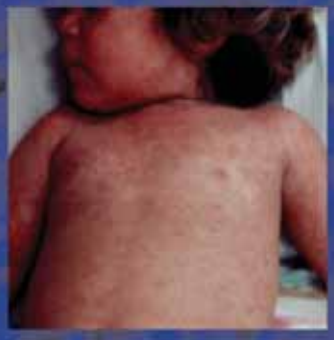
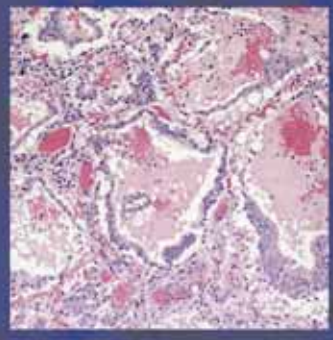
CLINICAL VIROLOGY

FOURTH EDITION



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CLINICAL VIROLOGY

FOURTH EDITION

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DEDICATION

To our families—Eva, Sara, Matthew and Isabella; Kevin, Sarah, Christopher, Jennifer, and Katherine; Melissa, Dan, Gabi, Gretta, Grant, Geoff, Mary, Cotes, and Anderson—and to our many colleagues and friends, who have inspired and supported us throughout the years.

Contents

Contributors

Conflicts of Interest

Preface

Important Notice (Please Read)

1. Introduction / 1
DOUGLAS D. RICHMAN, RICHARD J. WHITLEY, AND FREDERICK G. HAYDEN

Section I

Viral Syndromes and General Principles

2. Respiratory Infections / 9
JOHN J. TREANOR

3. Viral Infections of the Central Nervous System / 31
KEVIN A. CASSADY AND RICHARD J. WHITLEY

4. Gastrointestinal Syndromes / 47
EYAL LESHEM AND UMESH D. PARASHAR

5. Viral Hepatitis / 61
ZINA S. VALAYDON, STEPHEN A. LOCARNINI, AND ALEXANDER J.V. THOMPSON

6. Viral Infections in Organ Transplant Recipients / 75
JOHN A. ZAIA

7. Viral Heart Disease / 99
BRUCE M. McMANUS, MICHAEL SEIDMAN, KARIN KLINGEL, AND HONGLIN LUO

8. Viral Diseases of the Skin / 115
ZEENA Y. NAWAS AND STEPHEN K. TYRING

9. Viral Hemorrhagic Fevers / 141
GAIL CARSON, MIKE BRAY, AND CATHY ROTH

10. Viral Disease of the Eye / 151
HOWARD M. NEWMAN

11. Antiretroviral Agents / 169
CHRISTINE J. KUBIN, BARBARA S. TAYLOR, AND SCOTT M. HAMMER

12. Antiherpesvirus Agents / 215
CLAIRE L. GORDON, CHRISTINE J. KUBIN, AND SCOTT M. HAMMER

13. Anti–Hepatitis Virus Agents / 239
MATTHEW L. SCHERER, CHELSEA SAMMONS, BRIAN NELSON, SCOTT M. HAMMER, AND ELIZABETH VERNA

14. Antirespiratory Virus Agents / 271
MARCUS R. PEREIRA, BENJAMIN A. MIKO, MONICA MEHTA, AND SCOTT M. HAMMER

15. Diagnosis of Viral Infections / 291
GUY BOIVIN, TONY MAZZULLI, AND MARTIN PETRIC

16. Immune Responses to Viral Infection / 321
HENDRIK STREECK, TODD J. SUSCOVICH, AND GALIT ALTER

17. Immunization Against Viral Diseases / 351
JULIE E. LEDGERWOOD AND BARNEY S. GRAHAM

18. Chronic Fatigue and Postinfective Fatigue Syndromes / 371
ANDREW R. LLOYD

Section II

The Agents

Part A: DNA Viruses

19. Poxviruses / 387
STUART N. ISAACS AND R. MARK BULLER

20. Herpes Simplex Viruses / 415
RICHARD J. WHITLEY AND BERNARD ROIZMAN

21. Cercopithecine Herpesvirus 1 (B Virus) / 447
RICHARD J. WHITLEY

22. Varicella-Zoster Virus / 459
ANNE A. GERSHON AND MICHAEL D. GERSHON

23. Cytomegalovirus / 481
PAUL DAVID GRIFFITHS AND MATTHEW REEVES

24. Human Herpesvirus 6 and Human Herpesvirus 7 / 511
KOICHI YAMANISHI AND YASUKO MORI

25. Epstein-Barr Virus / 523
JOYCE FINGEROTH

26. Kaposi's Sarcoma-Associated Herpesvirus (KSHV/HHV8) / 549
YUAN CHANG, SHOU-JIANG GAO, AND PATRICK S. MOORE

27. Adenoviruses / 575
OLLI RUUSKANEN, JORDAN P. METCALF, MATTI WARIS, AND GÖRAN AKUSJÄRVI

28. Polyomaviruses / 599
JOHN E. GREENLEE AND HANS H. HIRSCH

29. Papillomavirus / 625
WILLIAM BONNEZ

30. Human Parvoviruses / 679
MARIA SÖDERLUND-VENERMO, KEVIN E. BROWN, AND DEAN D. ERDMAN

31. *Anelloviridae* / 701
PETER SIMMONDS AND COLIN P. SHARP

32. Hepatitis B Virus / 713
DARREN J. WONG, STEPHEN A. LOCARNINI, AND ALEXANDER J.V. THOMPSON

Part B: RNA Viruses

33. Human Lymphotropic Viruses: HTLV-1 and HTLV-2 / 771
ROBERTA L. BRUHN, RENAUD MAHIEUX, AND EDWARD L. MURPHY

34. Human Immunodeficiency Virus / 795
JOHN C. GUATELLI, ROBERT F. SILICIANO, DANIEL R. KURITZKES, AND DOUGLAS D. RICHMAN

35. Colorado Tick Fever and Other Arthropod Borne Reoviridae / 841
STEVEN YUKL AND JOSEPH K. WONG

36. Rotaviruses / 853
MANUEL A. FRANCO, JUANA ANGEL, AND HARRY B. GREENBERG

37. Respiratory Syncytial Virus, Human Metapneumovirus, and Parainfluenza Viruses / 873
JOHN V. WILLIAMS, PEDRO A. PIEDRA, AND JANET A. ENGLUND

38. Measles / 903
WILLIAM J. MOSS AND DIANE E. GRIFFIN

39. Mumps Virus / 929
JOHN W. GNANN, JR. AND DONALD R. LATNER

40. Zoonotic Paramyxoviruses / 949
DANIELLE E. ANDERSON AND LIN-FA WANG

41. Rhabdoviruses / 967
ALAN C. JACKSON

42. Filoviruses / 981
MIKE BRAY AND DANIEL S. CHERTOW

43. Influenza Virus / 1009
FREDERICK G. HAYDEN AND PETER PALESE

44. *Bunyaviridae:* Orthobunyaviruses, Phleboviruses, Nairoviruses, and Hantaviruses / 1059
GREGORY J. MERTZ, CLAS AHLM, AND COLLEEN B. JONSSON

45. Arenaviruses / 1089
DANIEL G. BAUSCH

46. Enteroviruses / 1113
JOSÉ R. ROMERO

47. Rhinovirus / 1143
WAI-MING LEE AND JAMES E. GERN

48. Hepatitis A Virus / 1165
SARA E. WILLIFORD AND STANLEY M. LEMON

49. Human Caliciviruses / 1189
ROBERT L. ATMAR AND MARY K. ESTES

50. Hepatitis E Virus / 1209
HARRY R. DALTON, NASSIM KAMAR, AND JACQUES IZOPET

51. Astrovirus / 1231
CARLOS F. ARIAS AND TOMÁS LÓPEZ

52. Coronaviruses / 1243
J.S.M. PEIRIS

53. Arthropod-Borne Flaviviruses / 1267
LYLE R. PETERSEN AND ALAN D.T. BARRETT

54. Hepatitis C Virus / 1313
CHRISTOPHER KOH, QISHENG LI, AND JAKE LIANG

55. Alphaviruses / 1347
DAVID W. SMITH, JOHN S. MACKENZIE, ILYA V. FROLOV, AND SCOTT C. WEAVER

56. Rubella Virus / 1381
DAVID W. KIMBERLIN

57. Infections Caused by Bornaviruses / 1395
RALF DÜRRWALD, NORBERT NOWOTNY, MARTIN BEER, AND JENS H. KUHN

Part C: Subviral Agents

58. Hepatitis D / 1409
MARIO RIZZETTO, ANTONINA SMEDILE, AND ALESSIA CIANCIO

59. Prion Diseases / 1425
CHRISTINA J. SIGURDSON, MEE-OHK KIM, AND MICHAEL D. GESCHWIND

Subject Index / 1449

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Conflicts of Interest

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Yuan Chang (chapter 26) holds patents that are assigned to his university on KSHV-related inventions.

Harry R. Dalton (chapter 50) has received travel and accommodation costs and consultancy fees from GlaxoSmithKline, Wantai, and Roche; travel, accommodation, and lecture fees from Merck, Gilead, and GFE Blut GmbH; and travel and accommodation fees from the Gates Foundation.

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Gao Shou-Jiang (chapter 26) holds patents that are assigned to his university on KSHV-related inventions.

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John Williams (chapter 37) serves on the Scientific Advisory Board of Quidel and an Independent Data Monitoring Committee for GlaxoSmithKline.

Preface

Virology is currently one of the most dynamic areas of clinical medicine. Challenges related to novel viruses, changing epidemiologic patterns, new syndromes, unmet vaccine needs, antiviral drug resistance, and threats of bioterrorism are balanced against improved insights into viral pathogenesis, better diagnostic tools, novel immunization strategies, and an expanding array of antiviral agents. The demands on clinicians, public health workers, and laboratorians will continue to increase as will the opportunities for effective intervention. This text, now in its fourth edition, is designed to inform scientists and health care professionals about the medically relevant aspects of this rapidly evolving field.

Clinical Virology has two major sections. The first addresses infections and syndromes related to particular organ systems, as well as the fundamentals of modern medical virology, including immune responses and vaccinology, diagnostics, and antivirals. The second provides agent-specific chapters that detail the virology, epidemiology, pathogenesis, clinical manifestations, laboratory diagnosis, and prevention and treatment of important viral pathogens. In a multiauthored text like *Clinical Virology,* the selection of authors is key. The senior authors for individual chapters were chosen because of their internationally recognized expertise and active involvement in their respective fields. In addition, common templates for the syndrome-specific and separately for the agent-specific chapters allow the reader to readily access material. Since publication of the third edition in 2009, all of the chapters have been extensively revised to incorporate new information and relevant citations. The timeliness and presentation of the fourth edition have been enhanced by publication of chapters online as they have become available and by the increased numbers and incorporation of color figures into the text. New chapters on Bornaviruses and Anelloviruses have been added, and the rapidly expanding field of antiviral drugs demanded dividing the subject into four chapters.

We have been particularly fortunate in receiving invaluable help from our administrative assistants, Mayra Rodriguez, Dunia Ritchey, and Lisa Cook. In addition, we express our appreciation for the enthusiastic professional support provided by Christine Charlip, Lauren Luethy, and Larry Klein of ASM Press.

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Important Notice (Please Read)

This book is intended for qualified medical professionals who are aware that medical knowledge is constantly changing. As new information becomes available, changes in treatment, diagnostic procedures, equipment, and the use of drugs and biologicals become necessary. The editors, authors, and publisher have, as far as it possible, taken care to ensure that the information is up-to-date but cannot guarantee that it is.

Consequently, readers are strongly advised to confirm that the information, especially with regard to drug usage, complies with the latest legislation and standards of practice. The authors, editors, and publisher make no warranty, expressed or implied, that the information in this book is accurate or appropriate or represents the standard of care for any particular facility or environment or any individual's personal situation.

Introduction

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1

Clinical virology incorporates a spectrum of disciplines and information ranging from the x-ray crystallographic structure of viral proteins to the global socioeconomic impact of disease. Clinical virology is the domain of molecular biologists, geneticists, pharmacologists, microbiologists, vaccinologists, immunologists, practitioners of public health, epidemiologists, and clinicians, including both pediatric and adult health care providers. It encompasses events impacting history that range from pandemics and Jennerian vaccination to the identification of new pathogens, mechanisms of disease, and modern countermeasures like antiretrovirals. For example, since the previous edition of this text, sequencing techniques from human specimens have led to the identification of numerous new members of several virus families, including polyomaviruses, orthomyxoviruses, and bunyaviruses (1–3). New viral pathogens have emerged or been recognized, including a camel-associated coronavirus causing the SARS-like Middle East respiratory syndrome, the tick-borne zoonotic orthomyxovirus (Bourbon virus) (2), the bunyaviruses (severe fever with thrombocytopenia virus) (3) and Heartland virus (4, 5), and newly emerged avian and swine influenza viruses causing zoonotic infections (H7N9, H5N6, H6N1, H10N8, H3N2v) (6–10). A bornavirus, belonging to a virus family known to cause disease in animals but with an unproven role in human disease, has been isolated in a cluster of encephalitis cases (11). Well-recognized pathogens like Chikungunya and Zika viruses have spread geographically to cause major outbreaks in the Western Hemisphere (12, 13). The political and social consequences of vaccine denialism have delayed the eradication of polio and measles globally and resulted in re-emerging outbreaks of measles in Europe and North America. Most dramatically, the pattern of relatively limited, albeit lethal, outbreaks of Ebola virus in central Africa over the past 40 years changed in 2014 with the West African outbreak that caused over 28,000 infections leading to over 11,000 fatalities, including more than 500 health care workers, before coming under apparent control in 2016 (http://www.who.int/csr/disease/ebola/en/).

