive care is a vital part of the management of tetanus, as full recovery may take several weeks. Many patients require respiratory support, and early tracheostomy should be considered to avoid complications of prolonged intubation. Early enteral nutrition and prompt initiation of physical therapy may speed recovery. Because of the extreme potency of small amounts of tetanus toxin, tetanus disease does not confer lasting protective immunity, and all patients should immediately receive appropriate immunization.

Prognosis

The prognosis of people with tetanus is dependent on the availability of supportive care, as well as the age and underlying health of the patient. In general, the shorter the incubation period and the time to onset of spasms, the worse the prognosis. Recovery from tetanus requires regrowth of axonal nerve terminals, and therefore the duration of disease can be prolonged (typically 4 to 6 weeks). Because of the availability of supportive care, most patients in developed countries recover. In contrast, in developing countries, without access to intensive care, the case fatality rates vary from 10% to 70%, nearing 100% in the youngest and oldest patients. Most adults and children who survive recover fully, but neonates may have varying degrees of neurologic damage, including intellectual deficits and cerebral palsy.

PREVENTION AND CONTROL OF DIPHTHERIA AND TETANUS

Vaccination with diphtheria and tetanus toxoids is the basis of prevention and control of these two diseases. Measurement of antitoxin antibodies is possible; however, interpretation of the antibody concentrations is complex and may not readily predict the protection status of the individual. More important than a specific antibody concentration, the key to protection is assurance of the appropriate series, including booster doses, of vaccinations.

In addition to routine vaccinations, tetanus immunizations have a role in management after potential exposure from an injury. Anyone with a clean, minor wound should receive a dose of a tetanus toxoid–containing vaccine if he or she has not had a booster dose in the past 10 years. For all other injuries, including but not limited to dirty, penetrating, or burn wounds, a dose of tetanus toxoid–containing vaccine should be given if the individual has not received a booster in the past 5 years, has received fewer than three vaccinations, or has unknown vaccination status. In addition, prophylactic administration of TIG is recommended for underimmunized patients with serious wounds.

Tetanus toxoid is available as a single antigen (TT) or in combination with pediatric or adult formulations of diphtheria toxoid (DT or Td, respectively) and acellular pertussis antigens (DTaP and Tdap). The diphtheria toxoid component of childhood vaccines has a higher toxoid content (represented by capital *D*) and is designed to induce a good antibody response in immunologically naïve individuals younger than 7 years of age. For older and previously immunized individuals, a lower toxoid content vaccine (designated by lowercase *d*) is used because it induces a good antibody response while yielding fewer reactions. Products available vary by country and age, and national agencies should be consulted for the currently recommended products. In the United States the current recommendation is for an initial five-dose series in childhood, with doses at 2, 4, and 6 months, a fourth dose at 15 to 18 months, and a fifth dose at 4 to 6 years of age. At least three doses of each toxoid are required for development of immunity, and additional doses are recommended to maintain this immunity. In the United States, booster doses of diphtheria and tetanus toxoid vaccines are recommended at age 11 to 12 years (combined with reduced dose acellular pertussis vaccines, Tdap) and then every 10 years to maintain protection. For individuals at least 11 years of age who are eligible to receive acellular pertussis vaccine, one dose of Tdap is recommended instead of Td; this can be given earlier than the 10-year mark. Since 2012, the CDC's Advisory Council on Immunization Practices (ACIP) has recommended Tdap immunization in the third trimester of every pregnancy and in October of 2019, the ACIP voted to update vaccine recommendations for booster doses to include Tdap immunization at any point when Td might be administered, anticipated to be incorporated into the CDC's 2020 Immunization Schedules. Anyone with uncertain vaccination history should be considered unvaccinated and receive the recommended age-appropriate series.

ACKNOWLEDGMENT

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3

Bordetella pertussis and Pertussis (Whooping Cough)

Sylvia H. Yeh

ABSTRACT

Despite the availability of vaccines against pertussis in most developed and developing countries, pertussis remains a significant cause of morbidity and mortality worldwide due to immunity following vaccination and clinical disease waning with time. Routine use of pertussis vaccines has shifted the burden of disease from middle childhood to young infants and older children, adolescents, and adults. The changing epidemiology dictates the need for new vaccines and new vaccine programs targeting these age groups.

CLINICAL VIGNETTE

A 9-year-old child presents with approximately 2 weeks of coughing. She reports that coughing comes on suddenly and has been increasingly forceful and prolonged, to the point where she feels she cannot breathe. She is anxious about going to sleep for fear of having a coughing fit. She is presently without rhinorrhea and has had no fever or other associated symptoms. There have been no ill contacts at home. Her immunizations are current, and there have been no new exposures to second-hand smoke, pets, or other allergens. There has been no travel outside the area she lives in. On exam, she is afebrile with normal vital signs. No abnormalities are noted on examination.

COMMENT: Due to changing pertussis epidemiology, children 7 to 10 years of age increasingly present with pertussis symptoms, presumably due to waning immunity from their last diphtheria toxoid and tetanus toxoid (DTaP) vaccination and before the recommended adolescent vaccination of tetanus toxoid and reduced-dose diphtheria toxoid (Tdap). Frequently, the illness progresses insidiously over time before it is recognizable as pertussis.

GEOGRAPHIC DISTRIBUTION AND DISEASE BURDEN

The World Health Organization (WHO) estimates, based on modeling data, that in 2014 worldwide there were 24.1 million pertussis cases and 167,000 deaths in children younger than 5 years of age. This is significantly greater than the 150,000 passively reported cases and approximately 80,000 to 90,000 annual deaths. Global vaccination coverage rate with three doses of pertussis vaccine stands at 86%. Pertussis is endemic globally, with epidemic peaks every 2 to 5 years. This cycling is unchanged even in the postvaccine era, likely because of both an accumulation of susceptible individuals, and in part a result of waning immunity.

RISK FACTORS

Bordetella pertussis is strictly a human pathogen and is readily transmitted by aerosolized droplets. It is the primary cause of clinical whooping cough, with *B. parapertussis, B. bronchiseptica*, and *B. holmseii* creating a similar, although typically milder, spectrum of illness. The attack rate for susceptible individuals is estimated to be more than 80%. Globally, as vaccination coverage has increased, the overall disease burden has declined (Fig. 3.1). In the United States, after the introduction of whole-cell pertussis vaccines in the 1940s, disease burden was the lowest in 1976 but has had a steady increase since 1980 (Fig. 3.2). The incidence of disease has increased in infants, especially those too young to have completed the primary immunization series, and in adolescents and adults who experience waning immunity from either vaccination or natural exposure. In the mid-2000s, following the transition to acellular pertussis vaccine, there was an age-specific increase in pertussis clustering among those 7 to 10 years of age, presumably due to waning immunity from acellular pertussis vaccine (Fig. 3.3). This was then followed by an increased disease burden among adolescents 13 to 14 years of age in 2012.

Infants younger than 12 months of age have the greatest risk of morbidity and mortality due to pertussis compared with all other age groups, with those younger than 2 months of age with the highest pertussis-related hospitalization and deaths. Studies from industrialized countries have reported rates of hospitalization because of pertussis ranging from 17 (6- to 11-month-old infants) to 280 (0- to 5-month-old infants) per 100,000 population. From 2004 to 2016, the Centers for Disease Control and Prevention (CDC) reports that among infants hospitalized for pertussis, 54.4% were younger than 2 months of age, and among infants who died, 85.5% were younger than 2 months of age. A study of pertussis deaths in the 1990s revealed a higher than expected rate of death in Hispanic infants and infants born at less than 37 weeks of gestation. Some preliminary data suggest this is due to limited maternal immunity in Hispanic mothers, and for preterm infants it is speculated that the cause is due to decreased placental transfer of maternal immunoglobulin G (IgG). Data suggest that administration of two to three doses of pertussis vaccine within the first 6 months of life is protective against severe disease. With the changes in pertussis epidemiology over time, mothers were originally the most common source of pertussis transmission to infants, whereas siblings are currently the most common source of pertussis infection for infants.

Since 2013, there have been reports of disease-causing strains of *B. pertussis* being deficient in a specific antigen, pertactin, which is one of the common antigenic targets of acellular pertussis vaccine. Subsequent vaccine efficacy studies suggest that the currently available acellular vaccines remain effective regardless of current circulating strains, even those deficient in pertactin. In addition, data do not suggest the pertactin-deficient strains differ in severity of disease compared with non–pertactin-deficient strains.

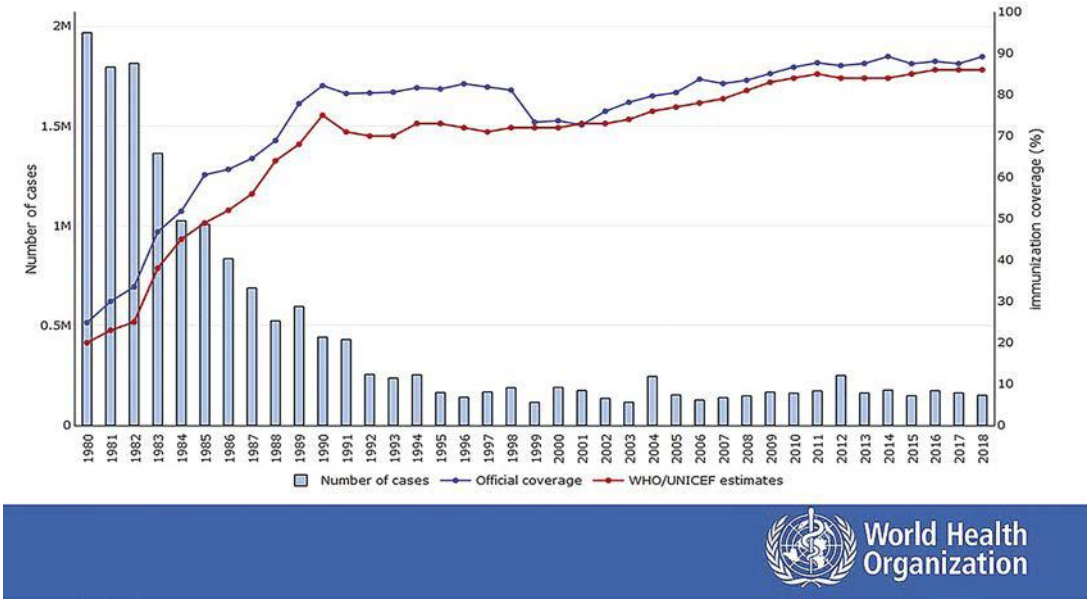

Fig. 3.1 World Health Organization (WHO) pertussis global annual reported cases and DTP3 coverage 1980–2018. (Reused with permission from WHO/UNICEF, Joint Reporting From July 8, 2019, Immunization, Vaccines, and Biological [IVB], World Health Organization. https://www.who.int/immunization/monitoring_surveillance/burden/vpd/surveillance_type/passive/pertussis_coverage_2018.jpg?ua=1.)

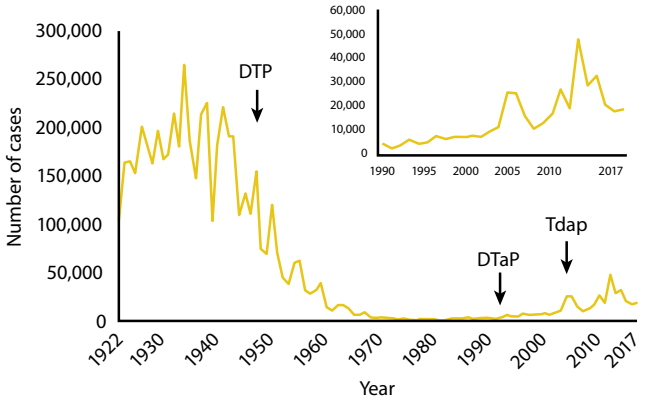

Fig. 3.2 Centers for Disease Control and Prevention (CDC) reported National Notifiable Diseases Surveillance System (NNDS) pertussis cases: 1922–2017. *DTaP,* Diphtheria toxoid, tetanus toxoid, acellular pertussis; *DTP,* diphtheria toxoid, tetanus toxoid, whole-cell pertussis *Tdap,* tetanus toxoid, reduced dose diphtheria toxoid, reduced dose acellular pertussis. (Reused with permission from CDC, National Notifiable Diseases Surveillance System and 1922–1949, passive reports to the Public Health Service. https://www.cdc.gov/pertussis/images/incidence-graph-2017.jpg.)

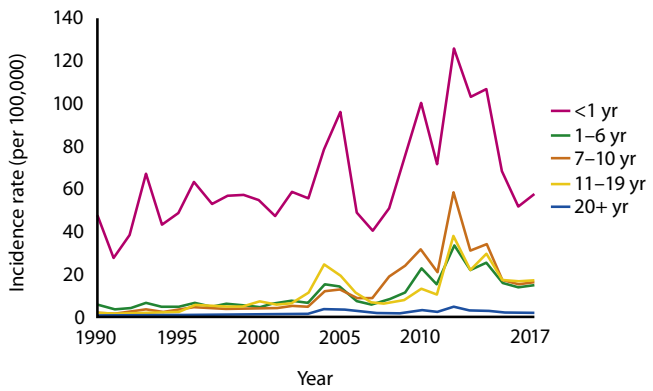

Fig. 3.3 Centers for Disease Control and Prevention (CDC) reported pertussis incidence by age group: 1990–2017. (Reused with permission from CDC. National Notifiable Diseases Surveillance System, 2017. https://www.cdc.gov/pertussis/images/incidence-graph-age-2017.jpg.)

CLINICAL FEATURES

After exposure to the bacteria, the average incubation period is 7 to 10 days, which is then followed by onset of symptoms. The clinical illness is divided into three stages: catarrhal, paroxysmal, and convalescent.

Catarrhal Stage

The catarrhal stage appears similar to the "common cold," with mild cough and coryza, and generally lasts 1 to 2 weeks. Fever is uncommon, and if present it is usually low grade. Unlike a common viral upper respiratory infection, which resolves quickly, in pertussis the cough gradually increases, and infected individuals are most contagious during this phase.

