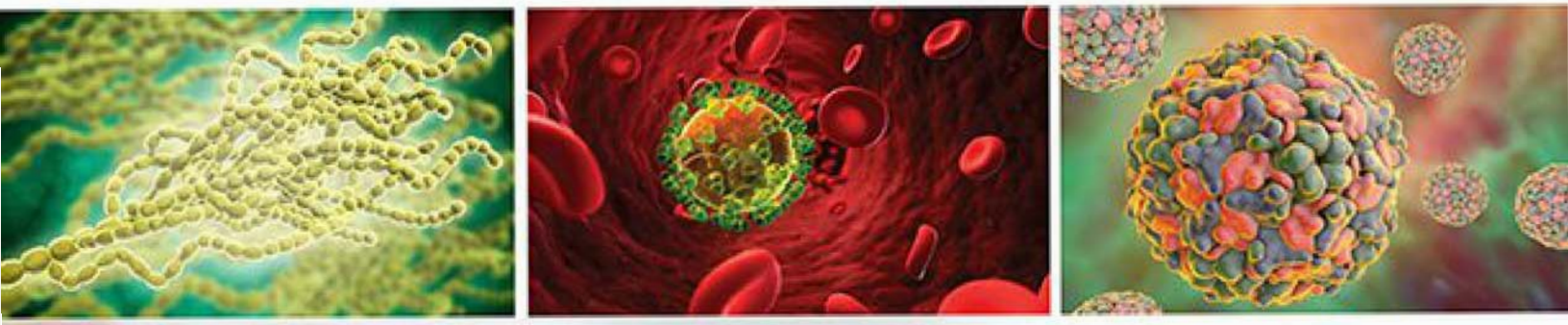
Second Edition

Pediatric INFECTIOUS DISEASES

ESSENTIALS FOR PRACTICE



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Pediatric Infectious Diseases: Essentials for Practice

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Pediatric Infectious Diseases: Essentials for Practice

Second Edition

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To our mentors for sharing their wisdom and knowledge
To our families for providing love and support for all of our endeavors
To our patients for teaching us and to their families for trusting us

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Preface

Our understanding of infectious diseases has increased exponentially over the past few decades with invention of new diagnostic tests and identification of new pathogens and diseases. We also have the recognition of new syndromes caused by well-known pathogens and the resurgence of "old" diseases, once thought conquered. The complexity of children receiving medical care in both the outpatient and inpatient settings has also increased substantially. Conditions that once required initial (e.g., pyelonephritis) or prolonged (e.g., osteomyelitis) hospitalization are now managed primarily in the outpatient setting. The survival of infants born prematurely and those with chronic illnesses has improved through advances in medical technology and systems of care. Healthcare delivery has also evolved with far greater emphasis on both achieving better outcomes at lower cost and improving the experiences of our patients and their families. Consequently, the amount of knowledge required to manage even common childhood infections can sometimes feel mind boggling. This book was written in order to provide general and specialty child-health clinicians—generalists and specialists—a practical, reliable, and evidence-based resource to diagnose and treat commonly encountered pediatric infections in the inpatient and outpatient settings.

The revised edition begins by addressing practical aspects such as basics of the practice of infectious diseases, including information about clinical microbiology and virology laboratory tests, infection control in office and hospital settings, and important concepts in infectious diseases epidemiology. This latter chapter we hope will provide the reader with insight into interpretation of contemporary clinical research. New to this edition are chapters on quality improvement and chapters on anti-infective agents, emphasizing the growing importance of rigorous assessment of our interventions and the need to maximize knowledge of the growing number of agents available for treatment of childhood infections. Additionally, as an increasingly vocal anti-vaccine movement threatens to undermine hard-won public health gains, the revised chapter on vaccines places greater emphasis on communication about vaccine safety and risk. The next section covers common signs and symptoms for which infections are often part of the differential diagnosis. Subsequent sections review infections by anatomic site with emphasis on providing practical guidance for diagnosis and management. The book addresses many special situations that fall outside the scope of organ systems such as perinatally acquired infections and care of children with human immunodeficiency virus infection. We also cover topics such as infections in children with atopic dermatitis or neurologic impairment and infections in internationally adopted children that often fall outside the scope of traditional textbooks.

In organizing this book, we strove to ensure that chapters were sufficiently detailed and thoroughly referenced while also adhering to our philosophy of providing practical management strategies. Our expert authors, to whom we are extremely grateful, succeeded in reaching this objective in a timely manner. We hope this book will serve as a daily infectious diseases consultant to the practicing pediatrician.

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Abbreviations

AACN	American Association of Critical Care Nurses
AAD	antibiotic-associated diarrhea
AAO	American Academy of Otolaryngology
AAP	American Academy of Pediatrics
AAPOS	American Association for Pediatric Ophthalmology and Strabismus
ABC	acute bacterial conjunctivitis
ACE	angiotensin-converting enzyme
ACIP	Advisory Committee on Immunization Practices
ACOG	American College of Obstetrics and Gynecology
ADEM	acute disseminated encephalomyelitis
AD-HIES	autosomal dominant hyper-IgE syndrome
ADP	adenosine diphosphate
AER	Adverse Event Reporting
AFB	acid-fast bacill(us)(i)
AFM	acute flaccid myelitis
Ag	antigen
AGT	antiglobulin test
AHA	American Heart Association
AHO	acute hematogenous osteomyelitis
AHRQ	Agency for Healthcare Research and Quality
AIDS	acquired immunodeficiency syndrome
AIIR	airborne infection isolation room
ALL	acute lymphocytic leukemia
ALN	acute lobar nephronia
ALPS	autoimmune lymphoproliferative syndrome
ALT	alanine aminotransferase
AMPA	α-amino-3-hydroxy-5-methyl-4-isoxazolapropiomic acid
ANA	antinuclear antibody
ANC	absolute neutrophil count
ANCA	antineutrophil cytoplasmic antibody
AOE	acute otitis externa
AOM	acute otitis media
APECED	autoimmune polyendocrinopathy candidiasis ectodermal dystrophy (dysplasia)
APIC	Association for Professionals in Infection Control
APSAC	American Professional Society of the Abuse of Children
ARF	acute rheumatic fever
ARR	absolute risk reduction
ART	antiretroviral therapy
ASM	American Society for Microbiology
ASO	antistreptolysin O
AST	aspartate aminotransferase
AT	ataxia telangiectasia
ATM	acute transverse myelitis
ATS	American Thoracic Society
ATV	atazanavir
AUC	area under the (time–concentration *t*/*C*) curve
AUC/MIC	area under the (*t*/*C*) curve over the minimum inhibitory concentration (Ch 8; ratio of total drug exposure over time, represented as an area under the *t*/*C* curve, over MIC)
AUROC	area under receiver–operator characteristic curve
AVM	malformation
AWARE	Assessing Worldwide Antimicrobial Resistance Evaluation
AZT	zidovudine
BAL	bronchoalveolar lavage
BBB	blood–brain barrier
BCG	bacille Calmette–Guérin
BCPPS	Board Certified Pediatric Pharmacy Specialist
BCSA	*Burkholderia cepacia*–selective agar
BCYE	buffered charcoal–yeast extract
BGMK	buffalo green monkey kidney
BJI	bone–joint infection
BMI	body mass index
BNP	B-type natriuretic peptide
BRAT	bananas, rice, applesauce, toast
BRUE	brief, resolved, unexplained event
BSA	body surface area
BSEP	bile salt export pump
BSI	bloodstream infection
BSL	biosafety level
BTX	botulinum toxin
BUN	blood urea nitrogen
CA	community-acquired
CAA	coronary artery aneurysm
CAP	community-acquired pneumonia
CAPS	cryopyrin-associated periodic syndrome
CART	combination antiretroviral therapy
CBC	complete blood count
CBDI	Cancer and Blood Disease Institute
CDC	Centers for Disease Control and Prevention
CD4	cluster of differentiation 4
CDI	*Clostridium difficile* infection
CDR	*Candida* drug resistance
CE	Conformité Européenne
CERN	Chicago Ebola Response Network
CF	cystic fibrosis

