

1674 Part XVII ◆ Infectious Diseases

Table 279-1 Drugs for Parasitic Infections

Parasitic infections are found throughout the world. With increasing travel, immigration, use of immunosuppressive drugs, and the spread of AIDS, physicians anywhere may see infections caused by previously unfamiliar parasites. The table below lists first-choice and alternative drugs for most parasitic infections.

INFECTION	DRUG	ADULT DOSAGE	PEDIATRIC DOSAGE
Acanthamoeba keratitis			
Drug of choice:	See footnote 1		
Amebiasis (<i>Entamoeba histolytica</i>)			
Asymptomatic			
Drug of choice:	Iodoquinol	650 mg PO tid × 20 days	30-40 mg/kg/day (max 2 g) in 3 doses PO × 20 days
or	Paromomycin	25-35 mg/kg/day PO in 3 doses × 7 days	25-35 mg/kg/day PO in 3 doses × 7 days
Alternative:	Diloxanide furoate ²	500 mg tid PO × 10 days	20 mg/kg/day PO in 3 doses × 10 days
Mild to moderate intestinal disease³			
Drug of choice ⁴ :	Metronidazole	500-750 mg tid PO × 7-10 days	35-50 mg/kg/day PO in 3 doses × 7-10 days
or	Tinidazole ⁵	2 g PO once daily × 3 days	50 mg/kg/day PO (max 2 g) in 1 dose × 3 days
Either followed by:	Iodoquinol	650 mg PO tid × 20 days	30-40 mg/kg/day PO in 3 doses × 20 days (max 2 g)
or	Paromomycin	25-35 mg/kg/day PO in 3 doses × 7 days	25-35 mg/kg/day PO in 3 doses × 7 days
Severe intestinal and extraintestinal disease³			
Drug of choice:	Metronidazole	750 mg PO tid × 7-10 days	35-50 mg/kg/day PO in 3 doses × 7-10 days
or	Tinidazole ⁵	2 g PO once daily × 5 days	50 mg/kg/day PO (max 2 g) × 5 days
Either followed by:	Iodoquinol	650 mg PO tid × 20 days	30-40 mg/kg/day PO in 3 doses × 20 days (max 2 g)
or	Paromomycin	25-35 mg/kg/day PO in 3 doses × 7 days	25-35 mg/kg/day PO in 3 doses × 7 days
Amebic meningoencephalitis, primary and granulomatous			
Naegleria			
Drug of choice:	Amphotericin B ^{6,7}	1.5 mg/kg/day IV in 2 doses × 3 days, then 1.5 mg/kg/day IV × 6 days	1.5 mg/kg/day IV in 2 doses × 3 days, then 1 mg/kg/d IV × 6 days
or		1 mg/kg IV once/day plus 0.5 mg/day intraventricularly (max of 1.5 mg/kg by both routes)	1 mg/kg IV once/daily plus 0.5 mg/d intraventricularly (max of 1.5 mg/kg by both routes)
or	Rifampin Fluconazole Azithromycin	10 mg/kg IV once/daily (max 600 mg/d) 12 mg/kg IV once/daily 500 mg IV once/daily	10 mg/kg IV once/daily (max 600 mg/d) 12 mg/kg IV once/daily 20 mg/kg IV once/daily (max 500 mg/d)
Acanthamoeba			
Drug of choice:	See footnote 8		

¹For treatment of keratitis caused by *Acanthamoeba*, concurrent topical use of 0.1% propamidine isethionate (Brolene) plus neomycin-polymyxin B-gramicidin ophthalmic solution has been successful (Hargrave SL, et al: *Ophthalmology* 106:952, 1999). In some European countries, propamidine is not available and hexamidine (Desmodine) has been used (Seal DV: *Eye* 17:893, 2003). In addition, 0.02% topical polyhexamethylene biguanide (PHMB) and/or chlorhexidine has been used successfully in a large number of patients (Tabin G, et al: *Cornea* 20:757, 2001; Wysenbeek YS, et al: *Cornea* 19:464, 2000). PHMB is available from Leiter's Park Avenue Pharmacy, San Jose, CA (800-292-6773; www.leiterx.com). The combination of chlorhexidine, natamycin (pimaricin), and debridement also has been successful (Kitagawa K, et al: *Jpn J Ophthalmol* 47:616, 2003).

²The drug is not available commercially, but as a service can be compounded by Panorama Compounding Pharmacy, 6744 Balboa Blvd, Van Nuys, CA 91406 (800-247-9767) or Medical Center Pharmacy, New Haven, CT (203-688-6816).

³Treatment should be followed by a course of iodoquinol or paromomycin in the dosage used to treat asymptomatic amebiasis.

⁴Nitazoxanide is FDA approved as a pediatric oral suspension for treatment of *Cryptosporidium* in immunocompetent children younger than 12 yr old and for *Giardia* (*Med Lett* 2003;45:29). It may also be effective for mild to moderate amebiasis (Diaz E, et al: *Am J Trop Med Hyg* 68:384, 2003). Nitazoxanide is available in 500 mg tablets and an oral suspension; it should be taken with food.

⁵A nitroimidazole similar to metronidazole, tinidazole was recently approved by the FDA and appears to be as effective and better tolerated than metronidazole. It should be taken with food to minimize GI adverse effects. For children and patients unable to take tablets, a pharmacist may crush the tablets and mix them with cherry syrup (Humco, and others). The syrup suspension is good for 7 days at room temperature and must be shaken before use. Ornidazole, a similar drug, is also used outside the United States.

⁶*Naegleria* infection has been treated successfully with intravenous and intrathecal use of both amphotericin B and miconazole plus rifampin and with amphotericin B, rifampin, and ornidazole (Seidel J, et al: *N Engl J Med* 306:346, 1982; Jain R, et al: *Neural India* 50:470, 2002). Other reports of successful therapy are less-well documented.

⁷An approved drug, but considered investigational for this condition by the FDA.

⁸Strains of *Acanthamoeba* isolated from fatal granulomatous amebic meningoencephalitis are usually susceptible in vitro to pentamidine, ketoconazole, flucytosine, and (less so) to amphotericin B. Chronic *Acanthamoeba* meningitis has been successfully treated in 2 children with a combination of oral trimethoprim-sulfamethoxazole, rifampin, and ketoconazole (Singhal T, et al: *Pediatr Infect Dis J* 20:623, 2001), and in an AIDS patient with fluconazole, sulfadiazine, and pyrimethamine combined with surgical resection of the CNS lesion (Seijo Martinez M, et al: *J Clin Microbiol* 38:3892, 2000). Disseminated cutaneous infection in an immunocompromised patient has been treated successfully with IV pentamidine isethionate, topical chlorhexidine, and 2% ketoconazole cream, followed by oral itraconazole (Slater CA, et al: *N Engl J Med* 331:85, 1994).

Table 279-1 Drugs for Parasitic Infections—cont'd

INFECTION	DRUG	ADULT DOSAGE	PEDIATRIC DOSAGE
<i>Balamuthia mandrillaris</i>			
Drug of choice:	See footnote 9		
<i>Sappinia diploidea</i>			
Drug of choice:	See footnote 10		
<i>Ancylostoma caninum</i> (eosinophilic enterocolitis)			
Drug of choice:	Albendazole ⁷	400 mg PO once	400 mg PO once
or	Mebendazole	100 mg PO bid × 3 days	100 mg PO bid × 3 days
or	Pyrantel pamoate ⁷	11 mg/kg PO (max 1 g) × 3 days	11 mg/kg PO (max 1 g) × 3 days
or	Endoscopic removal		
<i>Ancylostoma duodenale</i> , see Hookworm			
<i>Angiostrongylasis</i> (<i>Angiostrongylus cantonensis</i> , <i>Angiostrongylus costaricensis</i>)			
Drug of choice:	See footnote 11		
<i>Anisakiasis</i> (<i>Anisakis</i> spp.)			
Treatment of choice ¹² :	Surgical or endoscopic removal		
<i>Ascariasis</i> (<i>Ascaris lumbricoides</i> , roundworm)			
Drug of choice:	Albendazole ⁷	400 mg PO once	400 mg PO once
or	Mebendazole	100 mg PO bid × 3 days or 500 mg PO once	100 mg PO bid × 3 days or 500 mg PO once
or	Ivermectin ⁷	150-200 µg/kg PO once	150-200 µg/kg PO once
<i>Babesiosis</i> (<i>Babesia microti</i>)			
Drugs of choice ¹³ :	Atovaquone ⁷ plus azithromycin ⁷	750 mg PO bid × 7-10 days 600 mg PO daily × 7-10 days	20 mg/kg PO bid × 7-10 days 10 mg/kg PO on day 1 (max 500 mg/dose), then 5 mg/kg/d (max 250 mg/dose) PO days 2-10
or	Clindamycin ⁷ plus quinine ⁷	300-600 mg IV qid or 600 mg tid PO × 7-10 days 650 mg tid PO × 7-10 days	20-40 mg/kg/day IV or PO in 3 or 4 doses × 7-10 days (max 600 mg/dose) 24 mg/kg/day PO in 3 doses × 7-10 days
<i>Balamuthia mandrillaris</i> , see Amebic meningoencephalitis, primary			
<i>Balantidiasis</i> (<i>Balantidium coli</i>)			
Drug of choice:	Tetracycline ^{7,14}	500 mg PO qid × 10 days	40 mg/kg/day PO (max 2 g) in 4 doses × 10 days
Alternatives:	Metronidazole ⁷ Iodoquinol ⁷	750 mg PO tid × 5 days 650 mg PO tid × 20 days	35-50 mg/kg/day PO in 3 doses × 5 days 40 mg/kg/day PO in 3 doses × 20 days

⁹A free-living leptomyxid ameba that causes subacute to fatal granulomatous CNS disease. Several cases of *Balamuthia* encephalitis have been successfully treated with flucytosine, pentamidine, fluconazole, and sulfadiazine plus either azithromycin or clarithromycin (phenothiazines were also used) combined with surgical resection of the CNS lesion (Deetz TR, et al: *Clin Infect Dis* 37:1304, 2003; Jung S, et al: *Arch Pathol Lab Med* 128:466, 2004). Miltefosine is another option currently being evaluated but it is not approved for any indication in the United States at this time. Case reports and in vitro data suggest it may have some antiamebic activity (AC Aichelburg et al., *Emerg Infect Dis* 2008; 14:1743; DY Martinez et al., *Clin Infect Dis* 2010; 51:e7; FL Schuster et al., *J Eukaryot Microbiol* 2006; 53:121). Miltefosine (Impavido) is manufactured in 10 or 50 mg capsules by Paladin (Canada) and is available in the United States from the CDC for treatment of infections with free-living amebas.

¹⁰A free-living ameba not previously known to be pathogenic to humans. It has been successfully treated with azithromycin, IV pentamidine, itraconazole, and flucytosine combined with surgical resection of the CNS lesion (Gelman BB, et al: *J Neuropathol Exp Neurol* 62:990, 2003).

¹¹Most patients have a self-limited course and recover completely. Analgesics, corticosteroids, and careful removal of CSF at frequent intervals can relieve symptoms from increased intracranial pressure (Lo Re V III, Gluckman SJ: *Am J Med* 114:217, 2003). No anthelmintic drug is proven to be effective, and some patients have worsened with therapy (Slom TJ, et al: *N Engl J Med* 346:668, 2002). Mebendazole or albendazole and corticosteroid appeared to shorten the course of infection (K Sawanyawisuth and K Sawanyawisuth, *Trans R Soc Trop Med Hyg* 2008; 102:990; V Chotmongkol et al. *Am J Trop Med Hyg* 2009;81:443).

¹²(Repiso Ortega A, et al: *Gastroenterol Hepatol* 26:341, 2003.) Successful treatment of a patient with *Anisakiasis* with albendazole has been reported (Moore DA, et al *Lancet* 360:54, 2002).

¹³Exchange transfusion has been used in severely ill patients and those with high (>10%) parasitemia (Hatcher JC, et al *Clin Infect Dis* 32:1117, 2001). In patients who were not severely ill, combination therapy with atovaquone and azithromycin was as effective as clindamycin and quinine and may have been better tolerated (Krause PJ, et al: *N Engl J Med* 343:1454, 2000). Highly immunocompromised patients should be treated for a minimum of 6 wk and at least 2 wk past the last positive smear (PJ Krause et al., *Clin Infect Dis* 2008; 46:370). High doses of azithromycin (600-1,000 mg) have been used in combination with atovaquone for the treatment of immunocompromised patients (LM Weiss et al., *N Engl J Med* 2001; 344:773). Resistance to atovaquone plus azithromycin has been reported in immunocompromised patients treated with a single subcurative course of this regimen (GP Wormser et al., *Clin Infect Dis* 2010; 50:381).

¹⁴Use of tetracyclines is contraindicated in pregnancy and in children younger than 8 yr old.

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Table 279-1 Drugs for Parasitic Infections—cont'd

INFECTION	DRUG	ADULT DOSAGE	PEDIATRIC DOSAGE
Baylisascariasis (<i>Baylisascaris procyonis</i>)			
Drug of choice:	See footnote 15		
<i>Blastocystis hominis</i> infection			
Drug of choice:	See footnote 16		
Capillariasis (<i>Capillaria philippinensis</i>)			
Drug of choice:	Mebendazole ⁷	200 mg PO bid × 20 days	200 mg PO bid × 20 days
Alternatives:	Albendazole ⁷	400 mg PO daily × 10 days	400 mg PO daily × 10 days
Chagas disease, see Trypanosomiasis			
<i>Clonorchis sinensis</i>, see Fluke infection			
Cryptosporidiosis (<i>Cryptosporidium</i>)			
Immunocompetent			
Drug of choice:	Nitazoxanide ⁴	500 mg PO bid × 3 days ⁷	1-3 yr: 100 mg PO bid × 3 days 4-11 yr: 200 mg PO bid × 3 days
HIV infected			
Drug of choice:	See footnote 17		
Cutaneous larva migrans (creeping eruption, dog and cat hookworm)			
Drug of choice ¹⁸ :	Albendazole ⁷	400 mg PO daily × 3 days	400 mg PO daily × 3 days
or	Ivermectin ⁷	200 µg/kg PO daily × 1-2 days	200 µg/kg PO daily × 1-2 days
Alternative:	Thiabendazole	Topically	Topically
Cyclosporiasis (<i>Cyclospora cayetanensis</i>)			
Drug of choice ¹⁹ :	Trimethoprim-sulfamethoxazole (TMP-SMX) ⁷	TMP 160 mg/SMX 800 mg (1 DS tab) PO bid × 7-10 days	TMP 5 mg/kg, SMX 25 mg/kg bid PO × 7-10 days
Alternative:	Ciprofloxacin	500 mg PO bid × 7 days	-
Cysticercosis, see Tapeworm infection			
Drug of choice:			
Cystoisosporiasis (<i>Cystoisospora belli</i>, formerly known as <i>Isospora</i>)			
Drug of choice:	Trimethoprim-sulfamethoxazole (TMP-SMX) ⁷	TMP 160 mg/SMX 800 mg (1 DS tab) PO bid × 10 days	TMP 5 mg/kg, SMX 25 mg/kg PO bid × 10 days
<i>Dientamoeba fragilis</i> infection²⁰			
	Paromomycin ⁷	25-35 mg/kg/day PO in 3 doses × 7 days	25-35 mg/kg/day PO in 3 doses × 7 days
or	Iodoquinol	650 mg PO tid × 20 days	30-40 mg/kg/day PO (max 2 g) in 3 doses × 20 days
or	Metronidazole	500-750 mg tid × 10 days	20-40 mg/kg/day in 3 doses × 10 days
<i>Diphyllobothrium latum</i>, see Tapeworm infection			

¹⁵No drugs have been consistently demonstrated to be effective. The combination of albendazole 37 mg/kg/d PO and high-dose steroids has been used successfully (JM Peters et al., *Pediatrics* 2012; 129:e806; S Haider, *Emerg Infect Dis* 2012; 18:347). Albendazole 25 mg/kg/d PO × 20 d started as soon as possible (up to 3 d after possible infection) might prevent clinical disease and is recommended for children with known exposure, such as in the setting of ingestion of raccoon stool or contaminated soil (WJ Murray and KR Kazacos, *Clin Infect Dis* 2004; 39:1484). Mebendazole, levamisole, or ivermectin could be tried if albendazole is not available. Ocular baylisascariasis has been treated successfully using laser photocoagulation therapy to destroy the intraretinal larvae.

¹⁶Clinical significance of these organisms is controversial; metronidazole 750 mg tid × 10 days, iodoquinol 650 mg tid × 20 days or trimethoprim-sulfamethoxazole 1 DS tab bid × 7 days have been reported to be effective (Stenzel DJ, Borenstein PFL: *Clin Microbiol Rev* 9:563, 1996; Ok UZ, et al: *Am J Gastroenterol* 94:3245, 1999). Metronidazole resistance may be common (Haresh K, et al: *Trop Med Int Health* 4:274, 1999). Nitazoxanide has been effective in children (Diaz E, et al: *Am J Trop Med Hyg* 68:384, 2003).

¹⁷Nitazoxanide has not consistently been shown to be superior to placebo in HIV-infected patients (Amadi B, et al: *Lancet* 360:1375, 2002). For HIV-infected patients, potent antiretroviral therapy (ART) is the mainstay of treatment. Nitazoxanide (treatment duration of 5-21 days), paromomycin, or a combination of paromomycin and azithromycin may be tried to decrease diarrhea and recalcitrant malabsorption of antimicrobial drugs, which can occur with chronic cryptosporidiosis (B Pantenburg et al., *Expert Rev Anti Infect Ther* 2009; 7:385).

¹⁸Albanese G, et al: *Int J Dermatol* 40:67, 2001.

¹⁹HIV-infected patients may need higher dosage and long-term maintenance (Kansouzidou A, et al: *J Trav Med* 11:61, 2004).

²⁰Norberg A, et al: *Clin Microbiol Infect* 9:65, 2003.

Table 279-1 Drugs for Parasitic Infections—cont'd

INFECTION	DRUG	ADULT DOSAGE	PEDIATRIC DOSAGE
<i>Dracunculus medinensis</i> (guinea worm) infection			
Drug of choice:	See footnote 21		
<i>Echinococcus</i> , see Tapeworm Infection			
<i>Entamoeba histolytica</i> , see Amebiasis			
<i>Enterobius vermicularis</i> (pinworm) infection			
Drug of choice ²² :	Albendazole ⁷	400 mg PO once; repeat in 2 wk	400 mg PO once; repeat in 2 wk
or	Mebendazole	100 mg PO once; repeat in 2 wk	100 mg PO once; repeat in 2 wk
or	Pyrantel pamoate	11 mg/kg base PO once (max 1 g); repeat in 2 wk	11 mg/kg base PO once (max 1 g); repeat in 2 wk
<i>Fasciola hepatica</i> , see Fluke infection			
Filariasis ²³			
<i>Wuchereria bancrofti</i> , <i>Brugia malayi</i> , <i>Brugia timori</i>			
Drug of choice ²⁴ :	Diethylcarbamazine	6 mg/kg PO in 3 doses × 14 days ²⁵	6 mg/kg PO in 3 doses × 14 days ²⁵
<i>Loa loa</i>			
Drug of choice ²⁶ :	Diethylcarbamazine	9 mg/kg PO in 3 doses × 14 days ²⁵	9 mg/kg PO in 3 doses × 14 days ²⁵
<i>Mansonella ozzardi</i>			
Drug of choice:	See footnote 27		
<i>Mansonella perstans</i>			
Drug of choice:	Doxycycline ^{7,14}	100 mg bid PO × 7 days	4 mg/kg/day in 2 doses PO × 7 days
<i>Mansonella streptocerca</i> ²⁸			
Drug of choice:	Diethylcarbamazine Ivermectin ⁷	6 mg/kg/day PO × 14 days 150 µg/kg PO once	6 mg/kg/day PO × 14 days 150 µg/kg PO once
Tropical pulmonary eosinophilia (TPE) ²⁹			
Drug of choice:	Diethylcarbamazine	6 mg/kg/day in 3 doses × 12-21 days	6 mg/kg/day in 3 doses × 12-21 days
<i>Onchocerca volvulus</i> (river blindness)			
Drug of choice:	Invermectin ³⁰	150 µg/kg PO once, repeated every 6-12 mo until asymptomatic	150 µg/kg PO once, repeated every 6-12 mo until asymptomatic
Fluke, hermaphroditic, infection			

²¹Treatment of choice is slow extraction of worm combined with wound care (MMWR Morbid Mortal Wkly Rep 2011; 60:1450). 10 days' treatment with metronidazole 250 mg tid in adults and 25 mg/kg/day in 3 doses in children is not curative, but decreases inflammation and facilitates removal of the worm. Mebendazole 400-800 mg/day × 6 days has been reported to kill the worm directly.