Paroxysmal Stage

In the paroxysmal stage the coughing persists and gradually increases in severity, resulting in the classic paroxysmal attacks. Whooping may be observed during the paroxysmal phase, which is characterized by the noise of the forced inspiratory effort after the coughing attacks (Fig. 3.4). Posttussive emesis may be observed. This stage may last 6 to 12 weeks and is the period in which complications are most likely to occur. The occurrence of complications is inversely related to age, with the youngest infants having the highest rate of complications. The most common complications include hospitalizations, apnea, pneumonia (primary and secondary), barotrauma events (e.g., subconjunctival hemorrhages, umbilical hernias, pneumothorax), and failure to thrive in infants who are unable to feed due to persistent coughing. Seizures, encephalopathy (likely related to generalized hypoxia), and death occur in less than 2% of patients and are generally seen in the youngest infants, although these events

Fig. 3.4 Child coughing.

have been reported in adults. Pneumonia is the most common complication of pertussis (from either primary pertussis or secondary bacterial infection) and also the most common cause of pertussis-associated deaths. Infants younger than 4 months of age who died from pneumonia have been found to have histopathologic findings consistent with pulmonary hypertension.

Convalescent Stage

During the convalescent stage the cough continues to decrease gradually over several weeks to months. Sporadic coughing paroxysms may reappear with subsequent upper respiratory infections during convalescence.

Atypical Pertussis

Infants younger than 6 months of age and previously immunized older children, adolescents, and adults are less likely to have the features of classic whooping cough. Young infants may have apnea as their only presenting feature, and a history of a coughing household member is often the diagnostic clue. Older children, teens, and adults may have chronic cough of varying severity as their primary sign. Persistent coughing has led to erroneous diagnoses such as asthma or reflux aspiration.

DIAGNOSTIC APPROACH

Clinical Diagnosis

Pertussis is a clinical diagnosis, and a high index of suspicion is essential in making the correct diagnosis. When the classic features of whooping cough are present, the diagnosis may be readily entertained. However, because the spectrum of illness is quite varied, pertussis may not be considered. The following clinical case definitions for pertussis have been established by the WHO and the CDC in conjunction with the Council of State and Territorial Epidemiologists:

- In the absence of a more likely diagnosis, a cough illness lasting 2 weeks or longer with one of the following symptoms: paroxysms of coughing, inspiratory "whoop," posttussive vomiting, or apnea with or without cyanosis for infants younger than 1 year of age.
- A probable case is one that meets the clinical case definition and has neither laboratory confirmation nor epidemiologically linkage to a laboratory confirmed cases. For infants younger than 1 year of age, probable cases are defined by meeting the clinical definition and having either a polymerase chain reaction (PCR) positive for pertussis or being a contact with a laboratory-confirmed case of pertussis.
- A confirmed case is one that meets the clinical case definition and is PCR positive for pertussis, or had a contact older than 1 year of age with a laboratory-confirmed case of pertussis, or is any acute cough illness of any duration with isolation of *B. pertussis* from a culture of a clinical specimen.

Laboratory Studies

Although bacterial culture remains the "gold standard" for laboratory confirmation of pertussis infection, the sensitivity is variable and takes a long time to result. In the past decade, many more cases are being diagnosed via PCR. Serology, preferably paired, is an option for epidemiologic evaluation or confirmation of pertussis cases 2 to 8 weeks following cough onset. Although direct fluorescent antibody (DFA) testing was previously used, it has largely been replaced with PCR due to rapid turnaround and improved sensitivity and specificity of PCR compared with DFA.

Bacterial Culture

Growth of *B. pertussis* on specialized media (Bordet-Gengou or Regan-Lowe charcoal agar) is considered the gold standard, and although it is 100% specific, the sensitivity is variable and may be quite low. Factors that contribute to the poor sensitivity of culture include (1) inadequate nasopharyngeal (NP) sample, (2) samples obtained late in the illness, (3) prior antibiotic therapy, (4) previous pertussis immunizations, and (5) difficulty growing and identifying this fastidious organism in the clinical microbiology laboratory. Growth of *B. pertussis* may take 3 to 5 days, but generally microbiology laboratories will maintain the culture plates for 7 to 14 days.

Polymerase Chain Reaction

PCR is an amplified molecular testing tool that often detects sequences in the pertussis toxin gene. In multiple trials evaluating NP samples, PCR has demonstrated higher sensitivity than culture, as well as a more rapid turnaround time. There are commercial assays that include *B. pertussis* in a panel of pathogens detected by multiplex PCR. The limitation of PCR is the potential for contamination yielding false-positive results. Testing via PCR can be done on NP samples up to 4 weeks after cough onset.

Serology

The most widely available serologic assay is an enzyme-linked immunosorbent assay (ELISA) for antibodies to purified antigens of *B. pertussis*. However, there is no established serologic correlate of immunity or serologic marker of acute infection, nor standardization between commercially available tests. Currently, serologic testing is most informative when simultaneous testing of acute and convalescent serum samples is performed; however, fold-rise in titers may not be observed if the first sample is obtained late in the illness. Serologic testing is most useful for laboratory diagnosis late in the disease, usually 2 to 12 weeks after cough onset.

Other Laboratory Findings

During the paroxysmal stage, leukocytosis and lymphocytosis are the characteristic hematologic findings, although these may not be seen, especially in older individuals. The degree of leukocytosis can exceed 50,000 cells/mm^3, and the absolute lymphocyte count may exceed 10,000 cells/mm^3. The degree of lymphocytosis has been shown to correlate with the severity of illness and may result in a hyperviscosity syndrome. Hypoglycemia has been reported in young infants, which may be related to their inability to eat because of coughing or possibly secondary to toxins produced by the organism. Chest radiographs may be normal or may have subtle abnormalities such as peribronchial

cuffing, perihilar infiltrates, or atelectasis. Pulmonary consolidation occurs in 20% of hospitalized patents.

CLINICAL MANAGEMENT

Supportive Care

Supportive care is the mainstay for management of *B. pertussis* infection in patients of all ages. Young infants are more likely to need hospitalization because of their risks for apnea, hypoxia, failure to thrive, and other complications. However, more than 3% of pertussis-associated hospitalizations in the United States have been in adults older than 20 years of age. Infants with severe or frequent coughing paroxysms or apnea may require assisted ventilation. Some infants benefit from oxygen supplementation during coughing spells, feedings, and other exertions. Although there are no established criteria for hospitalization for infants, inability to maintain O_2 saturation during feeding and paroxysms warrants hospitalization.

For infants younger than 3 months of age, some experts recommend hospitalization for close monitoring. Severe pertussis and death have been associated with extreme leukocytosis (>30,000 white blood cells [WBCs]/mm^3). Monitoring WBC counts closely over time is recommended by some experts, and they would recommend double volume exchange transfusion or leukapheresis if there is continuing increase or if counts are more than 30,000 cells/mm^3. Although there have been no controlled studies, data suggest that for exchange transfusion to be successful, it needs to be done before evidence of multiorgan failure has occurred. Extracorporeal membrane oxygenation (ECMO) may be required in some cases.

Maintaining adequate hydration and caloric intake may be difficult for infants because of the paroxysms, which often prohibit them from eating and may cause increased caloric expenditure. Thus close attention to fluid and nutritional status is imperative. In addition, whenever possible, known triggers (e.g., exercise, cold temperatures) that cause coughing paroxysms in the child should be avoided.

Antibiotic Therapy

Antibiotic therapy should be initiated based on a high degree of clinical suspicion, even without laboratory confirmation. Antibiotic treatment is recommended for all infected individuals, regardless of their age or immunization status. The duration of symptoms before treatment seems to be an important factor for the impact of antibiotics. Early treatment (e.g., during the first 7 days of symptoms) may decrease the severity of symptoms, as well as decrease the risk of spread to other susceptible individuals. After 21 days of symptoms, antibiotics may still decrease spread to contacts but likely do little to alter the clinical course. Unfortunately, most patients do not come to medical attention until the paroxysmal phase, when there is likely to be less of an impact on the disease progression.

Azithromycin taken for 5 days is the first line choice for treatment and postexposure prophylaxis. Azithromycin should be used with caution in persons with prolonged QT interval and any proarrhythmic conditions. Oral erythromycin and possibly azithromycin have been associated with infantile hypertrophic pyloric stenosis (IHPS) in infants younger than 1 month of age. In infants younger than 1 month old, the risk of pertussis and its complications outweighs the risks of azithromycin therapy. Therefore the American Academy of Pediatrics (AAP) currently recommends azithromycin for infants younger than 1 month of age even though this is not a US Food and Drug Administration (FDA)-approved indication. Depending on the age of the individual, alternatives may include doxycycline, fluoroquinolones, and trimethoprim-sulfamethoxazole (TMP-SMX). Neither doxycycline nor the fluoroquinolones are routinely recommended for use in young children. Although it has excellent in vitro activity, TMP-SMX has not been systematically evaluated, and its clinical efficacy is largely unproven. TMP-SMX should not be used in the first 6 weeks of life because of the risks of bilirubin displacement and kernicterus. The β-lactam antibiotics have variable activity against *B. pertussis* and are not recommended.

Adjunctive Therapies

Treatment with agents such as antitussives, steroids, and aerosolized bronchodilators have not demonstrated efficacy or benefit for pertussis and are not routinely recommended. Initial studies of *B. pertussis* immunoglobulin (BPIG) showed an improvement in cough paroxysms; however, development of this product has not been pursued and BPIG is not available.

PROGNOSIS

As described earlier, infants have the greatest risk of morbidity and mortality, although complications from pertussis have also been reported in adolescents and adults. The prognosis of infants and children appears to be related to the occurrence and severity of complications. For adults, although the illness may be prolonged, recovery is usually complete.

PREVENTION AND CONTROL: VACCINES

The original vaccines for pertussis were killed whole-cell pertussis organisms, which were later available in combination with diphtheria toxoid and tetanus toxoid (DTwP). These vaccines were effective in reducing the overall burden of pertussis. However, reported temporal associations of adverse events led to a decrease in acceptance of these vaccines in many industrialized nations. Subsequently, pertussis vaccines that were more purified or composed of acellular pertussis antigens (aP) were developed. Currently, several aP vaccines in combination with diptheria toxoid and tetanus toxoid (DTaP) are widely available for use in infants and young children. The aP vaccines have a reduced rate of adverse events compared with whole-cell pertussis vaccines.

Throughout the world, pertussis vaccination generally begins around 2 months of age and consists of three to five doses by age 5 years. In the United States, DTaP is recommended for routine administration to infants at 2, 4, 6, and 12 to 15 months, with a booster dose at 4 to 6 years of age.

Because of the increasing recognition of pertussis in persons 10 years of age and older, who may expose young infants, vaccines targeted to the older age groups have been developed. Reduced-dose acellular pertussis (ap) vaccines combined with tetanus toxoid and reduced dose diphtheria toxoid (Tdap) have been available for individuals 10 years of age and older in the United States since 2005. In the United States, Tdap is recommended for routine administration in early adolescents (11 to 12 years of age), and for one-time use to replace Td booster vaccination in older teens and adults. Tdap vaccines are also recommended for persons (e.g., pediatric healthcare workers; household contacts, and caregivers of young infants) who have contact with individuals at risk for severe pertussis.

For pregnant women, Tdap is recommended to be administered with each pregnancy regardless of prior Tdap receipt history. Ideally, Tdap should be given between 27 and 36 weeks gestation, with earlier in the time frame preferred to maximize the transfer of placental antibody. However, Tdap can be given at any time during pregnancy. For women who did not get Tdap during pregnancy, it is recommended that they receive Tdap in the postpartum period if there is no prior history of Tdap receipt.

After pertussis exposure, DTaP vaccine should be administered as soon as possible for unimmunized children 7 years of age and younger

with incomplete pertussis vaccine series or for those with four or fewer doses and for whom more than 3 years have elapsed since the last pertussis vaccine. Tdap should be administered to exposed individuals older than 10 years of age who are unimmunized. Tdap can be administered at intervals as short as 2 years after previous vaccines containing tetanus, diphtheria, or pertussis, during a community outbreak, or in persons with a high risk of complications with pertussis.

Universal immunization of infants and children with the whole-cell and acellular pertussis vaccines has been effective in reducing the disease burden of pertussis. However, with the shifting epidemiology, it has become apparent that new vaccines and delivery programs are necessary to control this human pathogen. Recently in many industrialized countries, routine immunization programs that included only vaccination of infants and children with DTwP or DTaP have been revised to include Tdap for adolescents and adults. The goals of expanding pertussis vaccinations to include individuals 10 years of age and older are not only to reduce infections in the older age groups but ultimately, by decreasing pertussis circulation in the community, to provide protection for infants too young to be immunized.

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4

Haemophilus influenzae Type b

Sylvia H. Yeh

ABSTRACT

Haemophilus influenzae type b (Hib) was a leading cause of bacterial sepsis and meningitis in children before the widespread availability of conjugate vaccines. Globally, the burden and incidence of Hib disease has dramatically declined with increases in vaccine uptake.

CLINICAL VIGNETTE

A 3-year-old boy presents to the emergency department with high fever and difficulty breathing for 1 day. There is mild rhinorrhea but no rash. The breathing problems began suddenly, and there are no ill contacts. His parents have previously refused routine vaccinations. On exam, he is febrile, tachycardic, and in obvious respiratory distress with his upper body leaning forward and head tilted up. There is audible stridor at rest.

COMMENT: With the widespread use of Hib vaccination, epiglottitis is a very rare clinical presentation in the United States. When present, it is a medical emergency, necessitating rapid availability of sedation and intubation to minimize airway collapse.