CFU	colony-forming unit
CGD	chronic granulomatous disease
CHD	congenital heart disease
CHG	chlorhexidine gluconate
CHIME	Collaborative Home Infant Monitoring Evaluation
CI	confidence interval
CIA	chemiluminescence immunoassay
CIAIS	cold-induced autoinflammatory syndrome
CIC	Certified Inpatient Coder
CINCA	chronic infantile neurologic cutaneous–articular (syndrome)
CLABSI	central line–associated bloodstream infection
CLIA	Clinical Laboratory Improvement Amendments
CLSI	Clinical and Laboratory Standards Institute
CMP	chemistry panel
CMR	cardiovascular magnetic resonance
CMV	cytomegalovirus
CNS	central nervous system
CoNS	coagulase-negative *Staphylococcus*
CoV	coronavirus
CPAM	congenital pulmonary airway malformation
CPE	cytopathic effect
CPIC	Clinical Pharmacogenetics Implementation Consortium
CPK	creatine phosphokinase
CPS	Canadian Paediatric Society
CRBSI	catheter-related bloodstream infection
CRE	carbapenem-resistant enterobacteriaceae
CRF	circulating recombinant form
CRMO	chronic recurrent multifocal osteomyelitis
CRMP	collapsing-responsive mediator protein
CRP	C-reactive protein
CRS	congenital rubella syndrome
CSF	cerebrospinal fluid
CST	cavernous sinus thrombosis
CT	computed tomography
CTBA	cystine tellurite blood agar
CVC	central venous catheter
CVID	common variable immunodeficiency
CXR	chest X-ray
CZS	congenital Zika syndrome
DAMP	damage-associated molecular pattern
DAT	direct antiglobulin test
DBS	deep-brain stimulation
DCI	data collection instrument
DCM	dilated cardiomyopathy
DCT	direct Coombs test
DEET	*N*,*N*-diethyl-*meta*-toluamide (also known as *diethyltoluamide*)
DES	dysfunctional elimination syndrome
DEXA	dual-energy X-ray absorptiometry
DFA	direct fluorescent antibody
DGI	disseminated gonococcal infection
DHHS	Department of Health and Human Services
DIC	disseminated intravascular coagulation
DIH	drug-induced hypersensitivity
DIRA	deficiency of IL (interleukin)-1 receptor agonist
DNA	deoxyribonucleic acid
DOCK8	dedicator of cytokinesis 8 gene
DOT	directly observed therapy
DRESS	drug reaction with eosinophilia and systemic symptoms
DRV	darunavir
ds	double strength (in prescriptions)
DSM	*Diagnostic and Statistical Manual*
DTaP	diphtheria–tetanus–acellular pertussis (vaccine)
DTG	dolutegravir
d-TGA	*dextro*-transposition of the great arteries
DWI	diffusion-weighted imaging
EAC	external auditory canal
EACTS	European Association of Cardio-Thoracic Surgery
EANM	European Association of Nuclear Medicine
EBNA	Epstein–Barr nuclear antigen
EBUS-NA	endobronchial ultrasound-guided needle aspiration
EBV	Epstein–Barr virus
ED	emergency department
EDTA	ethylenediamine tetra (acetic acid)
EEE	eastern equine encephalitis
EES	erythromycin ethylsuccinate
EFV	efavirenz
EGA	estimated gestational age
EHEC	enterohemorrhagic *Escherichia coli*
EIA	enzyme immunoassay
ELF	epithelial lung fluid
ELISA	enzyme-linked immunosorbent assay
EKG	electrocardiogram
EMLA	eutectic mixture of local anesthetics
EMR	electronic medical record
EMTCT	elimination of mother-to-child transmission (of HIV)
EPA	Environmental Protection Agency (US)
ERCP	endoscopic retrograde cholangiopancreatography
ESBL	extended-spectrum β-lactamase
ESC	European Society of Cardiology
ESCMID	European Society of Clinical Microbiology and Infectious Diseases
ESPGHAN	European Society of Pediatric Gastroenterology, Hepatology, and Nutrition
ESR	erythrocyte sedimentation rate
ESRD	end-stage renal disease
ETEC	enterotoxigenic *Escherichia coli*
ETV	etravirine

EUCAST	European Committee on Antimicrobial Susceptibility Testing
EV	enterovirus
EVD	external ventricular drain
FAUC/MIC	ratio of free (non-protein-bound) drug exposure over time, represented as area under the time–concentration (*t*/*C*) curve, over the minimum inhibitory concentration
FCAS	familial cold autoinflammatory syndrome
FCU	familial cold urticaria
FDA	Food and Drug Administration (US)
FESS	functional endoscopic sinus surgery
FI	fusion inhibitor
F&I	febrile and immunocompromised
FIRS	fetal inflammatory response syndrome
5-FC	5-fluorocytosine
5-FU	5-fluorouracil
FLAIR	fluid-attenuated inversion recovery
FMEA	failure modes and effects analysis
FMF	familial Mediterranean fever
FMT	fecal microbiota transplantation
FNA	fine-needle aspiration
FNAB	fine-needle aspiration biopsy
FP, FN	false positive, false negative
FTA-abs	fluorescent treponemal antibody absorption
FTC	emtricitabine
FTT	failure to thrive
FUO	fever of unknown origin
FWS	fever without a source
GABA	γ-aminobutyric acid
GABHS	group A β-hemolytic *Streptococcus*
GAS	group A *Streptococcus*
GBS	group B *Streptococcus*
GCSF	granulocyte colony-stimulating factor
GCV	ganciclovir
GDH	glutamate dehydrogenase
GEE	generalized estimating equation
GERD	gastroesophageal reflux disease
GFR	glomerular filtration rate
GGT	γ-glutamyltransferase
GHD	graft-versus-host disease
GI	gastrointestinal
Glut1	glucose transporter type 1
G6PD	glucose-6-phosphate dehydrogenase
GU	genitourinary
GWAS	genome-wide association study
HAART	highly active antiretroviral therapy
HACEK	*Haemophilus*, *Actinobacillus* (now *Aggregatibacter*), *Cardiobacterium*, *Eikenella*, *Kingella* (genera)
HAI	healthcare-associated infection
HAV	hepatitis A virus
HBcAg	hepatitis B core antigen
HBeAg	hepatitis B e-antigen
HBIG	hepatitis B immunoglobulin
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HCW	healthcare worker
HDAF	human decay–accelerating factor
HDV	hepatitis D virus
HEPA	high-efficiency particulate air
HEV	hepatitis E virus
HIDS	hyper-IgD (with periodic fever) syndrome
HFNC	high-flow nasal cannula
HHV	human herpesvirus
Hib	*Haemophilus influenzae* type b
HICPAC	Healthcare Infection Control Practices Advisory Committee
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
HLH	hemophagocytic lymphohistiocytosis
hMPV	human metapneumovirus
HNS	head and neck surgery
HPF	high-power field
HPLC	high-performance liquid chromatography
HPV	human papillomavirus
HRV	human rhinovirus
HSCT	hematopoietic stem cell transplant
HSP	Henoch–Schönlein purpura
HSV	herpes simplex virus
HTLV	human T-cell lymphotropic virus
HUS	hemolytic–uremic syndrome
hVISA	heterogeneous vancomycin intermediate *Staphylococcus aureus*
IAP	intrapartum antibiotic prophylaxis
IAT	indirect antiglobulin test
IBD	inflammatory bowel disease
IBI	invasive bacterial infection
ICP	intracranial pressure
ICU	intensive care unit
IDSA	Infectious Diseases Society of America
IDU	injection drug use(r)
IE	infective endocarditis
IFI	invasive fungal infection
Ig	immunoglobulin (IgA, IgG, IgM, etc)
IGRA	interferon-γ release assay
IHI	Institute for Healthcare Improvement
IM	intramuscular(ly)
INR	International Normalized Ratio
IPC	infection prevention and control
IPD	invasive pneumococcal disease
IPEX	immune dysregulation, polyendocrinopathy, enteropathy, X-linked
iPrEx	preexposure prophylaxis initiative (trial; initiativa profilaxis pre-exposicion)
IPV	inactivated polio vaccine

IQ	intelligence quotient
IQR	interquartile range
IRF	interferon regulatory factor
IRIS	immune reconstitution inflammatory syndrome
ISC	International Society of Chemotherapy
I/T	immature-to-total ratio (sepsis ratio)
ITB	intrathecal baclofen
IU	international unit
IUD	intrauterine device
IV	intravenous
IVIG	intravenous immunoglobulin
JCV	John Cunningham virus
JDMS	juvenile dermatomyositis
JEV	Japanese encephalitis virus
JIA	juvenile idiopathic arthritis
KD	Kawasaki disease
KID	Kids' Inpatient Database
KOH	potassium hydroxide
LAD	leukocyte adhesion deficiency
LAIV	live-attenuated intranasal influenza vaccine
LAM	lipoarabinomannan
LCA	left coronary artery
LCH	Langerhans cell histiocytosis
LCMV	lymphocytic choriomeningitis virus
LCV	LaCrosse virus
LDH	lactate dehydrogenase
LF	lateral flow
LFT	liver function test
LGBT	lesbian, gay, bisexual, transgender
LGl	leucine-rich glioma
LGli1	leucine-rich glioma inactivated 1
LIP	lymphoid interstitial pneumonia
LLQ	left lower quadrant
LN	lymph node
LoR	level of reliability
LOS	length of stay (in hospital)
LP	lumbar puncture
LPS	lipopolysaccharide
LPV/r	lopinavir/ritonavir
LR	likelihood ratio
LTBI	latent tuberculosis infection
LUQ	left upper quadrant
LV	left ventricular
MA	mevalonic aciduria
MAC	*Mycobacterium avium* complex
MAI	*Mycobacterium avium intracellulare*
MALDI-TOF	matrix-assisted laser desorption and ionization time-of-flight (mass spectrometry)
MAT	microscopic agglutination test
MBC	minimum bactericidal concentration
MDR	multidrug resistance
MDRO	multidrug-resistant organism
MEE	middle-ear effusion
MERS	Middle East respiratory syndrome
MFI	multiflex flow immunoassay
MGIT	mycobacteria growth indicator tube
MIBG	metaiodobenzylguanidine
MIC	minimum inhibitory concentration
MLM	multilevel model
MLS	macrolide–lincosamide–streptogramin
MMR	measles–mumps–rubella
MRI	magnetic resonance imaging
MRSA	methicillin-resistant *Staphylococcus aureus*
MSBP	Munchausen syndrome by proxy
MSG	Mycosis Study Group
MSM	men who have sex with men
MSSA	methicillin-susceptible *Staphylococcus aureus*
Mtb	*Mycobacterium tuberculosis*
N/A	not applicable or (data) not available (used in tables only)
NAAT	nucleic acid amplification test
NADPH	nicotinamide adenine dinucleotide phosphate
NASPGHAN	North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition
NBTE	nonbacterial thrombotic endocarditis
NCNGU	nonchlamydia, nongonococcal urethritis
NEMO	NF-κB-essential modulator
NF	nuclear factor
NFAT	nuclear factor of activated T cells
NHANES	National Health and Examination Survey
NHSN	National Healthcare Safety Network
NI	neurologic impairment
NICE	National Institute (for Health and) Clinical Excellence (UK)
NICU	neonatal (*or* newborn) intensive care unit
NMDA-R	*N*-methyl-D-aspartate receptor
NMO	neuromyelitis optica
NNRTI	nonnucleoside reverse transcriptase inhibitor
NNT	number needed to treat
NOMID	neonatal-onset multisystem inflammatory disease
NP	nasopharyngeal
NPA	nasopharyngeal aspirate
nPEP	nonoccupational postexposure prophylaxis
NPS	nasopharyngeal swab
NPUAP	National Pressure Ulcer Advisory Panel
NPV	negative predictive value
NPW	nasopharyngeal wash
NRTI	nucleoside reverse transcriptase inhibitor
NSAID	nonsteroidal anti-inflammatory drug
NTM	nontuberculous mycobacteria
NT-proBNP	*N*-terminal pro-B-type natriuretic peptide
NVP	nevirapine
ODT	orally disintegrating tablet
OE	otitis externa
OFPBL	oxidation–fermentation with polymyxin B, bacitracin, and lactose