²²Since all family members are usually infected, treatment of the entire household is recommended.

²³Antihistamines or corticosteroids may be required to decrease allergic reactions due to disintegration of microfilariae from treatment of filarial infections, especially those caused by *Loa loa*. Endosymbiotic *Wolbachia* bacteria may have a role in filarial development and host response, and may represent a new target for therapy. Treatment with doxycycline 100 or 200 mg/day × 4-6 wk in lymphatic filariasis and onchocerciasis has resulted in substantial loss of *Wolbachia* with subsequent block of microfilariae production and absence of microfilaria when followed for 24 mo after treatment (Hoerauf A, et al: Med Microbiol Immunol 192:211, 2003; Hoerauf A, et al: BMJ 326:207, 2003).

²⁴Most symptoms caused by adult worm. Single-dose combination of albendazole (400 mg) with either ivermectin (200 µg/kg) or diethylcarbamazine (6 mg/kg) is effective for reduction or suppression of *Wuchereria bancrofti* microfilaria but does not kill the adult forms (Addiss D, et al: Cochrane Database Syst Rev 2004;CD003753).

²⁵For patients with microfilaria in the blood, Medical Letter consultants would start with a lower dosage and scale up: day 1, 50 mg; day 2, 50 mg tid; day 3, 100 mg tid; day 4-14, 6 mg/kg in 3 doses (for *Loa loa* day 4-14, 9 mg/kg in 3 doses). Multidose regimens have been shown to provide more rapid reduction in microfilaria than single-dose diethylcarbamazine, but microfilaria levels are similar 6-12 mo after treatment (Andrade LD, et al: Trans R Soc Trop Med Hyg 89:319, 1995; Simonsen PE, et al: Am J Trop Med Hyg 53:267, 1995). A single dose of 6 mg/kg is used in endemic areas for mass treatment (Figueiredo-Silva J, et al: Trans R Soc Trop Med Hyg 90:192, 1996; Noroes J, et al: Trans R Soc Trop Med Hyg 91:78, 1997).

²⁶In heavy infections with *Loa loa*, rapid killing of microfilariae can provoke an encephalopathy. Apheresis has been reported to be effective in lowering microfilarial counts in patients heavily infected with *Loa loa* (Ottessen ES: Infect Dis Clin North Am 7:619, 1993). Albendazole or ivermectin have also been used to reduce microfilaremia; albendazole is preferred because of its slower onset of action and lower risk for encephalopathy (Klion AD, et al: J Infect Dis 168:202, 1993; Kombila M, et al: Am J Trop Med Hyg 58:458, 1998). Albendazole may be useful for treatment of loiasis when diethylcarbamazine is ineffective or cannot be used, but repeated courses may be necessary (Klion AD, et al: Clin Infect Dis 29:680, 1999). Diethylcarbamazine, 300 mg once/wk, has been recommended for prevention of loiasis (Nutman TB, et al: N Engl J Med 319:752, 1988).

²⁷Diethylcarbamazine has no effect. Ivermectin 200 µg/kg once has been effective.

²⁸Diethylcarbamazine is potentially curative because of activity against both adult worms and microfilariae. Ivermectin is only active against microfilariae. (The Medical Letter: Drugs for parasitic infections, ed 2, 2010).

²⁹Relapse occurs and can be treated with diethylcarbamazine.

³⁰Annual treatment with ivermectin, 150 µg/kg, can prevent blindness from ocular onchocerciasis (Mabey D, et al: Ophthalmology 103:1001, 1996). Diethylcarbamazine should not be used for treatment of this disease.

Continued

Table 279-1 Drugs for Parasitic Infections—cont'd

INFECTION	DRUG	ADULT DOSAGE	PEDIATRIC DOSAGE
<i>Clonorchis sinensis</i> (Chinese liver fluke)			
Drug of choice:	Praziquantel	75 mg/kg/day PO in 3 doses × 1 day	75 mg/kg/day PO in 3 doses × 1 day
or	Albendazole ⁷	10 mg/kg PO × 7 days	10 mg/kg PO × 7 days
<i>Fasciola hepatica</i> (sheep liver fluke)			
Drug of choice ³¹ :	Triclabendazole	10 mg/kg PO once or twice ³²	10 mg/kg PO once or twice ³²
Alternative:	Bithionol	30-50 mg/kg PO on alternate days × 10-15 doses	30-50 mg/kg PO on alternate days × 10-15 doses
or	Nitazoxanide	500 mg PO bid × 7 days	1-3 yr: 100 mg PO bid 4-11 yr: 200 mg PO bid
<i>Fasciolopsis buski</i>, <i>Heterophyes heterophyes</i>, <i>Metagonimus yokogawai</i> (intestinal flukes)			
Drug of choice:	Praziquantel ⁷	75 mg/kg/day PO in 3 doses × 1 day	75 mg/kg/day PO in 3 doses × 1 day
<i>Metorchis conjunctus</i> (North American liver fluke)³³			
Drug of choice:	Praziquantel ⁷	75 mg/kg/day PO in 3 doses × 1 day	75 mg/kg/day PO in 3 doses × 1 day
<i>Nanophyetus salmincola</i>			
Drug of choice:	Praziquantel ⁷	60 mg/kg/day PO in 3 doses × 1 day	60 mg/kg/day PO in 3 doses × 1 day
<i>Opisthorchis viverrini</i> (Southeast Asian liver fluke)			
Drug of choice:	Praziquantel	75 mg/kg/day PO in 3 doses × 2 days	75 mg/kg/day PO in 3 doses × 2 days
or	Albendazole	10 mg/kg/day PO × 7 days	10 mg/kg/day PO × 7 days
<i>Paragonimus westermani</i> (lung fluke)			
Drug of choice:	Praziquantel ⁷	75 mg/kg/day PO in 3 doses × 2 days	75 mg/kg/day PO in 3 doses × 2 days
or ³⁴	Bithionol	30-50 mg/kg PO on alternate days × 10-15 doses	30-50 mg/kg PO on alternate days × 10-15 doses
or	Triclabendazole	10 mg/kg PO once or twice	10 mg/kg PO once or twice
<i>Giardiasis</i> (<i>Giardia duodenalis</i>)			
Drugs of choice:	Metronidazole ⁷ Nitazoxanide ⁴	250 mg PO tid × 5 days 500 mg PO bid × 3 days	15 mg/kg/day PO in 3 doses × 5 days 1-3 yr: 100 mg PO every 12 hr × 3 days 4-11 yr: 200 mg PO every 12 hr × 3 days 50 mg/kg PO once (max 2 g)
	Tinidazole ⁵	2 g PO once	
Alternatives ³⁵ :	Paromomycin ^{7,36} Furazolidone Quinacrine ²	25-35 mg/kg/day PO in 3 doses × 7 days 100 mg PO qid × 7-10 days 100 mg PO tid × 5 days	25-35 mg/kg/day PO in 3 doses × 7 days 6 mg/kg/day PO in 4 doses × 7-10 days 2 mg/kg tid PO × 5 days (max 300 mg/day)
<i>Gnathostomiasis</i> (<i>Gnathostoma spinigerum</i>)			
Treatment of choice ³⁷ :	Albendazole ⁷	400 mg PO bid × 21 days	400 mg PO bid × 21 days
or	Ivermectin ⁷	200 µg/kg/day PO × 2 days	200 µg/kg/day PO × 2 days
±	Surgical removal		
<i>Gongylonemiasis</i> (<i>Gongylonema</i> sp.)³⁸			
Treatment of choice:	Surgical removal		
or	Albendazole ⁷	10 mg/kg/day PO × 3 days	10 mg/kg/day PO × 3 days

³¹Unlike infections with other flukes, *Fasciola hepatica* infections may not respond to praziquantel. Triclabendazole (Egaten, Novartis) may be safe and effective but data are limited (Graham CS, et al: *Clin Infect Dis* 33:1, 2001). It is available from Victoria Pharmacy, Zurich, Switzerland (www.pharmaworld.com; 41-1-211-24-32) and should be given with food for better absorption. A single study has found that nitazoxanide has limited efficacy for treating fascioliasis in adults and children (Favennec L, et al: *Aliment Pharmacol Ther* 17:265, 2003).

³²Richter J, et al: *Curr Treat Options Infect Dis* 2002;4:313.

³³MacLean JD, et al: *Lancet* 347:154, 1996.

³⁴Triclabendazole may be effective in a dosage of 5 mg/kg once/day × 3 days or 10 mg/kg bid + 1 day (Calvopiña M, et al: *Trans R Soc Trop Med Hyg* 92:566, 1998). See footnote ³¹ for availability.

³⁵Albendazole 400 mg daily × 5 days alone or in combination with metronidazole may also be effective (Hall A, Nahar Q: *Trans R Soc Trop Med Hyg* 87:84, 1993; Dutta AK, et al: *Indian J Pediatr* 61:689, 1994; Cacopardo B, et al: *Clin Ter* 146:761, 1995). Combination treatment with standard doses of metronidazole and quinacrine given for 3 wk has been effective for a small number of refractory infections (Nash TE, et al: *Clin Infect Dis* 33:22, 2001). In 1 study, nitazoxanide was used successfully in high doses to treat a case of *Giardia* resistant to metronidazole and albendazole (Abboud P, et al: *Clin Infect Dis* 32:1792, 2001).

³⁶Not absorbed; may be useful for treatment of giardiasis in pregnancy.

³⁷de Gorgolas M, et al: *J Travel Med* 10:358, 2003. All patients should be treated with a medication regardless of whether surgery is attempted.

³⁸Eberhard ML, Busillo C: *Am J Trop Med Hyg* 61:51, 1999; Wilson ME, et al: *Clin Infect Dis* 32:1378, 2001.

Table 279-1 Drugs for Parasitic Infections—cont'd

INFECTION	DRUG	ADULT DOSAGE	PEDIATRIC DOSAGE
Hookworm infection (<i>Ancylostoma duodenale</i>, <i>Necator americanus</i>)			
Drug of choice:	Albendazole ⁷	400 mg PO once	400 mg PO once
or	Mebendazole	100 mg PO bid × 3 days or 500 mg once	100 mg PO bid × 3 days or 500 mg once
or	Pyrantel pamoate ⁷	11 mg/kg (max 1 g) PO × 3 days	11 mg/kg (max 1 g) PO × 3 days
Hydatid cyst, see Tapeworm infection			
<i>Hymenolepis nana</i>, see Tapeworm infection			
<i>Leishmania</i> infection			
Visceral^{39, 40}			
Drugs of choice:	Sodium stibogluconate	20 mg Sb/kg/day IV or IM × 28 days ⁴¹	20 mg Sb/kg/day IV or IM × 28 days ⁴¹
or	Meglumine antimonate	20 mg pentavalent antimony/kg/day IV or IM × 28 days ⁴¹	20 mg pentavalent antimony/kg/day IV or IM × 28 days ⁴¹
or	Amphotericin B ⁷	0.5-1 mg/kg IV daily or every 2 days for up to 8 wk	0.5-1 mg/kg IV daily or every 2 days for up to 8 wk
or	Liposomal amphotericin B ⁴²	3 mg/kg/day IV (days 1-5) followed by 3 mg/kg/day on days 14 and 21 ⁴³	3 mg/kg/day IV (days 1-5) followed by 3 mg/kg/day on days 14 and 21 ⁴³
or	Miltefosine	2.5 mg/kg/day PO (max 150 mg/day) × 28 days	2.5 mg/kg/day PO (max 150 mg/day) × 28 days
Alternative ⁴⁴ :	Pentamidine ⁷	4 mg/kg IV or IM daily or every 2 days for 15-30 doses	4 mg/kg IV or IM daily or every 2 days for 15-30 doses
Cutaneous⁴⁵			
Drugs of choice:	Sodium stibogluconate	20 mg Sb/kg/day IV or IM × 20 days ⁴¹	20 mg Sb/kg/day IV or IM × 20 days ⁴¹
or	Meglumine antimonate	20 mg pentavalent antimony/kg/day IV or IM × 20 days ⁴¹	20 mg pentavalent antimony/kg/day IV or IM × 20 days ⁴¹
or	Miltefosine	2.5 mg/kg/day PO (max 150 mg/day) × 28 days	2.5 mg/kg/day PO (max 150 mg/day) × 28 days
Alternatives ⁴⁶ :	Pentamidine ⁷	2-3 mg/kg IV or IM daily or every 2 days × 4-7 doses ⁴⁷	2-3 mg/kg IV or IM daily or every 2 days × 4-7 doses ⁴⁷
or	Paromomycin ^{7,48}	Topically 2x/day × 10-20 days	Topically 2x/day × 10-20 days

³⁹Consultation with physicians experienced in management of this disease is recommended. To maximize effectiveness and minimize toxicity, the choice of drug, dosage and duration of therapy should be individualized based on the region of disease acquisition, likely infecting species, number, significance and location of lesions, and host factors such as immune status (HW Murray, Lancet 2005; 366:1561). Some of the listed drugs and regimens are effective only against certain *Leishmania* species/strains and only in certain areas of the world (S Sundar and J Chakravorty, Expert Opin Pharmacother 2013; 14:53).

⁴⁰Visceral infection is most commonly caused by the Old World species *Leishmania donovani* (kala-azar) and *Leishmania infantum* and the New World species *Leishmania chagasi*. Treatment duration may vary based on symptoms, host immune status, species, and area of the world where infection was acquired.

⁴¹May be repeated or continued; a longer duration may be needed for some patients (Herwaldt BL: Lancet 354:1191, 1999).

⁴²Three lipid formulations of amphotericin B have been used for treatment of visceral leishmaniasis. Largely based on clinical trials in patients infected with *Leishmania infantum*, the FDA approved liposomal amphotericin B (AmBisome) for treatment of visceral leishmaniasis (Meyerhoff A, Clin Infect Dis 1999;28:42). Amphotericin B lipid complex (Abelcet) and amphotericin B cholesterol sulfate (Amphotec) have also been used with good results but are considered investigational for this condition by the FDA.

⁴³The FDA-approved dosage regimen for immunocompromised patients (e.g., HIV infected) is 4 mg/kg/day (days 1-5) and 4 mg/kg/day on days 10, 17, 24, 31, and 38. The relapse rate is high; maintenance therapy may be indicated, but there is no consensus as to dosage or duration. (Russo R, Nigro LC, Minniti S, et al: Visceral leishmaniasis in HIV infected patients: treatment with high dose liposomal amphotericin B [AmBisome], J Infect 32:133-137, 1996).

⁴⁴For treatment of kala-azar in adults in India, oral miltefosine 100 mg/day (~205 mg/kg/day) for 3-4 wk was 97% effective after 6 mo (Jha TK, et al: N Engl J Med 341:1795, 1999; Sangraula H, et al: J Assoc Physicians India 51:686, 2003). Gastrointestinal adverse effects are common, and the drug is contraindicated in pregnancy. The dose of miltefosine in an open-label trial in children in India was 2.5 mg/kg/day × 28 days (Bhattacharya SK, et al: Clin Infect Dis 38:217, 2004). Miltefosine (Impavido) is available from the manufacturer (Zentaris, Frankfurt, Germany at Impavido@zentaris.de).

⁴⁵Cutaneous infection is most commonly caused by the Old World species *Leishmania major* and *Leishmania tropica* and the New World species *Leishmania mexicana*, *Leishmania (Viannia) brasiliensis* and others. Treatment duration may vary based on symptoms, host immune status, species, and area of the world where infection was acquired.

⁴⁶In a placebo-controlled trial in patients 12 yr old and older, oral miltefosine was effective for the treatment of cutaneous leishmaniasis caused by *Leishmania (Viannia) panamensis* in Colombia but not *L. (V.) brasiliensis* in Guatemala at a dosage of about 2.5 mg/kg/day for 28 days. "Motion sickness," nausea, headache and increased creatinine were the most frequent adverse effects (Soto J, et al: Clin Infect Dis 38:1266, 2004). See footnote 44 regarding miltefosine availability. For treatment of *L. major* cutaneous lesions, a study in Saudi Arabia found that oral fluconazole, 200 mg once/day × 6 wk, appeared to speed healing (Alrajhi AA, et al: N Engl J Med 346:891, 2002).

⁴⁷At this dosage pentamidine has been effective against leishmaniasis in Colombia where the likely organism was *L. (V.) panamensis* (Soto-Mancipe J, et al: Clin Infect Dis 16:417, 1993; Soto J, et al: Am J Trop Med Hyg 50:107, 1994); its effect against other species is not well established.

⁴⁸Topical paromomycin should be used only in geographic regions where cutaneous leishmaniasis species have low potential for mucosal spread. A formulation of 15% paromomycin/12% methylbenzethonium chloride (Leshcutan) in soft white paraffin for topical use has been reported to be partially effective in some patients against cutaneous leishmaniasis due to *L. major* in Israel and against *L. mexicana* and *L. (V.) brasiliensis* in Guatemala, where mucosal spread is very rare (Arana BA, et al: Am J Trop Med Hyg 65:466, 2001). The methylbenzethonium is irritating to the skin; lesions may worsen before they improve.

Continued

Table 279-1 Drugs for Parasitic Infections—cont'd

INFECTION	DRUG	ADULT DOSAGE	PEDIATRIC DOSAGE
Mucosal⁴⁹			
Drugs of choice:	Sodium stibogluconate	20 mg Sb/kg/day IV or IM × 28 days ⁴¹	20 mg Sb/kg/day IV or IM × 28 days ⁴¹
or	Meglumine antimonate	20 mg pentavalent antimony/kg/day IV or IM × 28 days ⁴¹	20 mg pentavalent antimony/kg/day IV or IM × 28 days ⁴¹
or	Amphotericin B ⁷	0.5-1 mg/kg IV daily or every 2 days for up to 8 wk	0.5-1 mg/kg IV daily or every 2 days for up to 8 wk
or	Miltefosine	2.5 mg/kg/day PO (max 150 mg/day) × 28 days	2.5 mg/kg/day PO (max 150 mg/day) × 28 days
Lice infestation (<i>Pediculus humanus</i>, <i>Pediculus capitis</i>, <i>Phthirus pubis</i>)⁵⁰			
Drugs of choice:	0.5% Malathion ⁵¹	Topically	Topically
or	1% Permethrin ⁵²	Topically	Topically
or	Pyrethrins with piperonyl butoxide ⁵²	Topically	Topically
or	0.5% Ivermectin lotion	Topically, once	Topically, once
or	0.9% Spinosad susp	Topically, 2 × at least 7 days apart	Topically, 2 × at least 7 days apart
or	Ivermectin ^{7,53}	200 µg/kg PO × 3 doses, on days 1, 2, and 10	200 µg/kg PO × 3 doses, on days 1, 2, and 10
<i>Loa loa</i>, see Filariasis			
Malaria, treatment of (<i>Plasmodium falciparum</i>, <i>Plasmodium ovale</i>, <i>Plasmodium vivax</i>, and <i>Plasmodium malariae</i>)			
<i>P. falciparum</i>⁵⁴ acquired in areas of chloroquine resistance			
Oral ⁵⁵			
Drugs of choice:	Atovaquone/ proguanil ⁵⁶	2 adult tabs PO bid ⁵⁸ or 4 adult tabs PO once daily × 3 days	<5 kg: not indicated 5-8 kg: 2 pediatric tabs PO once/day × 3 days 9-10 kg: 3 pediatric tabs PO once/day × 3 days 11-20 kg: 1 adult tab PO once/day × 3 days 21-30 kg: 2 adult tabs PO once/day × 3 days 31-40 kg: 3 adult tabs PO once/day × 3 days >40 kg: 4 adult tabs PO once/day × 3 days
or	Quinine sulfate plus doxycycline ^{7,14} or plus tetracycline ^{7,14} or plus clindamycin ^{7,59}	650 mg PO every 8 hr × 3-7 days ⁵⁷ 100 mg PO bid × 7 days 250 mg PO qid × 7 days 20 mg/kg/day PO in 3 doses × 7 days ⁶⁰	30 mg/kg/day PO in 3 doses × 3-7 days ⁵⁷ 4 mg/kg/day PO in 2 doses × 7 days 6.25 mg/kg PO qid × 7 days 20 mg/kg/day PO in 3 doses × 7 days

⁴⁹Mucosal infection is most commonly due to the New World species *L. (V.) braziliensis*, *L. (V.) panamensis*, or *L. (V.) guyanensis*. Treatment duration may vary based on symptoms, host immune status, species, and area of the world where infection was acquired.