GEOGRAPHIC DISTRIBUTION AND DISEASE BURDEN

Haemophilus influenzae is a pleomorphic, gram-negative coccobacillary human pathogen that can be transmitted person to person via respiratory droplets. It is the causative agent for a wide range of infections whose severity is related to the presence or lack of a bacterial capsule. Encapsulated (typeable) strains of *H. influenzae* account for the vast majority of invasive disease, with Hib being the predominant serotype, especially in children younger than 5 years of age. Before widespread availability of conjugate vaccine in 1991, Hib was a leading cause of bacterial meningitis, occult bacteremia, epiglottitis, pneumonia, empyema, cellulitis, septic arthritis, and pericarditis. Invasive Hib infections occurred in 1 in 200 children in the United States during the first 5 years of life. This incidence has dramatically declined to approximately 1 per 100,000 over the past 15 years, reflecting the success of Hib conjugate immunization. Among all age groups in the United States, nontypeable *H. influenzae* currently causes the majority of invasive *H. influenzae* disease. In 2012, the World Health Organization (WHO) estimated that Hib was the cause of 2% of child deaths younger than 5 years of age due to all causes. As of 2018, the WHO estimated the global vaccination coverage with three doses of Hib vaccine to be 72%.

RISK FACTORS

Antibodies against the Hib polysaccharide capsule, polyribosylribitol phosphate (PRP), are protective against invasive disease. Young age is a primary risk factor, with infants 6 to 18 months of age having the greatest risk for invasive Hib disease because of their paucity of PRP antibodies. Infants younger than 6 months of age likely have some protection from passively acquired maternal antibodies. Underlying conditions such as human immunodeficiency virus (HIV), sickle cell anemia, functional asplenia, antibody or complement deficiency syndromes, and malignancy are also risk factors for Hib disease. Environmental exposures such as crowding, household size, daycare attendance, low family income, and low parental education level are also risk factors. Conversely, breastfeeding has been demonstrated to be protective against invasive Hib disease. In the prevaccine era, Hib invasive disease was rare in children older than the age of 5 years, primarily related to antibody acquisition from natural exposure to the organism.

Significantly increased risk of invasive Hib disease has been reported in indigenous populations, including Australian Aboriginal children, Native Alaskan Eskimos, Native Americans, and Canadian First Nations children. These population differences potentially relate to a variety of factors, including early exposure, crowding, microbiologic differences in the circulating strains, socioeconomic factors, and possibly genetics. In adults, underlying conditions such as chronic obstructive pulmonary disease, smoking, HIV infection, alcoholism, pregnancy, splenectomy or functional asplenia, and malignancy increase the risk of invasive Hib disease.

CLINICAL FEATURES

Although Hib can cause a variety of respiratory tract infections, in the prevaccine era it was notorious for causing significant invasive disease in infants and young children and may occur simultaneously at multiple sites. Although these infections are currently rare in immunized populations, practitioners should be familiar with their clinical manifestations because of possible resurgence of disease related to vaccine shortages and the potential for caring for unimmunized children, either due to vaccine refusal or coming from areas of the world without access to Hib vaccines. The following features are described as classically seen in the prevaccine era.

Cellulitis

Cellulitis is a somewhat unique manifestation of Hib disease seen in infants younger than 1 year of age. Hib cellulitis rarely occurs on the extremities, with most cases (74%) occurring at buccal, periorbital, or cervical areas. Facial cellulitis in infants often manifests

with acute fever, with a unilateral area of induration, warmth, and tenderness, which may progress to have a violaceous hue. An aspirate of the point of maximal swelling will typically yield organisms. Facial cellulitis from Hib is often associated with bacteremia, and 10% to 20% of children will have a secondary focus, including meningitis.

Epiglottitis

Classically, epiglottitis from Hib occurs in older children, 2 to 7 years of age. Signs may begin with abrupt onset of high fever and drooling, with rapid progression to significant respiratory distress with children assuming a tripod position (sitting leaning forward, with mouth open and tongue and jaw protruding) (Fig. 4.1) to allow air entry. Approximately 70% to 90% of patients with epiglottitis have positive blood cultures. The mortality rate is 5% to 10%, and death is usually related to abrupt airway obstruction. Children in respiratory distress exhibiting the tripod position should not have their oropharynx examined without the presence of suitable personnel and equipment for rapid intubation. In children younger than 2 years of age, Hib epiglottitis typically has a rapid onset and progression leading to severe blockage of the airway.

Pneumonia

Hib pneumonia was common, often severe, and frequently associated with empyema, pericarditis, and multilobe involvement. Hib pneumonia is usually preceded by an upper respiratory infection such as a "common cold" with fever and cough and is clinically indistinguishable from pneumonia caused by other bacterial agents. Frequently a peripheral leukocytosis with a polymorphonuclear predominance is observed. Culture of blood, pleural fluid, tracheal aspirate, or lung aspirate may be positive in 75% to 90% of cases. The disease process is usually acute and not associated with long-term pulmonary dysfunction.

Septic Arthritis and Osteomyelitis

Hib was the leading cause of septic arthritis for children younger than 2 years of age and can be associated with contiguous osteomyelitis. Presenting signs include fever and limited limb use. Approximately 90% of septic arthritis cases involve a single large joint such as the knee, ankle, elbow, or hip. Long-term cartilage damage may result from Hib arthritic degeneration. Hib antigen detection is often positive from infected articular fluid.

Fig. 4.1 Tripod position assumed by child with epiglottitis.

Bacteremia and Sepsis

Hib was the second leading cause of occult bacteremia in febrile children 6 to 36 months of age. Unlike bacteremia with *Streptococcus pneumoniae* (the leading cause), which may spontaneously resolve, bacteremia with Hib is commonly associated with disseminated infections. Of children with occult Hib bacteremia, 30% to 50% had a focus (e.g., meningitis, pneumonia, or cellulitis).

Meningitis

Meningitis derives from high-grade bacteremia that seeds the cerebrospinal fluid (CSF) through the choroid plexus and eventually reaches the arachnoid villi to cause meningitis. There are no clinical features that differentiate Hib meningitis from meningitis from other bacterial causes (see Fig. 4.2A). Typically in bacterial meningitis the child demonstrates fever, irritability, and nuchal rigidity. Classical signs of involuntary flexion of the knees with passive flexion of the neck (Brudzinki sign) and inability to extend a flexed leg (Kernig sign) may be seen in older children and adults (see Fig. 4.2B). Altered mental status, vomiting, or seizures may also be presenting symptoms and signs. Hib meningitis can have a fulminant course with clinical sepsis, disseminated intravascular coagulation (DIC), and rapid neurologic deterioration leading to increased intracranial pressure, seizure, coma, and respiratory arrest. Approximately 10% to 20% of children with Hib meningitis will have additional foci of infection (e.g., cellulitis, arthritis, or pneumonia) with their concomitant bacteremia.

In fulminant meningitis, 80% of CSF Gram stain analyses will demonstrate the organism. However, the ability to identify the organisms on Gram stain is diminished with prior antibiotic administration. Although previous antibiotic administration may negatively affect the ability to isolate the organism from culture, it will not affect the overall CSF cell count differential, glucose, or protein, which have the usual abnormalities associated with bacterial meningitis. Peripheral blood may reveal anemia, leukocytosis, thrombocytosis, or thrombocytopenia.

DIAGNOSTIC APPROACH

Evaluation of a young child with fever should be directed by history, including vaccinations and risk factors for serious invasive disease (e.g., age or underlying condition), and physical findings. In young infants with fever without a specific source, complete blood count, urinalysis, and potentially a chest radiograph and lumbar puncture to assess for CSF pleocytosis should be considered, along with appropriate cultures of blood, urine, CSF, and any nidus found on physical examination. The diagnosis of infection due to Hib is usually made by isolation of the organism by culture. Most invasive Hib disease is associated with bacteremia; therefore blood cultures should be performed if Hib is a consideration, even if the probable primary focus of infection is thought to have been identified (e.g., pneumonia or buccal cellulitis). Culture specimens should be processed quickly because the organism is fastidious. Once *H. influenzae* has been isolated, it can be serotyped, usually in a public health laboratory facility.

Nucleic acid amplification tests (NAAT) have been developed for detection of *H. influenzae* organisms but are not serotype specific. At least one multiplex assay is licensed in the United States for the detection of *H. influenzae* in CSF samples. The American Academy of Pediatrics Committee on Infectious Diseases recommends NAATs be done in conjunction with bacterial culture to allow for serotype testing and surveillance and for monitoring antimicrobial susceptibilities. However, NAAT may be useful in the setting of antibiotic pretreatment when cultures may become negative before sampling.

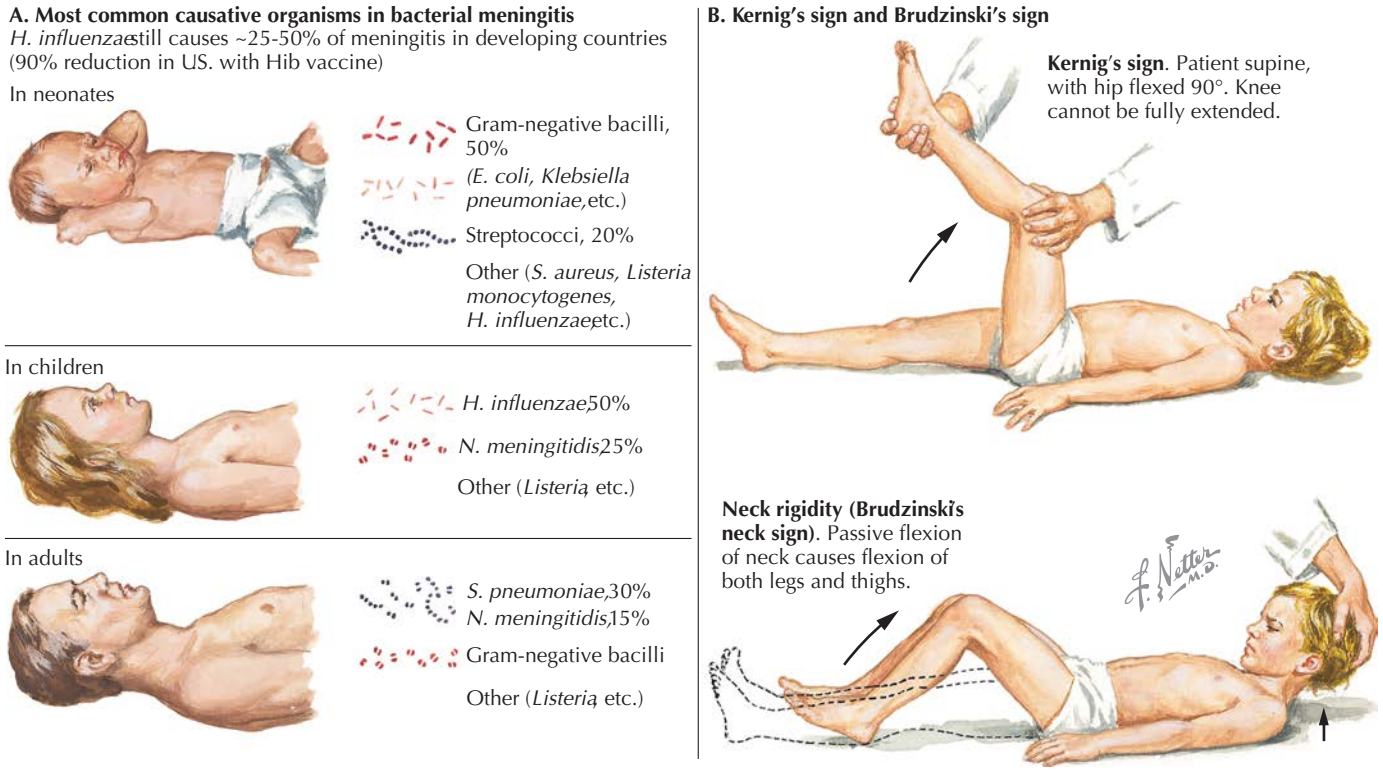

Fig. 4.2 (A) The most common causative organisms associated with bacterial meningitis vary according to age group. (B) Kernig's sign and Brudzinski's sign, if present during examination of older children and adults, have a high predictive value for bacterial meningitis.

CLINICAL MANAGEMENT

General Management

Increasing rates of Hib resistant to multiple antimicrobial agents have been reported worldwide. Approximately 50% of Hib isolates in the United States have evidence of plasmid-mediated β-lactamase production (greater for nontypeable strains than type b). This β-lactamase production renders the organism resistant to ampicillin and amoxicillin. Use of β-lactamase inhibitors, such as found in amoxicillin-clavulanic acid, restores the antibiotic killing activity against such strains. Second-, third-, and fourth-generation cephalosporins are generally active against Hib, including strains with β-lactamase production. Extended-spectrum macrolide antibiotics such as clarithromycin and azithromycin are also generally active against most strains of Hib, including those with resistance due to β-lactamase. Trimethoprim-sulfamethoxazole is active against Hib, but rates of resistance to this agent are increasing. Levofloxacin and other quinolones also have potent activity against Hib but are inappropriate for use in pediatric patients when there are safer alternative medications. The selection of antibiotic for treatment of Hib disease should be based on (1) suspected site of infection, (2) need for penetration of the blood-brain barrier and achievable bactericidal activity, (3) local antibiotic susceptibility of invasive isolates, and (4) duration needed for sterilization of both primary and secondary foci.

Invasive Disease

Pending determination of cause and susceptibility, the empiric treatment of suspected Hib meningitis should include a third-generation cephalosporin (cefotaxime or ceftriaxone) because of the ability of these agents to cross the blood-brain barrier and their resistance to β-lactamase activity. For other types of invasive Hib disease (pneumonia, septic arthritis, periorbital cellulitis), cefuroxime or a third-generation cephalosporin can be used for empiric therapy. Aminoglycosides are not recommended despite in vitro susceptibility.

Studies of pediatric patients with Hib meningitis suggest that adjunctive use of dexamethasone decreases the inflammatory response and may lessen the likelihood of hearing loss. The dose of dexamethasone is 0.6 mg/kg/day divided every 6 hours for a total of 4 days. Ideally, the first dose of dexamethasone should be administered just before or concurrently with the first antibiotic dose.

For abscesses, subdural empyema, pleural empyema, and pericardial effusions, percutaneous or surgical drainage is often necessary. In cases of septic arthritis, aspiration of infected joint fluid often is necessary for both diagnosis and reduction of intraarticular pressure. Repeated aspiration or placement of a surgical drain may also be necessary.