OI	opportunistic infection
OM	otitis media
OMAS	opsoclonus–myoclonus–ataxia syndrome
O&P	ova and parasite
oPEP	occupational postexposure prophylaxis
OR	odds ratio
ORS	oral rehydration solution
ORT	oral radiation therapy
OSHA	Occupational Safety and Health Administration
OTC	over the counter
PA	posterior–anterior (*also* posteroanterior)
PAE	postantibiotic effect (amount of time that bacterial regrowth is suppressed following removal of an antibiotic)
PaLoc	pathogenicity locus in *Clostridium difficile*
PAMP	pathogen-associated molecular pattern
PAN	polyarteritis nodosa
PANDAS	pediatric autoimmune neuropsychiatric disorder(s) associated with streptococcal infection
PANS	pediatric acute-onset neuropsychiatric syndrome
PaO_2	partial pressure of arterial oxygen
PAPA	pyogenic sterile arthritis; pyoderma gangrenosum and acne
PAPR	powered air-purified respirator
PAS	periodic acid–Schiff (stain)
PASOJAR	Pennsylvania Systemic Onset Juvenile Arthritis Registry
PBP	penicillin-binding protein
PCD	primary ciliary dyskinesia
PCF	pediatric condition falsification
PCN	penicillin
PCO_2	partial pressure of carbon dioxide
PCP	*Pneumocystis jiroveci* pneumonia
PCR	polymerase chain reaction
PCT	procalcitonin
PCV	pneumococcal (protein–polysaccharide) conjugate vaccine
PCV13	13-valent pneumococcal conjugate vaccine
PD	pharmacodynamic
PDC	potential diagnostic clue
PDSA	plan–do–study–act
PEACH	pelvic inflammatory disease (PID) Evaluation and Clinical Health Study
PedsQL	Pediatric Quality of Life
PEMCRC	Pediatric Emergency Medicine Collaborative Research Committee
PFAPA	periodic fever–adenitis–pharyngitis–aphthous ulcer
PfEMP1	*Plasmodium falciparum* erythrocyte membrane protein 1
PGM3	phosphoglucomutase 3 gene
PHIL	Public Health Image Library
PHMB	poly(hexamethyl biguanide)
PI	protease inhibitor
PICC	peripherally inserted central venous catheter
PICNIC	Pediatric Investigators Collaborative Network on Infections in Canada
PICU	pediatric intensive care unit
PID	pelvic inflammatory disease
PIDS	Pediatric Infectious Diseases Society
PK	pharmacokinetic
PLEX	plasma exchange
PLoS	Public Library of Science
PML	progressive multifocal leukoencephalopathy
PMN	polymorphonuclear neutrophil
PO	per os (orally; by mouth)
PPD	purified protein derivative
PPE	personal protective equipment
PPSV23	23-valent pneumococcal polysaccharide vaccine
PPV	positive predictive value
PrEP	preexposure prophylaxis
PRES	posterior reversible encephalopathy syndrome
PRIVENT	Prevention of Recurrent (urinary tract) Infection (in children with) Vesicoureteric (reflux) Normal (renal) Tract (mnemonic)
PROS	Pediatric Research Office Settings
PRP	poly(ribosylribitol phosphate)
PSRA	poststreptococcal reactive arthritis
PT	physical therapy
PTA	peritonsillar abscess
PVA	polyvinyl alcohol
PVL	periventricular leukomalacia
PZA	pyrazinamide
Q/D	quinupristin/dalfopristin
QI	quality improvement
RAD	reactive-airway disease
RADT	rapid antigen detection test
RAISE	Randomized controlled trial to Assess Immunoglobulin plus Steroid Efficiency
RAL	raltegravir
RBC	red blood cell
RBUS	renal bladder ultrasound
rCDI	recurrent *Clostridium difficile* infection
RCT	randomized controlled trial
REM	rapid eye movement
RIA	radioimmunoassay
RIG	rabies immunoglobulin
RIVUR	Randomized Intervention (for children with) Vesicourethral Reflux
RLQ	right lower quadrant
RMSF	Rocky Mountain spotted fever
RN	registered nurse
RNA	ribonucleic acid
RODEO	ROutine versus on DEmand removal Of the syndesmotic stabilization screw (trial)
RPA	retropharyngeal abscess
RPR	rapid plasma regain
RR	relative risk
RRR	relative risk reduction

RSV	respiratory syncytial virus
RT	real time
RUQ	right upper quadrant
RV	right ventricle
SARS	severe acute respiratory syndrome
SBECD	sulfobutylether-β-cydodextrin
SBI	serious bacterial infection
SCC	staphylococcal chromosome cassette
SCID	severe combined immunodeficiency
SCIWORA	spinal cord injury without radiographic abnormality
Scr	serum creatinine
SD	standard deviation
SDD	susceptible-dose-dependent
SDF	silver diamine fluoride
SEM	skin, eye, and mucous (*also* mouth) membranes
SES	socioeconomic status
SHEA	Society for Healthcare Epidemiology of America
SIADH	syndrome of inappropriate antidiuretic hormone (secretion)
SIDS	sudden infant death syndrome
SIM	simian immunodeficiency virus
SJIA	systemic juvenile idiopathic arthritis
SJS	Stevens–Johnson syndrome
SMART	specific, measurable, achievable, relevant, time-bound (mnemonic)
SNHL	sensorineural hearing loss
SPAG	small-particle aerosol generator
SPECT	single-photon emission computed tomography
SPG	sphenopalatine ganglion
SPIDS	Saudi Pediatric Infectious Diseases Society
SPS	sodium polyanetholsulfonate
SSI	surgical site infection
SSPE	subacute sclerosing panencephalitis
SSSS	staphylococcal scalded-skin syndrome
SSTI	skin and soft tissue infection
STAT3	signal transducer and activator of transcription 3 gene
STD	sexually transmitted disease
STEC	Shiga toxin–producing *Escherichia coli*
TB	tuberculosis
TBE	tickborne encephalitis
TCBS	thiosulfate citrate bile sucrose
Tdap	tetanus–diphtheria–acellular pertussis
TDF-FTC	tenofovir–emtricitabine
TDSA	thymidine-dependent *Staphylococcus aureus*
TEE	transesophageal echocardiography
TIG	tetanus immunoglobulin
TIV	trivalent inactivated influenza vaccine
TM	tympanic membrane
TMP-SMX	trimethoprim–sulfamethoxazole
TNFα	tumor necrosis factor alpha
TOA	tubo-ovarian abscess
TORCH	*Toxoplasma gondii*, Other microorganisms, Rubella, Cytomegalovirus, Herpes simplex virus (mnemonic)
TP, TN	true positive, true negative
TPPA	*Treponema pallidum* particle agglutination
TRAPS	tumor necrosis factor (TNF)–receptor–associated periodic syndrome
TRUST	Tracking Resistance in US Today (mnemonic)
TSS	toxic shock syndrome
TST	tuberculin skin test
TTE	transthoracic echocardiography
TUBC	transurethral bladder catheterization
UA	urinalysis
UGI	upper gastrointestinal (barium series)
URI	upper respiratory infection
USPHSTF	US Public Health Service Task Force
UV	ultraviolet
VAC	ventilator-associated condition
VAERS	Vaccine Adverse Event Reporting System
VATS	video-assisted therascopic surgery
VCA	viral capsid antigen
VCUG	voiding cystourethrogram
V_d	volume of distribution
VDRL	venereal disease research laboratory
VFR	visiting friends and relatives
VP	ventriculoperitoneal
V/Q	ventilation/perfusion
VRE	vancomycin-resistant enterococcus
VSD	Vaccine Safety Datalink
VUR	vesicourethral reflux
VZV	varicella zoster virus
WASP	wait-and-see prescription
WBC	white blood cell
WHIM	warts, hypogammaglobulinemia, infections, and myelokathexis
WHO	World Health Organization
WNV	West Nile virus
XLA	X-linked agammaglovulinemia
XLP	X-linked lymphoproliferative (disease)
YMSM	young men who have sex with men
ZDV	zidovudine

SECTION

1 Practical Aspects

1. Laboratory Diagnosis of Bacterial, Parasitic, and Fungal Infections
2. Laboratory Diagnosis of Viral Infections
3. Vaccine Safety and Risk Communication
4. Infection Prevention and Control in the Office
5. Infection Prevention and Control in the Hospital
6. Infectious Diseases Epidemiology
7. Quality Improvement in Infectious Diseases
8. Antibacterial Agents
9. Antifungal Agents
10. Antiviral Agents

CHAPTER 1

Laboratory Diagnosis of Bacterial, Parasitic, and Fungal Infections

Alexander J. McAdam

INTRODUCTION

The appropriate use of tests for infectious diseases in children is critical to determining the correct diagnosis. The keys to successful testing are collection and transport of an appropriate specimen to the laboratory and correct performance of the appropriate test in the laboratory. Communication between the clinician and the laboratory staff is important in diagnostic testing, particularly if a rare or fastidious organism is suspected. General guidelines for specimen collection and transport are included in this chapter, but it is important to seek guidance from the laboratory that will perform the test, as practice and test availability may vary among laboratories.