⁵⁰For infestation of eyelashes with *Phthirus pubis* lice, use petrolatum; TMP-SMX has also been used (Meinking TL: *Curr Probl Dermatol* 24:157, 1996). For pubic lice, treat with 5% permethrin or ivermectin as for scabies. TMP-SMX has also been effective together with permethrin for head lice (Hipolito RB, et al: *Pediatrics* 107:E30, 2001).

⁵¹Yoon KS, et al: *Arch Dermatol* 139:994, 2003.

⁵²A second application is recommended 1 wk later to kill hatching progeny. Some lice are resistant to pyrethrins and permethrin (Meinking et al: *Arch Dermatol* 2002;138:220).

⁵³Ivermectin is effective against adult lice but has no effect on nits (Jones KN, JC English III: *Clin Infect Dis* 36:1355, 2003).

⁵⁴Chloroquine-resistant *P. falciparum* occurs in all malarious areas except Central America west of the Panama Canal Zone, Mexico, Haiti, the Dominican Republic, and most of the Middle East (chloroquine resistance has been reported in Yemen, Oman, Saudi Arabia, and Iran). For treatment of multidrug-resistant *P. falciparum* in Southeast Asia, especially Thailand, where resistance to mefloquine is frequent, atovaquone/proguanil, artesunate plus mefloquine, or artemether plus mefloquine may be used (Luxemburger JC, et al: *Trans R Soc Trop Med Hyg* 88:213, 1994; Karbwang J, et al: *Trans R Soc Trop Med Hyg* 89:296, 1995).

⁵⁵Uncomplicated or mild malaria may be treated with oral drugs.

⁵⁶Atovaquone/proguanil is available as a fixed-dose combination tablet: adult tablets (Malarone; atovaquone 250 mg/proguanil 100 mg) and pediatric tablets (Malarone Pediatric; atovaquone 62.5 mg/proguanil 25 mg). To enhance absorption and reduce nausea and vomiting, it should be taken with food or a milky drink. Safety in pregnancy is unknown and use is generally not recommended. In a few small studies outcomes were normal in women treated with the combination in the 2nd and 3rd trimester (B Paternak et al., *Arch Intern Med* 2011; 171:259; AK Boggild et al., *Am J Trop Med Hyg* 2007; 76:208). The drug should not be given to patients with severe renal impairment (creatinine clearance <30 mL/min). There have been isolated case reports of resistance in *P. falciparum* in Africa, but Medical Letter consultants do not believe there is a high risk for acquisition of Malarone-resistant disease (E Schwartz et al., *Clin Infect Dis* 2003; 37:450; A Farnert et al., *BMJ* 2003; 326:628; S Kuhn et al., *Am J Trop Med Hyg* 2005; 72:407; CT Happi et al., *Malar J* 2006; 5:82).

⁵⁷In Southeast Asia, relative resistance to quinine has increased and treatment should be continued for 7 days.

⁵⁸Although approved for once daily dosing, Medical Letter consultants usually divide the dose in 2 to decrease nausea and vomiting.

⁵⁹For use in pregnancy.

⁶⁰Lell B, Kremsner PG: *Antimicrob Agents Chemother* 46:2315, 2002.

Table 279-1 Drugs for Parasitic Infections—cont'd

INFECTION	DRUG	ADULT DOSAGE	PEDIATRIC DOSAGE
or	Coartem (Artemether-lumefantrine)	1 tablet = 20 mg artemether and 120 mg lumefantrine A 3 day treatment schedule with a total of six oral doses is recommended for both adult and pediatric patients based on weight. These six doses should be administered over 3 days (4 tabs/dose at 0, 8, 24, 36, 48, and 60 hr)	5 to <15 kg: 1 tablet PO per dose 15 to <25 kg: 2 tablets PO per dose 25 to <35 kg: 3 tablets per dose ≥35 kg: 4 tablets PO per dose
Alternative:	Mefloquine ^{61,62}	750 mg PO followed 12 hr later by 500 mg	15 mg/kg PO followed 12 hr later by 10 mg/kg
<i>P. vivax</i> ⁶³ acquired in areas of chloroquine resistance			
Oral ⁵⁵			
Drug of choice:	Quinine sulfate plus doxycycline ^{7,14}	650 mg PO every 8 hr × 3-7 days ⁵⁷ 100 mg PO bid × 7 days	30 mg/kg/day PO in 3 doses × 3-7 days ⁵⁷ 4 mg/kg/day PO in 2 doses × 7 days
	plus primaquine ⁶⁴	30 mg base PO daily × 14 days	0.5 mg/kg/day PO × 14 days
or	Mefloquine ⁶¹	750 mg PO followed 12 hr later by 500 mg PO	15 mg/kg PO followed 12 hr later by 10 mg/kg PO
Alternatives:	Chloroquine plus primaquine ⁶⁴	25 mg base/kg PO in 3 doses over 48 hr 30 mg base PO daily × 14 days	25 mg base/kg PO in 3 doses over 48 hr 0.5 mg/kg/day PO × 14 days
All <i>Plasmodium</i> except chloroquine-resistant <i>P. falciparum</i> ⁵⁴ and chloroquine-resistant <i>P. vivax</i> ⁶³ (areas without chloroquine resistance)			
Oral ⁵⁵			
Drug of choice:	Chloroquine phosphate ⁶⁵	1 g (600 mg base), then 500 mg (300 mg base) 6 hr later PO, then 500 mg (300 mg base) at 24 and 48 hr	10 mg base/kg (max 600 mg base), then 5 mg base/kg 6 hr later PO, then 5 mg base/kg at 24 and 48 hr
All <i>Plasmodium</i>			
Parenteral (severe infection; chloroquine-sensitive and resistant)			
Drugs of choice ⁶⁶ :	Quinidine gluconate ⁶⁷	10 mg/kg IV loading dose (max 600 mg) in normal saline over 1-2 hr, followed by continuous infusion of 0.02 mg/kg/min until PO therapy can be started	10 mg/kg IV loading dose (max 600 mg) in normal saline over 1-2 hr, followed by continuous infusion of 0.02 mg/kg/min until PO therapy can be started
or	Quinine dihydrochloride ⁶⁷	20 mg/kg IV loading dose in 5% dextrose over 4 hr, followed by 10 mg/kg over 2-4 hr every 8 hr (max 1,800 mg/day) until PO therapy can be started	20 mg/kg IV loading dose in 5% dextrose over 4 hr, followed by 10 mg/kg over 2-4 hr every 8 hr (max 1,800 mg/day) until PO therapy can be started

⁶¹At this dosage, adverse effects including nausea, vomiting, diarrhea, dizziness, disturbed sense of balance, toxic psychosis, and seizures can occur. Mefloquine should not be used for treatment of malaria in pregnancy unless there is no other treatment option because of increased risk for stillbirth (Nosten F, et al: *Clin Infect Dis* 28:808, 1999). It should be avoided for treatment of malaria in persons with active depression or with a history of psychosis or seizures and should be used with caution in persons with psychiatric illness. Mefloquine can be given to patients taking β blockers if they do not have an underlying arrhythmia; it should not be used in patients with conduction abnormalities. Mefloquine should not be given together with quinine, quinidine, or halofantrine, and caution is required in using quinine, quinidine, or halofantrine to treat patients with malaria who have taken mefloquine for prophylaxis. Resistance to mefloquine has been reported in some areas, such as the Thailand-Myanmar and Thailand-Cambodia borders and in the Amazon basin, where 25 mg/kg should be used. In the United States, a 250 mg tablet of mefloquine contains 228 mg mefloquine base. Outside the United States, each 275 mg tablet contains 250 mg base.

⁶²*P. falciparum* with resistance to mefloquine is a significant problem in the malarious areas of Thailand and in areas of Myanmar and Cambodia that border on Thailand. It has also been reported on the borders between Myanmar and China, Laos and Myanmar, and in Southern Vietnam. In the United States, a 250 mg tablet of mefloquine contains 228 mg mefloquine base. Outside the United States, each 275 mg tablet contains 250 mg base.

⁶³*P. vivax* with decreased susceptibility to chloroquine is a significant problem in Papua New Guinea and Indonesia. There are also a few reports of resistance from Myanmar, India, the Solomon Islands, Vanuatu, Guyana, Brazil, Colombia, and Peru.

⁶⁴Primaquine phosphate can cause hemolytic anemia, especially in patients whose red cells are deficient in glucose-6-phosphate dehydrogenase (G6PD). This deficiency is most common in African, Asian, and Mediterranean peoples. Patients should be screened for G6PD deficiency before treatment. Primaquine should not be used during pregnancy.

⁶⁵If chloroquine phosphate is not available, hydroxychloroquine sulfate is as effective; 400 mg of hydroxychloroquine sulfate is equivalent to 500 mg of chloroquine phosphate.

⁶⁶Exchange transfusion has been helpful for some patients with high-density (>10%) parasitemia, altered mental status, pulmonary edema, or renal complications (Miller KD, et al: *N Engl J Med* 321:65, 1989).

⁶⁷Continuous ECG, blood pressure, and glucose monitoring are recommended, especially in pregnant women and young children. For problems with quinidine availability, call the manufacturer (Eli Lilly, 800-545-5979) or the CDC Malaria Hotline (770-488-7788). Quinidine may have greater antimalarial activity than quinine. The loading dose should be decreased or omitted in those patients who have received quinine or mefloquine. If more than 48 hr of parenteral treatment is required, the quinine or quinidine dose should be reduced by 30-50%.

Continued

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Table 279-1 Drugs for Parasitic Infections—cont'd

INFECTION	DRUG	ADULT DOSAGE	PEDIATRIC DOSAGE
Alternative:	Artesunate ⁶⁸ Plus a second oral drug	2.4 mg/kg/dose IV × 3 days, at 0, 12, 24, 48, and 72 hr	2.4 mg/kg/dose IV × 3 days, at 0, 12, 24, 48, and 72 hr
Prevention of relapses: <i>P. vivax</i> and <i>P. ovale</i> only			
Drug of choice:	Primaquine phosphate ⁶⁴	30 mg base/day PO × 14 days	0.6 mg base/kg/day PO × 14 days
Malaria, prevention of⁶⁹			
Chloroquine-sensitive areas⁵⁴			
Drug of choice	Chloroquine phosphate ^{70,71}	500 mg (300 mg base), PO once/wk ⁷²	5 mg/kg base once/wk, up to adult dose of 300 mg base ⁷²
Chloroquine-resistant areas⁵⁴			
Drug of choice:	Atovaquone/proguanil ^{56,71}	1 adult tab PO q day ⁷³	11-20 kg: 1 pediatric tab PO/day ^{56,73} 21-30 kg: 2 pediatric tabs PO/day ^{56,73} 31-40 kg: 3 pediatric tabs PO/day ^{56,73} >40 kg: 1 adult tab PO/day ^{56,73}
or	Mefloquine ^{61,71,74}	250 mg PO once/wk ⁷²	<9 kg: 5 mg/kg salt once/wk ⁷² 9-19 kg: ¼ tab once/wk ⁷² 19-30 kg: ½ tab once/wk ⁷² 31-45 kg: ¾ tab once/wk ⁷² >45 kg: 1 tab once/wk ⁷²
or	Doxycycline ^{7,71}	100 mg PO daily ⁷⁵	2 mg/kg/day, up to 100 mg/day ⁷⁵
Alternatives:	Primaquine ⁷	30 mg base PO daily ⁷⁶	0.6 mg/kg base daily
Malaria, self-presumptive treatment⁷⁷			
Drug of choice:	Atovaquone/proguanil ^{7,56,78}	4 adult tabs PO daily × 3 days	<5 kg: not indicated 5-8 kg: 2 pediatric tabs PO once/day × 3 days 9-10 kg: 3 pediatric tabs PO once/day × 3 days 11-20 kg: 1 adult tab PO once/day × 3 days 21-30 kg: 2 adult tabs PO once/day × 3 days 31-40 kg: 3 adult tabs PO once/day × 3 days >40 kg: 4 adult tabs PO once/day × 3 days

⁶⁸Ooral artesunate is not available in the United States; the IV formulation is available through the CDC Malaria branch under an investigational new drug (IND) for patients with severe disease who do not have timely access or cannot tolerate, or fail to respond to IV quinidine (*Med Lett Drugs Ther* 2008; 50:37). To avoid development of resistance, adults treated with artesunate must also receive oral treatment doses of either atovaquone/proguanil, doxycycline, clindamycin, or mefloquine; children should take either atovaquone/proguanil, clindamycin, or mefloquine (F Nosten et al., *Lancet* 2000; 356:297; M van Vugt, *Clin Infect Dis* 2002; 35:1498; F Smithuis et al., *Trans R Soc Trop Med Hyg* 2004; 98:182). If artesunate is given IV, oral medication should be started when the patient is able to tolerate it (SEAQUAMAT group, *Lancet* 2005; 366:717; PE Duffy and CH Sibley, *Lancet* 2005; 366:1908). Reduced susceptibility to artesunate characterized by slow parasitic clearance has been reported in Cambodia (WO Rogers et al., *Malar J* 2009; 8:10; AM Dundorp et al., *N Engl J Med* 2009; 361:455).

⁶⁹No drug regimen guarantees protection against malaria. If fever develops within a year (particularly within the first 2 mo) after travel to malarious areas, travelers should be advised to seek medical attention. Insect repellents, insecticide-impregnated bed nets, and proper clothing are important adjuncts for malaria prophylaxis (*Med Lett* 45:41, 2003). Malaria in pregnancy is particularly serious for both mother and fetus; therefore, prophylaxis is indicated if exposure cannot be avoided.

⁷⁰In pregnancy, chloroquine prophylaxis has been used extensively and safely.

⁷¹For prevention of attack after departure from areas where *P. vivax* and *P. ovale* are endemic, which includes almost all areas where malaria is found (except Haiti), some experts prescribe in addition primaquine phosphate 30 mg base/day or, for children, 0.6 mg base/kg/day during the last 2 wk of prophylaxis. Others prefer to avoid the toxicity of primaquine and rely on surveillance to detect cases when they occur, particularly when exposure was limited or doubtful. See also footnote 64.

⁷²Beginning 1-2 wk before travel and continuing weekly for the duration of stay and for 4 wk after leaving malarious zone. Most adverse events occur within 3 doses. Some Medical Letter consultants favor starting mefloquine 3 wk prior to travel and monitoring the patient for adverse events; this allows time to change to an alternative regimen if mefloquine is not tolerated. Mefloquine should not be taken on an empty stomach; it should be taken with at least 8 oz of water. For pediatric doses less than ½ tablet, it is advisable to have a pharmacist crush the tablet, estimate doses by weighing, and package them in gelatin capsules. There are no data for use in children weighing <5 kg, but based on dosages in other weight groups, a dose of 5 mg/kg can be used.

⁷³Beginning 1-2 days before travel and continuing for the duration of stay and for 1 wk after leaving. In 1 study of malaria prophylaxis, atovaquone/proguanil was better tolerated than mefloquine in nonimmune travelers (Overbosch D, et al: *Clin Infect Dis* 33:1015, 2001).

⁷⁴Mefloquine has not been approved for use during pregnancy. However, it has been reported to be safe for prophylactic use during the 2nd or 3rd trimester of pregnancy and possibly during early pregnancy as well. Mefloquine is not recommended for patients with cardiac conduction abnormalities, and patients with a history of depression, seizures, psychosis, or psychiatric disorders should avoid mefloquine prophylaxis. Resistance to mefloquine has been reported in some areas, such as the Thailand-Myanmar and Thailand-Cambodia borders; in these areas, atovaquone/proguanil or doxycycline should be used for prophylaxis.

⁷⁵Beginning 1-2 days before travel and continuing for the duration of stay and for 4 wk after leaving. Use of tetracyclines is contraindicated in pregnancy and in children younger than 8 yr old. Doxycycline can cause gastrointestinal disturbances, vaginal moniliasis, and photosensitivity reactions.

⁷⁶Studies have shown that daily primaquine beginning 1 day before departure and continued until 3-7 days after leaving the malaria area provides effective prophylaxis against chloroquine-resistant *P. falciparum* (Baird JK, et al: *Clin Infect Dis* 37:1659, 2003). Some studies have shown less efficacy against *P. vivax*. Nausea and abdominal pain can be diminished by taking with food.

⁷⁷A traveler can be given a course of atovaquone/proguanil, mefloquine, or quinine plus doxycycline for presumptive self-treatment of febrile illness. The drug given for self-treatment should be different from that used for prophylaxis. This approach should be used only in very rare circumstances when a traveler cannot promptly get to medical care.

⁷⁸Beginning 1-2 days before travel and continuing for the duration of stay and for 1 wk after leaving malarious zone. In 1 study of malaria prophylaxis, atovaquone/proguanil was better tolerated than mefloquine in nonimmune travelers (D Overbosch et al., *Clin Infect Dis* 2001; 33:1015). The protective efficacy of Malarone against *P. vivax* is variable ranging from 84% in Indonesian New Guinea (J Ling et al., *Clin Infect Dis* 2002; 35:825) to 100% in Colombia (J Soto et al., *Am J Trop Med Hyg* 2006; 75:430). Some Medical Letter consultants prefer alternate drugs if traveling to areas where *P. vivax* predominates.