In addition, adjunctive and supportive therapies are important in the management of children with invasive Hib disease. For meningitis, careful evaluation and anticipation of potential complications, such as shock, syndrome of inappropriate secretion of antidiuretic hormone (SIADH), seizures, subdural empyema, and evaluation for development of secondary foci are important. Fever may persist for prolonged periods in Hib meningitis, with approximately 10% of children remaining febrile for at least 10 days. For epiglottitis, airway management is critical, often dictating the need for intubation before the occurrence of airway obstruction.

Duration of therapy is determined by the site of infection, clinical response, and underlying host factors. For bacteremia, sepsis, and uncomplicated Hib meningitis, 10 days of antibiotics is generally sufficient. For cellulitis treatment, transition to oral antibiotics after a period of parenteral antibiotics can be made if there is a good clinical response. Similarly, for septic arthritis, pericarditis, empyema, and osteomyelitis, although they may require a longer duration of antibiotics (3 to 6 weeks), antibiotics may be switched from parenteral to

TABLE 4.1 *Haemophilus influenzae* Type b Conjugate Vaccines

Hib CONJUGATE	PRP-OMP	PRP-T
Carrier protein	*Neisseria meningitides* group B outer membrane protein	Tetanus toxoid
Trade name (manufacturer)	PedvaxHIB (Merck)	ActHIB (Sanofi Pasteur) Hiberix (GlaxoSmithKline)
Dosing schedule in United States (age in months)	2, 4, 12–15	2, 4, 6, 12–15
Available combinations (trade name)		DTaP/PRP-T/IPV (Pentacel, Sanofi Pasteur for 2, 4, 6, 12–15 months of age)

DTaP, Diphtheria, tetanus, acellular pertussis; *Hib, Haemophilus influenzae* type b; *IPV,* inactivated poliovirus vaccine; *PRP-OMP,* polyribosylribitol phosphate conjugated to outer membrane protein; *PRP-T,* polyribosylribitol phosphate conjugated to tetanus toxoid.

oral administration after documentation of susceptibility, good therapeutic response, adequate antimicrobial blood levels, and ensured compliance.

PROGNOSIS

With the exception of meningitis and fulminant sepsis, patients with invasive Hib disease, if treated early with appropriate antibiotics, may recover with minimal to no long-term sequelae. However, even with prompt intensive care, mortality from Hib meningitis is approximately 5%. Complications occur early in the disease course and include seizure, cerebral edema, subdural effusions or empyema, SIADH, cortical infarction, cerebritis, intracerebral abscess, hydrocephalus, and, rarely, herniation. Routine imaging such as head computed tomography or magnetic resonance imaging is not necessary but can help to clarify focal neurologic findings or complications that occur during the clinical course, especially subdural empyema. Small sterile subdural effusions are common findings on imaging but are usually of no clinical significance.

Long-term sequelae occur in approximately 15% to 30% of meningitis survivors. These sequelae include sensorineural hearing loss, delay in language acquisition, developmental delay, gross motor abnormalities, vision impairment, and behavior abnormalities. A substantial proportion of these abnormalities may resolve over time, and therefore long-term monitoring is necessary. Evaluation of hearing during the initial hospitalization and follow-up if a hearing loss is detected are necessary to provide the earliest interventional services necessary should a hearing deficit become permanent.

PREVENTION AND CONTROL

Haemophilus influenzae Type b Immunoprophylaxis

The first vaccine developed for the prevention of invasive Hib was a purified Hib capsular PRP polysaccharide vaccine. However, polysaccharide vaccines are poorly immunogenic in young children, especially those younger than 18 months of age, owing to the polysaccharide's inability to induce T cell–dependent response. Linking a polysaccharide antigen to an immunogenic carrier protein allows for T-cell recognition, leading to inducible antibody responses and long-term protection in young infants.

Four Hib conjugate vaccines have been developed, but only two conjugate formulations are used in the United States, with three manufacturers and one available in a combination vaccine (Table 4.1). In general, it is ideal to complete the primary series with the same Hib conjugate vaccine; however, if this is not possible, the vaccines can be interchanged. In this instance three doses of the primary series are required. The booster dose at 12 to 15 months of age can be with any Hib conjugate vaccine, regardless of the type used in the primary series. Unimmunized children older than 59 months of age with underlying conditions that increase the individual risk of Hib disease should receive a single dose of Hib conjugate vaccine. For individuals who are younger than 59 months of age with HIV or immunoglobulin G2 (IgG2) subclass deficiency, and who are unimmunized, two doses of Hib conjugate vaccine given 4 to 8 weeks apart are suggested.

Chemoprophylaxis

Postexposure chemoprophylaxis is recommended for all household members of cases, if there is a contact younger than 4 years of age who has not received all Hib vaccinations appropriate for his or her age or if there is an immunocompromised child contact regardless of his or her immunization status. Prophylaxis should be initiated as soon as possible and ideally within 2 weeks of the onset of disease in the index case. Rifampin is the drug of choice for chemoprophylaxis in the dose of 20 mg/kg once daily (maximum daily dose of 600 mg) for 4 days. Other agents such as ampicillin, trimethoprim-sulfamethoxazole, erythromycin-sulfisoxazole, and cefaclor have been shown to be ineffective for chemoprophylaxis. Recommendations for treatment of contacts in daycare centers are controversial, but most experts recommend prophylaxis if two or more cases of Hib disease have occurred among attendees within 60 days.

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5

Pneumococcal Disease: Infections Caused by *Streptococcus pneumoniae*

R. Douglas Pratt

ABSTRACT

Streptococcus pneumoniae (pneumococcus) is a gram-positive encapsulated bacterium that causes significant morbidity and mortality across all age groups. *S. pneumoniae* can be carried asymptomatically in the nasopharynx, and it can cause a wide range of diseases from upper respiratory infections including sinusitis and otitis media, lower respiratory infections (most commonly pneumonia), and invasive disease, including bacteremia and meningitis. Children younger than age 2 years, the elderly, and individuals with immunocompromise or anatomic or functional asplenia are most susceptible to invasive disease. Treatment is guided by severity of disease, site of infection, and susceptibility to antimicrobials. A 23-valent polysaccharide vaccine has been available in the United States for use in adults and high-risk children ages 2 years and older since 1983. A polysaccharide-protein conjugate vaccine covering 7 serotypes became available in the United States in 2000, followed by a 13-valent vaccine in 2010. Conjugate pneumococcal vaccines have been highly effective in preventing invasive disease in infants and young children, as well as affording indirect protection of the elderly population via herd immunity. The 13-valent vaccine was also shown to prevent pneumococcal pneumonia and invasive disease by active immunization in an elderly population. Pneumococcal conjugate vaccines are recommended for routine immunization of infants and young children globally.

CLINICAL VIGNETTE

A 22-month-old child was admitted to the hospital with complaints of high (39.4°C) fever, headache, vomiting, and impaired consciousness. On the basis of findings from physical examination and initial laboratory results, a working diagnosis of bacterial meningitis was made and empirical ceftriaxone and vancomycin therapy were initiated. The cerebrospinal fluid culture yielded penicillin-susceptible pneumococci, and the isolate was identified as serotype 35F by quellung reaction. The patient fully recovered with 14 days of tailored therapy without any complications during follow-up.

COMMENT: Following the introduction of the 13-valent pneumococcal conjugate vaccine (PCV13) into mass infant vaccination programs, invasive pneumococcal disease (IPD) due to the vaccine serotypes has tended to decrease in both vaccinated young children and nonvaccinated age groups due to herd immunity. However, IPD remains a risk, particularly in vaccinated children younger than 2 years of age, children with primary/secondary immunodeficiencies, and adults older than the age of 65. PCV13 serotypes currently comprise a minority of all IPC cases, with non-PCV13 serotypes now predominant.

GEOGRAPHIC DISTRIBUTION AND BURDEN OF DISEASE

The World Health Organization (WHO) estimates that pneumococcal infections accounted for approximately 5% of all-cause child mortality in children younger than 5 years of age in 2008. Countries implementing routine use of pneumococcal conjugate vaccines in infancy have seen a marked reduction in the incidence of serious diseases due to pneumococcal serotypes in the vaccines. Still, pneumonia is the single largest infectious cause of death in children worldwide. The WHO estimated that pneumonia accounted for 15% of all deaths of children younger than 5 years old, *S. pneumoniae* being the most common cause of bacterial pneumonia in children. Among adults living in Europe and the United States, *S. pneumoniae* is the most common cause of community-acquired bacterial pneumonia.

Distribution of serotypes varies temporally and geographically. Outbreaks of pneumococcal disease caused by the same serotypes have been reported in institutional settings; however, epidemics in the general population are rare in developed countries.

In temperate regions, invasive pneumococcal disease (IPD), defined as an infection of a normally sterile body site, is more common during winter. Close proximity indoors and spread of viral respiratory pathogens facilitate transmissibility and invasiveness.

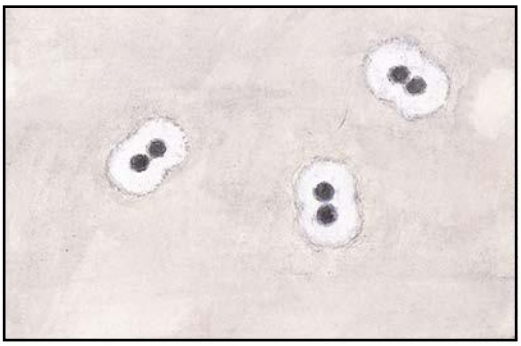
In low-income countries, data about the burden of pneumococcal disease are limited. Using information from hospital-based studies and vaccine efficacy trials and inferring from disease patterns among native populations, the estimated burden of disease is high. Rates of IPD among young children have been reduced substantially in countries in which the conjugate vaccines are in widespread use. After introduction of conjugate vaccines in the United States, annual rates of IPD in children young decreased from 100 cases per 100,000 people in 1998 to 9 cases per 100,000 in 2015, and IPD caused by the 13 conjugate vaccine serotypes decreased from 91 cases per 100,000 people in 1998 to 2 cases per 100,000 people in 2015.

S. pneumoniae is a common pathogen in middle ear aspirates from children with acute otitis media (AOM). AOM is also the leading reason for prescribing antibiotics during childhood, and this use contributes substantially to increased antimicrobial resistance.

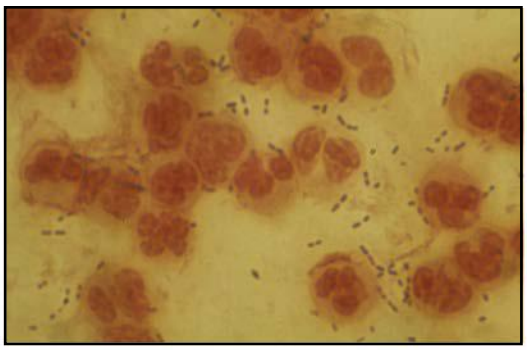
MICROBIOLOGY AND PATHOGENESIS

S. pneumoniae is a strictly human pathogen consisting of gram-positive, encapsulated, lancet-shaped bacteria occurring in pairs (called *diplococci*) and chains (Fig. 5.1). At least 90 serotypes have been identified based on differences in the polysaccharide capsule, as observed with the quellung reaction, in which serotype-specific antibodies bind to the bacterial capsule causing the bacteria to appear opaque and enlarged on microscopy (see Fig. 5.1).

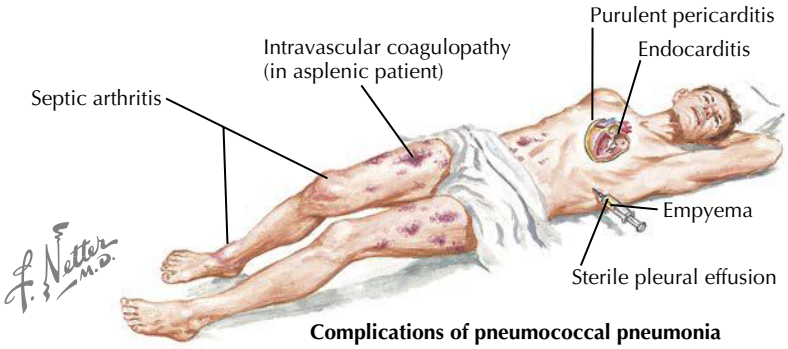
The polysaccharide capsule is considered the primary virulence factor of *S. pneumoniae.* Nonencapsulated strains are less likely to cause severe disease. The capsule contributes to pathogenesis by protecting the organism from phagocytosis. Antibody binding to the capsule can facilitate phagocytosis and bacterial killing by phagocytic cells. Some pneumococcal proteins, including hyaluronate lyase, pneumolysin,



Quellung reaction. Swelling of bacterial capsule when exposed to antibody



Purulent sputum with pneumococci (Gram stain)



Complications of pneumococcal pneumonia

Fig. 5.1 Pneumococcal disease.

neuraminidase, major autolysin, choline-binding protein A, and pneumococcal surface protein A (PspA) have functions that also contribute to pathogenicity. These virulence proteins have also been considered for development as vaccine antigen candidates.

RISK FACTORS

Children younger than age 2 years carry the highest burden of *S. pneumoniae* disease worldwide. Other groups at increased risk of invasive disease include the elderly, people with impaired immunity (e.g., humoral immunodeficiency, complement deficiency, human immunodeficiency virus [HIV] infection, and anatomic or functional asplenia [e.g., sickle cell disease]), cigarette smokers, those with cochlear implants and cerebrospinal fluid (CSF) leaks, and individuals with chronic diseases such as diabetes and heart, kidney, and lung disorders. IPD occurs at higher rates among certain ethnic groups; for example, prior to widespread use of conjugate pneumococcal vaccines, Native Americans and Eskimos had rates of IPD that were several-fold higher than in the general population in the United States.

CLINICAL PRESENTATION

S. pneumoniae organisms are transmitted person to person via contact with infected respiratory droplets. Asymptomatic nasopharyngeal (NP) carriage is common in children 6 months to 5 years of age, and they are a source of transmission among close contacts by projecting droplets (>5 μm) across a short distance (1 m).