SPECIMEN COLLECTION AND TRANSPORT FOR BACTERIA AND FUNGI

Bacteria and fungi are living organisms that can proliferate or die during specimen transport to the laboratory. Survival of the pathogen is required for culture; however, growth of organisms during transport is undesirable if the quantity of bacteria is important in making a diagnosis (e.g., in urine culture) or if overgrowth by normal microbiota makes detection of a pathogen less likely (e.g., in stool culture). The time taken for transport to the laboratory should be minimized to reduce death or growth of organisms. When transport time exceeds 1–2 hours, as in the outpatient office where transport times of up to 24 hours are sometimes required, use of specialized transport media may be required.[1]

If it is practical to obtain them, body fluids, tissues, and purulent material are generally preferred to specimens collected on a swab.[1] The quantity of material that can be collected on a swab is small, and bacteria may remain trapped on the swab, where they cannot be detected. Throat and genital specimens for bacterial culture are exceptions to this rule, and adequate specimens can be collected from these sites using swabs. If swabs must be submitted, submit one swab for each stain or culture ordered.

Many commercial transport systems include a swab and transport media in a tube. These systems work well for most medically important bacteria and fungi. Organisms that do not survive well during transport even with transport media include *Neisseria* spp., *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Campylobacter* spp., and obligate anaerobic bacteria.[1-3] If these organisms are suspected, transport time to the laboratory should be minimized (<12 hours), or media should be inoculated and incubated immediately after specimen collection. Alternatively, nonculture methods of detection should be used. Submission of swabs without transport media to the microbiology laboratory should be avoided, except for throat cultures for group A *Streptococcus* (*S. pyogenes*), which survives well for 24 hours on either dry swabs or in commercial transport media.[1,4]

Obligate anaerobic bacteria die in the presence of oxygen, so special transport containers are used for specimens from infections that are likely to include these organisms. Such infections include deep abscesses, fasciitis, and infections that have spread from body sites heavily colonized by anaerobic bacteria, including the oropharynx and intestine. Specimens from the oropharynx, intestine, and vagina generally should not be submitted for anaerobic culture because these body sites are normally colonized by obligate anaerobic bacteria. In addition, superficial skin and wound infections are unlikely to include obligate anaerobic bacteria, and so anaerobic culture is rarely useful for these infections. Unless the specimen will reach the laboratory very quickly (minutes for small specimens and ≤2 hours for larger specimens), a commercial anaerobic transport tube, jar, or bag should be used to protect the viability of the bacteria.

Specimens for yeast culture can be transported as described for bacterial culture. The following comments apply to specimens in which a hyphal fungus (i.e., mold) is suspected, although yeast, if present, will also remain viable. Tissue, fluids (respiratory, urine, sterile body fluids), hair, or nail specimens for fungal culture can generally be transported in a clean, dry container without transport media.[1] If the specimen will not reach the laboratory within 2 hours, specimens from normally sterile sites can be kept at 37°C, while those from body sites with bacterial microbiota can be kept at 4°C.[1]

LABORATORY METHODS FOR DETECTION, IDENTIFICATION, AND SUSCEPTIBILITY TESTING OF BACTERIA

Detection and identification of bacteria can be performed by several methods, including microscopic examination of stained specimens, culture, antigen detection, and nucleic acid amplification tests (NAAT). Examples of NAAT include polymerase chain reaction (PCR) and transcription-mediated amplification.

MICROSCOPIC DETECTION OF BACTERIA

The Gram stain remains a valuable tool for rapid detection and preliminary identification of bacteria. Gram-positive bacteria appear dark blue or purple because they have a thick peptidoglycan cell wall that retains crystal violet and iodine during destaining with alcohol. In contrast, Gram-negative bacteria have a thin layer of peptidoglycan surrounded by an outer membrane, and the alcohol rinse removes the crystal violet and iodine. After a counterstain with safranin, Gram-negative bacteria appear pink. The Gram stain also reveals the shape and arrangement of bacteria. The morphologies of commonly isolated bacteria are summarized in **Table 1-1**. Yeast usually stain Gram-positive, and they are easily differentiated from bacteria by their greater size.

Stains for mycobacteria include the acid-fast stain (carbol fuchsin) and auramine-O. These stains can be routinely performed on respiratory specimens and tissue and might be performed on other specimens at the discretion of the physician and laboratory staff. The modified acid-fast stain is less stringent than the acid-fast stain and is useful in detection and identification of *Nocardia*, *Rhodococcus*, *Tsukamurella*, and *Gordonia*, all of which are positive by modified acid-fast stain, but negative by regular acid-fast stain.

TABLE 1-1 Morphology of Organisms Frequently Detected by Gram Stain

Morphology	Likely Organisms
Gram-positive cocci in pairs and short chains	*Streptococcus pneumoniae*, *Enterococcus* species
Gram-positive cocci in chains	*Streptococcus* species other than *S. pneumoniae*
Gram-positive cocci in clusters	*Staphylococcus* species
Gram-positive bacilli	*Listeria monocytogenes* (small, regular rods) *Corynebacterium* species (small, irregular rods) *Bacillus* and *Clostridium* species (large, regular rods, may have spores)
Gram-negative cocci	*Neisseria* species (pairs) *Moraxella catarrhalis* (pairs, short chains)
Gram-negative bacilli	*Escherichia coli*, *Yersinia enterocolitica*, *Salmonella* species, *Shigella* species, and many other enteric bacteria *Pseudomonas aeruginosa*

IDENTIFICATION OF BACTERIA

Culture is the mainstay for detection of most bacteria. Most aerobic and facultative anaerobic bacterial pathogens will grow rapidly in routine culture; however, some species require the use of special media. Laboratory personnel should be informed if these are suspected. Identification of bacteria grown in culture is primarily done using either biochemical tests or matrix-assisted laser desorption and ionization time-of-flight mass spectrometry (MALDI-TOF).[5] Identification by biochemical testing usually takes 1–2 days to identify aerobic bacteria, and 4 or more days to identify anaerobic bacteria. MALDI-TOF identification can be performed in minutes, greatly reducing the time needed to identify most bacteria.[6] MADI-TOF testing is performed by placing a small spot of bacteria or yeast on a solid grid, and then overlaying the spot with a chemical matrix. The grid is placed in the MALDI-TOF device, which directs a laser at the bacteria and matrix, "desorbing" the bacteria and releasing charged fragments of bacterial proteins. The masses of the protein fragments are analyzed by mass spectrometry, resulting in a species-specific spectrum, or fingerprint, that is used to identify the bacterium. Infections with some organisms which require special culture are better detected by serology, NAAT, or antigen tests and these are noted in the tables later in this chapter.

Detection of mycobacteria in culture usually requires specific media, although rapid-growing mycobacteria (e.g., *M. fortuitum, M. chelonae, M. abscessus*) may be detected in routine bacterial culture. *Mycobacterium tuberculosis* often takes several weeks to grow in culture, although the time for growth is significantly reduced by using liquid culture media. Identification of mycobacteria by biochemical methods is time-consuming and slow. Much faster results can be obtained using nucleic acid probes or MALDI-TOF, and these methods are standard in most laboratories.[7,8]

Antigen detection assays use antibodies specific for bacterial proteins or carbohydrates to test for bacteria. Rapid antigen tests for *S. pyogenes* (group A *Streptococcus*) are highly specific (>95%).[9] These tests have sensitivities of approximately 70–85%, although the sensitivity is considerably lower (approximately 50%) when performed by nonlaboratory personnel.[9] Because of the moderate sensitivities of these tests, specimens with negative results by antigen tests for *S. pyogenes* should be submitted for culture. The *S. pneumoniae* antigen test in urine is highly sensitive (100%) for pneumococcal disease in children; however, it may also be positive in asymptomatic children colonized with *S. pneumoniae*, and so it has a specificity of only 50–60%.[10,11] Antigen tests performed on cerebrospinal fluid (CSF) are discussed below in the section on meningitis.

Both PCR and other NAAT are very sensitive because they amplify nucleic acid from the pathogen in logarithmic fashion, doubling the number of DNA or RNA molecules several times. As a result, NAAT can be more sensitive than culture, particularly for fastidious organisms. Clinical tests for many organisms are now done by NAATs, including *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, *Bordetella pertussis*, *S. agalactiae* (group B *Streptococcus*), *Streptococcus pyogenes* (group A *Streptococcus*), methicillin-resistant *S. aureus*, and *M. tuberculosis*. NAAT are now available in syndromic panels.[12,13] These panels detect several pathogens associated with a syndrome in a single test. Syndromic panels can include diverse pathogens in one test, including bacteria, viruses, parasites, and molds. Some panels also detect genetic markers of antimicrobial resistance in bacteria, such as methicillin resistance in *S. aureus* and carbapenem resistance in Gram-negative bacilli. Additional antibiotic susceptibility results beyond those few induced in the syndromic panel require conventional culture of the organism. There are several FDA-approved syndromic panels for detection of respiratory pathogens or intestinal pathogens, and a single such panel is available for testing cerebrospinal fluid for pathogens that cause meningitis or encephalitis. There are also NAAT panels that permit testing of blood culture bottle broth (from positive samples) for identification of bacteria, antimicrobial resistance genes, and yeast. Several of these panels are discussed in more detail in the sections on testing specific body sites later in this chapter.