Table 279-1 Drugs for Parasitic Infections—cont'd

INFECTION	DRUG	ADULT DOSAGE	PEDIATRIC DOSAGE
or	Quinine sulfate plus doxycycline ^{7,14}	650 mg PO every 8 hr × 3-7 days ⁵⁷ 100 mg bid PO × 7 days	30 mg/kg/day PO in 3 doses × 3-7 days ⁵⁷ 4 mg/kg/day in 2 PO doses × 7 days
or	Mefloquine ⁶¹	750 mg PO followed 12 hr later by 500 mg	15 mg/kg followed 12 hr later by 10 mg/kg
Microsporidiosis			
Ocular (<i>Encephalitozoon hellem</i> , <i>Encephalitozoon cuniculi</i> , <i>Vittaforma corneae</i> [<i>Nosema corneum</i>])			
Drug of choice:	Albendazole ⁷ plus fumagillin ⁷⁹	400 mg PO bid	
Intestinal (<i>Enterocytozoon bieneusi</i> , <i>Encephalitozoon [Septata] intestinalis</i>)			
<i>E. bieneusi</i> ⁸⁰	Fumagillin	60 mg/day PO × 14 days in 3 divided doses	
<i>E. intestinalis</i>			
Drug of choice	Albendazole ⁷	400 mg PO bid × 21 days	
Disseminated (<i>E. hellem</i> , <i>E. cuniculi</i> , <i>E. intestinalis</i> , <i>Pleistophora</i> sp., <i>Trachipleistophora</i> sp., and <i>Brachiola vesicularum</i>)			
Drug of choice ⁸¹ :	Albendazole ⁷	400 mg PO bid	
Mites, see Scabies			
<i>Moniliformis moniliformis</i> infection			
Drug of choice:	Pyrantel pamoate ⁷	11 mg/kg PO once, repeat twice, 2 wk apart	11 mg/kg PO once, repeat twice, 2 wk apart
<i>Naegleria</i> species, see Amebic meningoencephalitis, primary			
<i>Necator americanus</i> , see Hookworm infection			
<i>Oesophagostomum bifurcum</i>			
Drug of choice:	See footnote 82		
<i>Onchocerca volvulus</i> , see Filariasis			
<i>Opisthorchis viverrini</i> , see Fluke infection			
<i>Paragonimus westermani</i> , see Fluke infection			
<i>Pediculus capitidis</i> , <i>Pediculus humanus</i> , <i>Phthirus pubis</i> , see Lice			
<i>Pinworm</i> , see Enterobius			
<i>Pneumocystis jiroveci</i> (formerly <i>Pneumocystis carinii</i>) pneumonia (PCP) ⁸³			
Moderate to severe disease			
Drug of choice:	Trimethoprim-sulfamethoxazole (TMP-SMX)	TMP 15-20 mg/kg/day, SMX 75-100 mg/kg/day, PO or IV (change to PO after clinical improvement) in 3 or 4 doses × 21 days	TMP 15-20 mg/kg/day, SMX 75-100 mg/kg/day, PO or IV (change to PO after clinical improvement) in 3 or 4 doses × 21 days
Alternatives:	Pentamidine or Primaquine plus clindamycin ⁷	3-4 mg IV daily × 21 days 30 mg base PO daily × 21 days 600-900 mg IV tid or qid × 21 days, or 300-450 mg PO tid or qid × 21 days (change to PO after clinical improvement)	3-4 mg IV daily × 21 days 0.3 mg/kg base PO (max 30 mg) daily × 21 days 15-25 mg/kg IV tid or qid × 21 days, or 10 mg/kg PO tid or qid (max 300-450 mg/dose) × 21 days (change to PO after clinical improvement)

⁷⁹Ocular lesions caused by *E. hellem* in HIV-infected patients have responded to fumagillin eyedrops prepared from Fumidil-B (bicyclohexyl ammonium fumagillin) used to control a microsporidial disease of honey bees (Diesenhouse MC: *Am J Ophthalmol* 115:293, 1993), available from Leiter's Park Avenue Pharmacy (see footnote 1). For lesions caused by *V. corneae*, topical therapy is generally not effective and keratoplasty may be required (Davis RM, et al: *Ophthalmology* 97:953, 1990).

⁸⁰Oral fumagillin (Sanofi Recherche, Gentilly, France) has been effective in treating *E. bieneusi* (Molina J-M, et al: *N Engl J Med* 346:1963, 2002), but has been associated with thrombocytopenia. HAART may lead to microbiologic and clinical response in HIV-infected patients with microsporidial diarrhea (Benson CA, Kaplan JE, Masur H, et al: Treating opportunistic infections among HIV-infected adults and adolescents: recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association/Infectious Diseases Society of America, *MMWR Recomm Rep* 53([RR-15]:1-112, 2004). Octreotide (Sandostatin) has provided symptomatic relief in some patients with large-volume diarrhea.

⁸¹Molina J-M, et al: *J Infect Dis* 171:245, 1995. There is no established treatment for *Pleistophora*. For disseminated disease caused by *Trachipleistophora* or *Brachiola*, itraconazole 400 mg PO once/day plus albendazole may also be tried (Coyle CM, et al: *N Engl J Med* 351:42, 2004).

⁸²Albendazole or pyrantel pamoate may be effective (Ziem JB, et al: *Ann Trop Med Parasitol* 98:385, 2004).

⁸³*Pneumocystis* has been reclassified as a fungus. In severe disease with room air $\text{PO}_2 \leq 70$ mm Hg or $A-a\text{O}_2$ gradient ≥ 35 mm Hg, prednisone should also be used (Gagnon S, et al: *N Engl J Med* 323:1444, 1990; Caumes E, et al: *Clin Infect Dis* 18:319, 1994).

Continued

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Table 279-1 Drugs for Parasitic Infections—cont'd

INFECTION	DRUG	ADULT DOSAGE	PEDIATRIC DOSAGE
Mild to moderate disease			
Drug of choice:	Trimethoprim-sulfamethoxazole (TMP-SMX)	2 DS tablets (160 mg/800 mg each) PO tid × 21 days	TMP 15-20 mg/kg/day SMX 75-100 mg/kg/day PO in 3 or 4 doses × 21 days
Alternative:	Dapsone plus trimethoprim or primaquine plus clindamycin or atovaquone	100 mg PO daily × 21 days 15 mg/kg/day PO in 3 doses 30 mg base PO daily × 21 days 300-450 mg PO tid or qid × 21 days 750 mg PO bid × 21 days	2 mg/kg/day (max 100 mg) PO × 21 days 15 mg/kg/day PO in 3 doses 0.3 mg/kg base PO daily (max 30 mg) × 21 days 10 mg/kg PO tid or qid (max 300-450 mg/dose) × 21 days 1-3 mo: 30 mg/kg/day PO in 2 doses × 21 days 4-24 mo: 45 mg/kg/day PO in 2 doses × 21 days >24 mo: 30 mg/kg/day PO in 2 doses × 21 days
Primary and secondary prophylaxis⁸⁴			
Drug of choice:	Trimethoprim-sulfamethoxazole (TMP-SMX)	1 tab (single or double strength) PO daily or 1 DS tab PO 3 doses/wk	TMP 150 mg/m ² , SMX 750 mg/m ² PO in 2 doses on 3 consecutive days per wk
Alternatives ⁸⁵ :	Dapsone ⁷	50 mg PO bid, or 100 mg PO daily	2 mg/kg/day (max 100 mg) PO or 4 mg/kg (max 200 mg) PO each wk
or	Dapsone ⁷ plus pyrimethamine ⁸⁶	50 mg PO daily or 200 mg PO each wk 50 mg PO or 75 mg PO each wk	
or	Pentamidine aerosol	300 mg inhaled monthly via Respigrad II nebulizer	≥5 yr: 300 mg inhaled monthly via Respigrad II nebulizer
or	Atovaquone ⁷	1,500 mg/d PO in 1 or 2 doses	1-3 mo: 30 mg/kg/day PO 4-24 mo: 45 mg/kg/day PO >24 mo: 30 mg/kg/day PO
Roundworm, see Ascariasis			
Sappinia diploidea , see Amebic meningoencephalitis, primary			
Scabies (<i>Sarcoptes scabiei</i>)			
Drug of choice:	5% Permethrin	Topically, 2x at least 7 days apart ⁸⁷	Topically, 2x at least 7 days apart ⁸⁷
Alternatives ⁸⁸ :	Ivermectin ^{7,89} 10% Crotamiton	200 µg/kg PO 2x at least 7 days apart ⁸⁷ Topically overnight on days 1, 2, 3, 8	200 µg/kg PO 2x at least 7 days apart ⁸⁷ Topically overnight on days 1, 2, 3, 8
Schistosomiasis (Bilharziasis)			
<i>Schistosoma haematobium</i>			
Drug of choice:	Praziquantel	40 mg/kg/day PO in 1 or 2 doses × 1 day	40 mg/kg/day PO in 1 or 2 doses × 1 day
<i>Schistosoma intercalatum</i>			
Drug of choice:	Praziquantel	40 mg/kg/day PO in 1 or 2 doses × 1 day	40 mg/kg/day PO in 1 or 2 doses × 1 day
<i>Schistosoma japonicum</i>			
Drug of choice:	Praziquantel	60 mg/kg/day PO in 2 or 3 doses × 1 day	60 mg/kg/day PO in 3 doses × 1 day

⁸⁴Primary/secondary prophylaxis in patients with HIV can be discontinued after CD4 count increases to >200 × 10⁹/L for longer than 3 mo.⁸⁵An alternative trimethoprim-sulfamethoxazole regimen is 1 DS tab 3x/wk. Weekly therapy with sulfadoxine 500 mg/pyrimethamine 25 mg/leucovorin 25 mg was effective *Pneumocystis carinii* pneumonia (PCP) prophylaxis in liver transplant patients (Torre-Cisneros J, et al: *Clin Infect Dis* 29:771, 1999).⁸⁶Plus leucovorin 25 mg with each dose of pyrimethamine.⁸⁷In some cases, treatment may need to be repeated in 10-14 days. BJ Currie and JS McCarthy, *N Engl J Med* 2010; 362:717. A second ivermectin dose taken 2 wk later increased the cure rate to 95%, which is equivalent to that of 5% permethrin (V Usha et al., *J Am Acad Dermatol* 2000; 42:236). Ivermectin, either alone or in combination with a topical scabicide, is the drug of choice for crusted scabies in immunocompromised patients (P del Giudice, *Curr Opin Infect Dis* 2004; 15:123).⁸⁸Lindane (γ -benzene hexachloride; Kwell) should be reserved as a second-line agent. The FDA has recommended it should not be used for immunocompromised patients, young children, the elderly, and patients who weigh <50 kg.⁸⁹Ivermectin, either alone or in combination with a topical scabicide, is the drug of choice for crusted scabies in immunocompromised patients (del Giudice P: *Curr Opin Infect Dis* 15:123, 2004). The safety of oral ivermectin in pregnancy and young children has not been established.

Table 279-1 Drugs for Parasitic Infections—cont'd

INFECTION	DRUG	ADULT DOSAGE	PEDIATRIC DOSAGE
<i>Schistosoma mansoni</i>			
Drug of choice:	Praziquantel	40 mg/kg/day PO in 1 or 2 doses × 1 day	40 mg/kg/day PO in 1 or 2 doses × 1 day
Alternative:	Oxamniquine ⁹⁰	15 mg/kg PO once ⁹¹	20 mg/kg/day PO in 2 doses × 1 day ⁹¹
<i>Schistosoma mekongi</i>			
Drug of choice:	Praziquantel	60 mg/kg/day PO in 2 or 3 doses × 1 day	60 mg/kg/day PO in 3 doses × 1 day
Sleeping sickness, see Trypanosomiasis			
<i>Strongyloidiasis (Strongyloides stercoralis)</i>			
Drug of choice ⁹² :	Ivermectin	200 µg/kg/day PO × 2 days	200 µg/kg/day PO × 2 days
Alternative:	Albendazole ^{7, 93}	400 mg PO bid × 7 days	400 mg bid PO × 7 days
Tapeworm infection			
Adult (intestinal stage)			
<i>Diphyllobothrium latum</i> (fish), <i>Taenia saginata</i> (beef), <i>Taenia solium</i> (pork), <i>Dipylidium caninum</i> (dog)			
Drug of choice:	Praziquantel ⁷	5-10 mg/kg PO once	5-10 mg/kg PO once
Alternative:	Niclosamide	2 g PO once	50 mg/kg PO once
<i>Hymenolepis nana</i> (dwarf tapeworm)			
Drug of choice:	Praziquantel ⁷	25 mg/kg PO once	25 mg/kg PO once
Alternative:	Niclosamide	2 g PO daily × 7 days	11-34 kg: 1 g PO on day 1 then 500 mg/day PO × 6 days ⁹⁴ >34 kg: 1.5 g PO on day 1 then 1 g/d PO × 6 days ⁹⁴
Larval (tissue stage)			
<i>Echinococcus granulosus</i> (hydatid cyst)			
Drug of choice ⁹⁵ :	Albendazole	400 mg PO bid × 1-6 mo	15 mg/kg/day PO (max 800 mg) × 1-6 mo
<i>Echinococcus multilocularis</i>			
Treatment of choice:	See footnote 96		
<i>Taenia solium</i> (cysticercosis)			
Treatment of choice		See footnote 97	
Alternative:	Albendazole	400 mg bid PO × 8-30 days; can be repeated as necessary	15 mg/kg/day PO (max 800 mg) in 2 doses × 8-30 days; can be repeated as necessary
or	Praziquantel ⁷	50 mg/kg/day PO in 3 doses × 15 days	50 mg/kg/day PO × 15 day
Toxocariasis, see Visceral larva migrans			

⁹⁰Oxamniquine has been effective in some areas in which praziquantel is less effective (Stelma FF, et al: *J Infect Dis* 176:304, 1997). Oxamniquine is contraindicated in pregnancy.

⁹¹In East Africa, the dose should be increased to 30 mg/kg, and in Egypt and South Africa to 30 mg/kg/day × 2 days. Some experts recommend 40-60 mg/kg over 2-3 days in all of Africa (Shekhar KC: *Drugs* 42:379, 1991).

⁹²In immunocompromised patients or disseminated disease, it may be necessary to prolong or repeat therapy, or to use other agents. Veterinary parenteral and enema formulations of ivermectin have been used in severely ill patients unable to take oral medications (Chiodini PL, et al: *Lancet* 355:43, 2000; Orem J, et al: *Clin Infect Dis* 37:152, 2003; Tarr PE: *Am J Trop Med Hyg* 68:453, 2003).

⁹³Albendazole must be taken with food; a fatty meal increases oral bioavailability.

⁹⁴Niclosamide must be thoroughly chewed or crushed and swallowed with a small amount of water. Nitazoxanide may be an alternative (JJ Ortiz et al., *Trans R Soc Trop Med Hyg* 2002; 96:193; JC Chero et al., *Trans R Soc Trop Med Hyg* 2007; 101:203; E Diaz et al., *Am J Trop Med Hyg* 2003; 68:384).

⁹⁵Patients may benefit from surgical resection or percutaneous drainage of cysts. Praziquantel is useful preoperatively or in case of spillage of cyst contents during surgery. Percutaneous aspiration-injection-respiration (PAIR) with ultrasound guidance plus albendazole therapy has been effective for management of hepatic hydatid cyst disease (Smego RA Jr, et al: *Clin Infect Dis* 37:1073, 2003).

⁹⁶Surgical excision is the only reliable means of cure. Reports have suggested that in nonresectable cases use of albendazole or mebendazole can stabilize and sometimes cure infection (Craig P: *Curr Opin Infect Dis* 16:437, 2003).

⁹⁷Initial therapy for patients with inflamed parenchymal cysticercosis should focus on symptomatic treatment with antiseizure medication. Treatment of parenchymal cysticerci with albendazole or praziquantel is controversial (Maguire JM: *N Engl J Med* 350:215, 2004). Patients with live parenchymal cysts who have seizures should be treated with albendazole together with steroids (6 mg dexamethasone or 40-60 mg prednisone daily) and an antiseizure medication (Garcia HH, et al: *N Engl J Med* 350:249, 2004). Patients with subarachnoid cysts or giant cysts in the fissures should be treated for at least 30 days (Proaño JV, et al: *N Engl J Med* 345:879, 2001). Surgical intervention or CSF diversion is indicated for obstructive hydrocephalus; prednisone 40 mg/day may be given with surgery. Arachnoiditis, vasculitis, or cerebral edema is treated with prednisone 60 mg/day or dexamethasone 4-6 mg/day together with albendazole or praziquantel (White Jr AC: *Annu Rev Med* 51:187, 2000). Any cysticercocidal drug may cause irreparable damage when used to treat ocular or spinal cysts, even when corticosteroids are used. An ophthalmic exam should always precede treatment to rule out intraocular cysts.

Continued

Table 279-1 Drugs for Parasitic Infections—cont'd

INFECTION	DRUG	ADULT DOSAGE	PEDIATRIC DOSAGE
Toxoplasmosis (<i>Toxoplasma gondii</i>)⁹⁸			
Drugs of choice ^{99,100} :	Pyrimethamine ¹⁰¹ plus Sulfadiazine or plus Clindamycin or plus Atovaquone	200 mg PO × 1, then 50-75 mg/day × 3-6 wk 1-1.5 g PO qid × 3-6 wk 1.8-2.4 g/day IV or PO in 3 or 4 doses 1,500 mg PO bid	2 mg/kg/d × 3 days, then 1 mg/kg/day (max 25 mg/day) × 4 wk ¹⁰² 100-200 mg/kg/day × 3-4 wk 5-7.5 mg/kg/day IV or PO in 3 or 4 doses (max 600 mg/dose) 1,500 mg PO bid
Alternative:	Trimethoprim-sulfamethoxazole (TMP-SMX)	TMP 15-20 mg/kg/day; SFX 75-100 mg/kg/day PO or IV in 3 or 4 doses	TMP 15-20 mg/kg/day; SFX 75-100 mg/kg/day PO or IV in 3 or 4 doses
Trichinellosis (<i>Trichinella spiralis</i>)			
Drugs of choice:	Steroids for severe symptoms plus Albendazole ⁷	Prednisone 30-60 mg PO daily × 10-15 days 400 mg PO bid × 8-14 days	400 mg PO bid × 8-14 days
Alternative:	Mebendazole ⁷	200-400 mg PO tid × 3 days, then 400-500 mg PO tid × 10 days	200-400 mg PO tid × 3 days, then 400-500 mg PO tid × 10 days
Trichomoniasis (<i>Trichomonas vaginalis</i>)			
Drug of choice ¹⁰³ :	Metronidazole or Tinidazole ⁵	2 g PO once or 500 mg PO bid × 7 days 2 g PO once	15 mg/kg/day PO in 3 doses × 7 days 50 mg/kg PO once (max 2 g)
Trichostrongylus infection			
Drug of choice:	Pyrantel pamoate ⁷	11 mg/kg base PO once (max 1 g)	11 mg/kg PO once (max 1 g)
Alternative:	Mebendazole ⁷ or Albendazole ⁷	100 mg PO bid × 3 days 400 mg PO once	100 mg PO bid × 3 days 400 mg PO once
Trichuriasis (<i>Trichuris trichiura</i>, whipworm)			
Drug of choice:	Mebendazole	100 mg PO bid × 3 days	100 mg PO bid × 3 days
Alternative:	Albendazole ⁷ Ivermectin ⁷	400 mg PO × 3 days 200 µg/kg PO × 3 days	400 mg PO × 3 days 200 µg/kg PO × 3 days
Trypanosomiasis¹⁰⁴			
<i>Trypanosoma cruzi</i> (American trypanosomiasis, Chagas disease)			
Drug of choice:	Benznidazole	5-7 mg/kg/day PO in 2 divided doses × 60 days	≤12 yr: 10 mg/kg/day PO in 2 or 3 doses × 60 days
or	Nifurtimox ¹⁰⁵	8-10 mg/kg/day PO in 3-4 doses × 90 days	1-10 yr: 15-20 mg/kg/day PO in 4 doses × 90 days 11-16 yr: 12.5-15 mg/kg/day in 4 doses × 90 days

⁹⁸In ocular toxoplasmosis with macular involvement, corticosteroids are recommended in addition to antiparasitic therapy for an antiinflammatory effect.⁹⁹To treat CNS toxoplasmosis in HIV-infected patients, some clinicians have used pyrimethamine 50-100 mg/day (after a loading dose of 200 mg) with sulfadiazine and, when sulfonamide sensitivity developed, have given clindamycin 1.8-2.4 g/day in divided doses instead of the sulfonamide. Atovaquone plus pyrimethamine appears to be an effective alternative in sulfa-intolerant patients (Chirgwin K, et al: *Clin Infect Dis* 34:1243, 2002). Treatment is followed by chronic suppression with lower-dosage regimens of the same drugs. For primary prophylaxis in HIV patients with <100 × 10⁶/L CD4 cells, either trimethoprim-sulfamethoxazole, pyrimethamine with dapsone, or atovaquone with or without pyrimethamine can be used. Primary or secondary prophylaxis may be discontinued when the CD4 count increases to >200 × 10⁶/L for more than 3 mo (Benson CA, Kaplan JE, Masur H, et al: Treating opportunistic infections among HIV-infected adults and adolescents: recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association/Infectious Diseases Society of America, *MMWR Recomm Rep* 53(RR-15):1-112, 2004).¹⁰⁰Women who develop toxoplasmosis during the 1st trimester of pregnancy can be treated with spiramycin (3-4 g/day). After the 1st trimester, if there is no documented transmission to the fetus, spiramycin can be continued until term. If transmission has occurred in utero, therapy with pyrimethamine and sulfadiazine should be started (Montoya JG, Liesenfeld O: *Lancet* 363:1965, 2004). Pyrimethamine is a potential teratogen and should be used only after the 1st trimester.¹⁰¹Plus leucovorin 10-25 mg with each dose of pyrimethamine.¹⁰²Congenitally infected newborns should be treated with pyrimethamine every 2 or 3 days and a sulfonamide daily for about 1 yr (Remington JS, Klein JO, editors: *Infectious disease of the fetus and newborn infant*, ed 5, Philadelphia, 2001, WB Saunders, p. 290).¹⁰³Sexual partners should be treated simultaneously. Metronidazole-resistant strains have been reported and can be treated with higher doses of metronidazole (2-4 g/day × 7-14 days) or with tinidazole (Hager WD: *Sex Transm Dis* 31:343, 2004).¹⁰⁴Barrett MP, et al: *Lancet* 362:1469, 2003.¹⁰⁵The addition of γ-interferon to nifurtimox for 20 days in experimental animals and in a limited number of patients appears to shorten the acute phase of Chagas disease (McCabe RE, et al: *J Infect Dis* 163:912, 1991).