On the positive side, the development of new diagnostic technologies has provided dramatic advances for the detection of new pathogens and the diagnosis and management of virus infections in the clinic. Human "virome" projects based on high-throughput serologic screening, sequencing, and other technologies have documented the frequent but individually unique patterns of infection that we have with these microbes (14–16). Since the previous edition we have seen the revolutionary impact of combination antiviral therapy for HIV, with approximately 15 million people under treatment globally in 2015, followed by the development of 8- to 12-week interferon-free regimens for hepatitis C, with cure rates of over 95%. Modified viruses have become therapeutic tools in treating some forms of malignancy (e.g., herpes simplex virus for glioblastoma) (17, 18). In addition, promising new antiviral drugs and vaccines are in development for many other virus infections. The editors hope that the fascinating breadth and importance of the subject of clinical virology will be conveyed by this text. In this fourth edition, the editors have attempted to update and expand upon the information in the previous edition, while making the content more accessible with Internet-based technology.

A few words about nomenclature are necessary. Students (among others) are plagued by virus classification. Historically, classification reflected the information available from general descriptive biology. Viruses were thus classified by host (e.g., plant, insect, murine, avian), by disease or target organ (e.g., respiratory, hepatitis, enteric), or by vector (e.g., arboviruses). These classifications were often overlapping and inconsistent. Molecular biology now permits us to classify viruses by genetic sequence and biophysical structure, which can be quantitative and evolutionarily meaningful. Table 1, which shows the taxonomy of human viruses, is derived from the comprehensive Ninth Report of the International Committee on Taxonomy of Viruses (19).

The list in Table 1 represents viruses known to infect humans. Many of the agents are primarily animal viruses that accidentally infect humans: herpesvirus B, rabies, the Arenoviridae, the Filoviridae, the Bunyaviridae, and many arthropod-borne viruses. The role of intraspecies transmission of viruses is becoming increasingly appreciated. Although its contribution to zoonotic infections like H5N1 and antigenic shift of influenza A virus is well documented, the role of intraspecies transmission is a major consideration in the "emerging" diseases caused by Sin Nombre virus and related hantaviruses, Nipah virus, Ebola virus, arenavirus, hemorrhagic fevers, variant bovine spongiform encephalopathy, and most importantly, the human immunodeficiency viruses.

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TABLE 1 Taxonomy of human viruses

Family	Subfamily	Type species or example	Morphology	Envelope	Chapter
	Genus				
DNA viruses					
dsDNA viruses					
Poxviridae			Pleomorphic	+	19
	Chordopoxvirinae				
	Orthopoxvirus	Vaccinia virus, variola			
	Parapoxvirus	Orf virus			
	Molluscipoxvirus	Molluscum contagiosum virus			
	Yatapoxvirus	Yaba monkey tumor virus			
Herpesviridae			Icosahedral	+	
	Alphaherpesvirinae				
	Simplexvirus	Human herpesvirus 1 and 2			20
		Cercopithecine herpesvirus 1 (herpesvirus B)			21
	Varicellovirus	Human herpesvirus 3			22
	Betaherpesvirinae				
	Cytomegalovirus	Human herpesvirus 5			23
	Roseolovirus	Human herpesvirus 6 and 7			24
	Gammaherpesvirinae				
	Lymphocryptovirus	Human herpesvirus 4			25
	Rhadinovirus	Human herpesvirus 8			26
Adenoviridae	*Mastadenovirus*	Human adenoviruses	Icosahedral	–	27
Polyomaviridae	*Polyomavirus*	JC virus	Icosahedral	–	28
Papillomaviridae	*Papillomavirus*	Human papillomaviruses	Icosahedral	–	29
ssDNA viruses					
Parvoviridae			Icosahedral	–	
	Parvovirinae				30
	Erythrovirus	B19 virus			
	Dependovirus	Adeno-associated virus 2[a]			
	Bocavirus	Human bocavirus			
Anelloviridae	*Alphatorquevirus*	Torque teno virus[a]	Icosahedral	–	31
DNA and RNA reverse transcribing viruses					
Hepadnaviridae	*Orthohepadnavirus*	Hepatitis B virus	Icosahedral with envelope	+	32
Retroviridae			Spherical	+	

	Deltaretrovirus	HTLV 1 and 2			33
	Lentivirus	Human immunodeficiency viruses 1 and 2			34
	Spumavirus	Spumavirus (foamy virus)[a]			
RNA viruses					
dsRNA viruses					
Reoviridae			Icosahedral	–	
	Orthoreovirus	Reovirus 3[a]			
	Orbivirus	Kemerovo viruses			35
	Coltivirus	Colorado tick fever virus			35
	Seadornavirus	Banna virus			35
	Rotavirus	Human rotavirus			36
Negative-stranded ssRNA viruses					
Paramyxoviridae			Spherical	+	
	Paramyxovirinae				
	Respirovirus	Human parainfluenza viruses			37
	Morbillivirus	Measles virus			38
	Rubulavirus	Mumps virus			39
	Henipavirus	Nipah virus			40
	Pneumoniavirinae				
	Pneumovirus	Human respiratory syncytial virus			37
	Metapneumovirus	Human metapneumovirus			37
Rhabdoviridae			Bacilliform	+	41
	Vesiculovirus	Vesicular stomatitis virus			
	Lyssavirus	Rabies virus			
Filoviridae	*Filovirus*	Ebola virus	Bacilliform	+	42
Orthomyxoviridae			Spherical	+	43
	Influenzavirus A	Influenza A virus			
	Influenzavirus B	Influenza B virus			
	Influenzavirus C	Influenza C virus			
Bornaviridae	*Bornavirus*	Borna disease virus	Spherical	+	57
Bunyaviridae			Amorphic	+	44
	Orthobunyavirus	Bunyamwera virus, LaCrosse virus			
	Hantavirus	Hantaan virus, Sin Nombre virus			
	Nairovirus	Congo-Crimean hemorrhagic fever virus			
	Phlebovirus	Rift Valley fever virus			
Arenaviridae	*Arenavirus*	Lymphocytic choriomeningitis virus	Spherical	+	45

(*Continued on next page*)

TABLE 1 Taxonomy of human viruses (*Continued*)

Family	Subfamily	Type species or example	Morphology	Envelope	Chapter
Positive-stranded ssRNA viruses					
Picornaviridae			Icosahedral	–	
	Enterovirus	Polioviruses			46
	Rhinovirus	Human rhinoviruses			47
	Hepatovirus	Hepatitis A virus			48
Caliciviridae	*Calicivirus*	Norwalk virus	Icosahedral	–	49
Hepeviridae	*Hepevirus*	Hepatitis E virus	Icosahedral	-	50
Astroviridae	*Mamastrovirus*	Human astrovirus 1	Icosahedral	–	51
Coronaviridae	*Coronavirus*	Human coronavirus	Pleomorphic	+	52
Flaviviridae			Spherical	+	
	Flavivirus	Yellow fever virus			53
	Hepacivirus	Hepatitis C virus			54
Togaviridae			Spherical	+	
	Alphavirus	Western equine encephalitis virus			55
	Rubivirus	Rubella virus			56
Subviral agents: satellites, viroids, and agents of spongiform encephalopathies					
Subviral agents					
Satellites (single-stranded RNA)	*Deltavirus*	Hepatitis delta (D) virus	Spherical	+	58
Prion protein agents		Creutzfeld-Jakob agent	?	–	59

[a]Human virus with no recognized human disease.

Although not a documented risk, the theoretical threats of organ transplants from primates and pigs prompted a section on xenotransplantation in the chapter on transplantation. In addition, a number of human viruses have not been recognized to cause human disease, including spumaretroviruses, reoviruses, anelloviruses, and the adeno-associated parvoviruses. The text does not elaborate on these viruses in detail, but the editors did elect to include a chapter on Torque teno virus and related anelloviruses, despite any proven disease association, because of their remarkably high prevalence in human populations globally and the remarkably high titers achieved in blood. We have also added a new chapter on bornaviruses, which may represent either a newly recognized zoonosis or an emerging infection.

In order to provide a comprehensive yet concise treatment of the diverse agents and diseases associated with human viral infections, the editors have chosen to organize the textbook into two major sections. The first provides information regarding broad topics in virology, including immune responses, vaccinology, laboratory diagnosis, and principles of antiviral therapy, and detailed considerations of important organ system manifestations and syndromes caused by viral infections. The second section provides overviews of specific etiologic agents and discusses their biology, epidemiology, pathogenesis of disease causation, clinical manifestations, laboratory diagnosis, and management. We have attempted to ensure that the basic elements are covered for each of the viruses of interest, but it is the authors of each of these chapters that have done the real work and to whom we owe our gratitude and thanks.

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Section I

Viral Syndromes and General Principles

Respiratory Infections

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2

Respiratory viral infections have a major impact on health. Acute respiratory illnesses, largely caused by viruses, are the most common illness experienced by otherwise healthy adults and children. Data from the United States, collected in the 1992 National Health Interview Survey, suggest that such illnesses are experienced at a rate of 85.6 illnesses per 100 persons per year and account for 54% of all acute conditions exclusive of injuries (1). A total of 44% of these illnesses require medical attention and result in 287 days of restricted activity, 94.4 days lost from work, and 182 days lost from school per 100 persons per year. The morbidity of acute respiratory disease in the family setting is significant. The Tecumseh study, a family-based surveillance study of respiratory illness, estimated that approximately one-quarter of respiratory illnesses result in consultation with a physician (2). Illness rates for all acute respiratory conditions are highest in young children, and children below the age of 9 have been estimated to experience between five and nine respiratory illnesses per year (3).

Mortality due to acute viral respiratory infection in otherwise healthy individuals in economically developed countries is rare, with the exception of epidemic influenza and possibly respiratory syncytial virus. However, acute respiratory infection is a major cause of childhood mortality in low- and middle-income countries (4), and it is estimated that 4.5 million children under 5 years of age die annually from acute respiratory infection. Viruses are estimated to play a contributing role in approximately 20% to 30% of these deaths (4). In response, the World Health Organization has undertaken a major new initiative, the Battle against Respiratory Viruses (or BRaVe) to foster research on these pathogens (5).

Both RNA and DNA viruses are responsible for these infections, producing clinical syndromes ranging in severity from merely uncomfortable to life threatening. Each of these viruses may be responsible for different clinical syndromes depending on the age and immune status of the host. Furthermore, each of the respiratory syndromes associated with viral infection may be caused by a variety of specific viral pathogens (Table 1; also see Table 1 in Chapter 52). This chapter describes the clinical syndromes of respiratory virus infection, the spectrum of viruses associated with these syndromes, and the pathophysiology of these illnesses. Specific features of the virology and pathophysiology of disease induced by individual viral agents are described in greater detail in each of the virus-specific chapters.

SEASONAL PATTERNS OF RESPIRATORY VIRUS INFECTION

Many of the viruses associated with acute respiratory disease display significant seasonal variation in incidence (Fig. 1). Although the exact seasonal arrival of each virus in the community cannot be predicted with precision, certain generalizations are useful diagnostically and in planning control strategies. For example, both influenza and respiratory syncytial virus epidemics occur predominantly in the winter months, with a peak prevalence in January to March in the northern hemisphere. Although the periods of peak incidence for these two viruses usually do not coincide, there is often overlap between the two seasons. Parainfluenza virus type 3 (PIV-3) infections show a predominance in the spring, while types 1 and 2 (PIV-1 and PIV-2) cause outbreaks in the fall to early winter. Rhinoviruses may be isolated throughout the year, with increases in frequency in the spring and fall. The peak prevalence of enteroviral isolations is in late summer and early fall, while adenoviruses are isolated at roughly equal rates throughout the year. The herpesviruses do not show significant seasonal variation in incidence, except for varicella, which occurs throughout the year, but more commonly in late winter and early spring.