ANTIBIOTIC SUSCEPTIBILITY TESTING

Antibiotic susceptibility can be tested directly by phenotypic methods, or it can be predicted using NAAT to detect genes that mediate antibiotic resistance. Phenotypic tests measure inhibition of growth or killing of bacteria by antibiotics. The *minimum inhibitory concentration* (MIC) is the concentration of antibiotic that inhibits visible growth of bacteria. The MIC can be determined by several methods, including culturing bacteria in a titration of antibiotics in agar or broth, or by using automated devices. The *minimum bactericidal concentration* (MBC) is the concentration of an antibiotic that kills 99.9% of bacteria. In practice, the MIC is easily determined and predicts the susceptibility of bacteria to antibiotics, while determination of the MBC is technically cumbersome and rarely adds information beyond that obtained from the MIC or disk diffusion testing. Thus, MBC testing is seldom performed. Disk diffusion susceptibility testing is performed by coating an agar plate with bacteria and then placing paper disks impregnated with antibiotics onto the plate. The diameter of the zone of growth inhibition around the disk is measured. The zone of growth inhibition around the disk is inversely proportional to the MIC, and the relationship between these values is the basis for interpretation of disk diffusion testing results.

Nucleic acid amplification tests are used for rapid detection of genes that cause antibiotic resistance. These can be performed in just a few hours, and are currently used for a small number of well-characterized antibiotic resistance genes, including those causing methicillin resistance in *S. aureus*, vancomycin resistance in *Enterococcus* species, carbapenem resistance in Gram-negative bacilli, and rifampin resistance in *Mycobacterium tuberculosis*. The availability and use of these tests varies greatly between laboratories.

The interpretation of MIC values or disk diffusion zones as "susceptible," "susceptible-dose-dependent," "intermediate," or "resistant" is performed according to guidelines published by the Clinical and Laboratory Standards Institute (CLSI) in the United States. An organism is considered susceptible if it is inhibited by concentrations of antibiotic that are likely to be achieved at the relevant body site with the recommended dosage, and it is considered resistant if it is not inhibited by such concentrations. A "susceptible-dose-dependent" interpretation indicates that the organism will be susceptible when larger or more frequent antibiotic doses are administered. Cefepime is currently the only antibacterial drug with an interpretation of susceptible-dose-dependent. An "intermediate" interpretation means that failure of antibiotic therapy is more likely than if the organism is susceptible, but that drugs that are normally concentrated at the site of infection (e.g., penicillin in urine) or drugs given at higher doses than usual (e.g., penicillin for intermediate *S. pneumoniae* in meningitis) may be effective. The intermediate range also includes a buffer zone for technical variation in the test. The concentration that antibiotics reach can be different at various body sites, so laboratories selectively report susceptibility testing according to the body site from which bacteria are isolated. For example, susceptibility results with nitrofurantoin are reported for bacteria isolated only from urine, because nitrofurantoin is concentrated in urine while reaching subtherapeutic levels in serum and tissue. Furthermore, the interpretation of antibiotic susceptibility may depend on the body site infected. Interpretations of the MICs of *S. pneumoniae* with penicillin, cefotaxime, and ceftriaxone depend on whether the patient has meningitis or infection only outside the central nervous system (CNS) because routinely achievable levels of these drugs in the CNS and the rest of the body differ.

Laboratory testing can, in a few cases, be used to predict whether there is a significant risk that an organism that is apparently susceptible to an antibiotic is likely to develop resistance to that antibiotic. An increased chance of developing resistance to clindamycin in *Staphylococcus* and β-hemolytic streptococci can be detected by testing for erythromycin-inducible clindamycin resistance. This is done by placing clindamycin and erythromycin disks close together in disk diffusion susceptibility testing and looking for a flattening of the zone of growth inhibition around the clindamycin disk (the *D-test*). Organisms with a positive D-test are reported as clindamycin resistant, although the laboratory may report that clindamycin may still be effective in some patients.

The only test for antibiotic synergy that is routinely performed is a screen for synergy of the aminoglycosides gentamicin and streptomycin with the cell wall synthesis inhibitors penicillin, ampicillin, and vancomycin against *Enterococcus*. This is done by testing the growth of the *Enterococcus* isolate with a high level of the aminoglycoside. Although synergy testing is available for antibiotic-resistant Gram-negative organisms from patients with cystic fibrosis, there is no evidence that use of these results leads to improved patient outcomes.

LABORATORY METHODS FOR DETECTION, IDENTIFICATION, AND SUSCEPTIBILITY TESTING OF FUNGI

Fungi include both molds and yeasts. Molds grow primarily as hyphae (elongated structures that form a fuzzy-appearing colony) and spore-forming structures. *Aspergillus*, the Zygomycetes (e.g., *Mucor* and *Rhizopus*) and the dermatophytes (e.g., *Trichophyton*) are all molds. Yeast grow as round or oval forms and divide by budding. Colonies of yeast can appear smooth or rough, but not fuzzy. Yeast include *Candida* spp. and *Cryptococcus neoformans*. Dimorphic fungi grow as yeast at body temperature (including in tissue), but as molds at 25–30°C, and these include *Histoplasma capsulatum*, *Coccidioides immitis*, *Blastomyces dermatitidis*, *Sporothrix schenckii*, *Paracoccidioides brasiliensis*, and *Penicillium marneffei*.

MICROSCOPIC DETECTION OF FUNGI

Microscopic examination of specimens for fungi requires specific stains because Gram stain may stain these organisms poorly. Treatment of specimens with potassium hydroxide (KOH) renders most host tissues clear, but fungi remain visible. Calcofluor white stain, which can be combined with KOH, binds to fungal cell walls and fluoresces under ultraviolet (UV) light, making it easy to detect fungal structures. Giemsa or Wright stains are useful for detecting *Histoplasma capsulatum* in blood or bone marrow smears. Gomori methenamine silver stain is used to stain fungi in fixed tissue

IDENTIFICATION OF FUNGI

Several different media are available for fungal culture, and the choice of appropriate media depends on the specimen type and suspected fungus. It is therefore important that the specimen type (body site) be specified. Growth of *Malassezia* requires addition of lipids to the media, and so it is also important to notify the laboratory if *Malassezia* is suspected. *Malassezia* cause catheter-related infections in children receiving lipid-rich parenteral nutrition, tinea versicolor, and, less commonly, folliculitis, seborrheic dermatitis, and intravascular catheter-associated sepsis.

Identification of fungi, particularly molds and dimorphic fungi, is based primarily on the macroscopic and microscopic morphology of the organism. It may take several days to weeks for a mold to develop the distinctive morphology required for identification. Yeast can usually be identified more quickly. The germ tube assay is a test for identification of *Candida albicans*, which can be completed within a few hours after isolation of the organism in culture. MALDI-TOF can be used to identify most yeast very quickly, but is used for identification of molds by only a few laboratories.[14,15] Biochemical and morphological identification of other types of yeast can usually be accomplished in less than a week.

Several antigen tests for fungal infections are available. The galactomannan assay detects a fungal cell wall structure and is FDA-approved for detection of invasive *Aspergillus* infection. The assay has also been reported to be positive in some cases of infection with *Histoplasma capsulatum*, *Penicillium*, *Paecilomyces*, and *Alternaria* species.[16,17] Most studies of the utility of galactomannan testing in children have included few patients with invasive *Aspergillus* infection, and estimates of sensitivity and specificity of the test vary widely among these studies. A systematic review that combined several studies performed in children found an overall pooled sensitivity of the galactomannan test on blood of 81% and specificity of 88% for invasive fungal disease.[17] Galactomannan testing can also be performed on bronchoalveolar lavage fluid, although the sensitivity and specificity are low, and results should be interpreted with particular care.[18–20] A study of 72 bronchoalveolar lavage samples from children found sensitivity of 82.4% and specificity of 87.5%.[21] Positive results in this assay are associated with administration of enteral nutrition and some antibiotics, so results must be interpreted with caution.[22] The (1,3)-β-D-glucan assay (Fungitell) detects an antigen produced by many fungi, including *Candida*, *Aspergillus*, *Fusarium*, *Trichosporon*, and *Pneumocystis jirovecii*. Infections with *Cryptococcus neoformans* and the Zygomycetes (*Rhizopus*, *Mucor*, *Rhizomucor*, *Cunninghamella*, and *Absidia*) cannot be detected by the (1,3)-β-D-glucan tests.[23,24] Studies of the use of the Fungitell assay for detection of invasive fungal infections in children are small, and estimates of the test's performance vary widely. If specimens are collected twice weekly in neutropenic adults with acute myelogenous leukemia or myelodysplastic syndrome, the sensitivity of the test is 100% in those with proven or probable invasive fungal infections if a single abnormally high value is counted as positive, and a positive value occurs a median of 10 days before a clinical diagnosis.[25] A larger, multicenter study showed a sensitivity of 64.4% and specificity of 92.4% for invasive fungal infections in adults.[23] (1,3)-β-D-glucan is common in the environment and in medical devices or solutions, and positive results have been reported following dialysis, administration of immunoglobulin, surgical gauze, or bandages.