Table 279-1 Drugs for Parasitic Infections—cont'd

INFECTION	DRUG	ADULT DOSAGE	PEDIATRIC DOSAGE
<i>Trypanosoma brucei gambiense</i> (West African trypanosomiasis, sleeping sickness)			
Hemolympathic stage			
Drug of choice ¹⁰⁶ :	Pentamidine isethionate ⁷	4 mg/kg/day IM × 7 days	4 mg/kg/day IM or IV × 7 days
Alternative:	Suramin	100-200 mg (test dose) IV, then 1 g IV on days 1, 3, 5, 14, and 21	2 mg/kg (test dose) IV, then 20 mg/kg IV on days 1, 3, 5, 14, and 21
Late disease with CNS involvement			
Drug of choice:	Melarsoprol ¹⁰⁷	2.2 mg/kg/day IV × 10 days	2.2 mg/kg/day IV × 10 days
or	Eflornithine ¹⁰⁸	400 mg/kg/day IV in 4 doses × 14 d	400 mg/kg/day in 4 doses × 14 days
<i>Trypanosoma brucei rhodesiense</i> (East African trypanosomiasis, sleeping sickness)			
Hemolympathic stage			
Drug of choice:	Suramin	100-200 mg (test dose) IV, then 1 g IV on days 1, 3, 5, 14, and 21	2 mg/kg (test dose), then 20 mg/kg IV on days 1, 3, 5, 14, and 21
Late disease with CNS involvement			
Drug of choice:	Melarsoprol ¹⁰⁷	2.2 mg/kg/day × 10 days	2.2 mg/kg/day × 10 days
<i>Visceral larva migrans</i> ¹⁰⁹ (Toxocariasis)			
Drugs of choice:	Albendazole ⁷ Mebendazole ⁷	400 mg PO bid × 5 days 100-200 mg PO bid × 5 days	400 mg PO bid × 5 days 100-200 mg PO bid × 5 days
Whipworm, see Trichuriasis			
<i>Wuchereria bancrofti</i> , see Filariasis			

¹⁰⁶For treatment of *T. b. gambiense*, pentamidine and suramin have equal efficacy but pentamidine is better tolerated.

¹⁰⁷In frail patients, begin with as little as 18 mg and increase the dose progressively. Pretreatment with suramin has been advocated for debilitated patients. Corticosteroids have been used to prevent arsenical encephalopathy (Pepin J, et al: *Trans R Soc Trop Med Hyg* 89:92, 1995). Up to 20% of patients with *T. b. gambiense* fail to respond to melarsoprol (Barrett MP: *Lancet* 353:1113, 1999).

¹⁰⁸Eflornithine is highly effective in *T. b. gambiense* but not against *T. b. rhodesiense* infections. It is available in limited supply only from the WHO and the CDC. Eflornithine dose may be reduced to 400 mg/kg IV in 2 doses for 7 d when used in conjunction with nifurtimox at a dose of 15 mg/kg/d PO in 3 doses × 10 d.

¹⁰⁹Optimum duration of therapy is not known; some *Medical Letter* consultants would treat for 20 days. For severe symptoms or eye involvement, corticosteroids can be used in addition.

CDC, Centers for Disease Control and Prevention; CNS, central nervous system; CSF, cerebrospinal fluid; DS, double strength; ECG, electrocardiography; FDA, U.S. Food and Drug Administration; GI, gastrointestinal; HAART, highly active antiretroviral therapy; SMX, sulfamethoxazole; TMP, trimethoprim; WHO, World Health Organization.

From: Drugs for parasitic infection. *Med Lett* 11(Suppl):e1-e23, 2013. Available at <http://www.medicalletter.org>.

Table 281-1 Drug Treatment for Amebiasis

MEDICATION	ADULT DOSAGE (ORAL)	PEDIATRIC DOSAGE (ORAL)*
INVASIVE DISEASE		
Metronidazole	Colitis or liver abscess: 750 mg tid for 7-10 days	Colitis or liver abscess: 35-50 mg/kg/day in 3 divided doses for 7-10 days
or		
Tinidazole	Colitis: 2 g once daily for 3 days Liver abscess: 2 g once daily for 3-5 days	Colitis: 50 mg/kg/day once daily for 3 days Liver abscess: 50 mg/kg/day once daily for 3-5 days
Followed by:		
Paromomycin (preferred)	500 mg tid for 7 days	25-35 mg/kg/day in 3 divided doses for 7 days
or		
Diloxanide furoate [†]	500 mg tid for 10 days	20 mg/kg/day in 3 divided doses for 7 days
or		
Iodoquinol	650 mg tid for 20 days	30-40 mg/kg/day in 3 divided doses for 20 days
ASYMPTOMATIC INTESTINAL COLONIZATION		
Paromomycin (preferred)	As for invasive disease	As for invasive disease
or		
Diloxanide furoate [†]		
or		
Iodoquinol		

*All pediatric dosages are up to a maximum of the adult dose.

[†]Not available in the United States.

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Table 282-2 Drug Treatment for Giardiasis

MEDICATION	ADULT DOSAGE (ORAL)	PEDIATRIC DOSAGE (ORAL)*
RECOMMENDED		
Tinidazole	2 g once	>3 yr: 50 mg/kg once
Nitazoxanide	500 mg bid for 3 days	1-3 yr: 100 mg (5 mL) bid for 3 days 4-11 yr: 200 mg (10 mL) bid for 3 days >12 yr: 500 mg bid for 3 days
Metronidazole	250 mg tid for 5-7 days	15 mg/kg/day in 3 divided doses for 5-7 days
ALTERNATIVE		
Albendazole	400 mg once a day for 5 days	>6 yr: 400 mg once a day for 5 days
Paromomycin	25-35 mg/kg/day in 3 divided doses for 5-10 days	Not recommended
Quinacrine [†]	100 mg tid for 5-7 days	6 mg/kg/day in 3 divided doses for 5 days

*All pediatric dosages are up to a maximum of the adult dose.

[†]Not commercially available. Can be compounded by Medical Center Pharmacy in New Haven, CT (203-688-6816) or Panorama Compounding Pharmacy in Van Nuys, CA (800-247-9767).

Table 282-1 Clinical Signs and Symptoms of Giardiasis

SYMPTOM	FREQUENCY (%)
Diarrhea	64-100
Malaise, weakness	72-97
Abdominal distention	42-97
Flatulence	35-97
Abdominal cramps	44-81
Nausea	14-79
Foul-smelling, greasy stools	15-79
Anorexia	41-73
Weight loss	53-73
Vomiting	14-35
Fever	0-28
Constipation	0-27

Table 288-2

CDC Guidelines for Treatment of Malaria in the United States (Based on Drugs Currently Available for Use in the United States—Updated July 1, 2013)

(CDC Malaria Hotline: [770] 488-7788 or [855] 856-4713 toll-free Monday–Friday 9 AM to 5 PM EST; [770] 488-7100 after hours, weekends, and holidays)

CLINICAL DIAGNOSIS/ PLASMODIUM SPECIES	REGION INFECTION ACQUIRED	RECOMMENDED DRUG AND ADULT DOSE ¹	RECOMMENDED DRUG AND PEDIATRIC DOSE ¹ PEDIATRIC DOSE SHOULD NEVER EXCEED ADULT DOSE
Uncomplicated malaria/ <i>P. falciparum</i> or Species not identified If “species not identified” is subsequently diagnosed as <i>P. vivax</i> or <i>P. ovale</i> : see <i>P. vivax</i> and <i>P. ovale</i> (below) regarding treatment with primaquine	Chloroquine-resistant or unknown resistance ² (All malarious regions except those specified as chloroquine-sensitive listed in the box below)	A. Atovaquone-proguanil (Malarone) ³ Adult tab = 250 mg atovaquone/100 mg proguanil 4 adult tabs PO qd × 3 days B. Artemether-lumefantrine (Coartem) ³ 1 tablet = 20 mg artemether and 120 mg lumefantrine A 3 day treatment schedule with a total of 6 oral doses is recommended for both adult and pediatric patients based on weight. The patient should receive the initial dose, followed by the second dose 8 hr later, then 1 dose PO bid for the following 2 days 5–<15 kg: 1 tablet per dose 15–<25 kg: 2 tablets per dose 25–<35 kg: 3 tablets per dose ≥35 kg: 4 tablets per dose C. Quinine sulfate plus 1 of the following: doxycycline, tetracycline, or clindamycin Quinine sulfate: 542 mg base (=650 mg salt) ⁴ PO tid × 3 or 7 days ⁵ Doxycycline: 100 mg PO bid × 7 days Tetracycline: 250 mg PO qid × 7 days Clindamycin: 20 mg base/kg/day PO divided tid × 7 days D. Mefloquine (Lariam and generics) ⁷ 684 mg base (=750 mg salt) PO as initial dose, followed by 456 mg base (=500 mg salt) PO given 6–12 hr after initial dose Total dose = 1,250 mg salt	A. Atovaquone-proguanil (Malarone) ³ Adult tab = 250 mg atovaquone/100 mg proguanil Pediatric (ped) tab = 62.5 mg atovaquone/25 mg proguanil 5–8 kg: 2 ped tabs PO qd × 3 days 9–10 kg: 3 ped tabs PO qd × 3 days 11–20 kg: 1 adult tab PO qd × 3 days 21–30 kg: 2 adult tabs PO qd × 3 days 31–40 kg: 3 adult tabs PO qd × 3 days > 40 kg: 4 adult tabs PO qd × 3 days B. Artemether-lumefantrine (Coartem) ³ 1 tablet = 20 mg artemether and 120 mg lumefantrine A 3 day treatment schedule with a total of 6 oral doses is recommended for both adult and pediatric patients based on weight. The patient should receive the initial dose, followed by the second dose 8 hr later, then 1 dose PO bid for the following 2 days 5–<15 kg: 1 tablet per dose 15–<25 kg: 2 tablets per dose 25–<35 kg: 3 tablets per dose ≥35 kg: 4 tablets per dose C. Quinine sulfate ⁴ plus 1 of the following: doxycycline ⁶ , tetracycline ⁶ , or clindamycin ⁶ Quinine sulfate: 8.3 mg base/kg (=10 mg salt/kg) PO tid × 3 or 7 days ⁵ Doxycycline: 2.2 mg/kg PO every 12 hr × 7 days Tetracycline: 25 mg/kg/day PO divided qid × 7 days Clindamycin: 20 mg base/kg/day PO divided tid × 7 days D. Mefloquine (Lariam and generics) ⁷ 13.7 mg base/kg (=15 mg salt/kg) PO as initial dose, followed by 9.1 mg base/kg (=10 mg salt/kg) PO given 6–12 hr after initial dose. Total dose = 25 mg salt/kg
Uncomplicated malaria/ <i>P. falciparum</i> or Species not identified	Chloroquine-sensitive (Central America west of Panama Canal; Haiti; the Dominican Republic; and most of the Middle East)	Chloroquine phosphate (Aralen and generics) ⁸ 600 mg base (=1,000 mg salt) PO immediately, followed by 300 mg base (=500 mg salt) PO at 6, 24, and 48 hr Total dose: 1,500 mg base (=2,500 mg salt) or Hydroxychloroquine (Plaquenil and generics) 620 mg base (=800 mg salt) PO immediately, followed by 310 mg base (=400 mg salt) PO at 6, 24, and 48 hr Total dose: 1,550 mg base (=2,000 mg salt)	Chloroquine phosphate (Aralen and generics) ⁸ 10 mg base/kg PO immediately, followed by 5 mg base/kg PO at 6, 24, and 48 hr Total dose: 25 mg base/kg or Hydroxychloroquine (Plaquenil and generics) 10 mg base/kg PO immediately, followed by 5 mg base/kg PO at 6, 24, and 48 hr Total dose: 25 mg base/kg

¹If a person develops malaria despite taking chemoprophylaxis, that particular medicine should not be used as a part of their treatment regimen. Use 1 of the other options instead.

²NOTE: There are 4 options (A, B, C, or D) available for treatment of uncomplicated malaria caused by chloroquine-resistant *P. falciparum*. Options A, B, and C are equally recommended. Because of a higher rate of severe neuropsychiatric reactions seen at treatment doses, we do not recommend option D (mefloquine) unless the other options cannot be used. For option C, because there is more data on the efficacy of quinine in combination with doxycycline or tetracycline, these treatment combinations are generally preferred to quinine in combination with clindamycin.

³Take with food or whole milk. If patient vomits within 30 min of taking a dose, then patient should repeat the dose.

⁴U.S. manufactured quinine sulfate capsule is in a 324 mg dosage; therefore 2 capsules should be sufficient for adult dosing. Pediatric dosing may be difficult because of unavailability of noncapsule forms of quinine.

⁵For infections acquired in Southeast Asia, quinine treatment should continue for 7 days. For infections acquired elsewhere, quinine treatment should continue for 3 days.

⁶Doxycycline and tetracycline are not indicated for use in children younger than 8 yr old. For children younger than 8 yr old with chloroquine-resistant *P. falciparum*, atovaquone-proguanil and artemether-lumefantrine are recommended treatment options; mefloquine can be considered if no other options are available. For children younger than 8 yr old with chloroquine-resistant *P. vivax*, mefloquine is the recommended treatment. If it is not available or is not being tolerated and if the treatment benefits outweigh the risks, atovaquone-proguanil or artemether-lumefantrine should be used instead.

⁷Treatment with mefloquine is not recommended in persons who have acquired infections from Southeast Asia as a consequence of drug resistance.

⁸When treating chloroquine-sensitive infections, chloroquine and hydroxychloroquine are recommended options. However, regimens used to treat chloroquine-resistant infections may also be used if available, more convenient, or preferred.

Continued

Table 288-2 CDC Guidelines for Treatment of Malaria in the United States (Based on Drugs Currently Available for Use in the United States—Updated July 1, 2013)—cont'd

CLINICAL DIAGNOSIS/ PLASMODIUM SPECIES	REGION INFECTION ACQUIRED	RECOMMENDED DRUG AND ADULT DOSE ¹	RECOMMENDED DRUG AND PEDIATRIC DOSE ¹ PEDIATRIC DOSE SHOULD NEVER EXCEED ADULT DOSE
Uncomplicated malaria/ <i>P. malariae</i> or <i>P. knowlesi</i>	All regions	Chloroquine phosphate: ⁸ treatment as above or Hydroxychloroquine: treatment as above	Chloroquine phosphate: ⁸ treatment as above or Hydroxychloroquine: treatment as above
Uncomplicated malaria/ <i>P. vivax</i> or <i>P. ovale</i>	All regions Note: for suspected chloroquine-resistant <i>P. vivax</i> , see row below	Chloroquine phosphate ⁸ plus primaquine phosphate ⁹ Chloroquine phosphate: treatment as above Primaquine phosphate: 30 mg base PO qd × 14 days or Hydroxychloroquine plus primaquine phosphate ⁹ Hydroxychloroquine: treatment as above Primaquine phosphate: 30 mg base PO qd × 14 days	Chloroquine phosphate ⁸ plus primaquine phosphate ⁹ Chloroquine phosphate: treatment as above Primaquine: 0.5 mg base/kg PO qd × 14 days or Hydroxychloroquine plus primaquine phosphate ⁹ Hydroxychloroquine: treatment as above Primaquine phosphate: 0.5 mg base/kg PO qd × 14 days
Uncomplicated malaria/ <i>P. vivax</i>	Chloroquine-resistant ¹⁰ (Papua New Guinea and Indonesia)	A. Quinine sulfate plus either doxycycline or tetracycline plus primaquine phosphate ⁹ Quinine sulfate: treatment as above Doxycycline or tetracycline: Treatment as above Primaquine phosphate: treatment as above B. Atovaquone-proguanil plus primaquine phosphate ⁹ Atovaquone-proguanil: treatment as above Primaquine phosphate: treatment as above C. Mefloquine plus primaquine phosphate ⁹ Mefloquine: treatment as above Primaquine phosphate: treatment as above	A. Quinine sulfate plus either doxycycline ⁶ or tetracycline ⁶ plus primaquine phosphate ⁹ Quinine sulfate: treatment as above Doxycycline or tetracycline: treatment as above Primaquine phosphate: treatment as above B. Atovaquone-proguanil plus primaquine phosphate ⁹ Atovaquone-proguanil: treatment as above Primaquine phosphate: treatment as above C. Mefloquine plus primaquine phosphate ⁹ Mefloquine: treatment as above Primaquine phosphate: treatment as above
Uncomplicated malaria: alternatives for pregnant women ¹¹⁻¹³	Chloroquine-sensitive (See uncomplicated malaria sections above for chloroquine-sensitive species by region) Chloroquine-resistant (See sections above for regions with chloroquine-resistant <i>P. falciparum</i> and <i>P. vivax</i>)	Chloroquine phosphate: treatment as above or Hydroxychloroquine: treatment as above Quinine sulfate plus clindamycin Quinine sulfate: treatment as above Clindamycin: treatment as above or Mefloquine: treatment as above	Not applicable Not applicable

⁹Primaquine is used to eradicate any hypnozoites that may remain dormant in the liver, and thus prevent relapses, in *P. vivax* and *P. ovale* infections. Because primaquine can cause hemolytic anemia in glucose-6-phosphate dehydrogenase (G6PD)-deficient persons, G6PD screening must occur prior to starting treatment with primaquine. For persons with borderline G6PD deficiency or as an alternate to the above regimen, primaquine may be given 45 mg orally 1 time per week for 8 wk; consultation with an expert in infectious disease and/or tropical medicine is advised if this alternative regimen is considered in G6PD-deficient persons. Primaquine must not be used during pregnancy.

¹⁰NOTE: There are 3 options (A, B, or C) available for treatment of uncomplicated malaria caused by chloroquine-resistant *P. vivax*. High treatment failure rates as a result of chloroquine-resistant *P. vivax* are well documented in Papua New Guinea and Indonesia. Rare case reports of chloroquine-resistant *P. vivax* are also documented in Burma (Myanmar), India, and Central and South America. Persons acquiring *P. vivax* infections outside of Papua New Guinea or Indonesia should be started on chloroquine. If the patient does not respond, the treatment should be changed to a chloroquine-resistant *P. vivax* regimen and CDC should be notified (Malaria Hotline number listed above). For treatment of chloroquine-resistant *P. vivax* infections, options A, B, and C are equally recommended.

¹¹For pregnant women diagnosed with uncomplicated malaria caused by chloroquine-resistant *P. falciparum* or chloroquine-resistant *P. vivax* infection, treatment with doxycycline or tetracycline is generally not indicated. However, doxycycline or tetracycline may be used in combination with quinine (as recommended for non-pregnant adults) if other treatment options are not available or are not being tolerated, and the benefit is judged to outweigh the risks.

¹²Atovaquone-proguanil and artemether-lumefantrine are generally not recommended for use in pregnant women, particularly in the 1st trimester because of a lack of sufficient safety data. For pregnant women diagnosed with uncomplicated malaria caused by chloroquine-resistant *P. falciparum* infection, atovaquone-proguanil or artemether-lumefantrine may be used if other treatment options are not available or are not being tolerated, and if the potential benefit is judged to outweigh the potential risks.