COMMON COLDS

Clinical Features and Syndrome Definition

Common colds are familiar to most adults and are usually self-diagnosed. Most observers consider colds to include symptoms of rhinitis with variable degrees of pharyngitis; the predominant associated symptoms include nasal stuffiness, sneezing, runny nose, and sore throat. Patients often report chills, but significant fever is unusual. Cough and hoarseness are variably present and may be more frequent in the elderly (6). Headache and mild malaise may occur. Although a multitude of viruses may be associated with this syndrome, the pattern of symptoms associated with colds does not appear to vary significantly among agents. Physical findings are nonspecific and most commonly include nasal discharge and

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TABLE 1 Estimated frequency[a] with which individual viral respiratory syndromes are caused by specific common viral pathogens

Virus	Colds	Pharyngitis	Tracheobronchitis	Croup	Bronchiolitis	Pneumonia		
						Children[b]	Adults	Immuno-compromised
RNA viruses								
Influenza virus								
Type A	+[b]	++	+++	++	+	++	++++	++
Type B	+	++	++	+	+	+	++	+
Parainfluenza virus								
Type 1	+	++	+	++++	+			
Type 2	+	++	+	++	+			
Type 3	+	++	+	+++	++	+++	+	+
Respiratory syncytial virus	++	+		++	++++	++++	++	++
Human metapneumovirus	+				++	++	+	±
Measles virus			+	+		+	+	+
Rhinovirus	++++	++	+	+	+++	++	++	+
Enterovirus	++	++			+	+	±	
Coronavirus	++	+		++	+		+	+
DNA viruses								
Adenovirus		++	+	++	++	++	++	++
Herpes simplex virus		+	±		+	+		++
Varicella virus						+	+	+
Epstein-Barr virus		++					±	+
Cytomegalovirus		+				++	±	+++

[a]The relative frequency of causation is graded semiquantitatively as follows: ±, rarely if ever reported, occasional case reports; +, causes some cases (1%-5% of cases); ++; fairly common cause, (5%-15% of cases); +++; common cause, (15%-25% of cases); ++++, major cause (>25% of cases)
[b]Individuals under the age of 5.
[c]In affected regions during outbreaks.

pharyngeal inflammation. More severe disease, with higher fever, may be seen in children.

Overall, colds are one of the most common of disease experiences. Adults average 6 to 8 colds per 1,000 person-days during the peak cold season and from 2 to 4 colds per person per year (7). Rates of colds are higher in children, who average 6 to 8 colds per year. Adults with children at home have a higher frequency of colds, and women are generally affected more often then men.

Colds are self-limited, with a median duration of illness of approximately 9 to 10 days in adults (8) and longer in children (9). Recognized complications of colds include secondary bacterial infections of the paranasal sinuses and middle ear and exacerbations of asthma, chronic bronchitis, and emphysema. Involvement of the middle ear is common, and changes in middle ear pressures have been documented following both experimentally induced as well as naturally occurring rhinovirus (10) and influenza virus (11) infection. These abnormalities are likely due to eustachian tube dysfunction and probably account for the frequency with which otitis media complicates colds. Colds are associated with symptomatic otitis media in approximately 2% of cases in adults (12) and in a higher proportion in young children (13). Rhinoviruses and other common cold viruses have been detected in middle ear fluids in approximately 20% to 40% of cases of otitis media with effusion in children (14). Infections with RSV, influenza, and adenoviruses are often also associated with otitis media (13).

Colds are also associated with detectable abnormalities of the paranasal sinuses that may or may not be evident clinically. Mucosal thickening and/or sinus exudates have been observed by computerized tomography in as many as 77% of subjects with colds (15, 16). However, clinically manifest acute sinusitis is seen only in a small (0.5% to 5%) proportion of adults with naturally occurring colds.

Clinical colds in atopic individuals may be more severe or more likely to result in wheezing than in normal individuals, and rhinoviruses have been identified as major causes of asthma exacerbations in children and adults (17). The mechanism of this increased susceptibility is unclear but may be related to an altered immune response to infection. Rhinovirus colds may increase asthma by augmenting airway allergic responses such as histamine release and eosinophil influx after antigen challenge. Rhinoviruses have also been identified as important causes of exacerbations of chronic obstructive pulmonary disease (18, 19).

Etiology and Differential Diagnostic Features

The majority of common colds are associated with infection with rhinoviruses or other picornaviruses, particularly when very sensitive techniques, such as reverse-transcriptase-polymerase chain reaction (RT-PCR), are used for diagnosis (8). Other agents frequently associated with common colds include coronaviruses and nonprimary infections with parainfluenza and respiratory syncytial viruses, with a variety of other agents implicated occasionally (Table 1).

The differential diagnosis of individuals presenting with typical signs and symptoms is limited. However, in the presence of additional signs or symptoms which are not part of this clinical description, such as high, persistent fever, signs of respiratory distress, or lower respiratory tract disease, alternative diagnoses should be sought. Allergic causes

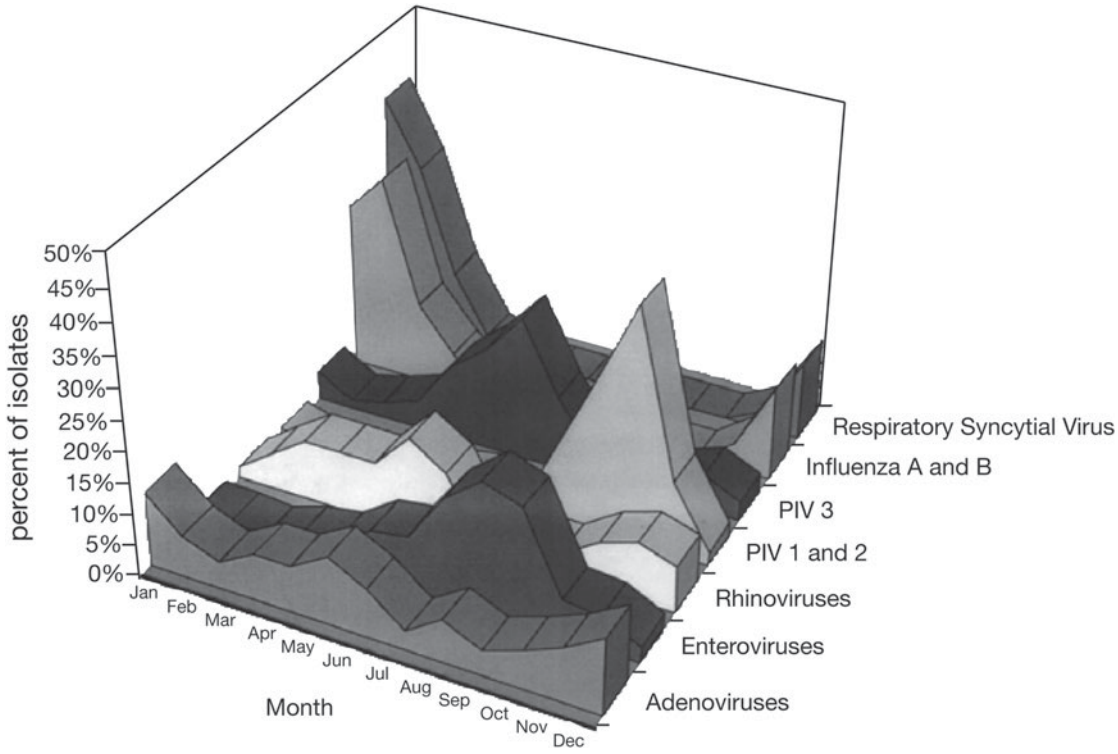

FIGURE 1 Many of the viruses that affect the respiratory tract exhibit a seasonal variation in prevalence. In this figure, numbers of virus isolates from children seen in private pediatric practices in Rochester, NY, are plotted by month of isolation. Data represent the 6-year average from 1990 to 1995 and are expressed as the percentage of all isolates of that virus that occurred in the given month.

should be considered in individuals who present with recurrent symptoms restricted to the upper respiratory tract.

Pathogenesis

Studies of the pathogenesis of the common cold have largely focused on rhinoviruses, the most commonly implicated viral etiology. Transmission of most of the viruses responsible for the common cold is by direct contact, with inoculation of virus into the upper respiratory tract. *In situ* hybridization studies of nasal biopsy specimens from rhinovirus-infected subjects demonstrate that infection is largely confined to relatively small numbers of ciliated nasal mucosal epithelial cells (20), although occasional non-ciliated cells are also infected (20). Sloughing of these epithelial cells is seen in naturally occurring colds, but the epithelial lining remains intact, with structurally normal cell borders (21). Infection is not associated with significant increases in the numbers of lymphocytes in the nasal mucosa (22), but increases in the numbers of polymorphonuclear leukocytes have been detected in nasal mucosa and secretions, probably due to elaboration of IL-8 by infected cells (23). Although rhinoviruses are not able to grow efficiently at core body temperature, virus can be detected within cells of the lower airway even in uncomplicated colds in healthy subjects (24).

In general, the number of infected cells appears to be quite limited, even in fairly symptomatic individuals (20). Such findings suggest that virus-induced cellular injury is not the direct cause of symptoms in rhinovirus colds and that inflammatory mediators and neurogenic reflexes play important roles. The nasal secretions during the initial response to rhinovirus infection are predominantly the result of increased vascular permeability, as demonstrated by elevated levels of plasma proteins in nasal secretions (25). Glandular secretions (lactoferrin, lysozyme, and secretory IgA) predominate later in colds (25). Similar observations have been made in allergic rhinitis. However, in contrast to the situation in allergic rhinitis, histamine does not appear to play a role in the induction of symptoms in colds, because nasal histamine levels do not increase, and therapy with selective (nonsedating) H1 antihistamines is not effective (26–28).

Local cytokine production is associated with symptoms in colds. Nasal secretion of kinin, IL-1, IL-6, and IL-8 levels increases during colds, and kinin and IL-8 concentrations correlate with symptoms (26). The low IL-6 production polymorphism has been associated with greater symptom magnitude following experimental rhinovirus challenge in susceptible adults (29) while polymorphisms in I-L10 or TNFα do not have a discernable effect. Intranasal administration of bradykinin mimics the induction of signs and symptoms in the common cold, including increased nasal vascular permeability, rhinitis, and sore throat (27, 30). Enhanced synthesis of proinflammatory cytokines and cell adhesion molecules in the middle ear may also contribute to the pathogenesis of otitis media associated with colds (31).

Treatment and Prevention

Treatment of colds in clinical practice is directed toward alleviation of symptoms. Symptoms of sneezing and rhinorrhea can be alleviated with nonselective antihistamines such as brompheniramine, chlorpheniramine, or clemastine fumarate, at the cost of some sedation (32, 33). The effect is probably due to the anticholinergic properties of these drugs because, as mentioned earlier, treatment with selective H1 inhibitors is not effective. Topical application of

vasoconstrictors such as phenylephrine or ephedrine provides temporary relief of nasal obstruction but may be associated with a rebound of symptoms upon discontinuation if used for more than a few days. Studies of pseudoephedrine have demonstrated measurable improvements in nasal air flow consistent with a decongestant effect (34, 35). Nonsteroidal anti-inflammatory drugs such as naproxen moderate the systemic symptoms of rhinovirus infection (36). Symptomatic therapy with systemic anticholinergic drugs or anticholinergic-sympathomimetic combinations has not been shown to confer any benefit and to be associated with significant side effects (37). In particular, the use of the decongestant phenylproponolamine has been shown to be associated with an increased risk of hemorrhagic stroke (38, 39), and this drug has been removed from over-the-counter cold remedies. However, topical application of ipratropium, a quaternary anticholinergic agent that is minimally absorbed across biologic membranes, reduces rhinorrhea significantly in naturally occurring colds (40). This agent probably exerts its major effect on the parasympathetic regulation of mucous and seromucous glands.

As expected, there is no benefit in treatment of colds with antibacterial agents, although they are frequently prescribed in colds, particularly in children. Echinacea has been suggested as having efficacy in colds, but a recent randomized trial showed no benefit (41), and administration of this remedy is not associated with a shorter duration of symptoms (42). Zinc gluconate may slightly reduce the duration of colds but does not reduce symptom severity and is associated with a high frequency of adverse events (43).

Clinical Features and Syndrome Definition

Pharyngitis is a common complaint of both adults and children and is one of the more common reasons for seeking outpatient medical care. In general, this syndrome refers to individuals who present with the primary complaint of sore throat and should probably be reserved for those individuals who manifest some objective evidence of pharyngeal inflammation as well. The clinical manifestations of pharyngitis are dominated by the specific causative agent and can be divided into those cases in which nasal symptoms accompany pharyngitis, which are predominantly viral in nature, and those cases without nasal symptoms, which have a somewhat more diverse spectrum of etiologic considerations, including both group A and nongroup A streptococci, chlamydia (strain TWAR), mycoplasma, and other agents (44).

Etiology and Differential Diagnostic Features

Viral pathogens associated with acute pharyngitis are summarized in Table 1. Rhinovirus colds are frequently accompanied by pharyngitis, although objective signs of pharyngeal inflammation are uncommon. Adenovirus infections are frequently associated with pharyngitis, and a specific syndrome of pharyngoconjunctival fever, consisting of fever, pharyngitis, and bilateral conjunctivitis is associated with adenovirus types 3 and 7. A variety of enteroviral serotypes are associated with febrile pharyngitis. Herpangina is a specific coxsackievirus-induced pharyngitis in which small (1 to 2 mm) vesicular lesions of the soft palate rupture to become small white ulcers. Pharyngitis is a typical component of acute influenza in which individuals experience the sudden onset of systemic symptoms of fever, myalgias, and malaise accompanied by upper respiratory signs and symptoms including pharyngitis. Primary oral infection with herpes simplex virus may present with pharyngitis, typically with vesicles and shallow ulcers of the palate, and cervical lymphadenopathy.