Invasive Pneumococcal Disease

S. pneumoniae infection can manifest as fever and bacteremia without a focus or as an infection of any organ system, including AOM, sinusitis, conjunctivitis, periorbital cellulitis, soft-tissue infection, pyogenic arthritis, osteomyelitis, community-acquired pneumonia (CAP), empyema, endocarditis, peritonitis, sepsis, and meningitis (see Fig. 5.1).

Onset of fever is typical for infections in all tissues and may be the only sign in young children with bacteremia. Otitis media typically causes pain in the ears. Pneumonia can cause fever, cough, pleuritic chest pain, and purulent or blood-tinged sputum.

Pneumococcal meningitis is characterized by high fever, headache, neck stiffness, and altered mental status. Other symptoms include nausea, vomiting, photophobia, and lethargy. Infants and young children may have nonspecific symptoms, including irritability or poor feeding. In later stages, patients of any age may have seizures or focal neurologic findings or may be comatose.

The differential diagnosis for IPD includes other bacterial pathogens, such as *Haemophilus influenzae* type b (Hib), *Neisseria meningitidis*, and *Staphylococcus aureus*. In the United States and other areas using Hib vaccines, most cases of bacterial meningitis are caused by *S. pneumoniae* and *N. meningitidis*. Viral meningitis caused by enteroviruses can manifest like bacterial meningitis but is generally less severe.

Before the widespread use of the conjugate vaccine in the United States, *S. pneumoniae* was the most common bacterial cause of pneumonia in young children. Other bacterial causes of CAP in children include *H. influenzae* (nontypeable), *Moraxella catarrhalis*, *Streptococcus pyogenes*, and *S. aureus* (including methicillin-resistant *S. aureus* [MRSA]). However, respiratory viruses (e.g., respiratory syncytial virus [RSV], influenza, human metapneumovirus) cause most cases of pneumonia in children.

DIAGNOSTIC APPROACH

When *S. pneumoniae* is suspected as a cause of invasive disease, specimens should be obtained from the site(s) of infection for culture and

Gram stain. Cultures provide highly specific diagnostic information, the ability to test for antibiotic susceptibility, and specimens for serotype-specific epidemiology. However, because pneumococci can colonize the upper respiratory tract, recovery of *S. pneumoniae* from the nasopharynx does not confirm it as the causative agent.

Most patients with IPD have leukocytosis (>12,000 cells/μL) and elevated markers of inflammation (e.g., C-reactive protein, erythrocyte sedimentation rate). Leukopenia may be seen with meningitis and other severe pneumococcal infections.

Diagnosing pneumococcal pneumonia can be challenging and treatment is typically empiric. Typical chest radiographs show consolidation of a segment, an entire lobe, or multiple lobes (see Fig. 26.1). In hospitalized patients with pneumonia, blood cultures are positive in 10% of children and up to 25% of adults. Respiratory specimens, such as sputum (in adolescents and adults) and endotracheal or bronchoalveolar lavage samples, showing gram-positive diplococci and many polymorphonuclear neutrophils suggest a pneumococcal cause pending culture results. Thoracentesis may be needed to drain pleural effusions or empyemas and to obtain specimens for culture.

In cases of fever without a focus and suspected IPD, blood should be obtained for culture. Depending on the signs and symptoms, specimens of CSF should be obtained for laboratory evaluation including cultures. Gram stain of the CSF sediment may reveal the characteristic gram-positive diplococci. The CSF will usually show a pleocytosis with a predominance of polymorphonuclear leukocytes (PMNs), although early in the disease lymphocytes may predominate. Typically, CSF protein is elevated and glucose is low relative to blood glucose levels.

A rapid in vitro diagnostic test based on the presence of pneumococcal capsular C polysaccharide in urine has been approved by the US Food and Drug Administration (FDA) for diagnosing pneumococcal pneumonia in adults. The test is 70% to 80% sensitive and greater than 90% specific when compared with conventional methods and is not affected by antibiotics. However, this test is not for use in children as it lacks specificity, probably because of higher rates of NP carriage. This rapid test is also used for detecting pneumococci in CSF of patients with meningitis. Multiplex polymerase chain reaction (PCR) tests have been approved by the FDA for detection of respiratory pathogens, including *S. pneumoniae*, in sputum and bronchioalveolar specimens, and a similar test is available for CSF specimens, making this the preferred non–culture-based approach to diagnosis.

TREATMENT

Adjunctive and supportive treatments of IPD are similar to therapies used for Hib infections, as described in Chapter 4.

Pneumococcal infections are treated with antimicrobials to which the organism is susceptible. All cultures of *S. pneumoniae* from sterile body sites should be evaluated for antimicrobial susceptibilities, but in most cases empirical therapy should begin before susceptibilities are known.

The prevalence of *S. pneumoniae* strains that are not fully susceptible to penicillin varies by region, but the proportion of such strains has decreased in the United States since introduction of the conjugate vaccine. Penicillin-resistant strains are defined as intermediately resistant (minimum inhibitory concentration [MIC] > 0.1 to 1 mcg/mL) or highly resistant (MIC ≥ 2 mcg/mL). *S. pneumoniae* strains that are resistant to penicillin are often resistant to other antimicrobials, including cephalosporins and macrolides, and these multidrug-resistant strains have been identified throughout the world. *S. pneumoniae* strains resistant to vancomycin have not been identified in the United States.

Bacterial meningitis is treated with higher doses of antibiotics than used for other infections to ensure adequate drug levels in the CSF. The initial regimen for suspected pneumococcal meningitis in all ages should include vancomycin and ceftriaxone or cefotaxime until the antimicrobial susceptibilities are known. Meropenem may be an alternative. Corticosteroids have been used in the treatment of bacterial meningitis to reduce intracerebral inflammation; however, evidence of improved outcomes in children is equivocal. If used, corticosteroids should be given before or concurrently with the first dose of antimicrobials.

In CAP, the specific pathogen is usually not known and patients are treated presumptively with antimicrobials that are effective against *S. pneumoniae,* as well as other common bacterial pathogens. For inpatient adults, combination therapy with a cephalosporin and a macrolide or fluroquinolone antibiotic is recommended while awaiting specific bacterial diagnosis. In children with mild-to-moderate CAP suggestive of bacterial infection, amoxicillin can be used for empirical treatment in an outpatient setting. If the clinical presentation is consistent with both bacterial and atypical pneumonia, a macrolide may be considered. For hospitalized children, empirical treatment with intravenous ampicillin or a third-generation parenteral cephalosporin (e.g., cefotaxime, ceftriaxone) is effective in most settings. Cefotaxime or ceftriaxone is recommended for children hospitalized with pneumonia caused by pneumococci suspected or proven to be penicillin-resistant strains, for serious infections including empyema, or in those not fully immunized with PCV13. Vancomycin should be included in those with life-threatening infection.

First line treatment for uncomplicated AOM is amoxicillin (80 to 90 mg/kg/day). If initial therapy fails, antibiotics active against penicillin-nonsusceptible pneumococci and β-lactamase–producing *H. influenzae* and *M. catarrhalis* should be used (e.g., amoxicillin-clavulanic acid, second- and third-generation oral cephalosporins). In severe cases and when second line therapy fails, parenteral ceftriaxone may be given and/or tympanocentesis may be used to drain infected middle ear fluid, obtain cultures, and guide therapy, as well as to provide pain relief.

PROGNOSIS

Early diagnosis and treatment with appropriate antimicrobials are keys to better clinical outcomes.

Nearly all children with ear infections recover, although recurrent infections can lead to hearing loss and delayed language development. In the United States and other high-income countries, pneumococcal pneumonia may result in hospitalization, although the mortality rate is low. In children who have bacteremia without a focus, 10% will develop focal complications, 3% to 6% will develop meningitis, and approximately 1% will die. Of children younger than 5 years of age with pneumococcal meningitis, approximately 5% will die and 25% of survivors may have long-term problems such as hearing loss or learning disability. Sequelae in patients with meningitis are associated with the presence of coma and low CSF glucose level (<0.6 mmol/L).

The incidence of IPD and mortality resulting from bacterial infections in sickle cell disease have been declining due to use of penicillin prophylaxis, implementation of new vaccination strategies using conjugate vaccines, and improved medical care.

PREVENTION

Good respiratory hygiene and active immunization are effective prevention strategies. Risk of IPD may be reduced by improvement in predisposing conditions such as diabetes and HIV, smoking cessation, and avoidance of crowded living conditions.

Immunoprophylaxis

The first vaccines developed against *S. pneumonia* were composed of polysaccharides extracted from common invasive serotypes. In the United States a tetravalent polysaccharide vaccine was licensed in 1946 but was discontinued in 1951 owing to the increasing use of penicillin. In 1977 a 14-valent polysaccharide vaccine became available, and a 23-valent polysaccharide vaccine that covers serotypes responsible for more than 90% of pneumococcal disease has been available since 1983.

The pneumococcal polysaccharide vaccine provides only limited protection in children younger than 2 years of age. Polysaccharide antigens do not elicit T-cell help for antibody production efficiently, particularly in young children. Protein-polysaccharide conjugate vaccines, manufactured by chemical linkage of bacterial polysaccharides to protein antigens such as diphtheria and tetanus toxoids, are able to elicit T-cell help and induce protective immune responses, even in infants and young children. In clinical trials, a conjugate vaccine composed of seven serotypes (4, 6B, 9V, 14, 18C, 19F, and 23F), which accounted for approximately 80% of invasive disease in young children in the United States at the time of the trial, was proven highly effective in preventing invasive disease. Since licensure in the United States in 2000, high rates of vaccine coverage have resulted in a marked reduction in IPD in infants and small children, as well as adult and elderly populations, likely because of decreased transmission and herd immunity. In addition, rates of antimicrobial resistance have fallen because the conjugate vaccine includes serotypes associated with high rates of resistance.

As disease caused by conjugate vaccine serotypes diminished with wide use of the vaccine, some nonvaccine serotypes emerged as important causes of disease in children. Pneumococcal conjugate vaccines formulated with additional serotypes, including serotypes important globally, became available in 2009 and 2010. A 13-valent vaccine containing the seven original serotype plus serotypes 1, 3, 5, 6A, 7F, and 19A was licensed in the United States for use in children 6 weeks through 5 years of age. Subsequently, the 13-valent vaccine was evaluated in adults and shown to be effective in preventing invasive disease, and nonbacteremic and bacteremic pneumonia due to vaccine serotypes. A 10-valent conjugate vaccine containing additional serotypes 1, 5, and 7F is available in Europe, Canada, and elsewhere. Investigational vaccines targeting proteins common to most pneumococci and conjugate vaccines with additional serotypes hold promise in providing broad protection against pneumococcal disease.

The WHO recommends that all infants and young children receive at least three doses of a pneumococcal conjugate vaccine. In the United States, the Centers for Disease Control and Prevention (CDC) recommends that all infants and toddlers receive the conjugate pneumococcal vaccine at 2, 4, 6, and 12 to 15 months of age. Both the conjugate and 23-valent polysaccharide vaccines are recommended for certain groups of children (ages 2 years and older) and adults who are at increased risk of pneumococcal disease.

CDC vaccine recommendations may be viewed at: https://www.cdc.gov/vaccines/schedules/index.html.

Chemoprophylaxis

Chemoprophylaxis is not routinely recommended for contacts of individuals with IPD or for travelers.

Penicillin chemoprophylaxis is recommended by the CDC for persons with functional or anatomic asplenia because of the high risk of severe infections. For children with sickle cell hemoglobinopathy, oral penicillin V (125 mg, twice daily) is recommended beginning before 4 months of age. The optimal duration of penicillin prophylaxis in these children has not been determined; however, stopping at age 5 years in children who are fully vaccinated and who have been free of severe pneumococcal infections has not resulted in increased infections.

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6

Infections Caused by *Neisseria meningitidis*

Margaret C. Bash

ABSTRACT

Neisseria meningitidis is both a commensal organism of the upper respiratory tract and a significant pathogen for humans. It causes devastating disease with significant morbidity and mortality worldwide. Infections caused by *N. meningitidis* can have various clinical presentations ranging from asymptomatic carriage or a mild upper respiratory illness to purulent meningitis and/or disseminated disease with fulminant sepsis. Strains with capsule types belonging to groups A, B, C, Y, W, and recently X are associated with invasive disease. The majority of patients infected with *N. meningitidis* are children, usually younger than 5 years old, adolescents, young adults, and adults older than 65 years of age. Effective polysaccharide and polysaccharide conjugate vaccines are available for prevention of serogroup A, C, Y, and W disease. The serogroup B polysaccharide is poorly immunogenic, and outer membrane protein–based vaccines have been developed and recently licensed.

CLINICAL VIGNETTE

A 17-year-old previously healthy female university student was brought to the emergency room with symptoms of fever, headache, and malaise. She had been well until the prior evening, when her symptoms began with generalized fatigue causing her to leave her friends early to go to sleep in her dormitory. She felt too ill to join them for breakfast, and when they returned to her room they were concerned to find her confused and febrile.

Her exam was significant for a temperature of 102°F, photophobia, and positive Kernig and Brudzinski signs (pain with hip flexion and knee extension, and flexion of the hips and knees when the neck is flexed by the examiner, respectively). Rare, fine petechiae were present on her trunk and upper extremities, and the rash progressed during the evaluation. Laboratory investigations revealed a total leukocyte count of 19000/mm^3 and a platelet count of 10000/mm^3. Blood cultures and lumbar puncture were performed. Cerebrospinal fluid (CSF) white blood cell (WBC) count was 15 with 80% neutrophils. Gram stain revealed gram-negative diplococci.

The patient was initially treated with vancomycin (1 g intravenously every 12 hours) and ceftriaxone (1 g intravenously every 12 hours). The patient showed early signs of hemodynamic instability (systolic blood pressure of 80 mm Hg and heart rate of 140/min) in spite of an initial intravenous fluid bolus, and she was transferred to the intensive care unit for continued fluid and inotropic support. Norepinephrine was required at a rate of 1 mcg/kg/min during the first 8 hours of admission but was successfully discontinued during the first hospital day. Dexamethasone was administered for the first 4 days because the CSF gram stain and subsequent culture confirmed *Neisseria meningitidis* meningitis in addition to sepsis. Vancomycin was stopped following culture confirmation of *N. meningitidis*.