¹³For *P. vivax* and *P. ovale* infections, primaquine phosphate for radical treatment of hypnozoites should not be given during pregnancy. Pregnant patients with *P. vivax* and *P. ovale* infections should be maintained on chloroquine prophylaxis for the duration of their pregnancy. The chemoprophylactic dose of chloroquine phosphate is 300 mg base (=500 mg salt) orally once per week. After delivery, pregnant patients who do not have G6PD deficiency should be treated with primaquine.

Table 288-2

CDC Guidelines for Treatment of Malaria in the United States (Based on Drugs Currently Available for Use in the United States—Updated July 1, 2013)—cont'd

CLINICAL DIAGNOSIS/ PLASMODIUM SPECIES	REGION INFECTION ACQUIRED	RECOMMENDED DRUG AND ADULT DOSE ¹	RECOMMENDED DRUG AND PEDIATRIC DOSE ¹ PEDIATRIC DOSE SHOULD NEVER EXCEED ADULT DOSE
Severe malaria ¹⁴⁻¹⁶	All regions	<p>Quinidine gluconate¹⁴ plus 1 of the following: doxycycline, tetracycline, or clindamycin</p> <p>Quinidine gluconate: 6.25 mg base/kg (=10 mg salt/kg) loading dose IV over 1-2 hr, then 0.0125 mg base/kg/min (=0.02 mg salt/kg/min) continuous infusion for at least 24 hr. An alternative regimen is 15 mg base/kg (=24 mg salt/kg) loading dose IV infused over 4 hr, followed by 7.5 mg base/kg (=12 mg salt/kg) infused over 4 hr every 8 hr, starting 8 hr after the loading dose (see package insert). Once parasite density <1% and patient can take oral medication, complete treatment with oral quinine, dose as above. Quinidine/quinine course = 7 days in Southeast Asia; =3 days in Africa or South America</p> <p>Doxycycline: treatment as above. If patient not able to take oral medication, give 100 mg IV every 12 hr and then switch to oral doxycycline (as above) as soon as patient can take oral medication. For IV use, avoid rapid administration. Treatment course = 7 days</p> <p>Tetracycline: treatment as above</p> <p>Clindamycin: treatment as above. If patient not able to take oral medication, give 10 mg base/kg loading dose IV followed by 5 mg base/kg IV every 8 hr. Switch to oral clindamycin (oral dose as above) as soon as patient can take oral medication. For IV use, avoid rapid administration. Treatment course = 7 days</p> <p><i>Investigational new drug (contact CDC for information):</i> Artesunate followed by 1 of the following: atovaquone-proguanil (Malarone), clindamycin, or mefloquine</p>	<p>Quinidine gluconate¹⁴ plus one of the following: doxycycline⁴, tetracycline⁴, or clindamycin</p> <p>Quinidine gluconate: same mg/kg dosing and recommendations as for adults</p> <p>Doxycycline: treatment as above. If patient not able to take oral medication, may give IV. For children <45 kg, give 2.2 mg/kg IV every 12 hr and then switch to oral doxycycline (dose as above) as soon as patient can take oral medication. For children >45 kg, use same dosing as for adults. For IV use, avoid rapid administration. Treatment course = 7 days</p> <p>Tetracycline: treatment as above</p> <p>Clindamycin: treatment as above. If patient not able to take oral medication, give 10 mg base/kg loading dose IV followed by 5 mg base/kg IV every 8 hr. Switch to oral clindamycin (oral dose as above) as soon as patient can take oral medication. For IV use, avoid rapid administration. Treatment course = 7 days.</p> <p><i>Investigational new drug (contact CDC for information):</i> Artesunate followed by 1 of the following: atovaquone-proguanil (Malarone), clindamycin, or mefloquine</p>

¹⁴Persons with a positive blood smear or history of recent possible exposure and no other recognized pathology who have 1 or more of the following clinical criteria (impaired consciousness/coma, severe normocytic anemia, renal failure, pulmonary edema, acute respiratory distress syndrome, circulatory shock, disseminated intravascular coagulation, spontaneous bleeding, acidosis, hemoglobinuria, jaundice, repeated generalized convulsions, and/or parasitemia of >5%) are considered to have manifestations of more severe disease. Severe malaria is most often caused by *P. falciparum*.

¹⁵Patients diagnosed with severe malaria should be treated aggressively with parenteral antimalarial therapy. Treatment with IV quinidine should be initiated as soon as possible after the diagnosis has been made. Patients with severe malaria should be given an intravenous loading dose of quinidine unless they have received more than 40 mg/kg of quinine in the preceding 48 hr or if they have received mefloquine within the preceding 12 hr. Consultation with a cardiologist and a physician with experience treating malaria is advised when treating malaria patients with quinidine. During administration of quinidine, blood pressure monitoring (for hypotension) and cardiac monitoring (for widening of the QRS complex and/or lengthening of the QTc interval) should be monitored continuously and blood glucose (for hypoglycemia) should be monitored periodically. Cardiac complications, if severe, may warrant temporary discontinuation of the drug or slowing of the intravenous infusion.

¹⁶Pregnant women diagnosed with severe malaria should be treated aggressively with parenteral antimalarial therapy.

From the Centers for Disease Control and Prevention. Available at: <http://www.cdc.gov/malaria/resources/pdf/treatmenttable.pdf>

Table 288-3 Treatment of Uncomplicated Malaria

REGIMENS	
All <i>Plasmodium falciparum</i> malaria	Artemether-lumefantrine 1.5 mg/kg-9 mg/kg twice daily for 3 days with food or milk Artesunate 4 mg/kg daily for 3 days and mefloquine 25 mg base per kg (8 mg/kg/daily for 3 days)*† Dihydroartemisinin-piperaquine 2.5 mg/kg-20 mg/kg daily for 3 days
Sensitive <i>P. falciparum</i> malaria	Artesunate 4 mg/kg daily for 3 days and a single dose of sulfadoxine-pyrimethamine 25 mg/kg-1.25 mg/kg Artesunate 4 mg/kg and amodiaquine* 10 mg base per kg daily for 3 days
Chloroquine-sensitive <i>Plasmodium vivax</i> ‡, <i>Plasmodium malariae</i> ‡, <i>Plasmodium ovale</i> ‡, <i>Plasmodium knowlesi</i> ‡	Chloroquine 10 mg base per kg immediately, followed by 10 mg/kg at 24 hr and 5 mg/kg at 48 hr

*World Health Organization prequalified fixed dose formulations are preferable to loose tablets. A taste masked dispersible pediatric tablet formulation of artemether-lumefantrine is available.

†High failure rates with artesunate-mefloquine have been reported on the Thailand-Myanmar border.

‡Any of the artemisinin combination treatments can be given except for artesunate-sulfadoxine-pyrimethamine where *P. vivax* is resistant. Patients with *P. vivax* or *P. ovale* infections should also be given a 14 day course of primaquine to eradicate hypnozoites (radical cure). However, severe glucose-6-phosphate dehydrogenase deficiency is a contraindication because a 14 day course of primaquine can cause severe hemolytic anemia in this group.

From White NJ, Pukrittayakamee S, Hien TT, et al: *Malaria*. Lancet 383:723-732, 2014.

Table 288-4 Treatment of Severe Malaria in Adults and Children

- Artesunate 2.4 mg/kg by intravenous or intramuscular* injection, followed by 2.4 mg/kg at 12 hr and 24 hr; continue injection once daily if necessary†
 - Artemether 3.2 mg/kg by immediate intramuscular* injection, followed by 1.6 mg/kg daily
 - Quinine dihydrochloride 20 mg salt per kg infused during 4 hr, followed by maintenance of 10 mg salt per kg infused during 2-8 hr every 8 hr (can also be given by intramuscular injection* when diluted to 60-100 mg/mL)
- Artesunate is the treatment of choice. Artemether should only be used if artesunate is unavailable. Quinine dihydrochloride should be given only when artesunate and artemether are unavailable.

*Intramuscular injections should be given to the anterior thigh.

†Young children with severe malaria have lower exposure to artesunate and its main biologically active metabolite dihydroartemisinin than do older children and adults. Revised dose regimens to ensure similar drug exposures have been suggested.

Table 290-1 Signs and Symptoms Occurring Before Diagnosis or During the Course of Untreated Acute Congenital Toxoplasmosis in 152 Infants (A) and in 101 of These Same Children After They Had Been Followed 4 Yr or More (B)

SIGNS AND SYMPTOMS	Frequency of Occurrence in Patients with	
	"Neurologic" Disease*	"Generalized" Disease†
A. INFANTS	108 PATIENTS (%)	44 PATIENTS (%)
Chorioretinitis	102 (94)	29 (66)
Abnormal cerebrospinal fluid	59 (55)	37 (84)
Anemia	55 (51)	34 (77)
Convulsions	54 (50)	8 (18)
Intracranial calcification	54 (50)	2 (4)
Jaundice	31 (29)	35 (80)
Hydrocephalus	30 (28)	0 (0)
Fever	27 (25)	34 (77)
Splenomegaly	23 (21)	40 (90)
Lymphadenopathy	18 (17)	30 (68)
Hepatomegaly	18 (17)	34 (77)
Vomiting	17 (16)	21 (48)
Microcephalus	14 (13)	0 (0)
Diarrhea	7 (6)	11 (25)
Cataracts	5 (5)	0 (0)
Eosinophilia	6 (4)	8 (18)
Abnormal bleeding	3 (3)	8 (18)
Hypothermia	2 (2)	9 (20)
Glaucoma	2 (2)	0 (0)
Optic atrophy	2 (2)	0 (0)
Microphthalmia	2 (2)	0 (0)
Rash	1 (1)	11 (25)
Pneumonitis	0 (0)	18 (41)
B. CHILDREN ≥4 YR OF AGE	70 PATIENTS (%)	31 PATIENTS (%)
Mental retardation	62 (89)	25 (81)
Convulsions	58 (83)	24 (77)
Spasticity and palsies	53 (76)	18 (58)
Severely impaired vision	48 (69)	13 (42)
Hydrocephalus or microcephalus	31 (44)	2 (6)
Deafness	12 (17)	3 (10)
Normal	6 (9)	5 (16)

*Patients with otherwise undiagnosed central nervous system disease in the 1st yr of life.

†Patients with otherwise undiagnosed nonneurologic diseases during the 1st 2 mo of life.

Adapted from Eichenwald H: A study of congenital toxoplasmosis. In Slim JC, editor: Human toxoplasmosis, Copenhagen, 1960, Munksgaard, pp. 41-49. Study performed in 1947. The most severely involved institutionalized patients were n

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Table 288-5 Chemoprophylaxis of Malaria for Children

AREA	DRUG	DOSAGE (ORAL)	ADVANTAGES	DISADVANTAGES	BEST USE
Chloroquine-resistant area	Mefloquine*†	<10 kg: 4.6 mg base (5 mg salt)/kg/wk 10-19 kg: $\frac{1}{4}$ tab/wk 20-30 kg: $\frac{1}{2}$ tab/wk 31-45 kg: $\frac{3}{4}$ tab/wk >45 kg: 1 tab/wk (228 mg base)	Once weekly dosing	Bitter taste No pediatric formulation Side effects of sleep disturbance, vivid dreams	Children going to malaria endemic area for 4 wk or more Children unlikely to take daily medication
	Doxycycline‡	2 mg/kg daily (max 100 mg)	Inexpensive	Cannot give to children <8 yr Daily dosing Must take with food or causes stomach upset Photosensitivity	Children going to area for <4 wk who cannot take or cannot obtain atovaquone-proguanil
	Atovaquone/proguanil§ (Malarone)	Pediatric tabs: 62.5 mg atovaquone/25 mg proguanil Adult tabs: 250 mg proguanil/100 mg proguanil 5-8 kg: pediatric tab once daily (off-label) 9-10 kg: pediatric tab once daily (off-label) 11-20 kg: 1 pediatric tab once daily 21-30 kg: 2 pediatric tabs once daily 31-40 kg: 3 pediatric tabs once daily >40 kg: 1 adult tab once daily	Pediatric formulation Generally well tolerated	Daily dosing Expensive Can cause stomach upset	Children going to malaria endemic area for <4 wk
Chloroquine-susceptible area	Chloroquine phosphate	5 mg base/kg/wk (max: 300 mg base)	Once weekly dosing Inexpensive Generally well tolerated	Bitter taste No pediatric formulation	Best medication for children traveling to areas with <i>Plasmodium falciparum</i> or <i>Plasmodium vivax</i> that is chloroquine susceptible
Drugs used for chloroquine-resistant areas can also be used in chloroquine-susceptible areas					

*Chloroquine and mefloquine should be started 1-2 wk prior to departure and continued for 4 wk after last exposure.

†Mefloquine resistance exists in western Cambodia and along the Thailand-Cambodia and Thailand-Myanmar borders. Travelers to these areas should take doxycycline or atovaquone-proguanil. See text for precautions about mefloquine use.

‡Doxycycline should be started 1-2 days prior to departure and continued for 4 wk after last exposure. Do not use in children younger than 8 yr of age or in pregnant women.

§Atovaquone/proguanil (Malarone) should be started 1-2 days prior to departure and continued for 7 days after last exposure. Should be taken with food or a milky drink. Not recommended in pregnant women, children weighing <5 kg, and women breastfeeding infants who weigh <5 kg. Contraindicated in individuals with severe renal impairment (creatinine clearance <30 mL/min).

The Digestive System

Table 306-2 Causes of Oropharyngeal Dysphagia

NEUROMUSCULAR DISORDERS
Cerebral palsy
Brain tumors
Cerebrovascular accidents
Polio and postpolio syndromes
Multiple sclerosis
Myositis
Dermatomyositis
Myasthenia gravis
Muscular dystrophies
Acquired or inherited dystonia syndrome
Dysautonomia
METABOLIC AND AUTOIMMUNE DISORDERS
Hyperthyroidism
Systemic lupus erythematosus
Sarcoidosis
Amyloidosis
INFECTIOUS DISEASE
Meningitis
Botulism
Diphtheria
Lyme disease
Neurosyphilis
Viral infection: polio, Coxsackievirus, herpes, cytomegalovirus
STRUCTURAL LESIONS
Inflammatory: abscess, pharyngitis
Congenital web
Cricopharyngeal bar
Dental problems
Bullous skin lesions
Plummer-Vinson syndrome
Zenker diverticulum
Extrinsic compression: osteophytes, lymph nodes, thyroid swelling
OTHER
Corrosive injury
Side effects of medications
After surgery
After radiation therapy

Table 306-1 Some Nondigestive Tract Causes of Gastrointestinal Symptoms in Children

ANOREXIA
Systemic disease: inflammatory, neoplastic
Cardiorespiratory compromise
Iatrogenic: drug therapy, unpalatable therapeutic diets
Depression
Anorexia nervosa
VOMITING
Inborn errors of metabolism
Medications: erythromycin, chemotherapy, nonsteroidal anti-inflammatory drugs
Increased intracranial pressure
Brain tumor
Infection of the urinary tract
Labyrinthitis
Adrenal insufficiency
Pregnancy
Psychogenic
Abdominal migraine
Toxins
Renal disease
DIARRHEA
Infection: otitis media, urinary
Uremia
Medications: antibiotics, cisapride
Tumors: neuroblastoma
Pericarditis
Adrenal insufficiency
CONSTIPATION
Hypothyroidism
Spina bifida
Developmental delay
Dehydration: diabetes insipidus, renal tubular lesions
Medications: narcotics
Lead poisoning
Infant botulism
ABDOMINAL PAIN
Pyelonephritis, hydronephrosis, renal colic
Pneumonia (lower lobe)
Pelvic inflammatory disease
Porphyria
Angioedema
Endocarditis
Abdominal migraine
Familial Mediterranean fever
Sexual or physical abuse
Systemic lupus erythematosus
School phobia
Sickle cell crisis
Vertebral disk inflammation
Psoas abscess
Pelvic osteomyelitis or myositis
Medications
ABDOMINAL DISTENTION OR MASS
Ascites: nephrotic syndrome, neoplasm, heart failure
Discrete mass: Wilms tumor, hydronephrosis, neuroblastoma, mesenteric cyst, hepatoblastoma, lymphoma
Pregnancy
JAUNDICE
Hemolytic disease
Urinary tract infection
Sepsis
Hypothyroidism
Panhypopituitarism

Table 306-3 Causes of Esophageal Dysphagia

NEUROMUSCULAR DISORDERS
GERD
Achalasia cardia
Diffuse esophageal spasm
Scleroderma
MECHANICAL
Intrinsic Lesions
Foreign bodies including pills
Esophagitis: GERD, eosinophilic esophagitis
Stricture: corrosive injury, pill induced, peptic
Esophageal webs
Esophageal rings
Esophageal diverticula
Neoplasm
Extrinsic Lesions
Vascular compression
Mediastinal lesion
Cervical osteochondritis
Vertebral abnormalities

Table 306-4 Causes of Abdominal Distention or Mass

Ascites: nephrotic syndrome, neoplasm, heart failure

Discrete mass: Wilms tumor, hydronephrosis, neuroblastoma,

mesenteric cyst, hepatoblastoma, lymphoma

Pregnancy

Table 306-5 Causes of Jaundice

Hemolytic disease

Urinary tract infection

Sepsis

Hypothyroidism

Panhypopituitarism

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Table 306-4 Differential Diagnosis of Emesis During Childhood

INFANT	CHILD	ADOLESCENT
COMMON Gastroenteritis Gastroesophageal reflux Overfeeding Anatomic obstruction* Systemic infection† Pertussis syndrome Otitis media	Gastroenteritis Systemic infection Gastritis Toxic ingestion Pertussis syndrome Medication Reflux (GERD) Sinusitis Otitis media Anatomic obstruction* Eosinophilic esophagitis	Gastroenteritis GERD Systemic infection Toxic ingestion Gastritis Sinusitis Inflammatory bowel disease Appendicitis Migraine Pregnancy Medications Ipecac abuse, bulimia Concussion
RARE Adrenogenital syndrome Inborn errors of metabolism Brain tumor (increased intracranial pressure) Subdural hemorrhage Food poisoning Rumination Renal tubular acidosis Ureteropelvic junction obstruction Pseudoobstruction	Reye syndrome Hepatitis Peptic ulcer Pancreatitis Brain tumor Increased intracranial pressure Middle ear disease Chemotherapy Achalasia Cyclic vomiting (migraine) Esophageal stricture Duodenal hematoma Inborn error of metabolism Pseudoobstruction	Reye syndrome Hepatitis Peptic ulcer Pancreatitis Brain tumor Increased intracranial pressure Concussion Middle ear disease Chemotherapy Cyclic vomiting (migraine) Biliary colic Renal colic Diabetic ketoacidosis Pseudoobstruction Intestinal tumor Achalasia

*Includes malrotation, pyloric stenosis, intussusception, Hirschsprung disease.

†Meningitis, sepsis.

GERD, gastroesophageal reflux disease, inguinal hernia.