Molecular tests for fungal pathogens are limited. There is an FDA-approved test, T2Candida Panel, for five common *Candida* species that is performed directly on blood, without the need for culture. The sensitivity of the test is reported to be high, although few actual clinical blood samples have been available for study.[26] Some PCR panels performed on positive blood culture samples include detection of *Candida albicans*, and a syndromic panel for use with CSF includes detection of *Cryptococcus* species.[27] There are NAAT for *Aspergillus* species available at some commercial and reference laboratories. These tests are not approved by the FDA but have been found to be useful ancillary tests in some studies.[28]

ANTIFUNGAL SUSCEPTIBILITY TESTING

Susceptibility testing for fungi is performed by phenotypic tests. MIC cutoffs for determination of susceptibility of most *Candida* species are available for triazoles and echinocandins, but not for amphotericin B. There are no guidelines for interpretation of testing amphotericin B susceptibility, although organisms with an MIC of >1 μg/mL are probably resistant. Antifungal susceptibly testing of molds is difficult and is performed in a small number of reference laboratories. Interpretive cutoffs are limited, and only *epidemiological cutoffs*, which indicate whether acquired mechanisms of antifungal resistance are present, may be available.

LABORATORY METHODS FOR DETECTION AND IDENTIFICATION OF PARASITES

SPECIMEN COLLECTION AND TRANSPORT FOR PARASITES

It is important to use one or more preservatives for transport of stool for parasite examination because some parasites rapidly become undetectable. Many laboratories request that the stool be sent in two separate preservatives for conventional, microscopic, detection of parasites: 10% buffered formalin for preparation of a stool concentrate and a preservative with poly(vinyl alcohol) (PVA) for preparation of a permanent stained slide. Commercial kits with these preservatives are available, and these have convenient tight-fitting screw caps and "fill to" lines. Preservatives that can be used for both the concentrate and permanent stained slide are available, but the laboratory should be consulted before these are used.

Pinworms (*Enterobius vermicularis*) and their eggs are not readily found in stool because the female worms exit the anus and lay their eggs on the adjacent skin. To collect the eggs for diagnosis, the sticky side of cellulose (clear) tape can be applied repeatedly to different areas of

TABLE 1-2 Special Stains for Parasites

Parasite(s)	Stain	Specimen
Acanthamoeba species	Calcofluor white, Giemsa, Papanicolaou, or trichrome stain (poorly stained by Gram stain)	Tissue (corneal scrapings or biopsy of lesions of cornea, brain, or skin), transport quickly to laboratory at room temperature
Cryptosporidium parvum, Cyclospora cayetanensis, Isospora belli	Modified acid-fast stain	Stool in commercial 10% buffered formalin parasite transport kit
Microsporidia	Modified trichrome stain, Weber green stain, Ryan blue stain	

the perianal skin, preferably first thing in the morning (before passing stool). The tape is then applied to a microscope slide, with the sticky side against the glass, and is submitted to the laboratory. Opaque or frosted tape should not be used.

If bloodborne parasites, such as malaria or babesia, are suspected, blood anticoagulated with EDTA (purple-top tube) should be submitted for preparation of blood smears.

TESTS FOR PARASITIC INFECTIONS

Routine testing for intestinal parasites includes microscopic examination of a wet concentrate and a permanent stained slide of stool or, for *E. vermicularis*, tape preparation specimens. Routine examination of stool includes a concentrated wet preparation for detection of helminths, protozoan cysts, coccidia, and microsporidia, and a permanent stain smear for protozoa. A few intestinal parasites require special stains to be detected. If these parasites are suspected, it is important to inform the microbiology laboratory so that the appropriate methods will be used. These parasites, along with the method used for detection and the recommended specimen, are listed in **Table 1-2**. Most syndromic panels for testing stool samples include more common parasites such as *Giardia*, *Cryptosporidium*, *Cyclospora cayetanensis*, and *Entamoeba histolytica*.[13,29]

Bloodborne parasites include *Plasmodium* (malaria), *Babesia*, *Trypanosoma*, and several species of filaria. These pathogens can be detected by microscopic examination of Giemsa-stained blood smears. The use of thick blood films increases the sensitivity for *Plasmodium* and *Babesia*; however, thin smears should also be made because the morphology of the parasites is better preserved in this preparation so that species identification can be made. The Binax NOW ICT malaria test is an FDA-approved rapid immunochromatographic test that differentiates *P. falciparum* from the other *Plasmodium* species. It is sensitive for *P. falciparum* (96%) and *P. vivax* (87%), but less sensitive for *P. ovale* and *P. malariae* (both 62%) and has an overall specificity of 99%.[30]

SPECIMEN COLLECTION AND TESTING FOR SELECTED BODY SITES

BLOOD

Blood culture bottles specifically intended for pediatric use may provide some advantage over use of adult blood culture bottles in children, although the data supporting this possibility are limited.[31] Pediatric blood culture bottles contain a smaller volume of media than those intended for use in adults, and they also have a lower concentration of sodium polyanetholsulfonate (SPS), an anticoagulant that also inhibits the antibacterial effects of blood. SPS has been suggested to inhibit growth of some bacteria (e.g., *Neisseria meningitidis*); however, the antibacterial effect of SPS does not appear to be significant in practice.[32,33]

The concentration of bacteria in the blood of a bacteremic child can be quite low, so the chance of detecting a bacterial pathogen is significantly increased by culturing a larger volume of blood.[31] The concentration of bacteria in blood is less than one colony-forming unit (CFU) of viable bacteria per milliliter of blood in 23.1% of children, and <10 CFU/mL of blood in 60.3% of children with culture-confirmed bacteremia.[34] The sensitivity of blood culture in children increases when higher volumes of blood are cultured (e.g., sensitivity increases by approximately 20% when the volume is increased from 2 to 6 mL).[35]

Because limited blood volume is available from children and because the yield of aerobic culture is much greater than that of anaerobic culture from children, anaerobic culture is recommended primarily in children with risk factors for sepsis with obligate anaerobes, although one small study contradicts this.[31,36] Widely used automated continuous-monitoring pediatric blood culture systems reliably detect facultative but not obligate anaerobes. Although data are limited, risk factors for sepsis with obligate anaerobic bacteria in children may include decubitus ulcers, abdominal processes (pain, breakdown of the anatomic barrier of the intestinal tract), and neutropenia. Obligate anaerobic bacteria are also associated with deep abscesses and infections of the head and neck that extend from the oropharynx, and so anaerobic culture may also be useful in children with such infections.

Several bacteria and fungi in blood require special culture conditions or alternative methods of detection (**Table 1-3**). Yeast, including *Candida*, can be detected in conventional blood culture bottles and do not require use of isolator bottles.[37]

CEREBROSPINAL FLUID

Cerebrospinal fluid (CSF) culture and Gram stain should be routinely sent if bacterial meningitis is suspected. CSF should be transported to the microbiology laboratory at room temperature within one hour of specimen collection. Routine Gram stain and culture will detect most common and uncommon causes of meningitis in children. Gram stain will detect approximately half of cases of bacterial meningitis, and false-positive CSF Gram stain results, although uncommon, may be caused by observer misinterpretation, reagent contamination, or the use of an occluded lumbar needle that leads to contamination of the specimen with skin.[38] Tests for bacterial antigens in CSF should not be performed routinely, as these are insensitive and nonspecific and do not generally add information to that obtained from Gram stain and culture results.[39] Even when bacterial antigens are detected in CSF, the result rarely affects patient care because the Gram stain is also nearly always positive in these patients. Obligate anaerobic bacteria are an uncommon cause of meningitis in children. Anaerobic culture of CSF should be considered, particularly when there are other infections that may give anaerobes access to the meninges or blood (e.g., sinusitis, chronic ear infections, or gastrointestinal disease) or when the anatomic protection of the meninges is compromised (e.g., due to ventricular shunt or skull fractures). *Propionibacterium acnes*, an anaerobe, is frequently isolated from CSF of patients who have a ventricular shunt.[40]

Tests for fungi in CSF should be sent in selected patients. Immunocompromised patients, particularly those with HIV infection or prolonged corticosteroid treatment, are at risk for meningitis caused by *C. neoformans*.[41] Tests for cryptococcal antigen in CSF and blood can be done quickly and are sensitive and specific.[41] In adults, tests cryptococcal antigen tests on CSF have >95% sensitivity for identification of cryptococcal meningitis. Serum tests for cryptococcal antigen to diagnose cryptococcal meningitis are approximately 75% sensitive in adults without HIV and 95% sensitive in adults with HIV.[42] India ink stains have variable sensitivity for cryptococcal meningitis and should not be done unless cryptococcal antigen tests are not available.[43,44] *Histoplasma capsulatum* and *C. immitis* may also be detected by antigen tests, and these results will often be available more quickly than culture results. It is reasonable to do fungal culture in addition to antigen assays if fungi are suspected, but it is important to note that fungi often take weeks to grow in culture.