Pharyngitis will be a significant complaint in approximately one-half of cases of the acute mononucleosis syndrome due to Epstein-Barr virus (45). Pharyngitis in this syndrome is generally exudative and is accompanied by cervical and generalized lymphadenopathy, as well as fever, hepatosplenomegaly, and other systemic symptoms. The heterophile antibody test is typically positive in the second week of illness. Cytomegalovirus can cause an identical syndrome that is monospot-negative and may be associated with pharyngitis more commonly in children than in adults. An acute mononucleosis-like syndrome with pharyngitis may also be the presenting manifestation of primary HIV infection. Viruses associated with hemorrhagic fever, such as Ebola, Marburg, or Lassa, produce an acute pharyngitis that occurs early in the disease, before skin lesions appear.

The differential diagnosis of acute pharyngitis generally centers upon the differentiation of streptococcal from viral etiologies. Features suggestive of streptococcal pharyngitis include tonsillar swelling, moderate to severe tenderness on palpation, enlargement of lymph nodes, presence of scarlatiniform rash, and absence of coryza (46). The bacterium *Fusobacter necrophorum* has also been recognized as frequently associated with acute pharyngitis in adults and has a clinical presentation similar to that of streptococcal pharyngitis (47).

The presence of nasal symptoms or of conjunctivitis favors a viral etiology, and as described above, some viral syndromes may present with distinguishing characteristics that help in their identification. Generally, acute pharyngitis in children less than 3 years of age is predominantly viral in origin. The presence of exudate is suggestive of bacterial etiology, but exudates may also be seen with adenovirus or EBV. Rapid diagnostic tests for the office identification of group A streptococci are widely available and are indicated in most cases where the etiology is uncertain. When highly sensitive tests are used, backup cultures are generally not necessary (48).

Pathogenesis

The pathophysiology of those virus infections for which pharyngitis is part of the clinical presentation is described in the individual virus-specific chapters of this book. As described above, pharyngitis in the common cold is probably the result of chemical mediators of inflammation, which are potent stimulators of pain nerve endings. Potentially similar mechanisms may account for pharyngitis in other viral syndromes as well. Direct viral damage and other host inflammatory responses may also contribute.

Treatment and Prevention

The treatment of most cases of viral pharyngitis is symptomatic, as noted in the section on common colds. Patients suspected of having influenzal pharyngitis who are seen within the first 2 days of illness can be treated with antiviral therapy (see Chapters 14 and 43). In immunosuppressed patients with chronic herpetic pharyngitis or normal hosts with primary gingivostomatitis, acyclovir therapy is recommended (see the discussion on herpes simplex virus).

Treatment of group A streptococcal infections with antimicrobial agents is generally initiated to prevent rheumatologic complications of this infection and is associated with more rapid resolution of symptoms, although the absolute benefits are rather modest (49). Rapid diagnostic tests are widely available for the office identification of group A

streptococci and are indicated in most cases where the etiology is uncertain. Antibiotic treatment based on only positive rapid test or throat culture results can reduce unnecessary use of antibiotics for treatment of pharyngitis (50).

CROUP (ACUTE LARYNGOTRACHEOBRONCHITIS)

Clinical Features and Syndrome Definition

Croup, or viral laryngotracheobronchitis, is a clinically distinct illness that predominantly affects children under the age of three. The illness typically begins with upper respiratory tract symptoms of rhinorrhea and sore throat, often with a mild cough. After 2 or 3 days, the cough deepens and develops a characteristic brassy, barking quality, which is similar to a seal's bark. Fever is usually present, generally between 38° and 40°C, although those with croup due to respiratory syncytial virus may have normal temperatures. The child may appear apprehensive and most comfortable sitting forward in bed. The respiratory rate is elevated but usually not over 50; this contrasts with bronchiolitis, in which more severe tachypnea is often seen. Chest wall retractions, particularly in the supraclavicular and suprasternal areas, may be observed. Children with this finding on presentation have a higher risk of hospitalization or of requiring ventilatory support.

The characteristic physical finding of croup is inspiratory stridor. Inspiration is prolonged, and in very severe cases, some degree of expiratory obstruction may also be seen. Rales, rhonchi, and wheezing, which reflect the characteristic involvement of the lower respiratory tract, may be heard on physical examination. A fluctuating course is typical, and the child may appear to worsen or improve within an hour. Hypoxemia occurs in 80% of children with croup severe enough to require hospitalization. The degree of hypoxia is generally difficult to ascertain clinically, but continuous monitoring of pulse oximetry does not correlate with respiratory distress and may lead to increased hospitalization rates.

Children who develop respiratory insufficiency as a result of increasing fatigue also may have elevations in $PaCO_2$. Other routine laboratory assays are generally unremarkable. Children with croup characteristically exhibit subglottic narrowing of the tracheal air shadow on PA films of the neck, the so-called "steeple" sign (Fig. 2). This finding may be useful in differentiating croup from epiglottitis. Chest X-rays may reveal parenchymal infiltrates which are part of the characteristic involvement of the lower respiratory tract in this syndrome.

Croup is predominantly a disease of young children, with a peak age incidence in the second year of life. In the Seattle virus watch family study, the annual incidence of croup was 5.2 per 1,000 in the first 6 months of life, 11.0 per 1,000 in the second 6 months, 14.9 per 1,000 in the second year of life, and 7.5 per 1,000 in those 2 to 3 years of age, with a marked drop after that age (51). Boys are somewhat more likely to be affected than girls (52).

Etiology and Differential Diagnostic Features

Overall, viruses are recovered from croup cases more frequently than from other types of respiratory illnesses. An estimate of the relative importance of individual infectious agents in croup is shown in Table 1. The parainfluenza viruses are the most common viruses responsible for croup, accounting for about 75% of cases (52). Of the parainfluenza viruses, types 1 and 2 are most commonly associated with croup (52), and the seasonal incidence of croup reflects the seasonal variations in parainfluenza virus incidence (Fig. 1). Less common causes of croup include respiratory syncytial virus, influenza A or B viruses, rhinoviruses, and adenoviruses, as well as *Mycoplasma pneumoniae*. Recent studies have also shown a strong association with the novel coronavirus NL63 (53). Measles is a relatively less common cause of croup but is associated with especially severe disease (54). Mycoplasma pneumoniae and influenza viruses tend to be isolated more commonly from older children with croup (52). Parainfluenza virus type 2 and influenza A viruses are associated with more severe disease (55), but generally the clinical presentation of the croup syndrome due to individual agents is similar. Specific viral diagnosis is not routinely performed since the clinical syndrome is sufficient for diagnosis, and management generally does not depend on identification of the specific agent.

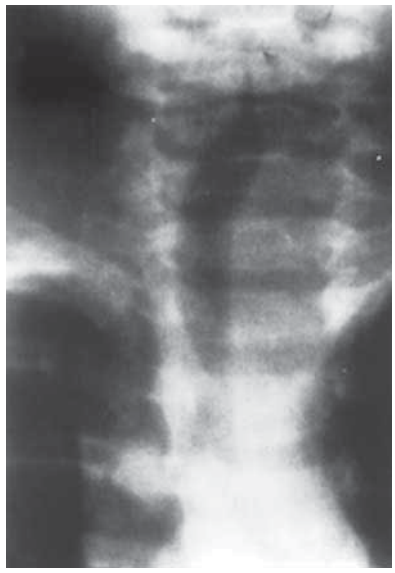

FIGURE 2 Posteroanterior roentgenogram of the neck of a child with viral croup that shows the characteristic narrowing of the air shadow of the trachea in the subglottic area. (Courtesy of Dr. Carolyn B. Hall, University of Rochester)

The majority of cases of inspiratory stridor in children are caused by viral croup. However, it is critical to distinguish these syndromes from other, potentially more serious causes of airway obstruction such as bacterial epiglottitis and tracheitis early in clinical management. Epiglottitis is an acute cellulitis of the epiglottis and surrounding structures. Patients present with acute respiratory distress and drooling, but the barking cough of croup is absent. Epiglottitis in children is usually caused by *Hemophilus influenzae* type b (Hib). The incidence of invasive Hib infections has declined remarkably since the introduction of polysaccharide-conjugate vaccines, and the incidence of epiglottitis in children has also declined considerably (56). In adults, and rarely in children, epiglottitis may be caused by a variety of other bacterial agents such as *Haemophilus parainfluenzae* or β-hemolytic streptococci, which may spread from a contiguous focus of infection. Bacterial tracheitis is a relatively rare syndrome that mimics croup. Abundant purulent sputum is often present. Bacterial tracheitis is usually caused by *Staphylococcus aureus* or Hib; other bacteria such as β-hemolytic streptococci and *Streptococcus pneumoniae* have also been associated with this syndrome. Other infectious causes of stridor, including peritonsillar or retropharyngeal

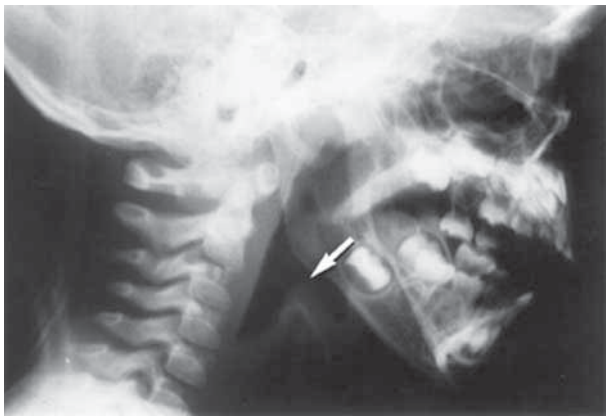

FIGURE 3 Lateral neck films of the neck in a child with epiglottitis demonstrates the characteristic thickening of the epiglottis in this disease and may be helpful in distinguishing this illness from croup or retropharyngeal abscess. (Courtesy of Dr. Caren B. Hall, University of Rochester)

abscess or diphtheria, and noninfectious causes of stridor such as trauma or aspiration of a foreign body, should be considered.

Direct visualization of the epiglottis may be necessary to exclude bacterial etiologies, and facilities and personnel for this procedure and for emergency airway management should be available. Lateral neck radiographs may show edema of the epiglottis in epiglottitis (Fig. 3) or thickening of the retropharyngeal space in individuals with retropharyngeal abscess. However, radiographs are limited in accuracy and should be performed with caution in individuals with respiratory distress. It may be useful to administer racemic epinephrine, because a rapid response is suggestive of croup.

Pathogenesis

The severity of clinical symptoms in viral croup appears to be directly related to the level of virus replication (57). This results in inflammation in both the upper respiratory tract and the lung parenchyma. The classic signs of croup, including the barking cough and inspiratory stridor, arise mostly from inflammation occurring in the larynx and trachea. Inflammatory changes are seen by histology in the epithelial mucosa and submucosa of the larynx and trachea. The cellular infiltrate includes histiocytes, lymphocytes, plasma cells, and polymorphonuclear leukocytes. The inflammation and obstruction are greatest at the subglottic level, which is the least distensible part of the airway because it is encircled by the cricoid cartilage. Consequently, localized inflammation and edema lead to obstruction of airflow. The impeded flow of air through this narrowed area produces the classic high-pitched vibration. Obstruction is greater during inspiration because the narrowing occurs in the extrathoracic portion of the airway and is enhanced in small children because the walls of the airways in these individuals are relatively compliant and can collapse to a greater extent. Obstruction of airflow results in an initial decline in tidal volume, which is compensated by an increase in respiratory rate to maintain adequate alveolar ventilation. However, if the obstruction increases, the work of breathing may increase until the child tires, and as the respiratory rate declines, the child develops hypercarbia and respiratory failure.

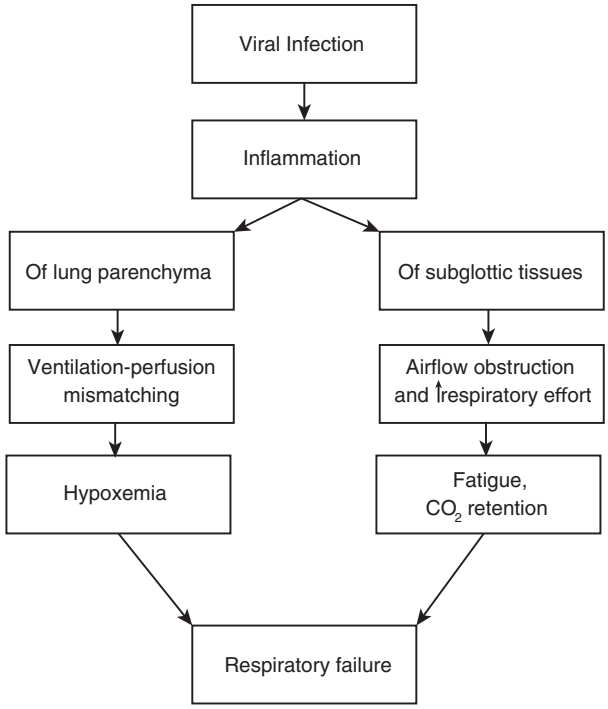

FIGURE 4 Pathophysiology of croup. Both mechanical obstruction of airflow and ventilation-perfusion mismatching due to parenchymal infection of the lung are responsible for the hypoxia and respiratory distress of croup. (Modified from Hall, Reference 206, with permission)

Involvement of the lower respiratory tract is integral to the pathophysiology of croup (Fig. 4) (58). Inflammatory changes are noted throughout the respiratory tract, including the linings of the bronchi, bronchioles, and even the alveoli. Consistent with these findings, hypoxemia is detected in about 80% of children hospitalized with croup. Although some degree of hypoxia can be explained on the basis of hypercarbia, the major pathophysiologic mechanism is ventilation-perfusion mismatching. Pulmonary edema may complicate severe croup and upper airway obstruction (59). The onset of pulmonary edema often occurs immediately following intubation. Pulmonary edema in these cases does not appear to be due to pulmonary artery hypertension but to local hypoxia and increased alveolar-capillary transmural pressure.