Table 306-5 Causes of Gastrointestinal Obstruction

ESOPHAGUS <i>Congenital</i> Esophageal atresia Vascular rings Schatzki ring Tracheobronchial remnant <i>Acquired</i> Esophageal stricture Foreign body Achalasia Chagas disease Collagen vascular disease	Ileal atresia Meconium ileus Meckel diverticulum with volvulus or intussusception Inguinal hernia Internal hernia Intestinal duplication Pseudoobstruction <i>Acquired</i> Postsurgical adhesions Crohn disease Intussusception Distal ileal obstruction syndrome (cystic fibrosis) Duodenal hematoma Superior mesenteric artery syndrome
STOMACH <i>Congenital</i> Antral webs Pyloric stenosis <i>Acquired</i> Bezoar, foreign body Pyloric stricture (ulcer) Chronic granulomatous disease of childhood Eosinophilic gastroenteritis Crohn disease Epidermolysis bullosa	COLON <i>Congenital</i> Meconium plug Hirschsprung disease Colonic atresia, stenosis Imperforate anus Rectal stenosis Pseudoobstruction Volvulus Colonic duplication <i>Acquired</i> Ulcerative colitis (toxic megacolon) Chagas disease Crohn disease Fibrosing colonopathy (cystic fibrosis)
SMALL INTESTINE <i>Congenital</i> Duodenal atresia Annular pancreas Malrotation/volvulus Malrotation/Ladd bands	

Table 306-8 Pharmacologic Therapies for Vomiting Episodes

THERAPEUTIC DRUG CLASS	DRUG	DOSAGE
REFLUX Dopamine antagonist	Metoclopramide (Reglan)	0.1-0.2 mg/kg PO or IV qid
GASTROPARESIS Dopamine antagonist Motilin agonist	Metoclopramide (Reglan) Erythromycin	0.1-0.2 mg/kg PO or IV qid 3-5 mg/kg PO or IV tid-qid
INTESTINAL PSEUDOOBSTRUCTION Stimulation of intestinal migratory myoelectric complexes	Octreotide (Sandostatin)	1 µg/kg SC bid-tid
CHEMOTHERAPY Dopamine antagonist	Metoclopramide	0.5-1.0 mg/kg IV qid, with antihistamine prophylaxis of extrapyramidal side effects
Serotonergic 5-HT ₃ antagonist Phenothiazines (extrapyramidal, hematologic side effects) Steroids Cannabinoids	Ondansetron (Zofran) Prochlorperazine (Compazine) Chlorpromazine (Thorazine) Dexamethasone (Decadron) Tetrahydrocannabinol (Nabilone)	0.15-0.3 mg/kg IV or PO tid ≈0.3 mg/kg PO bid-tid ≥6 mo of age: 0.5 mg/kg PO or IV tid-qid 0.1 mg/kg PO tid 0.05-0.1 mg/kg PO bid-tid
POSTOPERATIVE	Ondansetron, phenothiazines	See under chemotherapy
MOTION SICKNESS, VESTIBULAR DISORDERS Antihistamine Anticholinergic	Dimenhydrinate (Dramamine) Scopolamine (Transderm Scop)	1 mg/kg PO tid-qid Adults: 1 patch/3 days
ADRENAL CRISIS Steroids	Cortisol	2 mg/kg IV bolus followed by 0.2-0.4 mg/kg/hr IV (±1 mg/kg IM)
CYCLOTHYMIC VOMITING SYNDROME Supportive Analgesic Anxiolytic, sedative Antihistamine, sedative Abortive Serotonergic 5-HT ₃ antagonist Nonsteroidal antiinflammatory agent (GI ulceration side effect) Serotoninergic 5-HT _{1D} agonist	Meperidine (Demerol) Lorazepam (Ativan) Diphenhydramine (Benadryl) Ondansetron Granisetron (Kytril) Ketorolac (Toradol) Sumatriptan (Imitrex)	1-2 mg/kg IV or IM q 4-6 hr 0.05-0.1 mg/kg IV q 6 hr 1.25 mg/kg IV q 6 hr See above 10 µg/kg IV q 4-6 hr 0.5-1.0 mg/kg IV q 6-8 hr ≥40 kg: 20 mg intranasally or 25 mg PO, 1 time only
PROPHYLACTIC* Antimigraine, β-adrenergic blocker Antimigraine, antihistamine Antimigraine, tricyclic antidepressant	Propranolol (Inderal) Cyproheptadine (Periactin) Amitriptyline (Elavil)	0.5-2.0 mg/kg PO bid 0.25-0.5 mg/kg/day PO + bid-tid 0.33-0.5 mg/kg PO tid, and titrate to maximum of 3.0 mg/kg/day as needed Obtain baseline ECG at start of therapy, and consider monitoring drug levels
Antimigraine antiepileptic	Phenobarbital (Luminal) Erythromycin (see above)	2-3 mg/kg qhs
Low-estrogen oral contraceptives	Consider for catamenial CVS episodes	

*If >1 CVS bout/mo or symptoms are extremely disabling; taken daily.

CVS, cyclic vomiting syndrome; ECG, electrocardiogram; GI, gastrointestinal.

From Kliegman RM, Greenbaum LA, Lye PS, editors: Practical strategies in pediatric diagnosis and therapy, ed 2, Philadelphia, 2004, Elsevier, p 317.

Table 306-7 Complications of Vomiting

COMPLICATION	PATHOPHYSIOLOGY	HISTORY, PHYSICAL EXAMINATION, AND LABORATORY STUDIES
Metabolic	Fluid loss in emesis HCl loss in emesis Na, K loss in emesis Alkalosis → • Na into cells	Dehydration Alkalosis; hypochloremia Hyponatremia; hypokalemia
Nutritional	Emesis of calories and nutrients Anorexia for calories and nutrients	Malnutrition; "failure to thrive"
Mallory-Weiss tear	Retching → tear at lesser curve of gastroesophageal junction	Forceful emesis → hematemesis
Esophagitis	Chronic vomiting → esophageal acid exposure	Heartburn; Hemoccult + stool
Aspiration	Aspiration of vomitus, especially in context of obtundation	Pneumonia; neurologic dysfunction
Shock	Severe fluid loss in emesis or in accompanying diarrhea Severe blood loss in hematemesis	Dehydration (accompanying diarrhea can explain acidosis?) Blood volume depletion
Pneumomediastinum, pneumothorax	Increased intrathoracic pressure	Chest x-ray
Petechiae, retinal hemorrhages	Increased intrathoracic pressure	Normal platelet count

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Table 306-9 Supportive and Nonpharmacologic Therapies for Vomiting Episodes

DISEASE	THERAPY
All	Treat cause <ul style="list-style-type: none"> • Obstruction: operate • Allergy: change diet (steroids) • Metabolic error: Rx defect • Acid peptic disease: H2RAs, PPIs, etc.
COMPLICATIONS	
Dehydration	IV fluids, electrolytes
Hematemesis	Transfuse, correct coagulopathy
Esophagitis	H2RAs, PPIs
Malnutrition	NG or NJ drip feeding useful for many chronic conditions
Meconium ileus	Gastrografin enema
DIOS	Gastrografin enema; balanced colonic lavage solution (e.g., GoLYTELY)
Intussusception	Barium enema; air reduction enema
Hematemesis	Endoscopic: injection sclerotherapy or banding of esophageal varices; injection therapy, fibrin sealant application, or heater probe electrocautery for selected upper GI tract lesions
Sigmoid volvulus	Colonoscopic decompression
Reflux	Positioning; dietary measures (infants: rice cereal, 1 tbs/oz of formula)
Psychogenic components	Psychotherapy; tricyclic antidepressants; anxiolytics (e.g., diazepam: 0.1 mg/kg PO tid-qid)

DIOS, distal intestinal obstruction syndrome; GI, gastrointestinal; H₂RA, H₂-receptor antagonist; NG, nasogastric; NJ, nasojejunal; PPIs, proton pump inhibitors; tbs, tablespoon.

From Kliegman RM, Greenbaum LA, Lye PS, editors: Practical strategies in pediatric diagnosis and therapy, ed 2, Philadelphia, 2004, Elsevier, p 319.

Table 306-10 Mechanisms of Diarrhea

PRIMARY MECHANISM	DEFECT	STOOL EXAMINATION	EXAMPLES	COMMENT
Secretory	Decreased absorption, increased secretion, electrolyte transport	Watery, normal osmolality with ion gap < 100 mOsm/kg	Cholera, toxicigenic <i>Escherichia coli</i> ; carcinoid, VIP, neuroblastoma, congenital chloride diarrhea, <i>Clostridium difficile</i> , cryptosporidiosis (AIDS)	Persists during fasting; bile salt malabsorption can also increase intestinal water secretion; no stool leukocytes
Osmotic	Maldigestion, transport defects ingestion of unabsorbable substances	Watery, acidic, and reducing substances; increased osmolality with ion gap > 100 mOsm/kg	Lactase deficiency, glucose-galactose malabsorption, lactulose, laxative abuse	Stops with fasting; increased breath hydrogen with carbohydrate malabsorption; no stool leukocytes
Increased motility	Decreased transit time	Loose to normal-appearing stool, stimulated by gastrocolic reflex	Irritable bowel syndrome, thyrotoxicosis, postvagotomy dumping syndrome	Infection can also contribute to increased motility
Decreased motility	Defect in neuromuscular unit(s) stasis (bacterial overgrowth)	Loose to normal-appearing stool	Pseudoobstruction, blind loop	Possible bacterial overgrowth
Decreased surface area (osmotic, motility)	Decreased functional capacity	Watery	Short bowel syndrome, celiac disease, rotavirus enteritis	Might require elemental diet plus parenteral alimentation
Mucosal invasion	Inflammation, decreased colonic reabsorption, increased motility	Blood and increased WBCs in stool	<i>Salmonella</i> , <i>Shigella</i> infection; amebiasis; <i>Yersinia</i> , <i>Campylobacter</i> infection	Dysentery evident in blood, mucus, and WBCs

VIP, vasoactive intestinal peptide; WBC, white blood cell.

From Kliegman RM, Greenbaum LA, Lye PS, editors: Practical strategies in pediatric diagnosis and therapy, ed 2, Philadelphia, 2004, Elsevier, p 274.

Ion gap = Stool osmolality - [(Stool Na + stool K) × 2]

Table 306-6 Criteria for Cyclical Vomiting Syndrome

All of the criteria must be met for the consensus definition of cyclical vomiting syndrome:

- At least 5 attacks in any interval, or a minimum of 3 episodes during a 6-mo period
- Recurrent episodes of intense vomiting and nausea lasting 1 hr to 10 days and occurring at least 1 wk apart
- Stereotypical pattern and symptoms in the individual patient
- Vomiting during episodes occurs ≥4 times/hr for ≥1 hr
- Return to baseline health between episodes
- Not attributed to another disorder

Li, B UK, Lefevre F, Chelimsky GG, et al: North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition consensus statement on the diagnosis and management of cyclic vomiting syndrome, *J Pediatr Gastroenterol Nutr* 47:379–393, 2008.

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Table 306-11 Differential Diagnosis of Diarrhea

INFANT	CHILD	ADOLESCENT
ACUTE		
Common		
Gastroenteritis (viral > bacterial > protozoal)	Gastroenteritis (viral > bacterial > protozoal)	Gastroenteritis (viral > bacterial > protozoal)
Systemic infection	Food poisoning	Food poisoning
Antibiotic associated	Systemic infection	Antibiotic associated
Overfeeding	Antibiotic associated	
Rare		
Primary disaccharidase deficiency	Toxic ingestion	Hyperthyroidism
Hirschsprung toxic colitis	Hemolytic uremic syndrome	Appendicitis
Adrenogenital syndrome	Intussusception	
Neonatal opiate withdrawal		
CHRONIC		
Common		
Postinfectious secondary lactase deficiency	Postinfectious secondary lactase deficiency	Irritable bowel syndrome
Cow's milk or soy protein intolerance (allergy)	Irritable bowel syndrome	Inflammatory bowel disease
Chronic nonspecific diarrhea of infancy	Celiac disease	Lactose intolerance
Excessive fruit juice (sorbitol) ingestion	Cystic fibrosis	Giardiasis
Celiac disease	Lactose intolerance	Laxative abuse (anorexia nervosa)
Cystic fibrosis	Excessive fruit juice (sorbitol) ingestion	Constipation with encopresis
AIDS enteropathy	Giardiasis	
	Inflammatory bowel disease	
	AIDS enteropathy	
Rare		
Primary immune defects	Primary and acquired immune defects	Secretory tumor
Autoimmune enteropathy	Secretory tumors	Primary bowel tumor
IPEX and IPEX-like syndromes	Pseudoobstruction	Parasitic infections and venereal diseases
Glucose-galactose malabsorption	Sucrase-isomaltase deficiency	Appendiceal abscess
Microvillus inclusion disease (microvillus atrophy)	Eosinophilic gastroenteritis	Addison disease
Congenital transport defects (chloride, sodium)	Secretory tumors	
Primary bile acid malabsorption		
Factitious syndrome by proxy		
Hirschsprung disease		
Shwachman syndrome		
Secretory tumors		
Acrodermatitis enteropathica		
Lymphangiectasia		
Abetalipoproteinemia		
Eosinophilic gastroenteritis		
Short bowel syndrome		

Table 306-14 Distinguishing Features of Acute Gastrointestinal Tract Pain in Children

DISEASE	ONSET	LOCATION	REFERRAL	QUALITY	COMMENTS
Pancreatitis	Acute	Epigastric, left upper quadrant	Back	Constant, sharp, boring	Nausea, emesis, tenderness
Intestinal obstruction	Acute or gradual	Perumbilical-lower abdomen	Back	Alternating cramping (colic) and painless periods	Distention, obstipation, emesis, increased bowel sounds
Appendicitis	Acute	Perumbilical, then localized to lower right quadrant; generalized with peritonitis	Back or pelvis if retrocecal	Sharp, steady	Anorexia, nausea, emesis, local tenderness, fever with peritonitis
Intussusception	Acute	Perumbilical-lower abdomen	None	Cramping, with painless periods	Hematochezia, knees in pulled-up position
Urolithiasis	Acute, sudden	Back (unilateral)	Groin	Sharp, intermittent, cramping	Hematuria
Urinary tract infection	Acute	Back	Bladder	Dull to sharp	Fever, costovertebral angle tenderness, dysuria, urinary frequency

Table 306-12 Causes of Constipation

NONORGANIC (FUNCTIONAL)—RETENTIVE
ANATOMIC
Anal stenosis, atresia with fistula
Imperforate anus
Anteriorly displaced anus
Intestinal stricture (postnecrotizing enterocolitis)
Anal stricture
ABNORMAL MUSCULATURE
Prune-belly syndrome
Gastroschisis
Down syndrome
Muscular dystrophy
INTESTINAL NERVE OR MUSCLE ABNORMALITIES
Hirschsprung disease
Pseudoobstruction (visceral myopathy or neuropathy)
Intestinal neuronal dysplasia
Spinal cord defects
Tethered cord
Spinal cord trauma
Spina bifida
DRUGS
Anticholinergics
Narcotics
Methylphenidate
Phenytoin
Antidepressants
Chemotherapeutic agents (vincristine)
Pancreatic enzymes (fibrosing colonopathy)
Lead
Vitamin D intoxication
METABOLIC DISORDERS
Hypokalemia
Hypercalcemia
Hypothyroidism
Diabetes mellitus, diabetes insipidus
INTESTINAL DISORDERS
Celiac disease
Cow's milk protein intolerance
Cystic fibrosis (meconium ileus equivalent)
Inflammatory bowel disease (stricture)
Tumor
Connective tissue disorders
Systemic lupus erythematosus
Scleroderma
PSYCHIATRIC DIAGNOSIS
Anorexia nervosa

Table 306-15 Differential Diagnosis of Gastrointestinal Bleeding in Childhood

INFANT	CHILD	ADOLESCENT
COMMON		
Bacterial enteritis	Bacterial enteritis	Bacterial enteritis
Milk protein allergy intolerance	Anal fissure	Inflammatory bowel disease
Intussusception	Colonic polyps	Peptic ulcer/gastritis
Swallowed maternal blood	Intussusception	Prolapse (traumatic) gastropathy secondary to emesis
Anal fissure	Peptic ulcer/gastritis	Mallory-Weiss syndrome
Lymphonodular hyperplasia	Swallowed epistaxis	Colonic polyps
	Prolapse (traumatic) gastropathy secondary to emesis	Anal fissure
	Mallory-Weiss syndrome	
RARE		
Volvulus	Esophageal varices	Hemorrhoids
Necrotizing enterocolitis	Esophagitis	Esophageal varices
Meckel diverticulum	Meckel diverticulum	Esophagitis
Stress ulcer, gastritis	Lymphonodular hyperplasia	Pill ulcer
Coagulation disorder (hemorrhagic disease of newborn)	Henoch-Schönlein purpura	Telangiectasia-angiodyplasia
Esophagitis	Foreign body	Graft-vs-host disease
	Hemangioma, arteriovenous malformation	Duplication cyst
	Sexual abuse	
	Hemolytic-uremic syndrome	
	Inflammatory bowel disease	
	Coagulopathy	
	Duplication cyst	

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Table 306-13 Chronic Abdominal Pain in Children

DISORDER	CHARACTERISTICS	KEY EVALUATIONS
NONORGANIC		
Functional abdominal pain Irritable bowel syndrome Nonulcer dyspepsia	Nonspecific pain, often periumbilical Intermittent cramps, diarrhea, and constipation Peptic ulcer-like symptoms without abnormalities on evaluation of the upper GI tract	Hx and PE; tests as indicated Hx and PE Hx; esophagogastroduodenoscopy
GASTROINTESTINAL TRACT		
Chronic constipation	Hx of stool retention, evidence of constipation on examination	Hx and PE; plain x-ray of abdomen
Lactose intolerance	Symptoms may be associated with lactose ingestion; bloating, gas, cramps, and diarrhea	Trial of lactose-free diet; lactose breath hydrogen test
Parasite infection (especially <i>Giardia</i>)	Bloating, gas, cramps, and diarrhea	Stool evaluation for O&P; specific immunoassays for <i>Giardia</i>
Excess fructose or sorbitol ingestion	Nonspecific abdominal pain, bloating, gas, and diarrhea	Large intake of apples, fruit juice, or candy or chewing gum sweetened with sorbitol
Crohn disease	See Chapter 336	
Peptic ulcer	Burning or gnawing epigastric pain; worse on awakening or before meals; relieved with antacids	Esophagogastroduodenoscopy, upper GI contrast x-rays, or MRI enteroscopy
Esophagitis	Epigastric pain with substernal burning	Esophagogastroduodenoscopy
Meckel diverticulum	Perumbilical or lower abdominal pain; may have blood in stool (usually painless)	Meckel scan or enteroclysis
Recurrent intussusception	Paroxysmal severe cramping abdominal pain; blood may be present in stool with episode	Identify intussusception during episode or lead point in intestine between episodes with contrast studies of GI tract
Internal, inguinal, or abdominal wall hernia Chronic appendicitis or appendiceal mucocele	Dull abdomen or abdominal wall pain Recurrent RLQ pain; often incorrectly diagnosed, may be rare cause of abdominal pain	PE, CT of abdominal wall Barium enema, CT
GALLBLADDER AND PANCREAS		
Cholelithiasis Choledochal cyst Recurrent pancreatitis	RUQ pain, might worsen with meals RUQ pain, mass ± elevated bilirubin Persistent boring pain, might radiate to back, vomiting	Ultrasound of gallbladder Ultrasound or CT of RUQ Serum amylase and lipase ± serum trypsinogen; ultrasound, CT, or MRI-ERCP of pancreas
GENITOURINARY TRACT		
Urinary tract infection Hydronephrosis Urolithiasis	Dull suprapubic pain, flank pain Unilateral abdominal or flank pain Progressive, severe pain; flank to inguinal region to testicle	Urinalysis and urine culture; renal scan Ultrasound of kidneys Urinalysis, ultrasound, IVP, CT
Other genitourinary disorders	Suprapubic or lower abdominal pain; genitourinary symptoms	Ultrasound of kidneys and pelvis; gynecologic evaluation
MISCELLANEOUS CAUSES		
Abdominal migraine Abdominal epilepsy	See text; nausea, family Hx migraine Might have seizure prodrome	Hx EEG (can require > 1 study, including sleep-deprived EEG) Serum bilirubin
Gilbert syndrome	Mild abdominal pain (causal or coincidental?); slightly elevated unconjugated bilirubin	
Familial Mediterranean fever	Paroxysmal episodes of fever, severe abdominal pain, and tenderness with other evidence of polyserositis	Hx and PE during an episode, DNA diagnosis
Sickle cell crisis Lead poisoning Henoch-Schönlein purpura	Anemia Vague abdominal pain ± constipation Recurrent, severe crampy abdominal pain, occult blood in stool, characteristic rash, arthritis	Hematologic evaluation Serum lead level Hx, PE, urinalysis
Angioneurotic edema	Swelling of face or airway, crampy pain	Hx, PE, upper GI contrast x-rays, serum C1 esterase inhibitor
Acute intermittent porphyria	Severe pain precipitated by drugs, fasting, or infections	Spot urine for porphyrins

EEG, electroencephalogram; GI, gastrointestinal; Hx, history; IVP, intravenous pyelography; O&P, ova and parasites; PE, physical exam; RLQ, right lower quadrant; RUQ, right upper quadrant.