An FDA-approved syndromic PCR panel for pathogens causing meningitis or encephalitis is available.[12,27] The assay detects bacteria (*E. coli*, *H. influenzae*, *L. monocytogenes*, *N. meningitidis*, *S. agalactiae*, and *S. pneumoniae*) and viruses (enterovirus, herpes simplex viruses, and others), as well as the yeast, *Cryptococcus*. It is highly sensitive for these pathogens, and occasionally detects them correctly even if culture is negative.[45] It is important to note that bacterial meningitis is now very

TABLE 1-3 Blood Pathogens Detected by Special Techniques

Pathogen	Culture	Comments
Bartonella species	Collect blood in isolator tube* Culture takes up to 5 weeks	Serology or NAAT recommended
Borrelia species (relapsing fever)	Seldom available (research use)	Collect blood during fever, submit for microscopic examination Serology recommended
Brucella species	Conventional blood culture bottles require extended incubation and blind subculture	Notify laboratory, as *Brucella* is a potential hazard to laboratory staff Consider bone marrow culture Serology recommended
Ehrlichia and *Anaplasma* species	Seldom available (research use)	Microscopic examination of blood for inclusions may be helpful but is insensitive Serology and NAAT recommended
Histoplasma capsulatum	Collect blood in isolator tube* for fungal culture or collect blood in Myco/F† lytic bottle	Specimen collected in isolator tube will yield growth faster Contact laboratory for preferred bottle
Leptospira interrogans	Inoculate oleic acid–albumin media with 1–2 drops of blood at bedside (preferred) or collect blood with sodium poly(amethol sulfonate) and submit to laboratory	Contact laboratory to determine whether culture is available Multiple cultures are needed to improve sensitivity Serology recommended
Malassezia species (catheter infections)	Inoculate fungal media with blood, overlay with olive oil	Contact laboratory so that media will be available Also submit blood from port for Gram stain
Mycobacterium species	Use an isolator tube* or culture bottles specific for mycobacteria	Contact laboratory for preferred bottle Specimen collected in isolator tube will yield growth slower
Streptobacillus moniliformis (rat-bite fever)	Collect blood in citrate anticoagulant, culture with serum-supplemented media	Contact laboratory to determine whether culture is available

Abbreviation: NAAT = nucleic acid amplification tests.

*Isolator system from Wampole Laboratories.

†Myco/F lytic bottle from Becton Dickinson and Company.

TABLE 1-4 Gastrointestinal Pathogens Detected by Special Techniques

Pathogen	Culture	Comments
Clostridium difficile (colitis)	Common flora in children, so presence may be normal	NAAT or immunoassays for glutamate dehydrogenase and *C. difficile* toxins are recommended Reflex testing protocols in use in many laboratories
Enterohemorrhagic *E. coli* (including 0157:H7)	Transport media (modified Cary–Blair) needed if transport time >1 hour Culture on sorbitol–MacConkey's agar for *E. coli* 0157	Stool preferred to swabs Other (non-0157) enterohemorrhagic *E. coli* can be detected by immunoassay for Shiga-like toxin NAAT, including syndromic panels, are available
Helicobacter pylori	Gastric antral biopsy (not stool) should be transported to laboratory as soon as possible in culture broth (e.g., tryptic soy broth) If transport time >1 hour, transport at 4°C Grows on 5% sheep blood agar or modified Thayer–Martin in humidified microaerobic environment (5% O_2)	Breath test, serology, or stool antigen tests are recommended
Vibrio species	Transport media (e.g., modified Cary–Blair) needed if transport time >1 hour Grow on MacConkey's or 5% sheep's blood media, but selective alkaline broth and thiosulfate citrate bile sucrose (TCBS) media enhance recovery	Stool preferred to swabs Contact laboratory to determine availability of selective broth and media NAAT, including syndromic panels, are available
Yersinia enterocolitica	Transport media (e.g., modified Cary–Blair) needed if transport time >1 hour Grow on MacConkey agar at 37°C, but culture at 25°C enhances recovery	Stool preferred to swabs Cold enrichment (4°C) enhances recovery from stool but takes weeks and so is of limited utility NAAT, including syndromic panels, are available

rare in immunized populations, and so the positive predictive value of this test is low for some pathogens, making false-positive results more likely.[12,27] Results of this assay should be interpreted in the context of other CSF values, such as glucose, protein, and white blood cell (WBC) levels.

STOOL

Routine stool culture usually includes *Salmonella*, *Shigella*, and *Campylobacter*. If other pathogens, such as enterohemorrhagic *E. coli* (EHEC, including *E. coli* O157:H7), *Yersinia enterocolitica*, or *Vibrio* are suspected, culture for these organisms should be specifically requested. Excreted stool is preferable to swab specimens; swab specimens should be collected only from infants or patients who are unable to produce a specimen. If a stool specimen cannot be transported to the laboratory in less than an hour, it should either transported at 4°C, or with transport media to preserve the bacteria. Enteric pathogens that require special culture conditions are shown in Table 1-4.

Enterohemorrhagic *E. coli* is among the most common bacterial causes of diarrhea in children.[46] It can be detected either by culture or by immunoassay for the Shiga toxins that it produces. Approximately half of EHEC are of the serotype O157:H7, and these can be detected using MacConkey agar containing sorbitol, which these organisms do not ferment. Most laboratories in the United States use sorbitol-containing media for detection of EHEC, although some may use more specific chromogenic agars.[47] Assays for Shiga toxins, which are produced by all serotypes of EHEC, will detect significantly more cases of EHEC infection.[46] Shiga-like toxins can be detected by immunoassays for the protein toxin, or by more sensitive NAAT for the genes encoding the toxins.[48] Most laboratories perform both a culture for *E. coli* O157:H7 and an assay for Shiga toxins, so they will detect most cases of EHEC.

There are several different methods available for detection of *Clostridium difficile*–associated diarrhea. Unfortunately, none of these tests performs perfectly, and the best test or group of tests for detecting *C. difficile* disease is an area of active investigation and debate.[49,50] The most common and recommended initial tests for *C. difficile* are NAAT

that detect the genes for *C. difficile* toxins, or immunoassays for the glutamate dehydrogenase (GDH) protein produced by all *C. difficile*. Both of these assays are highly sensitive for detection of *C. difficile*, but there are concerns about the specificity of the tests. NAAT will detect even small numbers of organisms and may be positive in people who are colonized with the organism. Most laboratories that perform NAAT as the initial test for *C. difficile* will not perform additional testing, but some laboratories will use an immunoassay for *C. difficile* toxin as a confirmatory test on NAAT-positive specimens to increase the stringency for detecting *C. difficile* disease. GDH is produced by all *C. difficile*, including a significant number of *C. difficile* that do not produce toxins, and so GDH assays should not be used alone but can be used along with an assay that detects *C. difficile* toxin, usually an immunoassay. Finally, if the GDH assay and toxin immunoassay give different results, one positive and the other negative, some laboratories will perform a NAAT for the toxin. Regardless of the method used, positive results for *C. difficile*, particularly in younger children, should be interpreted carefully in the context of the patient's history and testing for other appropriate pathogens. Diagnosis of *C. difficile*–associated diarrhea in young children is difficult because a large proportion of healthy children younger than one year are colonized by *C. difficile*, which can lead to positive test results in any of the available assays.[51]

There are several FDA-approved syndromic gastrointestinal panels available. All of these include detection of *Campylobacter*, *Salmonella*, *Shigella*, and ETEC.[12,13] The detection of other bacteria varies between assays. They can include detection of common pathogens, such as enterotoxigenic *E. coli*, the cause of traveler's diarrhea, as well as less common pathogens such as *Vibrio* species. Some panels detect organisms whose pathogenicity is poorly understood, such as enteropathogenic and enteroaggregative *E. coli*, both of which can be members of the normal microbiota, and so interpretation of the results can be difficult. These panels can also include detection of parasites, including *Giardia*, *Cryptosporidium*, *C. cayetanensis*, and *Entamoeba histolytica*, and some include detection of viral pathogens as well. A few of these panels include detection of *C. difficile*; however, many labs do not report *C. difficile* results from these assays because of the very different risk factors for *C. difficile* infection and other infectious forms of gastroenteritis.

RESPIRATORY SPECIMENS

Sputum samples are rarely performed in children, given the challenge of obtaining an adequate sample for testing and the preponderance of viruses as a cause of lower respiratory tract infection in otherwise healthy children. When obtained, sputum should be submitted for Gram stain and bacterial culture. Bacteria that commonly cause pneumonia, including streptococci, staphylococci, and *H. influenzae*, can be grown in routine respiratory culture. A sample collected by tracheal aspiration or bronchoalveolar lavage may be necessary in some circumstances (e.g., in a child with chronic granulomatous disease). As discussed above, the test for *S. pneumoniae* antigen is sensitive but not specific for invasive pneumococcal disease in children.[10,11] There are few studies on interpretation of respiratory Gram stains in children. In adults, a high number of polymorphonuclear leukocytes and a low number of epithelial cells on Gram stain suggests that a respiratory specimen is from the lower respiratory tract and that bacterial growth is likely to be significant. A study that evaluated the utility of Gram stain in endotracheal aspirates from mechanically ventilated children revealed that the absence of bacteria on Gram stain suggests that culture is unlikely to detect a pathogen, and a separate study indicated that omitting these cultures would have little effect on patient care.[52,53] Respiratory pathogens that are not detected by routine culture are listed in **Table 1-5**, and comments on some of these follow.