Treatment and Prevention

Because the majority of hospitalized children are hypoxic, oxygen is the mainstay of treatment for severe disease and should be given to all hypoxemic patients. Humidified air or mist therapy is commonly used and has several potential roles. Desiccation of the inflamed epithelial surfaces is decreased, and the viscosity of the exudate is reduced. However, the value of mist therapy has not been proven, and removal of the child from the parents and placement in a mist tent can be more distressing to the child than beneficial.

Corticosteroids have been shown to confer significant benefits in the management of mild, moderate, and severe croup, including more rapid improvement in symptoms, reduced length of hospital stay, and reduced rates of intubation. Administration of a single dose of 0.6 mg/kg dexamethasone

intramuscularly (60), an oral dose of between 0.6 to 0.15 mg/kg orally (61), or of 2 mg of budesonide by nebulizer (62) are all effective, and comparative trials have shown all three strategies to be equally effective (63, 64). Administration of single-dose corticosteroid therapy in this setting has not been associated with significant side effects and should probably be used in most patients with significant illness (65).

Administration of nebulized racemic epinephrine generally gives rapid, symptomatic relief in croup (66). It is believed that α-adrenergic stimulation by this drug causes mucosal vasoconstriction, leading to decreased subglottic edema. Several randomized trials have demonstrated a rapid beneficial effect on airway obstruction (67, 68). The onset of action is rapid, often within minutes, but the duration of relief is also limited, lasting 2 hours or less. Therefore, treated subjects should be observed closely for clinical deterioration. While symptomatic relief is considerable, use of epinephrine is not associated with improvements in oxygenation, probably because the defect in oxygen is associated with ventilation-perfusion mismatching due to lower respiratory tract involvement. In addition tachycardia may occur. Thus, inhaled epinephrine is generally reserved for children who fail to respond to more conservative management (69). Oxygen mixed with helium (heliox) has been suggested as an intervention to reduce the work of breathing; however, its role in the routine management of croup remains undetermined (70).

Antiviral agents effective against some of the viruses responsible for croup are available but have not been tested for efficacy in this situation. However, the potential benefit of the use of antiviral agents in the typical self-limited course of croup would likely be limited. Since croup is a viral illness, antibiotic therapy is of no benefit.

BRONCHIOLITIS

Clinical Features and Syndrome Definition

Bronchiolitis is a characteristic syndrome of infants whose presenting symptoms are dominated by the major pathophysiologic defect, obstruction to expiratory airflow (71). The onset of lower respiratory symptoms is usually preceded by rhinitis, often with nasal congestion and discharge. More severe symptoms characteristically occur 2 to 3 days later but in some cases are concurrent with the onset of upper respiratory symptoms. In many instances, there may be a history of exposure to an adult or sibling with a cold or other minor respiratory illness or history of exposure to other cases of bronchiolitis in the daycare setting.

The hallmark of disease is wheezing, which can be quite marked, with flaring of the nostrils and use of accessory muscles of respiration. Cough may or may not be prominent initially, and when cough is present, it may be paroxysmal in nature. Slight cyanosis is often observed, but the presence or absence of cyanosis is not a reliable indicator of the degree of oxygenation or of the severity of disease. Physical findings are generally confined to the chest, with development of rales, which are usually musical in the beginning and then become more moist. Hyper-resonance of the chest may be observed, and the liver may be displaced downward due to hyperinflation. The respiratory rate is elevated, with rates of 50 to 80 breaths per minute. Fever is frequently present at the beginning of the illness but may no longer be present at the time lower respiratory tract involvement develops. Among hospitalized infants, one-third or more are afebrile, despite marked lower respiratory tract disease. Thus, the presence or absence of fever does not indicate the severity of the child's illness. Mild conjunctivitis is noted in about a third of cases, with pharyngitis of varied severity in about half, and otitis media in 5% to 10%. The hospital course is variable, but most infants will show improvement in 3 to 4 days (72).

Radiologic findings are generally nonspecific, with reported findings including air trapping, consolidation, and collapse (73). Air trapping is particularly indicative of respiratory syncytial virus (RSV)-associated bronchiolitis and may be the only radiologic finding (Fig. 5). However, there is no correlation between the radiographic findings and the clinical course (74). Chest radiographs should be obtained to rule out alveolar filling defects suggestive of bacterial pneumonia and in those infants with severe disease, sudden deterioration, or underlying disorders (75). Results of routine laboratory tests are generally unremarkable, and the peripheral white blood cell count is usually not elevated. Abnormal water, electrolyte, and endocrine homeostasis may be seen during acute illness, including elevated antidiuretic hormone secretion and low fractional excretion of sodium (76). Electrolyte disturbances, most notably hyponatremia, may be seen with severe disease, particularly if excessive amounts of hypotonic fluid are administered (77). Acute disease may be associated with elevations in pulmonary artery pressure, but echocardiographic studies are usually unremarkable in infants with structurally normal hearts (78).

Bronchiolitis is a disease predominantly of infancy, and the epidemiology of this disease closely parallels that of the major infectious cause, respiratory syncytial virus. The peak age incidence is between 2 and 6 months of age, with over 80% of cases occurring in the first year of life (79). The risk of hospitalization of infants during the first 12 months of life for bronchiolitis has been estimated to be approximately 10 per 1,000 population (80), with the peak age of hospitalization between 1 and 3 months. Hospitalization rates are highest in children who reside in industrialized urban settings (81). Among lower socioeconomic status groups, bronchiolitis hospitalization rates of 0.5% to 1% of the entire population of infants in the first year of life are not uncommon (82).

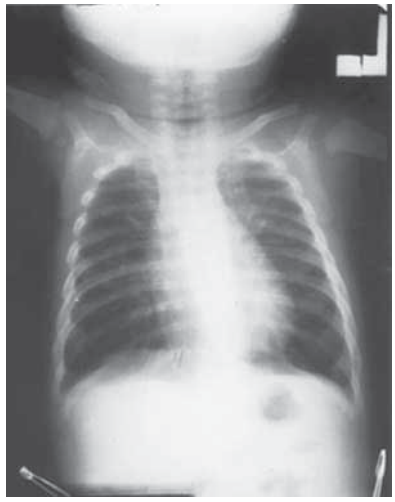

FIGURE 5 The CXR in bronchiolitis characteristically shows hyperinflation due to obstruction to airflow. A variety of other findings may be present, including interstitial infiltrates or lobar consolidation. (Courtesy of Dr. Caren B. Hall, University of Rochester)

The risk of hospitalization and severe bronchiolitis is particularly high in infants with congenital heart or lung disease or immunodeficiency (83, 84). In addition, infants born prematurely and those who are less than 6 weeks of age at the time of presentation are also at risk (85). More severe disease has also been documented in children with a family history of asthma (85) and those exposed to cigarette smoke in the family setting (86).

Etiology and Differential Diagnostic Features

The spectrum of viruses associated with bronchiolitis is shown in Table 1. RSV causes the majority of cases of bronchiolitis, and during the RSV epidemic season, essentially all cases are due to this virus (87). Overall, RSV is recovered from about three-fourths of all infants admitted to the hospital with bronchiolitis (71). Children hospitalized with bronchiolitis due to RSV tend to be younger than those with other viruses (88). Children with a higher viral load on nasopharyngeal aspirates have a higher risk of ICU admission (89). Human metapneumovirus (hMPV) is also a significant cause of bronchiolitis (90–92). The clinical picture most closely resembles that of RSV, and bronchiolitis is the major manifestation in children. Clinical features include wheezing and hypoxia. There are no clinical features that can distinguish between disease caused by hMPV and RSV, although generally RSV may be more severe.

Rhinoviruses have recently been recognized as associated with a significant proportion of cases of bronchiolitis and represent the second most common virus detected using sensitive nucleic acid tests in children with bronchiolitis. The true attribution of RV to this syndrome must take into account the frequent detection of this virus in asymptomatic children as well. Rhinoviruses can also mimic RSV infection in infants with bronchopulmonary dysplasia (93).

Other respiratory viruses causing bronchiolitis include parainfluenza viruses, influenza virus, mumps, and rhinoviruses. Adenoviruses types 3, 7, and 21 are relatively uncommon causes but may be associated with more severe disease, including bronchiolitis obliterans (94). Novel human coronaviruses, such as NL-63, have also been associated with lower respiratory tract disease in infants (95). An additional recently described human parvovirus, the human bocavirus, has been found in as many as 12% of cases of acute wheezing in young children (96).

The differential diagnosis of diseases characterized by expiratory airflow obstruction in infants is relatively small. Pertussis can occasionally be confused with bronchiolitis; more frequent vomiting, more paroxysmal cough, and lymphocytosis are clues to the diagnosis. Differentiation of acute infectious bronchiolitis from the initial presentation of allergic asthma is difficult and contributes to the difficulty in assessing therapeutic interventions in this disease. Anatomic defects such as vascular rings can cause obstruction of the airway. Foreign bodies should be considered strongly, especially in young infants. Gastroesophageal reflux is an additional consideration.

RSV and some of the other viral agents responsible for bronchiolitis can be isolated from nasopharyngeal secretions in cell culture, but nucleic acid detection techniques are more sensitive and detect a wider range of viruses (97). Rapid antigen detection techniques are widely used, but the sensitivity of such techniques is dependent on the quality of the nasopharyngeal specimen, with nasopharyngeal aspirates superior to brushings or swabs (98). Their utility in routine management is unclear, although they may be useful for infection control purposes.

Pathogenesis

The pathophysiology of infectious bronchiolitis has been described most completely in the case of infection with RSV. The basic pathophysiologic changes in bronchiolitis are summarized in Figure 6 (71). Viral infection of epithelial cells of the bronchioles leads to destruction and necrosis of the ciliated epithelium. Leucocytes, predominantly lymphocytes, can be seen in increased numbers in the peribronchial tissues (99). The submucosa becomes edematous, and there is increased production of mucus. Ultimately, dense plugs of alveolar debris and strands of fibrin form within small bronchi and bronchioles, which may partially or completely obstruct airflow. The pathogenic basis for respiratory difficulty in bronchiolitis is related to obstruction of these small airways (71). Hypoxemia is the major abnormality of gas exchange, with ventilation-perfusion imbalance the major cause of the hypoxemia. In addition to hypoxia, hypercarbia, and respiratory acidosis have been observed in some severely ill infants.

Infants appear to be particularly susceptible to the consequences of viral infection because the peripheral airways are disproportionately narrow in the early years of life. In addition, collateral channels of ventilation, such as the pores of Kohn, are deficient both in number and size in the infant lung. Finally, the airways of infants are intrinsically more reactive to bronchospastic stimuli than are the airways of older children (100). It is not clear how RSV infection results in the observed histologic damage, and the reasons some children experience relatively mild disease while others go on to respiratory failure are unknown.

The possibility that immune responses are involved in the pathogenesis of RSV bronchiolitis has received considerable attention. Factors identified as potentially playing a role include overproduction of IgE in response to infection, alteration in the cytokine phenotype of responding T cells, and release of leukotrienes in the airways (101). In addition, neural mechanisms of airway smooth muscle tone may be disrupted by RSV (102).

The innate immune response also plays an important role in the pathogenesis of RSV disease in infants, and it has been recognized that single nucleotide polymorphisms in several genes that control the inflammatory response have an important impact on the severity of RSV disease. Examples include polymorphisms in the genes for IL-4, IL-8, and IL-13, and in TLR-4 and the CCR5 receptor, among others (103).

Following recovery from acute bronchiolitis, some children experience continued episodes of wheezing, especially during apparently viral upper respiratory infections. Estimates are that the risk of either infrequent or frequent wheezing following recovery from documented RSV lower respiratory tract infection is increased by about 3- to 4-fold (104). The risk of subsequent wheezing is also increased in children with bronchiolitis associated with RSV. The mechanisms underlying this increased risk are unknown. Other studies have shown no difference in the rate of subsequent asthma in monozygotic twins discordant for RSV hospitalization (105). A history of maternal asthma may be associated with more severe disease in children with rhinovirus-associated bronchiolitis but not RSV (106, 107).