COMMENT: The patient recovered rapidly and continued antibiotics for 7 days. Close monitoring for sequelae of meningitis including hearing loss and cognitive dysfunction was planned. Antibiotic prophylaxis was administered to her roommates and boyfriend.

GEOGRAPHIC DISTRIBUTION AND BURDEN OF DISEASE

N. meningitidis has a worldwide distribution, but there are distinct regional characteristics of the microbiology and epidemiology of disease. The Centers for Disease Control and Prevention (CDC) has reported the worldwide incidence of invasive meningococcal disease to be 0.5 to 5 per 100,000 population per year. In the United States the overall incidence ranged from 0.5 to 1.5 per 100,000 population per year in the 1990s but has declined over the past two decades to 0.11 cases per 100,000 persons in 2017. Disease is primarily caused by serogroup B, although cases of C, Y, and W occur. European countries have a wide range of disease incidence (0.2 to 14 cases per 100,000). The majority of these cases are caused by serogroup B, especially in countries where meningococcal C conjugate (MCC) vaccines are used routinely. An epidemic of serogroup B meningococcal disease persisted for almost a decade in New Zealand (17.4 cases per 100,000 in 2001), but attack rates declined to 2.6 per 10,000 in 2007, at least in part as a result of a national vaccination campaign using an outer membrane vesicle (OMV) vaccine made from the outbreak strain.

Before World War II, serogroup A was the most common serogroup identified from disease isolates in industrialized countries. In the second half of the 20th century, this serogroup was primarily associated with epidemic meningitis, especially in the sub-Saharan region of Africa known as the *meningitis belt*. Countries in this region experienced recurrent epidemics every 5 to 10 years with incidence rates reaching 1000 per 100,000. Even in interepidemic years, serogroup A disease rates were as high as 25 per 100,000. Following introduction and widespread use of a serogroup A meningococcal conjugate vaccine (MenAfriVac) in national vaccination campaigns, serogroup A epidemics have disappeared from this region. Serogroup A epidemics also occurred in India, China, and Russia. Other areas of Africa have yearly rates of invasive serogroup A disease higher than in industrialized nations. Travel to the Hajj pilgrimage has been a significant risk factor for exposure to serogroup A meningococci.

Asymptomatic nasopharyngeal carriage of *N. meningitidis* is common and varies by age. Infants have a carriage rate of 1% to 2%, whereas adolescents and young adults have a carriage rate of 15% to 25%. Carriage of highly virulent strains occurs in less than 5% of the general population, even during outbreaks. Carriage isolates are often unencapsulated, or less virulent, than strains that cause invasive disease. Transmission of *N. meningitidis* is primarily through respiratory droplets. Invasive meningococcal disease is associated with recent acquisition of a new pathogenic strain rather than after extended colonization. Studies of military recruits in the 1970s helped to determine the infectivity and route of spread of the organism and established that preexisting antibodies that trigger complement-mediated killing of the bacteria provide protection against invasive disease.

The prevalence of bactericidal antibodies in the population increases with age and is inversely related to the rates of invasive disease. Infection rates are highest in children younger than age 5 years, especially 6 months to 1 year of age. A second period of increased risk is observed during adolescence and young adulthood. College freshman living in dormitories and military recruits are at moderate risk, whereas and individuals with close or intimate contact with an index case are at 500 times increased risk of invasive disease. Individuals with terminal complement component deficiencies or those who are receiving complement inhibitor therapies are at high risk of recurrent invasive meningococcal infections.

PATHOGENESIS

N. meningitidis, a gram-negative diplococcus, is an obligate human pathogen. Endemic sporadic disease is caused by highly diverse strains, but most disease isolates can be grouped by genetic analysis of housekeeping genes (multilocus sequence typing [MLST]) into one of several hypervirulent lineages. In contrast, local outbreaks and sustained epidemics can be caused by a single strain type and are considered clonal.

Surface structures of the bacterium are important for strain characterization, disease pathogenesis, and immunity. Capsular polysaccharide type defines the serogroup of a strain. Strains expressing serogroup A, B, C, Y, W, and more recently serogroup X capsules are associated with invasive disease, whereas unencapsulated strains and strains of the remaining serogroups are usually associated with asymptomatic nasopharyngeal colonization. The polysaccharide capsule enhances efficient transmission and inhibits phagocytosis. Lipooligosaccharide (LOS) is an endotoxin that induces an inflammatory cascade that leads to the clinical features seen in septicemia, septic shock, and meningitis.

N. meningitidis has extensive mechanisms for the uptake and incorporation of deoxyribonucleic acid (DNA), a process known as *horizontal exchange,* which allows the organism to adapt to the host and evade natural immunity. This process results in antigenic diversity of many surface proteins and occasionally capsule type switching. In addition, phase variation of surface structures such as Opa proteins and LOS also contribute to phenotypic diversity of the organism.

Genetic polymorphisms of the human host affect susceptibility to meningococcal infections and may affect disease outcomes. Genetic deficiencies of complement factors 5 to 9 (late complement component deficiency) are well recognized risk factors for recurrent or familial meningococcal disease. In addition, some case control studies have shown an association between meningococcal disease and polymorphisms of interleukin-1 receptor agonist (IL1RA), carcinoembryonic antigen cell adhesion molecules 3 and 6, surfactant proteins A and D, and factor H.

CLINICAL PRESENTATION

The spectrum of *N. meningitidis* infections can range from asymptomatic to fulminant septicemia and/or meningitis. The progression of invasive disease can be rapid, with circulatory collapse and death occurring within hours of presentation. In contrast, resolution of unsuspected culture-positive meningococcemia without treatment has been documented in adults and infants with fever and upper respiratory symptoms.

The hallmark features of meningococcal disease are fever and rash, classically a nonblanching petechial rash, which can progress to purpura associated with disseminated intravascular coagulation (DIC). The rash is not diagnostic; a macular or maculopapular rash can also be observed, and of note, rash is absent in almost one-third of culture-proven disease in children. Approximately 11% to 15% of children presenting with petechiae have meningococcemia.

The most common presentation of invasive meningococcal disease is meningitis. Typical clinical findings of meningitis are the result of inflammation in the subarachnoid space and include fever, headache, meningismus, photophobia, and lethargy. Older children may also have positive Kernig and Brudzinski signs (see Fig. 4.2B). Infants may not have these classic symptoms of meningitis but usually demonstrate irritability, inconsolable crying, poor feeding, and lethargy. Meningococcal meningitis can occur with or without associated septicemia.

Septicemia accounts for 15% to 20% of invasive meningococcal disease and results from significant levels of bacteria and endotoxin in the bloodstream. The onset of disease is rapid, and clinical decline with significant morbidity or mortality can occur within 24 to 48 hours. Bacteremia and increased endotoxin production initiate an intravascular inflammatory cascade that causes endothelial damage resulting in DIC and multiorgan failure (Fig. 6.1). The vascular damage initially results in petechiae and purpura and can ultimately lead to autoamputation of digits or entire limbs. The average duration from onset of symptoms to admission for patients with sepsis is 12 hours, which is less than half the time for patients with meningitis.

Other less common presentations of invasive disease include pneumonia, pyogenic arthritis, purulent pericarditis, osteomyelitis, and endophthalmitis. These clinical presentations are more often associated with serogroups Y or W-135 and are usually seen in older patients. Recently, outbreaks of meningococcal urethritis caused by unencapsulated strains that have acquired some genetic features of *N. gonorrhoeae* have been reported.

Chronic meningococcemia is a rare condition that manifests with recurrent intermittent fever, rash, and arthralgia or arthritis and may last for months. The presentation can be like that of many other viral, rheumatologic, or vasculitic conditions. *N. meningitidis* can be cultured from serum during acute episodes, and in the absence of appropriate treatment, some patients eventually progress to disseminated disease. The pathogenesis of chronic meningococcemia is not known; however, it is more commonly seen in patients with underlying terminal complement deficiency.

DIAGNOSTIC APPROACH

Invasive meningococcal disease should be considered in any patient with fever and signs or symptoms that are consistent with bacterial sepsis or meningitis. The initial evaluation includes cultures of blood and cerebrospinal fluid (CSF) and, in some instances, biopsies of skin lesions. The CSF cell count, protein level, and glucose concentrations are usually abnormal, although normal CSF profiles have been reported. CSF should also be examined for gram-negative diplococci. Peripheral leukocytosis with a predominance of polymorphonuclear cells is typical, but leukopenia, thrombocytopenia, and anemia may be present. Coagulopathy and metabolic abnormalities, such as hyponatremia, hypoglycemia, and metabolic acidosis, can complicate the clinical management of patients with invasive disease.

Viable *N. meningitidis* can be obtained from 40% to 75% of blood and 90% of CSF cultures when obtained before the administration of antibiotics. The microbiologic evaluation should not delay therapy when invasive meningococcal disease is suspected; in some circumstances, antibiotics must be administered empirically before cultures can be obtained. Blood and CSF can be rapidly sterilized after antibiotic administration; however, organisms have been identified in skin lesions up to 12 hours after antibiotics have been given. *N. meningitidis* antigen testing has been replaced by nucleic acid amplification–based

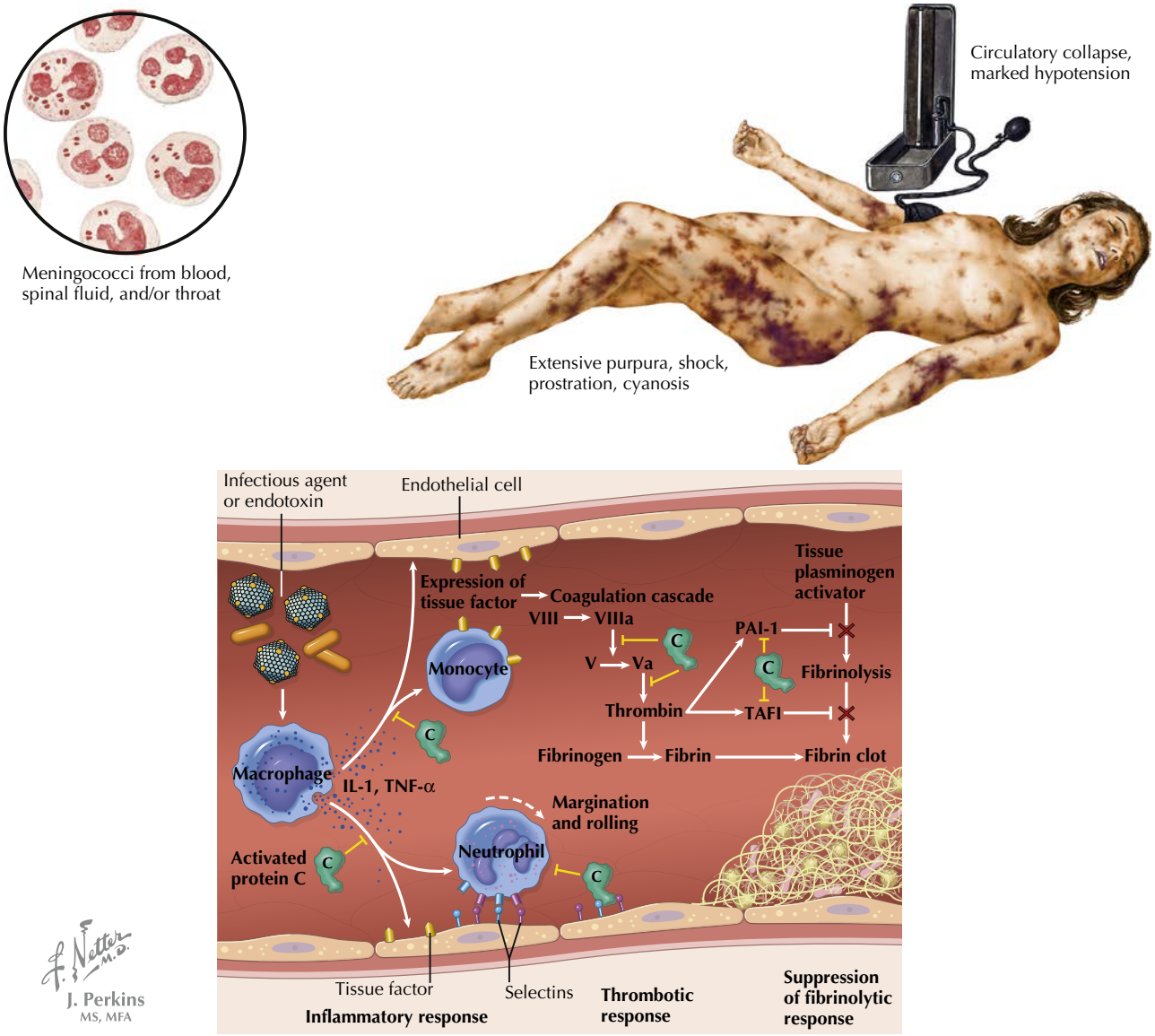

Fig. 6.1 Disseminated intravascular coagulation (DIC). *IL-1*, Interleukin-1; *PAI-1*, plasminogen activator inhibitor-1; *TAFI*, thrombin activatable fibrinolysis inhibitor; *TNF-α*, tumor necrosis factor alpha.

diagnostic methods, and these diagnostic tests can be informative, especially when treatment has been initiated prior to obtaining blood or CSF for culture; in locations where antigen testing is still performed, it is important to note that cross-reaction occurs between the serogroup B capsular antigen and *Escherichia coli* K1.

The differential diagnosis is influenced by the age and epidemiologic history of the patient and includes other causes of bacterial sepsis and meningitis including *Streptococcus pneumoniae, Haemophilus influenzae* type b, *Staphylococcus aureus,* and gram-negative enteric pathogens, as well as rickettsial disease, Henoch-Schönlein purpura, and other noninfectious causes of vasculitis.

TREATMENT

Prompt initiation of parenteral antibiotics is the mainstay of treatment for invasive meningococcal disease. Third-generation cephalosporins, such as ceftriaxone and cefotaxime, are bactericidal, have excellent central nervous system penetration, and are most often used as initial therapy of meningitis until culture results and susceptibility profiles are determined. Most meningococcal isolates are susceptible to penicillin G (250,000 units/kg/day IV or IM divided every 4 to 6 hours [maximum: 24 million units/day]).