The appropriate specimen for diagnosis of pulmonary tuberculosis depends on the child's age and ability to produce sputum. If sputum can be produced, three sputum samples collected on separate days should be submitted for stain and culture for acid-fast bacteria.[54,55] If sputum cannot be obtained, gastric aspirate specimens should be collected. The sensitivity of gastric aspirate culture can be increased by collection of the specimen first thing in the morning (before the patient eats), neutralization of the stomach acid by adding sodium bicarbonate or sodium carbonate to the specimen, and collection of three specimens on separate days before the initiation of therapy. The sensitivity of culture of gastric aspirates for *M. tuberculosis* is nearly 90% in infants, but is only approximately 50% in older children.[54] It is controversial whether gastric aspirate specimens should be stained for acid-fast bacilli, because oral acid-fast organisms can be detected in aspirates from patients who do not have pulmonary tuberculosis. In populations with a high prevalence of pulmonary tuberculosis, staining of gastric aspirates works well, but positive results should be interpreted with caution in patients at a low risk of pulmonary tuberculosis.[56]

Two NAAT tests have been approved by the FDA for detection of *M. tuberculosis* in respiratory specimens, and it is recommended that a single NAAT be performed routinely in patients suspected of having pulmonary tuberculosis.[54] These tests are sensitive and specific on respiratory specimens in which acid-fast bacilli are detectable on stain (i.e., "smear-positive" specimens).[54] If acid-fast bacilli are not detectable by stain, these tests are specific, but not very sensitive, and so a positive result is highly predictive of tuberculosis, but a negative result should

TABLE 1-5 Respiratory Pathogens Detected by Special Techniques

Pathogen	Culture	Comments
Bordetella pertussis	Requires enriched media, Regan–Lowe Transport media with charcoal (Amies with charcoal or Regan–Lowe transport media) will enhance survival	Consider serology or NAAT (more sensitive than culture) Direct fluorescent antibody (DFA) tests are not adequately sensitive or specific if used alone
Burkholderia cepacia complex	Requires selective media, *B. cepacia*–selective agar (BCSA) or oxidation–fermentation with polymyxin B, bacitracin, and lactose (OFPBL)	Consider in patients with cystic fibrosis Difficult to identify and so may require reference laboratory
Corynebacterium diphtheriae	Use commercial swab and transport media to swab beneath membrane, if possible Requires selective media, cystine tellurite blood agar (CTBA) or tinsdale agar	Contact laboratory to determine availability of media or need for sendout to reference laboratory
Legionella pneumophila	Requires enriched media, buffered charcoal-yeast extract (BCYE) If specimen must be transported before culture, transport at 4°C	Consider urine antigen tests (detects only serogroup 1, the cause of 80% of infections)
Mycobacterium species	Collect sputum if possible, or bronchoalveolar lavage or three gastric aspirates (see text) for culture Agarose media (e.g., Middlebrook agars) and broth media [mycobacteria growth indicator tube (MGIT) system, MB/BacT, Bactec Myco/F lytic bottles] both inoculated for fastest recovery Takes up to 8 weeks	Stain for acid-fast organisms recommended (carbol fuchsin or auramine-O stain) on sputum or bronchoalveolar lavage (BAL) NAAT recommended
Mycoplasma pneumoniae	If culture needed, use Mycoplasma transport media (2SP) or culture media (SP-4) Requires selective media, SP-4, methylene blue–glucose, or others Takes up to 4 weeks	Serology (IgM) or NAAT recommended Contact laboratory to determine availability of transport media and culture

not be used to rule out tuberculosis.[54] One of these NAAT also includes sensitive and specific testing for rifampin resistance in *M. tuberculosis*.[57] NAAT testing for resistance to rifampin with or without testing for resistance to isoniazid is recommended specimens that are positive for MTB by a NAAT test.[54]

Bordetella pertussis can be detected by culture or PCR. Direct fluorescent antibody (DFA) assays for *B. pertussis* are not sensitive or specific and should not be used if other tests are available. If the patient has been symptomatic for <2 weeks, PCR of a nasopharyngeal swab, aspirate, or wash specimen is very sensitive and typically detects two- to threefold more infections than does culture.[58,59] Dacron or rayon swabs with synthetic shafts are preferred because calcium alginate swabs and wooden shafts inhibit PCR. Most PCR tests detect a *B. pertussis* genetic sequence (IS481) that is also present in *B. holmesii,* which is occasionally found in human samples and can lead to false-positive PCR results for *B. pertussis*. The high sensitivity of PCR must be weighed against the potential for false-positive results, which have led to costly investigations of pseudo-outbreaks of pertussis.[60] PCR for pertussis can be made more sensitive by amplifying other DNA sequences, such as the pertussis toxin gene promoter.[61] There is no FDA approved serology test for antibodies to *B. pertussis*; however, some public health laboratories offer this test and it is reasonably accurate.[61]

Infection with *Mycoplasma pneumoniae* is best detected by NAAT of respiratory specimens or by serological testing. NAAT for *M. pneumoniae* will detect significantly more cases than detection of IgM, and both tests are reasonably specific.[62,63] Culture of *M. pneumoniae* is difficult and slower than NAAT or serology and is not recommended for routine clinical practice.

There are several syndromic NAAT panels available for detection of respiratory pathogens.[12] These panels include a variety of viruses (adenovirus, influenza viruses, respiratory syncytial virus). Some also include detection of one or more bacterial pathogens. *C. pneumoniae*, *M. pneumoniae*, and *Bordetella* spp. are found on some panels, although none of the FDA-approved panels include all three of these pathogens. These panels are expensive and are probably best reserved for immunocompromised and critically ill patients.[64]

SEXUALLY TRANSMITTED INFECTIONS (INCLUDING PERINATAL TRANSMISSION)

Diagnosis of sexually transmitted infections in adolescents can be done by the same methods used in adults. In younger children, bacteria associated with sexually transmitted infection can be acquired from the mother during delivery or as a result of sexual abuse. The body sites affected and the diagnostic tests can therefore differ between children and adults, because of the routes of transmission and social, legal, and psychological consequences of the diagnosis. The collection of genital specimens from a prepubertal girl should be done only by experienced practitioners as it can be painful when performed incorrectly.

Neisseria gonorrhoeae can be detected by Gram stain, culture, or NAAT. Gram stain of a urethral specimen in a symptomatic adolescent male is a sensitive and specific test for *N. gonorrhoeae* infection; however, it should not be used in females or asymptomatic males. Culture for *N. gonorrhoeae* can be performed using urethral, cervical, vaginal, anorectal, conjunctival, or pharyngeal swabs. The organism is labile, and every effort should be made to culture specimens correctly. Culture conditions and alternative tests for genital pathogens are listed in **Table 1-6**. Culture is a reasonably sensitive test for *N. gonorrhoeae* (80–86%), and it is the gold standard for specificity. Molecular tests, including NAAT, for *N. gonorrhoeae* and *C. trachomatis* are discussed together below, as these are usually performed together on a single specimen.

Chlamydia trachomatis can be detected by culture and molecular tests. Immunoassays for *C. trachomatis* should be avoided because of their poor sensitivity and specificity. *C. trachomatis* culture is performed by incubating the specimen with mammalian cells, which support replication of the bacteria, and then staining the cells by immunofluorescence with antibodies specific for *C. trachomatis* 2 or 3 days later. The advantages of culture are the high (gold-standard) specificity of the test and acceptability of multiple specimen sources, including urethral, cervical, vaginal, anorectal, conjunctival, or pharyngeal swabs. Unfortunately, the sensitivity of culture for genital infection with *C. trachomatis* ranges from only 52.3% (female) to 58.9% (male), which is significantly lower than that of NAAT.[65] As a result, culture is used primarily for conjunctival and pharyngeal sites, as most laboratories cannot perform NAAT on specimens from these sites and when sexual abuse is suspected since the very high specificity makes a false-positive result unlikely.

TABLE 1-6 Genital Pathogens Detected by Special Techniques

Pathogen	Culture	Comments
Chlamydia trachomatis	Requires cell culture If culture needed (e.g., suspected sexual abuse), use *Chlamydia* transport media (2SP or SPG)	NAAT recommended
Haemophilus ducreyi	Immediately inoculate conventional chocolate (5% lysed sheep blood) agar and, if available, chocolate agar supplemented with vancomycin and fetal bovine serum If specimen must be transported before culture, transport at 4°C	Culture is insensitive Contact laboratory to determine availability of media
Neisseria gonorrhoeae	Inoculate room-temperature-selective media (modified Thayer–Martin, Martin–Lewis, or NYC medium) and incubate at 35°C with 5% CO_2 immediately if possible If plates are transported, systems that generate CO_2 should be used (JEMBEC, Gono-Pak, InTray GC)	Consider NAAT Swabs should be cultured within 6 hours
Klebsiella (Calymmatobacterium) granulomatis	Seldom available (research use)	Collect scraping or biopsy of edge of lesion, submit for Wright's or Giemsa stain

There are several NAAT for *C. trachomatis* and *N. gonorrhoeae*. An advantage of NAAT over other tests for *C. trachomatis* and *N. gonorrhoeae* is that urine can be tested, in addition to vaginal (which can be self-collected), urethral, and cervical specimens. Other specimens (e.g., conjunctival and pharyngeal) are not approved by the FDA for testing in NAAT, but some large laboratories have validated their use and can test these specimens. Most studies of NAAT for diagnosis of these infections are performed in adults and adolescents, and data in prepubertal children are quite limited. It is difficult to compare the performance of the available NAAT because of the use of different and problematic gold standards, but NAAT are the most sensitive tests for both *C. trachomatis* and *N. gonorrhoeae*. Most studies of adults have revealed that the NAAT are >90% sensitive for both organisms and that the specificities are >97%.[66,67] Use of urine from females may be somewhat less sensitive for both organisms than for other acceptable specimens.[66]

The selection of tests for diagnosis of *C. trachomatis* and *N. gonorrhoeae* in children who may have been sexually abused is complex. Detection of these bacteria requires a sensitive test (e.g., NAAT), while the significant legal, social, and psychological consequences of a false-positive test require a very specific test (e.g., culture). A summary of the tests for bacteria and parasites recommended by the Centers for Disease Control and Prevention (CDC) at initial visit and to be considered 2 weeks later for children in cases of suspected sexual abuse is presented in **Table 1-7**.[68] The CDC does not recommend use of NAAT for *N. gonorrhoeae* if culture is available; however, NAAT can be used for detection of *C. trachomatis* in urine from girls and in vaginal secretions.