Treatment and Prevention

Recommendations regarding the treatment and prophylaxis of bronchiolitis have been summarized recently (108). Correction of hypoxemia is the most important aspect of

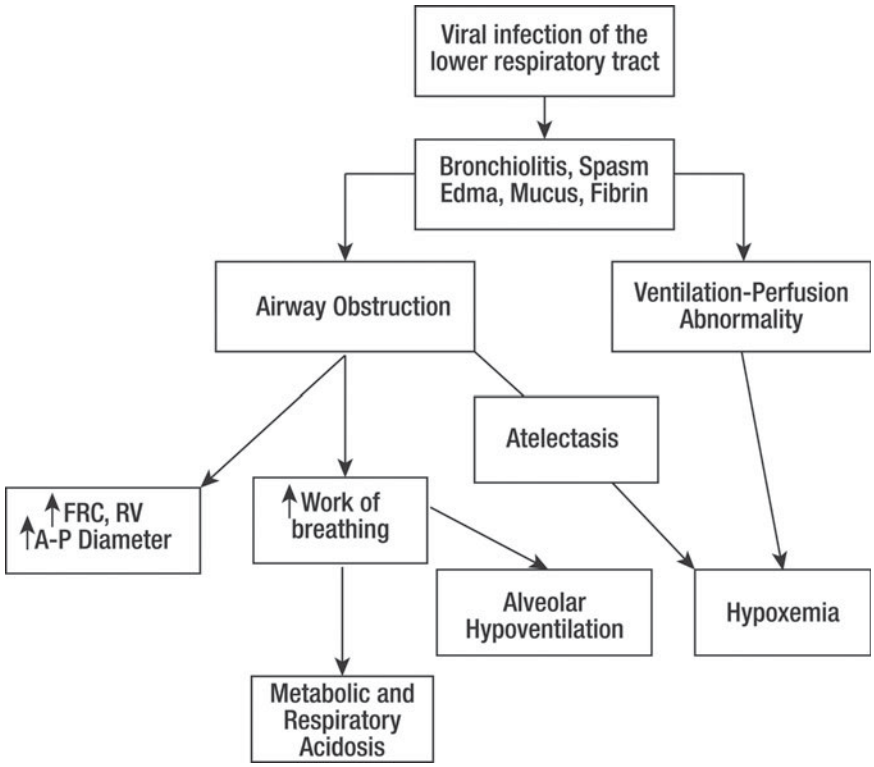

FIGURE 6 Pathophysiology of bronchiolitis. Viral infection of the lower respiratory tract results in inflammation and increased mucus production. Both airway obstruction and ventilation-perfusion mismatching are responsible for the clinical findings of hypoxia, hyperinflation, and hypoventilation. If uncorrected, these defects can lead to apnea or sudden death. (Modified from Wohl and Chernick, Reference 71, with permission)

managing RSV lower respiratory tract disease. Oxygen should be administered to infants whose saturation consistently falls below 90%, but the role of continuous monitoring of oxygen saturation is controversial. Inhaled hypertonic saline has been suggested as a modality to rehydrate the airway and may reduce the risk of hospitalization, although not affecting length of stay (109). Some studies have suggested that a humidified high-flow nasal cannula or continuous positive airway pressure may be useful in children who are at risk for respiratory failure (110).

Because of the dehydrating effect of tachypnea and reduced oral intake in some hospitalized infants, parenteral rehydration is often needed, but care must be taken to avoid inducing hyponatremia. Fluid intake and electrolyte concentrations should be carefully monitored in all infants with severe bronchiolitis, because hyponatremia and syndrome of inappropriate secretion of antidiuretic hormone (SIADH) may occur.

Other therapies are generally not routinely recommended in the treatment of bronchiolitis. Generally, bronchodilators produce modest short-term improvements in clinical scores but do not improve oxygenation, rates of hospitalization, or duration of hospital stay (111). The majority of studies of systemic corticosteroids have also failed to demonstrate a beneficial effect in acute bronchiolitis, and oral corticosteroids do not appear to have beneficial effects (112). Antibacterial drugs, including azithromycin, are of no benefit (113).

A humanized neutralizing monoclonal antibody to the RSV F protein, palivizumab (Synagis®), has had significant protective efficacy in a population of infants with prematurity or bronchopulmonary dysplasia, as well as in children with hemodynamically significant congenital heart disease. Administration of palivizumab intramuscularly at a dose of 0.15 mg/kg of body weight once per month resulted in a 55% reduction in RSV-related hospitalizations and a lower incidence of intensive care unit admissions in this population (114). Recommendations for the use of passive antibody prophylaxis in the United States have been recently revised (115). Palivizumab should generally be used only in the first year of life during the RSV epidemic season. Use is recommended in preterm infants who were born before 29 weeks' gestation (who would be expected to receive little placental transfer of maternal antibody), preterm infants of any gestational age who develop chronic lung disease of prematurity, and infants with hemodynamically significant chronic heart disease. Use can also be considered during the first year of life in infants with anatomic pulmonary disorders or neuromuscular disorders that impair clearing of secretions. The risk of severe RSV in the second year of life is considerably less, but use of palivizumab can be considered in infants with chronic lung disease of prematurity who continue to require medical support, and infants who are profoundly immunocompromised. Routine use in children with cystic fibrosis is not currently recommended.

Interruption of nosocomial transmission may be facilitated by thorough handwashing, decontamination of surfaces and inanimate objects, and isolation or cohorting of infected infants. Use of disposable eye-nose goggles by pediatric staff reduces the risk of nosocomial RSV infection in both staff and patients. Regular use of gowns, gloves, and possibly masks by hospital staff caring for infected children

may also reduce the risk of nosocomial RSV spread. Protective isolation of high-risk infants or deferring their elective admission has been recommended during institutional outbreaks of RSV.

Vaccines are available to prevent bronchiolitis due to influenza virus and mumps, but there is no vaccine currently available for prevention of bronchiolitis due to RSV or PIV. There are multiple significant hurdles to the development of such vaccines, including the very young age at which the disease presents, the suppressive effect of maternal antibody on vaccine responses, and in the case of RSV, the potential for enhanced disease in vaccine recipients (116).

TRACHEITIS AND TRACHEOBRONCHITIS

Clinical Features and Syndrome Definition

In addition to causing croup and bronchiolitis, viral infection of the trachea and bronchi may cause tracheitis or tracheobronchitis. Tracheitis is characterized by tracheal tenderness, which can be elicited by gentle pressure on the anterior trachea just below the cricoid cartilage. Substernal discomfort on inhalation, and nonproductive paroxysmal cough are noted. Paroxysmal nonproductive cough is also characteristic of tracheobronchitis and is usually much more severe at night. Later in the course of illness, small amounts of clear or whitish sputum may be produced. Accompanying symptoms may include fever, headache, myalgias, malaise and anorexia. After several days of coughing, chest wall or abdominal discomfort, which is muscular in nature, may be noted. Physical findings are generally nonspecific; examination of the chest may reveal no adventitious sounds but more commonly scattered rhonchi and occasional wheezing. Physical signs such as egophony, pleural friction rubs, or areas of dullness to percussion should suggest the presence of other diagnoses such as pneumonia or pleural effusion.

Etiology and Differential Diagnostic Features

Tracheobronchitis is most typically caused by influenza A or B virus (Table 1). Herpes simplex has been associated with necrotizing tracheobronchitis in non-immunocompromised hosts (117); this syndrome is often accompanied by refractory bronchospasm. The differential diagnosis of acute bronchitis includes nonviral infections and non-infectious etiologies such as cough-variant asthma. *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* infections cause prolonged cough. *Bordetella pertussis* infection should also be considered in the differential diagnosis of prolonged cough illness. In otherwise healthy persons, workup of acute cough should be directed toward determining the presence of pneumonia.

Treatment and Prevention

Treatment of bronchitis is primarily symptomatic with antipyretics, and cough suppression. In the absence of signs of pneumonia or documented bacterial infection such as pertussis, treatment of cough with antibacterial agents is of no benefit (118, 119).

VIRAL PNEUMONIA

Clinical Features and Syndrome Definition

The development of pneumonia is defined by the development of abnormalities of alveolar gas exchange accompanied by inflammation of the lung parenchyma, often associated with visible changes on radiologic studies. Although there can be considerable variety in the presentation of viral pneumonia depending on the age and immunologic competence of the host and the specific viral pathogen, there are certain general features of viral pneumonias. Physical findings are often nonspecific. The patient generally appears acutely ill, conjunctivitis and rhinitis may be noted, and the trachea may be somewhat tender if accompanied by viral tracheitis. Chest exam reveals increased respiratory rate, diffuse rales, and often wheezes. The sputum is relatively scant, generally shows few polymorphonuclear leukocytes, and Gram stain usually reveals minimal numbers of bacteria. The clinical presentation of viral pneumonia in children typically includes fever and lower respiratory tract signs and symptoms, such as difficulty breathing, nonproductive cough, and physical findings of wheezing or increased breath sounds. Young infants may present with apneic episodes with minimal fever. The clinical presentation may be dominated by the associated croup or bronchiolitis, which are frequently present.

A number of underlying conditions may increase the risk or severity of viral pneumonia. These features have been identified most clearly for influenza but probably impact the severity of other forms of viral pneumonia. Underlying cardiopulmonary diseases, such as valvular heart disease or chronic obstructive pulmonary disease, are well-recognized risk factors for viral pneumonia in adults and children. Neuromuscular conditions that impair clearance of respiratory secretions are also risk factors for influenza (120) and presumably other viral lower respiratory disease. Obesity has also been recognized as an important risk factor (121, 122). Individuals with compromised immune systems are susceptible to a range of pathogens that would not cause significant disease in immunologically intact individuals.

Pregnancy has long been recognized as a major risk for more severe influenza. The risks associated with pregnancy were dramatically demonstrated during the recent A(H1N1) pdm09 pandemic, where pregnant women were substantially over-represented among patients requiring hospitalization, ICU admission, and ventilatory support (123, 124). The increased risk of severe influenza extends throughout pregnancy and the immediate postpartum period. While the effects of pregnancy are most pronounced during pandemics, pregnancy has also been recognized as a risk factor for cardiopulmonary hospitalizations in the interpandemic period (125).

Bacterial superinfection is a common complication of viral lower respiratory tract infection, particularly in adults. The classic presentation is that of a typical episode of viral illness with more or less complete recovery, followed 2 to 14 days later by a recurrence of fever and development of cough and dyspnea (126). Chest X ray reveals lobar infiltrates, and the clinical course is typical of bacterial pneumonia. In addition, combined bacterial and viral pneumonia, with clinical features of each, are common. Bacterial superinfection of viral pneumonia can occur with many bacteria, but the most common bacterium responsible for bacterial pneumonia complicating influenza is *Streptococcus pneumoniae*. There are also increases in the relative frequency of *Staphylococcus aureus*, including methicillin-resistant *S. aureus* (MRSA) and *Hemophilus influenzae* (127).

The impact of viral pneumonia and the spectrum of associated viral agents are highly dependent on the age group and immune status of the host. Further details are provided in the pathogen-specific chapters. While viruses are clearly important and frequent causes of pneumonia in young children, their role is less apparent in older children. In

healthy adults, pure viral pneumonia is less common but may be associated with a variety of viruses. Elderly adults may experience more significant lower respiratory tract signs and symptoms following infection with agents that normally cause upper respiratory tract illness in younger adults. Finally, viral pneumonia is an important cause of morbidity and mortality in individuals with compromised immune systems, with a broader spectrum of viral agents than seen in immunologically intact individuals. The manifestations of viral lower respiratory tract disease in different populations are described below.

Immunocompetent Adults

Viruses are relatively less common causes of acute pneumonia in adults, but sensitive nucleic acid detection tests suggest that viruses can be detected in as many as one-third of adults with acute pneumonia (128). Influenza has been well recognized as a cause of pneumonia in adults, primarily during seasonal epidemics. In case series of community acquired pneumonia (CAP), viruses are detected in 20% to 30% of cases, frequently in combination with bacterial pathogens (129–134). RSV is generally the most commonly detected viral agent, but essentially all of the respiratory viruses have been associated with CAP (Table 2). Clinically, cases caused by RSV are not distinguishable from those associated with other viral pathogens.

Adenoviruses have been described as causes of significant outbreaks of atypical pneumonia in military recruits and less often in civilians. Illness is typically mild and clinically resembles that due to M. *pneumoniae*, but more severe disseminated infections and deaths have been reported (135). Multiple X-ray patterns are noted; there may be large pleural effusions. Prodromal symptoms of upper respiratory infection are reported by most patients, and pharyngitis is often found on presentation. Bacterial superinfection, particularly with *N. meningitidis*, may occur. Adenovirus serotypes 4 and 7 are most often implicated, but recent reports have emphasized the emergence of a relatively rare adenovirus serotype 14 responsible for severe community acquired pneumonia in adults and children (136).