Penicillin-resistant *N. meningitidis* strains have been described worldwide; however, the rate of penicillin resistance in the United States has remained low at approximately 3%. Ciprofloxacin-resistant isolates and clinical treatment and prophylaxis failures have been reported. Routine susceptibility testing is recommended for all *N. meningitidis* isolates from sterile body sites. The recommended duration of therapy for meningococcemia or meningitis is 7 to 10 days; however, there are reports of clinical and microbiologic resolution with shorter courses of therapy.

Emergent management of *N. meningitidis* infections involves fluid resuscitation, maintenance of blood pressure with pressor support, and early intubation if indicated to prevent circulatory collapse or increases in intracranial pressure. Adjuvant therapy with corticosteroids for patients with septic shock and meningitis has shown some benefit in adults and in pediatric patients with *H. influenzae* meningitis; however, there has been no proven benefit in meningococcal sepsis or meningitis. Activated protein C (APC), a component in the coagulation pathway, may be considered in adult patients

with invasive meningococcal disease and severe sepsis who present early in their disease course. In pediatric patients, the risk and benefits of this therapy should be weighed, although it is generally not recommended.

PROGNOSIS

The overall mortality rate from meningococcemia is approximately 10% in the United States, with most cases of death occurring in young infants and adolescents. Factors associated with poor outcome and high mortality rates include young age, absence of meningitis, presence of shock, clinical signs of ischemic damage, leukopenia, or thrombocytopenia. In less severe disease with prompt management, most patients have significant resolution of symptoms by the second day of illness and complete recovery within 1 week. After acute illness, less than 10% of patients develop postinfectious complications as a result of immune complex–induced inflammation such as arthritis, iritis, myocarditis, pericarditis, and vasculitis. These conditions usually manifest 4 or more days after onset of infection and can be managed with nonsteroidal antiinflammatory agents. Sequelae from invasive meningococcal disease occur in up to 19% of patients and can include hearing loss, neurologic dysfunction or motor deficits, digit or limb amputation, and skin scarring.

PREVENTION AND CONTROL

Prevention of secondary cases of invasive meningococcal disease involves patient isolation, chemoprophylaxis of exposed individuals, and in some situations vaccination. Respiratory droplet precautions should be used until the patient has received 24 hours of appropriate antimicrobial therapy to eradicate carriage. Patients who are treated with antibiotics other than ceftriaxone or cefotaxime should receive chemoprophylaxis to eradicate nasopharyngeal colonization. Chemoprophylaxis is essential for close contacts because their attack rate is 500 to 800 times higher than in the general population. This includes all individuals who have been directly exposed to oral secretions from the index case, all childcare or preschool contacts, and all individuals who slept in the same dwelling as the index case in the 7 days before onset of disease. Individuals who were seated next to the index case on a prolonged airplane flight (>8 hours) are also eligible for chemoprophylaxis. Routine prophylaxis is not given to medical personnel unless they had significant exposure to respiratory secretions. Ideally, chemoprophylaxis should be given within 24 hours after diagnosis in the index patient. Rifampin, ceftriaxone, ciprofloxacin, and azithromycin are effective chemoprophylactic medications. Rifampin or ceftriaxone can be used in younger children, but ciprofloxacin is recommended only for nonpregnant adults older than 18 years of age. Ciprofloxacin is not recommended in regions where resistant strains have been identified. In addition, vaccination of close contacts is recommended if the index case was caused by a serogroup included in current vaccines.

Vaccines are available for prevention of invasive disease caused by *N. meningitidis* groups A, C, Y, and W. Historically, the polysaccharide tetravalent meningococcal vaccine (MPSV4) was used for control of outbreaks and recommended for routine use in high-risk populations such as military recruits, individuals with terminal complement component deficiencies or asplenia, travelers to geographic regions with high rates of disease, and more recently college freshman living in dormitories. Polysaccharide vaccines are not generally immunogenic in children younger than 2 years of age except serogroup A meningococcal polysaccharide vaccine, which was used in infants 6 months of age and older in a two-dose series during serogroup A outbreaks.

Because polysaccharides do not induce memory and immunity wanes after 3 to 5 years, the MPSV4 has been replaced by conjugate vaccines. Chemical conjugation of polysaccharides to a protein carrier creates T cell–dependent antigens that are usually highly immunogenic in infant populations. After the licensure of a tetravalent glycoconjugate meningococcal vaccines (MCV4) in the United States, routine immunization of all children 11 years of age and older, and all individuals who are at increased risk of invasive meningococcal disease was recommended. A booster dose of MCV4 is administered 3 to 5 years after the initial immunization for high-risk children and routinely at 16 years of age for all adolescents who were initially immunized at 11 years of age. Monovalent serogroup C conjugate vaccines have been incorporated into routine infant immunization schedules in some countries where serogroup C disease was common. These vaccines have been shown to decrease colonization and provide herd immunity.

Management of epidemic serogroup A disease in Africa previously depended on a reactive vaccination strategy initiated when disease rates exceed certain thresholds. This approach provided some benefit in controlling outbreaks; however, it was not useful in their prevention. The Meningitis Vaccine Project, a public-private partnership, successfully developed and incorporated into widespread use an affordable effective serogroup A conjugate vaccine, eliminating the recurrent epidemics of this disease in the meningitis belt region of Africa.

Vaccines for the prevention of serogroup B meningococcal disease target subcapsular protein antigens because the serogroup B polysaccharide is poorly immunogenic. Vaccines using OMVs depleted of LOS have been used in the Netherlands, Cuba, Brazil, Chile, and most recently in New Zealand to address serogroup B epidemics. These OMV vaccines were made from the epidemic strain and, especially in young children or infants, are thought to have provided strain specific immunity. New vaccines that are designed to be broadly protective against the diverse strains associated with endemic disease have been developed. Two serogroup B vaccines have been approved for use in individuals 10 through 25 years of age in the United States. One vaccine, 4CMenB (Bexerso), contains four antigenic components: recombinant factor H binding protein (Fhbp), recombinant neisserial adhesin A (NadA), recombinant neisserial heparin-binding protein (NHBP), and OMVs from strain NZ98/254 that include a porin protein PorA (serosubtype P1.4). The other licensed vaccine, MenBFHbp (Trumenba), contains two lipidated recombinant FHbp antigens, one from each of two genetic subfamilies. In clinical studies, both vaccines elicited bactericidal antibodies against selected MenB strains measured with the human complement serum bactericidal activity. Serogroup B vaccines are recommended for people 10 years of age and older who are at increased risk for meningococcal disease. Although not routinely recommended for adolescents, these vaccines may be considered for immunization of individuals 16 through 23 years of age.

ACKNOWLEDGMENT

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Poliomyelitis (Polio) and Polioviruses

Alison M. Helfrich, Michael Rajnik

ABSTRACT

In the early 20th century, poliomyelitis was one of the most feared illnesses of humans, in part because it affected previously healthy individuals with little or no warning and could result in devastating paralysis. Although the disease was once endemic worldwide, with vaccines eradication has been achieved in all but two countries. In current times, acute flaccid paralysis (AFP) is associated with vaccine-derived poliovirus strains or other viral agents more commonly than wild-type polio virus. However, with disruption of proper sanitation or maintenance of vaccination within the population, outbreaks can quickly reemerge.

CLINICAL VIGNETTE

A 3-year-old male from Syria presents to the local health clinic for progressive leg weakness for 2 days. Yesterday, he collapsed after getting out of bed and has not been able to stand. His parents report a recent febrile illness with diarrhea that self-resolved. Prior to this illness, he appeared healthy. Due to recent unrest and violence in the region, the family relocated to a rural area where healthcare, including vaccines, is limited due to the civil war. His parents recall no vaccines administered in the past 2 years.

Exam revealed a thin child who appeared in pain but was without acute distress. Cranial nerves were intact, and he was controlling oral secretions with normal breathing. He was unable to move his left leg, and he only had 3/5 strength in his right leg. The lower extremity patellar and Achilles reflexes were 0/4 on the left and 2/4 on the right. He was transferred to a referral hospital for management. Stool polymerase chain reaction (PCR) ultimately confirmed poliomyelitis due to a circulating vaccine-derived poliovirus strain. After 6 months of physical therapy, he started to regain strength and function.

COMMENT: Oral polio vaccine (OPV) is used in mass vaccination campaigns worldwide because of ease in administration and fecal shedding of the vaccine viruses by vaccine recipients can promote herd immunity in the community. Rarely, the circulating vaccine-derived polioviruses (cVDPVs) cause paralytic polio.

EPIDEMIOLOGY, GEOGRAPHIC DISTRIBUTION, AND DISEASE BURDEN

Polioviruses are positive-sense, single-stranded ribonucleic acid (RNA) viruses that belong to the *Enterovirus C* species of the Picornaviridae family. They include three antigenically distinct serotypes (1, 2, and 3), with serotype 1 as the most common serotype leading to infection. The polioviruses were previously ubiquitous throughout the world and are highly infectious, spreading through contaminated fecal or respiratory secretions via the fecal-oral route. Humans are the only known natural hosts and reservoir. Although replication in other primates can occur, only humans are infected. Outbreaks were most common in summer and fall in temperate climates, whereas tropical climates have episodes year-round.

Poliomyelitis, often referred to as polio, was recognized by ancient Egyptians, as evidenced in hieroglyphics depicting people with deformed limbs. Throughout history, a majority of the infections were subclinical. Most of these infections occurred in infants and were attenuated by maternal antibodies, leading to subclinical disease but widespread immunity. With the improvement of sanitation in the United States, fewer infants were exposed to the virus and therefore not immune. This created a pool of susceptible individuals, specifically older children and adults, resulting in sporadic epidemics that occurred every few years, quickly increasing in frequency and size. The largest outbreak in the United States occurred in 1952, when nearly 58,000 cases of polio were diagnosed. In developing countries, polio remained endemic into the latter half of the 20th century. With improved sanitation in these regions, epidemics began to occur similar to the pattern observed in the turn-of-the-century United States.

The introduction of polio vaccines dramatically reduced the incidence of polio worldwide. The last case of naturally occurring polio in the United States was reported in 1979. The Western Hemisphere was certified free of wild-type poliovirus (WTPV) in 1994. In October 2019, the Polio Global Eradication Initiative announced that polio is on the verge of eradication, with only two countries (Pakistan and Afghanistan) reporting indigenous WTPV. Of the three serotypes of poliovirus, only serotype 1 remains endemic.

The OPV is a live-attenuated vaccine that has been used worldwide, but there is a risk in 1 in 2.5 million doses to develop vaccine-associated paralytic poliomyelitis (VAPP). The use of OPV also led to the development of cVDPVs, which have been the cause of numerous outbreaks of polio illnesses in parts of Africa, the Middle East, and Southeast Asia.

RISK FACTORS

In the prevaccine era, virtually all infants were exposed to the polioviruses by the age of 6 months, although very few developed the paralytic disease. Risk factors for the infection progressing to paralytic disease include young age, pregnancy, antibody deficiency states, male gender (prepuberty), strenuous exercise, and preceding limb injury within 4 weeks of infection. In adults, women have an increased risk of infection but do not necessarily have an increased risk of paralysis.

CLINICAL FEATURES

Even in the postvaccine era, approximately 70% of infections are asymptomatic. Clinically inapparent infections are defined as isolation of a poliovirus from stool or throat with concomitant fourfold rise in antibody titers. Less than 1% of infections progress to the weakness

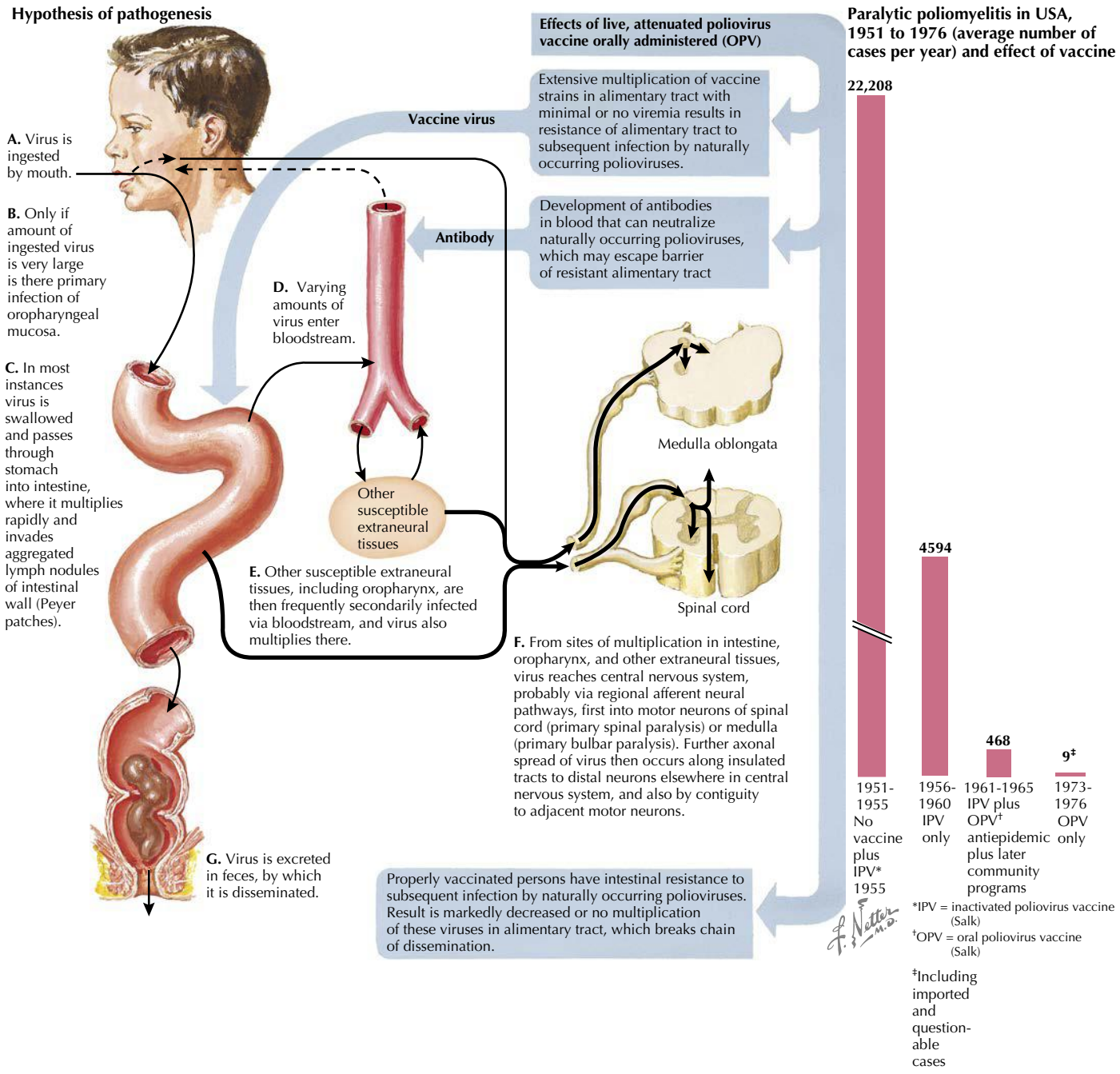

Fig. 7.1 Poliomyelitis.

and paralysis seen in paralytic poliomyelitis. The incubation period is 3 to 6 days; however, symptom onset varies depending on clinical presentation.