Varicella is generally more severe in adults than in children, especially among smokers. Chest radiographs taken in adults with varicella will reveal infiltrates in 10% to 20%, most frequently with a nodular infiltrate in a peribronchial distribution involving both lungs; however, the majority of these individuals are asymptomatic. More severe illness is seen occasionally, and fatal varicella pneumonia has been reported in pregnancy. The severity of the pulmonary lesions in varicella generally correlates better with the diffuseness of the rash than with findings on pulmonary exam. Following recovery from varicella, the development of diffuse pulmonary calcifications has been documented.

TABLE 2 Recovery of respiratory viruses from adults and children with community acquired pneumonia

Study	Karhu 2014 (131)	Gadsby 2016 (128)	Sangil 2012 (132)	Jain 2015 (130)	Garbino 2009 (134)	Garcia-Garcia 2012 (151)	Jain 2015 (150)
Time period	3/2008–5/2012	9/2012–2/2014	11/2009–10/2010	1/2010–6/2012	NR	9/2004–7/2010	1/2010–6/2012
Location	Finland	UK	Spain	US	SWZ	Spain	US
Population	Adults, intubated	Adults, 12% in ICU	Adults	Adults, 21% ICU	Adults, mostly transplant pts	Children <14 yo	Children (70% <4 y.o.)
Number tested	49	323	131	2259	522	884	2222
Sampling	BAL, swabs, bronchial aspirate	Sputum, tracheal aspirates	Sputum, NP swabs	Swabs, urine Ag, serology	BAL specimens	Nasal aspirates	Swabs, urine Ag, serology
Results (% positive)							
Pathogenic bacteria only	43	41	34	11	24	NT	8
Mixed bacterial/viral	39	35	19	3	2	NT	7
Viruses only	10	6	17	24	15	73	66
Percent positive for:							
Influenza A/B	2	7	5	6	2	5	7
RSV	2	1	5	3	1	31	28
PIV 1-4	2	3	2	3	3	5	7
hMPV	0	1	3	4	1	5	13
Entero/Rhino	35	13	4	9	4	19	27*
Coronavirus	4	3	2	2	5	1	5
Adenovirus	8	2	0	1	0	13	11
Bocavirus	0	0	0	NT	1	13	NT

*Also detected in 17% of healthy controls.
NR, not reported; NT, not tested.

RSV frequently causes detectably altered airway reactivity in adults (137), and on occasion, lower respiratory tract involvement becomes clinically manifest as pneumonia in otherwise healthy adults (138). RSV is being increasingly recognized as a cause of significant lower respiratory tract disease in the elderly (139). It has been estimated that 2% to 4% of pneumonia deaths among the elderly in the United States may be due to RSV (140). Parainfluenza viruses have also been reported as occasional causes of pneumonia in adults and in the elderly (141). Measles can be complicated by clinically severe pneumonitis in a small percentage of healthy adults, and bacterial superinfection is common. Diffuse pneumonitis and respiratory failure have been described in association with EBV acute mononucleosis in otherwise healthy adults.

Hantaviruses are associated with hantavirus cardiopulmonary syndrome (HCPS), characterized by the onset of severe pulmonary dysfunction after a 2- to 3-day prodrome of nonspecific influenza-like symptoms, fever, myalgias, cough, gastrointestinal symptoms, and headache (142). Coryza or upper respiratory tract symptoms suggest an alternative diagnosis. Laboratory abnormalities include leukocytosis, increased hematocrit due to hemoconcentration, and thrombocytopenia with coagulopathy. However, clinical bleeding is unusual, in contrast to other systemic hantavirus syndromes (142). Moderately elevated levels of serum lactate dehydrogenase and aspartate aminotransferase are typically seen. A variety of radiographic abnormalities have been described; those that may help to distinguish HPS from adult respiratory distress syndrome (ARDS) include early, prominent interstitial edema and nonperipheral distribution of initial airspace disease (143).

Novel human coronaviruses have been associated with severe lower respiratory tract disease and acute respiratory distress syndrome (ARDS) during outbreaks, including the severe acute respiratory syndrome (SARS) coronavirus or SARS CoV in 2003 (144), and more recently the Middle East respiratory syndrome (MERS) coronavirus, or MERS-CoV (145–147). Clinical characteristics of these illnesses are similar to those of progressive respiratory distress and hypoxia (147–149).

Children

Viruses are more commonly recognized causes of pneumonia in children than in adults (128) (Table 2). In one recent series, viruses were detected in 66% of children with radiographic pneumonia, with dual bacterial and viral pathogens detected in 7% of cases (150). The frequency of virus-associated CAP begins to decrease after age 5 years. RSV has been associated with the largest proportion of viral pneumonia in young children, particularly if accompanied by bronchiolitis (87, 150, 151) (Table 1). Bronchiolitis and pneumonia represent a spectrum of lower respiratory tract involvement with RSV virus, frequently coexist, and are not clearly distinguishable. The most typical radiographic finding is diffuse interstitial pneumonitis, although lobar or segmental consolidation are evident in about one-fourth of children with RSV lower respiratory tract disease, often involving the right upper or middle lobe.

The PIVs are second only to RSV as causes of pneumonia in this age group. As described earlier, lower respiratory tract involvement is integral to the pathophysiology of croup, but pneumonia with pulmonary infiltrates is most commonly associated with PIV-3 and 4 (152). Influenza A and B viruses are both significant causes of pneumonia in children, especially during periods of epidemic prevalence (153). In infants and children, the most frequent manifestation of influenza pneumonia is an interstitial pneumonitis similar in appearance and course to those of the other predominant viral agents of pneumonia in this age group, except that a secondary bacterial pneumonia may occur more frequently than with RSV or PIV.

Rhinoviruses have also been associated with a significant proportion of CAP in children, despite their apparent temperature sensitivity. Recent studies using sensitive PCR-based diagnostics have suggested that RV may be the second or third most common virus detected in acute pneumonia in children (150, 151, 154). However, RV is detected almost as frequently in age- and site-matched asymptomatic controls (150). Adenoviruses are also frequently isolated from children with respiratory disease and are implicated in about 10% of childhood pneumonias. However, the true impact of adenoviruses as causes of pneumonia in this age group is difficult to assess because of the long and intermittent asymptomatic respiratory shedding of these viruses in children. Hilar adenopathy on chest X ray is somewhat more common with this form of pneumonia than other types (155). Pneumonia is the most frequent serious complication of measles. Other viruses that may occasionally cause viral pneumonia in children include enteroviruses, rubella virus, and herpes simplex virus. Premature infants are at risk for pneumonia due to cytomegalovirus because of lack of maternal antibodies.

Pneumonia is the most frequent serious complication of measles. The prodrome of typical measles lasts 2 to 8 days and is characterized by fever, malaise, anorexia, cough, coryza, and conjunctivitis. Koplik's spots, which are erythematous macular lesions with central white-yellow or gray puncta, appear on the buccal or labial mucous membranes toward the end of the prodromal period. The maculopapular, erythematous eruption begins about the face and neck and progresses to involve the upper body, trunk, and extremities. The rash typically disappears after 5 to 6 days in the order in which it appeared. Defervescence and symptom improvement occur several days after the appearance of the rash, although persistent cough is common. Leukopenia is common during the prodromal and early exanthematous stages of measles. Pronounced leukopenia (less than 2,000 cells/mm^3) is associated with a poor prognosis. The development of neutrophilic leukocytosis suggests the possibility of bacterial superinfection or other complications.

Immunocompromised Individuals

Individuals with diminished host immunity may develop severe, life-threatening pulmonary infections with the entire spectrum of RNA and DNA viruses, including both viruses that are typical causes of lower respiratory tract disease in normal hosts and other more opportunistic viral pathogens (Table 1). DNA viruses have received the most recognition in this regard.

CMV is a frequent cause of severe pneumonitis in immunosuppressed individuals, particularly transplant recipients (156). The highest risk in the transplant population is 1 to 3 months post-transplantation, with the peak incidence at 8 weeks' post-transplantation. Diffuse interstitial pneumonitis is the most frequent manifestation, but multiple other radiographic presentations have been reported, including nodular infiltrates. Multiple associated findings are present in severe infection and reflect the disseminated nature of the infection; the presence of neutropenia, abnormalities of liver function tests, and mucosal ulcerations may be clinical clues to the diagnosis.

Herpes simplex virus pneumonia has been reported largely in immunocompromised or debilitated individuals. These cases are variably preceded by clinically evident mucocutaneous disease. The majority of cases present as a focal pneumonia as a result of contiguous spread from the upper respiratory tract; diffuse interstitial disease resulting from hematogenous spread occurs in up to 40% of cases (157). Risk groups include neonates, transplant recipients, burn patients particularly with inhalation injury, and those who have experienced prolonged mechanical ventilation, cardiothoracic surgery, or trauma.

Varicella-zoster virus is an important problem in individuals with hematological malignancies and others with iatrogenic immunosuppression, with the greatest risk seen in organ transplantation. Prolonged fever and recurrent crops of lesions are predictors of visceral dissemination, and pneumonia is generally seen in this setting. Pulmonary manifestations may include pleuritic chest pain due to vesicular lesions of the pleura, and, as also true in normal hosts, the chest radiographs may demonstrate diffuse nodular lesions.

Adenoviruses are significant causes of morbidity and mortality in immunocompromised patients, particularly after transplantation. In contrast to infection in normal hosts, infection in immunocompromised subjects tends to be disseminated, with isolation of virus from multiple body sites including lung, liver, gastrointestinal tract, and urine (158). In addition, the spectrum of serotypes includes both those found in immunocompetent individuals as well a markedly increased frequency of isolation of higher-numbered serotypes found rarely in immunologically normal subjects (159).

Common respiratory viruses have also received increasing recognition as potential causes of significant morbidity and mortality in this population (160). RSV has been well recognized as a cause of severe pneumonia in recipients of bone marrow (161) and solid organ transplantation (162). Nosocomial transmission of RSV in this setting has been well documented and may be the source of many infections in this susceptible population. The illness typically begins with nondescript upper respiratory symptoms that progress over several days to severe, life-threatening lower respiratory tract involvement. Mortality of 50% or higher is typical if pneumonia supervenes, particularly if disease occurs in the pre-engraftment period (163). Parainfluenza viruses have also been reported as an infrequent lower respiratory tract pathogen in both solid-organ and bone marrow transplantation. PIV-3 has been most common serotype isolated, but all four serotypes have been implicated (160). Influenza virus may also cause severe disease in transplant recipients (164) and patients with leukemia. Rhinoviruses and coronavirus infections in this population are also common but tend to be associated less frequently with lower respiratory tract disease (165). In transplant recipients, infections with community respiratory viruses may result in long-term impairment of respiratory function (166).

Measles giant cell pneumonia is a severe, usually fatal form of pneumonia in immunosuppressed individuals, including those who are severely malnourished. Most cases have occurred in those with hematological or other malignancies or in individuals with AIDS (167). Such hosts do not mount the cellular immune responses involved in the pathogenesis of measles rash or other typical manifestations of measles, and a high index of suspicion must be maintained (167). Giant cell pneumonia also occurs in significantly malnourished individuals. Multinuclear giant cells with intranuclear inclusions are seen and may be demonstrable in fluid obtained by bronchoalveolar lavage.

Diagnosis

Evaluation of the specific cause of acute pneumonia, and in particular, attribution of pneumonia to a particular viral etiology, is complicated by difficulty in obtaining appropriate samples of lower respiratory tract secretions, and the frequent asymptomatic shedding of some viruses, such as rhinovirus, herpes viruses, or adenoviruses in the upper respiratory tract.

The clinical presentation, epidemiology, and presence of associated features such as rash, may provide strong clues regarding the specific viral etiology of pneumonia, especially in children. However, distinguishing purely viral from bacterial or combined viral and bacterial lower respiratory tract disease remains an extremely difficulty challenge. This is a particularly important goal in reducing the unnecessary use of antibacterial therapy, and reducing rates of antibiotic resistance and complications such as *Clostridium difficile*.

Highly sensitive multiplex nucleic acid detection tests are now widely available in well-resourced settings and increasingly used to detect respiratory viruses in both upper and lower respiratory tract samples (see Chapter 15). Interpreting the results of such tests is complicated by the reality that detection of a virus does not rule out the presence of a coexisting bacterial infection nor represent compelling evidence that antibacterial therapy is not needed.

Radiologic findings also do not reliably distinguish viral from bacterial, or between viral causes of pneumonia (168). Recently, a number of biomarkers have been proposed for this purpose. The most widely used is probably the serum procalcitonin test, with the presence of a high pro-calcitonin associated with a higher likelihood of bacterial infection (169). The C reactive protein (CRP) is also sometimes used in the same way (170). However, there is debate whether the sensitivity and specificity of these tests is in the range to be able to guide decision-making for antimicrobial use (171). Recently, the use of a combination of markers, essentially developing a transcriptional profile of responding cells, has been demonstrated to have better sensitivity and specificity in this regard (172), and may pave the way for more accurate determination of the cause of pneumonia.

Pathogenesis

The pathogenesis of viral infections of the lower respiratory tract can be conveniently considered in terms of infections initiated in and primarily confined to the respiratory tract, such as with influenza or RSV; processes in which infection is initiated in the respiratory tract with subsequent systemic manifestations, such as in measles or varicella; and processes where respiratory tract involvement is secondary to a systemic infection, such as with cytomegalovirus. Each of these situations may lead to what is recognized clinically as a viral pneumonia. The general features of primary viral pneumonia are discussed below using influenza as a model, and pathogenesis of other forms of viral pneumonia is discussed briefly in comparison.

In primary viral pneumonia, virus infection reaches the lung either by contiguous spread from the upper respiratory tract or by inhalation of small particle aerosols. Infection initially occurs in ciliated respiratory mucosal epithelial cells of the trachea, bronchi, and lower respiratory tract and leads to widespread destruction of these cells. The mucosa is

hyperemic, and the trachea and bronchi contain bloody fluid. Tracheitis, bronchitis, and bronchiolitis are seen, with loss of normal ciliated epithelial cells. Submucosal hyperemia, focal hemorrhage, edema, and cellular infiltrate are present. The alveolar spaces contain varying numbers of neutrophils and mononuclear cells admixed with fibrin and edema fluid. The alveolar capillaries may be markedly hyperemic with intra-alveolar hemorrhage. Acellular, hyaline membranes line many of the alveolar ducts and alveoli (see Figure 10 in Chapter 43). Pathologic findings seen by lung biopsy in nonfatal cases during non-pandemic situations are similar to those described in fatal cases (173).

The pathologic changes in the lower respiratory tract in children with viral pneumonia due to RSV and PIV are nonspecific and include epithelial necrosis with bronchiolar mucus plugging and widespread inflammation and necrosis of lung parenchyma, and severe lesions of the bronchial and bronchiolar mucosa as well (99) (see Figures 4 and 5 in Chapter 37). In fatal cases of RSV pneumonia in children, hemorrhagic pneumonia with peribronchial mononuclear infiltration and cytoplasmic inclusion bodies in epithelial cells are seen. Giant cell pneumonia with virally induced multi-nucleated syncytial cells may be seen in RSV, PIV, or measles infections in immunocompromised hosts.

Bacterial superinfection is a well-recognized complication of viral pneumonia and accounts for a large proportion of the morbidity and mortality of viral lower respiratory tract disease, especially in adults. Consequently, the spectrum of disease and pathophysiology of bacterial superinfection has been studied intensively, and a number of factors in viral respiratory disease have been identified which could play a role in increasing the risk of bacterial infection. The disruption of the normal epithelial cell barrier to infection and loss of mucociliary clearance undoubtedly contribute the enhancement of bacterial pathogenesis (174). In addition, increased adherence of bacteria to virus-infected epithelial cells has been demonstrated. Polymorphonuclear leukocytes and mononuclear cells are susceptible to abortive infection by some respiratory viruses with resulting decreased function which may also contribute to enhanced bacterial infection (175). Virus-induced impairment of repair functions has also been proposed (176).

Infection with influenza, RSV, PIV, and adenoviruses is usually limited to the respiratory tract by mechanisms which are not completely clear. In contrast, respiratory tract infection with measles or varicella virus leads to dissemination and systemic manifestations. In more severe cases of varicella, vesicles may be found within the tracheobronchial tree and on pleural surfaces. Microscopic examination demonstrates interstitial pneumonitis with edema, and intranuclear inclusion bodies within septal cells, and peribronchiolar inflammation.

The Hantavirus pulmonary syndrome represents an additional example of a viral infection which involves the lung as part of a systemic infection. The pathogenesis of HPS involves extensive infection of endothelial cells throughout the body, which is particularly intensive within the vascular endothelial cells of the lung (177). Abundant viral antigen and nucleic acid can be detected within these cells. Microscopic examination of the lung reveals mild to moderate interstitial pneumonitis with variable degrees of congestion, edema, and mononuclear cell infiltration (see Figure 4 in Chapter 44). The cellular infiltrate is composed of a mixture of small and large mononuclear cells, which consist predominantly of T-lymphocytes, and macrophage/monocytes. The picture is one of immune mediated capillary leak and not of cell necrosis or inflammatory pneumonitis. High levels of cytokines have been detected in the blood and likely mediate the endothelial damage.

There are several features of CMV pneumonitis in the transplant setting that suggest that both host and viral factors interact in pathogenesis (178). CMV pathogenicity is enhanced in transplant recipients and frequently occurs at the site of the transplanted organ. The risk of CMV pneumonitis is also highest in individuals at the highest risk for graft versus host disease (179).

Treatment and Prevention

Therapy of viral pneumonia is dependent on the severity of disease, the age and immune status of the host, and the specific causative viral agent. General supportive measures, particularly the management of hypoxia, are critically important, and some patients have required high frequency ventilation or extracorporeal membrane oxygenation. Although inflammatory responses contribute to the pathogenesis of viral pneumonia, early corticosteroid treatment is generally associated with worse outcomes (180–182) Since mixed viral-bacterial infections or bacterial superinfections are common, antibacterial agents may be required as indicated by appropriate microbiologic studies.

Antiviral therapy should be guided by the results of diagnostic tests (Table 3). The neuraminidase inhibitors zanamivir and oseltamivir are active against both influenza A and B viruses (183). It should be noted that these agents have mostly been studied in uncomplicated influenza in healthy adults, where the main effect is in reduction of the duration of illness. However, observational studies in hospitalized patients (184, 185) have shown the mortality benefit of early oseltamivir therapy, and surveillance data suggesting that therapy as late as 5 days improved survival of hospitalized patients (186). Inhaled zanamivir may be difficult to reliably and safely deliver in severe influenza, but an intravenous formulation has been used with apparent benefit, including in infections due to oseltamivir resistant A (H1N1) viruses. The neuraminidase inhibitor peramivir has also recently been approved for intravenous use in the United States, although a small study did not demonstrate benefit in hospitalized patients (187). Although the M2 inhibitors are highly effective drugs for the prophylaxis and therapy of influenza A virus, currently circulating seasonal influenza A viruses are uniformly resistant to these agents (188). However, there may be a role for these drugs in combination therapy of influenza (189), and studies to evaluate this in humans are in progress.

The only option currently available for the other RNA viruses is ribavirin, but there is little evidence of efficacy of this agent for treating established viral pneumonia (see bronchiolitis, above). In immunocompromised hosts, treatment of RSV pulmonary infection associated with respiratory failure has not been successful. One approach that appears promising is treatment with ribavirin, possibly in combination with immunoglobulin, early in the illness when URI symptoms predominate (160). Controlled trials in parainfluenza virus infection are not available, although anecdotal reports suggest potential efficacy (190). Limited controlled trials have suggested that aerosolized ribavirin may reduce the severity of symptoms in children with measles, and some immunocompromised patients with measles pneumonia have done well following treatment with aerosolized (167) or intravenous forms of the drug (191). Intravenous ribavirin is effective in the treatment of hemorrhagic

TABLE 3 Therapies of potential benefit in viral pneumonia

Viral Etiology	Potential Therapies	Comments
Respiratory syncytial virus	Ribavirin	May be considered for use in high-risk or severely ill children. Premptive use in transplant patients.
	Palivizumab (Synagis)	Effective prevention of RSV bronchiolitis/pneumonia in high-risk premature infants who lack maternal antibody.
Parainfluenza virus	DAS-181	Case reports of efficacy in hematologic transplant, investigational, may be available for compassionate use.
	Ribavirin	Case reports of efficacy of IV or oral ribavirin in parainfluenza virus infection, aerosolized ribavirin not recommended. Addition of IVIG may be helpful.
Influenza virus	Neuraminidase inhibitors Oseltamivir (oral) Zanamivir (intravenous) Peramivir (intravenous)	Timely oseltamivir therapy associated with reduced rates of pneumonia development and mortality in hospitalized patients. Indicated for severe or progressive disease and in high-risk patients. IV zanamivir is active against most oseltamivir-resistant variants. IV peramivir also available.
Measles virus	Ribavirin	Aerosolized or IV ribavirin may shorten the duration of illness in children with measles. Use in measles pneumonia is unproved.
	IVIG	IVIG may decrease risk of measles when administered to susceptible individuals, and may decrease symptoms in those infected.
Adenovirus	Cidofovir, brincidofovir	Cidofovir is active *in vitro* and multiple case reports suggest efficacy. Brincidofovir has less renal toxicity; recent clinical trial suggests efficacy against adenovirus pneumonia in transplant patients.
Herpes simplex virus	Acyclovir (Valacyclovir, Famciclovir)	Controlled trials have demonstrated efficacy of acyclovir in a variety of HSV diseases. Cross resistance between agents.
	Foscarnet, cidofovir	May be useful for treatment of herpes viruses resistant to acyclovir.
Varicella-zoster virus	Acyclovir (Valacyclovir, Famciclovir)	Demonstrated efficacy of IV acyclovir in varicella and in varicella pneumonia, must use relatively high doses.
	Foscarnet	May be useful for management of acyclovir-resistant cases.
Cytomegalovirus	Ganciclovir	Clinical efficacy in CMV pneumonitis in AIDS and solid-organ transplantation. In bone marrow transplant patients, efficacious when combined with IVIG.
	Foscarnet, cidofovir	Predominant use in gancyclovir-resistance or in individuals who cannot tolerate gancyclovir due to hematological toxicity.

Note: Listing of potential therapies only, not to be considered a recommendation for use. Please see pathogen-specific chapters and Chapter 14 on antivirals for respiratory viruses for more detailed treatment recommendations.

fever with renal syndrome, but does not appear to be useful for treatment of the hantavirus pulmonary syndrome (192).

An experimental agent that has shown some promise in treatment of severe parainfluenza virus infection in immunosuppressed hematopoietic stem cell transplant recipients is the sialidase construct DAS-181 (193). The drug is administered by inhalation, and mechanism of action is thought to be removal of sialic acid receptors from the host respiratory tract. Two investigational RSV antivirals, the fusion inhibitor presatovir (GS-5806) and the polymerase ALS-8176, have shown promising activity in experimentally induced RSV infections in adults (194, 195) and are undergoing clinical trials in serious RSV infections at present.

Acyclovir is active *in vitro* against herpes simplex virus types 1 and 2 and against varicella-zoster virus, but it does not have clinically useful activity for treatment of cytomegalovirus or Epstein-Barr virus disease. Although controlled clinical trials of this drug in herpes simplex pneumonia have not been conducted, the drug has proven clinical efficacy in other herpesvirus infections and would be indicated in any serious HSV lower respiratory tract infection. Acyclovir is also effective in the therapy of varicella, and intravenous acyclovir has been effective when initiated early in the course of varicella pneumonia (196). The related drugs valacyclovir, famciclovir, and penciclovir are similar to acyclovir in their spectrum of activity against herpes and varicella viruses. Viruses resistant to the activity of these drugs have been isolated from treated immunocompromised patients, and may be susceptible to the antiherpes drug phosphonoformic acid (foscarnet).

Guidelines for management of CMV disease in transplant patients have recently been published (197, 198). Transplant candidates should be screened for evidence of CMV immunity, and CMV-seronegative recipients of transplants from CMV-positive donors are at the highest risk of CMV disease. One strategy for prevention of CMV disease is to provide prophylaxis with ganciclovir or valgancyclovir during the period of highest risk, over the first 3 to 6 months after transplantation. Alternatively, some centers favor a preemptive therapy approach, where patients are monitored with serial PCR and antiviral therapy is initiated when CMV PCR becomes positive and reaches a predefined threshold.

Once CMV pneumonitis is established, particularly in allogeneic bone marrow transplant patients, it can be very difficult to treat. Ganciclovir is highly active against CMV *in vitro*, and intravenous ganciclovir therapy is generally recommended in cases of severe disease, although the orally available drug valgancyclovir can be used in less-severe cases. Cidofovir and foscarnet are considerations for CMV resistant to ganciclovir. The combination of ganciclovir therapy and intravenous CMV immune globulin or IVIG can reduce mortality in stem cell transplant recipients (199, 200) and is generally recommended in this situation.

Antiviral treatment of proven value for adenovirus infection is not available. Cidofovir is active against adenovirus *in vitro*, and there are several case reports or case series of successful therapy of adenovirus infection in immunocompromised patients with cidofovir (201, 202). However, cidofovir has substantial renal toxicity, which limits its utility in this application. A newly derived series of lipid ester derivatives of cidofovir are orally bioavailable and have less renal toxicity. One of these agents, brincidofovir, has shown preliminary evidence of efficacy against adenovirus infections in bone marrow transplant recipients (203–205).

Although recent years have witnessed a significant increase in the spectrum and potency of available antiviral agents, drug therapy of viral pneumonia remains burdened by the toxicity of drugs, the development of antiviral resistance, and the complex pathogenesis of many viral syndromes in which viral replication is only part of the disease process. Vaccines of variable effectiveness currently exist for influenza, measles, and varicella virus. Development of additional effective vaccines for the viral pathogens causing pneumonia will contribute to the control of this important problem.

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