Nonparalytic Poliomyelitis

During the incubation period, the virus replicates in the lymphatic tissue, first in the tonsils and lymph nodes of the neck, then in the Peyer patches of the small intestine. After several days, a primary minor viremia occurs, with systemic spread of the poliovirus in the blood to muscle, fat, bone marrow, liver, and spleen (Fig. 7.1). This period is typically asymptomatic, but up to 24% of patients have a mild illness with gastrointestinal symptoms or a respiratory influenza-like illness. These individuals will typically recover in 5 to 10 days, without the development of antibodies to neutralize the virus. In 1% of patients, a secondary major viremia occurs, and the poliovirus spreads to the central nervous system (CNS) and causes an aseptic meningitis. This presents with a severe headache and meningeal irritation but also has a full recovery in 5 to 10 days.

Paralytic Poliomyelitis

Polioviruses replicate within neurons, with a strong predilection for the anterior horn cells of the spinal cord. Rarely, the posterior horn cells and dorsal root ganglia are infected also (Fig. 7.2). Once inside the neurons, the poliovirus will replicate and cause selective destruction of motor neurons; this results in paralysis of the muscle fibers of the infected neuron. It can spread within the CNS laterally to nearby neurons, or retrograde along the axonal transport and travel superiorly along the spine, even as far as the brainstem.

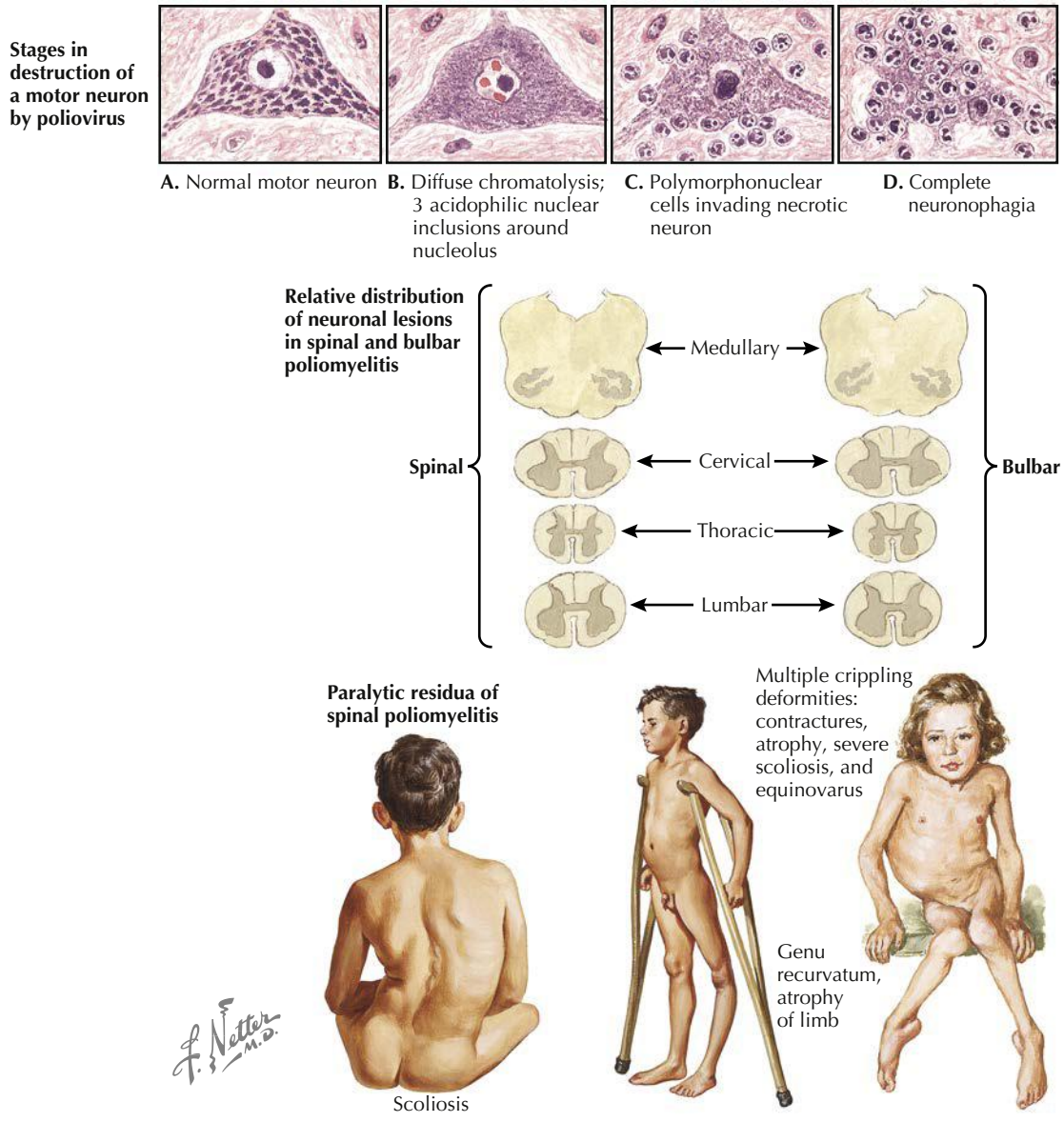

Fig. 7.2 Poliomyelitis.

Approximately 0.1% to 0.2% of the infected, symptomatic individuals develop paralytic poliomyelitis. The hallmark of paralytic poliomyelitis is asymmetric flaccid paresis or paralysis with areflexia. In children, classic paralytic poliomyelitis has a biphasic course, with an initial minor illness (as previously discussed), then a 7- to 10-day symptom-free period of presumed recovery. It is followed by a rapid, abrupt onset of a major illness characterized by severe back, neck, and muscle pain with the development of muscle weakness, loss of reflexes, and asymmetric flaccid paralysis. The maximal loss of function is typically seen within 3 to 5 days of onset but may progress for up to 1 week.

Lower extremities are more often involved than upper extremities, with the proximal muscles more often involved than distal muscles (see Fig. 7.2). Paralysis may diminish over time, with maximal improvement by 6 months after infection; some patients make a full recovery. Unfortunately, if motor dysfunction persists beyond 12 months, the patient will have lifelong disability. It is estimated up to 60% patients with poliomyelitis will have some residual deficit. Sensory loss with polio is extremely rare. Spastic paralysis suggesting upper motor neuron disease may be observed with polioencephalitis, which is a rare manifestation of infants.

Bulbar Poliomyelitis

During epidemics, bulbar poliomyelitis accounts for 5% to 35% of paralytic cases and is the most severe form of polio. Due to its brainstem involvement, including cranial nerves 9, 10, and 12, it results in respiratory compromise. The patient may have nasal speech, inability to swallow secretions, and dyspnea, often appearing anxious or distraught, attributable to difficulty breathing and the associated hypoxia. Prior to modern ventilators, it was associated with a 60% mortality; in contrast, paralytic poliomyelitis affecting only the spinal cord had a less than 7% mortality rate.

DIFFERENTIAL DIAGNOSIS

The World Health Organization defines AFP as any case of "sudden onset of paralysis/weakness in any part of the body of a child younger than 15 years of age." This definition is utilized in the global surveillance

of poliomyelitis, because it is the most common category of diagnoses that includes paralytic polio in the differential. Infectious agents are the leading identified cause of AFP, with up to 90% of cases occurring after a viral infection. Other nonpolio enteroviruses such as enterovirus A71, enterovirus D68, coxsackievirus A7, and coxsackievirus A16 cause AFP. Noninfectious causes of AFP include multiple sclerosis and spinal cord disorders (e.g., transverse myelitis and cord compression). The most common cause of AFP is Guillain-Barré syndrome (GBS), and it can easily be confused with poliomyelitis. However, GBS manifests as a bilateral process, with ascending paralysis, loss of sensory functions, and motor neuron dysfunction. The cerebrospinal fluid (CSF) in GBS generally has elevated protein, with minimal or no pleocytosis. Identifying GBS is important because management differs from poliomyelitis.

Laboratory Findings

Laboratory findings, such as the complete blood count and serum chemistry values, are usually normal or have nonspecific mild abnormalities. CSF findings with poliovirus infection are similar to those of other forms of viral/aseptic meningitis. The CSF pleocytosis is mild (20 to 300 cells/mm^3) with a lymphocyte predominance, although initially there may be a polymorphonuclear predominance. The total protein may be normal or mildly elevated, and the CSF glucose is normal.

Poliovirus is rarely detected in the CSF via culture, due to low viral loads and the presence of neutralizing antibodies. However, it can be rapidly and easily isolated from a throat swab or stool specimens. The poliovirus persists in the throat for 1 to 2 weeks post illness and is shed in the stool for 3 to 6 weeks. Viral culture from a throat swab or stool specimen is the preferred diagnostic tool to confirm diagnosis, preferably performed early in disease course. Molecular methods with real-time reverse-transcriptase polymerase chain reaction (RT-PCR) have a slightly higher sensitivity than viral cell culture and provide results quicker; RT-PCR can also differentiate between WTPV and vaccine-associated poliovirus, whereas viral culture cannot. Confirmatory testing requires two samples obtained greater than 24 hours apart. In addition, confirmation of polio infection may be obtained with serologic testing demonstrating a fourfold rise in antibody titers in paired acute and convalescent sera. Serum neutralizing antibodies develop about 1 week after infection and are lifelong. Immunity is type specific; however, serology cannot differentiate between infection with wild-type or vaccine-associated poliovirus.

CLINICAL MANAGEMENT AND DRUG TREATMENT

Supportive care is the mainstay of treatment, which may include pain management and physical therapy, as well as ventilation for patients who progress to respiratory failure. Surgical management may be required for long-term sequelae such as contractures. The role of antiviral therapy for polioviruses remains unclear. Pocapavir is a novel antiviral targeting picornaviruses, which acts as a capsid inhibitor to prevent virion uncoating upon entry into the cell. A double-blind placebo study in adults found that Pocapavir decreased the length of time of poliovirus shedding after OPV administration. This finding suggests that Pocapavir could be used to decrease transmission of the poliovirus and may be clinically useful in select groups such as patients with primary B-lymphocyte immune deficiencies, who were found to excrete the vaccine-derived poliovirus for up to 25 years.

PROGNOSIS

During the time of polio epidemics, approximately 50% mortality was observed in individuals with respiratory failure, but the overall mortality rate was approximately 5% to 10% of people who developed paralytic poliomyelitis. Approximately two-thirds of patients with AFP do not regain full strength and/or function. Approximately 25% to 40% of children infected with polio were at risk of developing a secondary complication called postpolio syndrome. This syndrome was a new onset of functional deterioration after a prolonged period of stability, occurring 15 to 40 years after the initial poliomyelitis infection. Clinical presentation is characterized by muscle weakness, atrophy, and fatigue in the same muscles that were involved in the original illness. Even without meeting the criteria for postpolio syndrome, many polio survivors have long-term sequelae including muscle weakness, chronic pain, contractures, fatigue, depression, and other disorders associated with a lower quality of life.

PREVENTION AND CONTROL

The polio vaccine was heralded as one of the greatest successes of medical research in the 20th century. In 1955, the inactivated polio vaccine (IPV) was introduced by Dr. Jonas Salk, followed by rapid decline in polio cases. In 1961 to 1962, the OPV, a live attenuated virus vaccine, was introduced by Dr. Albert Sabin and quickly replaced IPV, because of the ease of administration and potential benefits of herd immunity through fecal shedding of the vaccine viruses. After the introduction of both polio vaccines, the rates of wild-type polio dropped dramatically.

In the latter half of the 20th century, VAPP was observed more frequently than wild-type polio in the United States. This led to adoption of a sequential vaccine regimen, with two doses of IPV followed by two doses of OPV from 1997 through 1999. Ultimately, this was changed to an all-IPV dosage regimen in 2000. IPV is safe and generally well tolerated by recipients. It is contraindicated in individuals with previous adverse reaction to the vaccine or its components. Several combination vaccines for infants and children containing IPV are available and offer the benefit of fewer injections per round of vaccinations.

Due to VAPP, adjustments have been made to the OPV to decrease the risk of cVDPV. Serotype 2 WTPV was declared eradicated in 1999, but many of the cVDPV were related to serotype 2. In 2016 the trivalent-OPV was switched to the bivalent-OPV, to eliminate serotype 2 from the vaccine in efforts to decrease the cVDPV. With the recent eradication of serotype 3, further changes may occur and lead to the development of a monovalent OPV.

Currently, both versions of OPV are not routinely produced nor used in the United States; however, an emergency stockpile of OPV is maintained in the event of a polio outbreak. OPV is recommended as the vaccine of choice during a mass vaccination campaign. OPV should not be used in immunocompromised individuals, unvaccinated adults, or in those requiring vaccination but who have an immunocompromised household contact.

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