Table 323-2 Symptoms and Signs That May Be Associated with Gastroesophageal Reflux

Symptoms

- Recurrent regurgitation with or without vomiting
- Weight loss or poor weight gain
- Irritability in infants
- Ruminative behavior
- Heartburn or chest pain
- Hematemesis
- Dysphagia, odynophagia
- Wheezing
- Stridor
- Cough
- Hoarseness

Signs

- Esophagitis
- Esophageal stricture
- Barrett esophagus
- Laryngeal/pharyngeal inflammation
- Recurrent pneumonia
- Anemia
- Dental erosion
- Feeding refusal
- Dystonic neck posturing (Sandifer syndrome)
- Apnea spells
- Apparent life-threatening events

From Wyllie R, Hyams JS, Kay M, editors: Pediatric gastrointestinal and liver disease, ed 4, Philadelphia, 2011, WB Saunders, Table 22-1, p. 235.

Table 315-1 Differential Diagnosis of Oral Ulceration

CONDITION	COMMENT
COMMON	
Aphthous (canker sore)	Painful, circumscribed lesions; recurrences
Traumatic	Accidents, chronic cheek biter, or after dental local anesthesia
Hand, foot, mouth disease	Painful; lesions on tongue, anterior oral cavity, hands, and feet
Herpangina	Painful; lesions confined to soft palate and oropharynx
Herpetic gingivostomatitis	Vesicles on mucocutaneous borders; painful, febrile
Recurrent herpes labialis	Vesicles on lips; painful
Chemical burns	Alkali, acid, aspirin; painful
Heat burns	Hot food, electrical
UNCOMMON	
Neutrophil defects	Agranulocytosis, leukemia, cyclic neutropenia; painful
Systemic lupus erythematosus	Recurrent, may be painless
Behçet syndrome	Resembles aphthous lesions; associated with genital ulcers, uveitis
Necrotizing ulcerative gingivostomatitis	Vincent stomatitis; painful
Syphilis	Chancre or gumma; painless
Oral Crohn disease	Aphthous-like; painful
Histoplasmosis	Lingual
Pemphigus	May be isolated to the oral cavity
Stevens-Johnson syndrome	May be isolated or appear initially in the oral cavity

Table 308-1 Dental Problems Associated with Selected Medical Conditions

MEDICAL CONDITION	COMMON ASSOCIATED DENTAL OR ORAL FINDINGS
Cleft lip and palate	Missing teeth, extra (supernumerary) teeth, shifting of arch segments, feeding difficulties, speech problems
Kidney failure	Mottled enamel (permanent teeth), facial dysmorphology
Cystic fibrosis	Stained teeth with extensive medication, mottled enamel
Immunosuppression	Oral candidiasis with potential for systemic candidiasis, cyclosporine-induced gingival hyperplasia
Low birthweight	Palatal groove, narrow arch with prolonged oral intubation; enamel defects of primary teeth
Heart defects with susceptibility to bacterial endocarditis	Bacteremia from dental procedures or trauma
Neutrophil chemotactic deficiency	Juvenile periodontitis (loss of supporting bone around teeth)
Juvenile diabetes (uncontrolled)	Juvenile periodontitis
Neuromotor dysfunction	Oral trauma from falling; malocclusion (open bite); gingivitis from lack of hygiene
Prolonged illness (generalized) during tooth formation	Enamel hypoplasia of crown portions forming during illness
Seizures	Gingival enlargement if phenytoin is used
Maternal infections	Syphilis: abnormally shaped teeth
Vitamin D-dependent rickets	Enamel hypoplasia

Table 327-1 Ingestible Caustic Materials Around the House

CATEGORY	MOST DAMAGING AGENTS	OTHER AGENTS
Alkaline drain cleaners, milking machine pipe cleaners	Sodium or potassium hydroxide	Ammonia Sodium hypochlorite Aluminum particles
Acidic drain openers	Hydrochloric acid Sulfuric acid	
Toilet cleaners	Hydrochloric acid Sulfuric acid Phosphoric acid Other acids	Ammonium chloride Sodium hypochlorite
Oven and grill cleaners	Sodium hydroxide Perborate (borax)	
Denture cleaners	Persulfate (sulfur) Hypochlorite (bleach)	
Dishwasher detergent • Liquid • Powdered • Packaged	Sodium hydroxide Sodium hypochlorite Sodium carbonate	
Bleach	Sodium hypochlorite	Ammonia salt
Swimming pool chemicals	Acids, alkalis, chlorine	
Battery acid (liquid)	Sulfuric acid	
Disk batteries	Electric current	Zinc or other metal salts
Rust remover	Hydrofluoric, phosphoric, oxalic, and other acids	
Household delimers	Phosphoric acid Hydroxyacetic acid Hydrochloric acid	
Barbeque cleaners	Sodium and potassium hydroxide	
Glyphosate surfactant (RoundUp) acid	Glyphosate herbicide	Surfactants
Hair relaxer	Sodium hydroxide	
Weed killer	Dichlorophenoxyacetate, ammonium phosphate, propionic acid	

Source: National Library of Medicine: Health and safety information on household products (website). <http://householdproducts.nlm.nih.gov/>
 From Wylie R, Hyams JS, Kay M, editors: Pediatric gastrointestinal and liver disease, ed 4, Philadelphia, 2011, WB Saunders, Table 19-1, p. 198.

Table 327-2 Classification of Caustic Injury

GRADE	VISIBLE APPEARANCE	CLINICAL SIGNIFICANCE
Grade 0	History of ingestion, but no visible damage or symptoms	Able to take fluids immediately
Grade 1	Edema, loss of normal vascular pattern, hyperemia, no transmucosal injury	Temporary dysphagia, able to swallow within 0-2 days, no long-term sequelae
Grade 2a	Transmucosal injury with friability, hemorrhage, blistering, exudate, scattered superficial ulceration	Scarring, no circumferential damage (no stenosis), no long-term sequelae
Grade 2b	Grade 2a plus discrete ulceration and/or circumferential ulceration	Small risk of perforation, scarring that may result in later stenosis
Grade 3a	Scattered deep ulceration with necrosis of the tissue	Risk of perforation, high risk of later stenosis
Grade 3b	Extensive necrotic tissue	High risk of perforation and death, high risk of stenosis

From Wylie R, Hyams JS, Kay M, editors: Pediatric gastrointestinal and liver disease, ed 4, Philadelphia, 2011, WB Saunders, Table 19-2, p. 199.

Table 332-2 Chronic Constipation: Rome III Criteria**INFANTS AND TODDLERS**

Must include 1 mo of at least 2 of the following in infants up to 4 yr of age:

- ≤2 Defecations per week
 - ≥1 Episode of incontinence after the acquisition of toilet training skills
 - History of excessive stool retention
 - History of painful or hard bowel movements
 - Presence of a large fecal mass in the rectum
 - History of a large-diameter stool that might obstruct the toilet
- Accompanying symptoms may include irritability, decreased appetite, and/or early satiety. The accompanying symptoms disappear immediately following passage of a large stool.

CHILDREN WITH A DEVELOPMENTAL AGE OF 4-18 YR

Must include 2 or more of the following in a child with a developmental age of at least 4 yr with insufficient criteria for diagnosis of irritable bowel syndrome*:

- ≤2 Defecations per week
- ≥1 Episode of fecal incontinence per week
- History of retentive posturing or excessive volitional stool retention
- History of painful or hard bowel movements
- Presence of a large fecal mass in the rectum
- History of a large-diameter stool that might obstruct the toilet

*Criteria fulfilled at least once per week for at least 2 mo before diagnosis.

From Hyman P, Milla P, Benninga M, et al: Childhood functional gastrointestinal disorders: neonate/toddler, *Gastroenterology* 130:1519-1526, 2006; and Rasquin A, Dilorenzo C, Forbes D, et al: Childhood functional gastrointestinal disorders: child/adolescent, *Gastroenterology* 130:1527-1537, 2006.

Table 332-1 Findings in Pseudoobstruction

GI SEGMENT	FINDINGS*
Esophageal motility	Abnormalities in approximately half of CIPO, although in some series up to 85% demonstrate abnormalities Decreased LES pressure Failure of LES relaxation Esophageal body: low-amplitude waves, poor propagation, tertiary waves, retrograde peristalsis, occasionally aperistalsis
Gastric emptying	May be delayed
EGG	Tachygastria or bradygastria may be seen
ADM	Postprandial antral hypomotility is seen and correlates with delayed gastric emptying Myopathic subtype: low-amplitude contractions, <10-20 mm Hg Neuropathic subtype: contractions are uncoordinated, disorganized Absence of fed response Fasting MMC is absent, or MMC is abnormally propagated
Colonic	Absence of gastrocolic reflex because there is no increased motility in response to a meal
ARM	Normal rectoanal inhibitory reflex

*Findings can vary according to the segment(s) of the GI tract that are involved.

ADM, Antroduodenal manometry; ARM, anorectal manometry; CIPO, chronic intestinal pseudoobstruction; EGG, electrogastrography; GI, gastrointestinal; LES, lower esophageal sphincter; MMC, migrating motor complex.

From Steffen R: Gastrointestinal motility. In Wyllie R, Hyams JS, Kay M, editors: Pediatric gastrointestinal and liver disease, ed 3, Philadelphia, 2006, WB Saunders, p. 66.

Table 332-3 Suggested Medications and Dosages for Disimpaction

MEDICATION	AGE	DOSAGE
RAPID RECTAL DISIMPACTION		
Glycerin suppositories	Infants and toddlers	
Phosphate enema	<1 yr	60 mL
Milk of molasses enema	>1 yr	6 mL/kg bodyweight, up to 135 mL twice
	Older children	(1:1 milk:molasses) 200-600 mL
SLOW ORAL DISIMPACTION IN OLDER CHILDREN		
Over 2-3 Days		
Polyethylene glycol with electrolytes		25 mL/kg bodyweight/hr, up to 1000 mL/hr until clear fluid comes from the anus
Over 5-7 Days		
Polyethylene without electrolytes		1.5 g/kg bodyweight/day for 3 days
Milk of magnesia		2 mL/kg bodyweight twice/day for 7 days
Mineral oil		3 mL/kg bodyweight twice/day for 7 days
Lactulose or sorbitol		2 mL/kg bodyweight twice/day for 7 days

From Loening-Baucke V: Functional constipation with encopresis. In Wyllie R, Hyams JS, Kay M, editors: Pediatric gastrointestinal and liver disease, ed 3, Philadelphia, 2006, WB Saunders, p 183.

Table 332-4 Suggested Medications and Dosages for Maintenance Therapy of Constipation

MEDICATION	AGE	DOSE
FOR LONG-TERM TREATMENT (YEARS)		
Milk of magnesia	>1 mo	1-3 mL/kg bodyweight/day, divided into 1-2 doses
Mineral oil	>12 mo	1-3 mL/kg bodyweight/day, divided into 1-2 doses
Lactulose or sorbitol	>1 mo	1-3 mL/kg bodyweight/day, divided into 1-2 doses
Polyethylene glycol 3350 (MiraLAX)	>1 mo	0.7 g/kg bodyweight/day, divided into 1-2 doses
FOR SHORT-TERM TREATMENT (MONTHS)		
Senna (Senokot) syrup, tablets	1-5 yr	5 mL (1 tablet) with breakfast, max 15 mL daily
	5-15 yr	2 tablets with breakfast, maximum 3 tablets daily
Glycerin enemas	>10 yr	20-30 mL/day ($\frac{1}{2}$ glycerin and $\frac{1}{2}$ normal saline)
Bisacodyl suppositories	>10 yr	10 mg daily

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Table 332-5 Distinguishing Features of Hirschsprung Disease and Functional Constipation

VARIABLE	FUNCTIONAL	HIRSCHSPRUNG DISEASE
HISTORY		
Onset of constipation	After 2 yr of age	At birth
Encopresis	Common	Very rare
Failure to thrive	Uncommon	Possible
Enterocolitis	None	Possible
Forced bowel training	Usual	None
EXAMINATION		
Abdominal distention	Uncommon	Common
Poor weight gain	Rare	Common
Rectum	Filled with stool	Empty
Rectal examination	Stool in rectum	Explosive passage of stool
Malnutrition	None	Possible
INVESTIGATIONS		
Anorectal manometry	Relaxation of internal anal sphincter	Failure of internal anal sphincter relaxation
Rectal biopsy	Normal	No ganglion cells, increased acetylcholinesterase staining
Barium enema	Massive amounts of stool, no transition zone	Transition zone, delayed evacuation (>24 hr)

From Imseis E, Gariepy C: Hirschsprung disease. In Walker WA, Goulet OJ, Kleinman RE et al, editors: Pediatric gastrointestinal disease, ed 4, Hamilton, Ontario, 2004, BC Decker, p. 1035.

Table 335-2 Recommended Eradication Therapies for *Helicobacter pylori*—Associated Disease in Children

MEDICATIONS	DOSE	DURATION OF TREATMENT
Amoxicillin	50 mg/kg/day in 2 divided doses	14 days
Clarithromycin	15 mg/kg/day in 2 divided doses	14 days
Proton pump inhibitor	1 mg/kg/day in 2 divided doses	1 mo
or		
Amoxicillin	50 mg/kg/day in 2 divided doses	14 days
Metronidazole	20 mg/kg/day in 2 divided doses	14 days
Proton pump inhibitor	1 mg/kg/day in 2 divided doses	1 mo
or		
Clarithromycin	15 mg/kg/day in 2 divided doses	14 days
Metronidazole	20 mg/kg/day in 2 divided doses	14 days
Proton pump inhibitor	1 mg/kg/day in 2 divided doses	1 mo

Adapted from Gold BD, Colletti RB, Abbott M, et al: Medical position statement: The North American Society for Pediatric Gastroenterology and Nutrition. Helicobacter pylori infection in children: recommendations for diagnosis and treatment, J Pediatr Gastroenterol Nutr 31:490–497, 2000.

Table 335-3 Antisecretory Therapy with Pediatric Dosages

MEDICATION	PEDIATRIC DOSE	HOW SUPPLIED
H₂ RECEPTOR ANTAGONISTS		
Cimetidine	20-40 mg/kg/day Divided 2-4 x a day	Syrup: 300 mg/mL Tablets: 200, 300, 400, 800 mg
Ranitidine	4-10 mg/kg/day Divided 2 or 3 x a day	Syrup: 75 mg/5 mL Tablets: 75, 150, 300 mg
Famotidine	1-2 mg/kg/day Divided twice a day	Syrup: 40 mg/5 mL Tablets: 20, 40 mg
Nizatidine	5-10 mg/kg/day divided twice a day Older than 12 yr: 150 mg twice a day	Solution: 15 mg/ml Capsule 150, 300 Tablet: 75 mg
PROTON PUMP INHIBITORS		
Omeprazole	1.0-3.3 mg/kg/day weigh <20 kg: 10 mg/day weigh >20 kg: 20 mg/day Approved for use in those older than 2 yr	Capsules: 10, 20, 40 mg
Lansoprazole	0.8-4 mg/kg/day weigh <30 kg: 15 mg/day weigh >30 kg: 30 mg/day Approved for use in those older than 1 yr	Capsules: 15, 30 mg Powder packet: 15, 30 mg SoluTab: 15, 30 mg
Rabeprazole	1-11 yr(weigh <15 kg): 5 mg/day 1-11 yr (weigh >15 kg): 10 mg/day >12 yr: 20 mg tablet	Delayed release capsule: 5, 10 mg Delayed release tablet: 20 mg
Pantoprazole	1-5 yr: 0.3-1.2 mg/kg/day (limited data) >5 yr of age: weigh >15 kg to <40 kg: 20 mg/day weigh >40 kg: 40 mg/day	Tablet: 20, 40 mg Powder pack: 40 mg
CYTOPROTECTIVE AGENTS		
Sucralfate	40-80 mg/kg/day	Suspension: 1,000 mg/5 mL Tablet: 1,000 mg

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Table 336-3 Montreal Classification of Extent and Severity of Ulcerative Colitis

- E1 (proctitis): inflammation limited to the rectum
- E2 (left-sided; distal): inflammation limited to the splenic flexure
- E3 (pancolitis): inflammation extends to the proximal splenic flexure
- S0 (remission): no symptoms
- S1 (mild): 4 or less stools per day (with or without blood), absence of systemic symptoms, normal inflammatory markers
- S2 (moderate): 4 stools per day, minimum signs of systemic symptoms
- S3 (severe): 6 or more bloody stools per day, pulse rate of ≥90 beats per min, temperature ≥37.5°C (99.5°F), hemoglobin concentration <105 g/L, erythrocyte sedimentation rate ≥30 mm/hr⁻¹

E, extent; S, severity.

From Ordás I, Eckmann L, Talamini M, et al: *Ulcerative colitis*, Lancet 380:1606–1616, 2012 (Panel 2, p. 1610).

Table 335-1 Etiologic Classification of Peptic Ulcers

- Positive for *Helicobacter pylori* infection
- Drug (NSAID)-induced
- H. pylori* and NSAID-positive
- H. pylori* and NSAID-negative*
- Acid hypersecretory state (Zollinger-Ellison syndrome)
- Anastomosis ulcer after subtotal gastric resection
- Tumors (cancer, lymphoma)
- Rare specific causes
 - Crohn disease of the stomach or duodenum
 - Eosinophilic gastrroduodenitis
 - Systemic mastocytosis
 - Radiation damage
 - Viral infections (cytomegalovirus or herpes simplex infection, particularly in immunocompromised patients)
 - Colonization of stomach with *Helicobacter heilmannii*
 - Severe systemic disease
 - Cameron ulcer (gastric ulcer where a hiatal hernia passes through the diaphragmatic hiatus)
 - True idiopathic ulcer

*Requires search for other specific causes.

Table 336-6 Pediatric Ulcerative Colitis Activity Index

ITEM	POINTS
(1) Abdominal pain	
No pain	0
Pain can be ignored	5
Pain cannot be ignored	10
(2) Rectal bleeding	
None	0
Small amount only, in <50% of stools	10
Small amount with most stools	20
Large amount (>50% of the stool content)	30
(3) Stool consistency of most stools	
Formed	0
Partially formed	5
Completely unformed	10
(4) Number of stools per 24 h	
0-2	0
3-5	5
6-8	10
>8	15
(5) Nocturnal stools (any episode causing wakening)	
No	0
Yes	10
(6) Activity level	
No limitation of activity	0
Occasional limitation of activity	5
Severe restricted activity	10
Sum of Index (0-85)	

Table 336-1 Comparison of Crohn Disease and Ulcerative Colitis

FEATURE	CROHN DISEASE	ULCERATIVE COLITIS
Rectal bleeding	Sometimes	Common
Diarrhea, mucus, pus	Variable	Common
Abdominal pain	Common	Variable
Abdominal mass	Common	Not present
Growth failure	Common	Variable
Perianal disease	Common	Rare
Rectal involvement	Occasional	Universal
Pyoderma gangrenosum	Rare	Present
Erythema nodosum	Common	Less common
Mouth ulceration	Common	Rare
Thrombosis	Less common	Present
Colonic disease	50-75%	100%
Ileal disease	Common	None except backwash ileitis
Stomach–esophageal disease	More common	Chronic gastritis can be seen
Strictures	Common	Rare
Fissures	Common	Rare
Fistulas	Common	Rare
Toxic megacolon	None	Present
Sclerosing cholangitis	Less common	Present
Risk for cancer	Increased	Greatly increased
Discontinuous (skip) lesions	Common	Not present
Transmural involvement	Common	Unusual
Crypt abscesses	Less common	Common
Granulomas	Common	None
Linear ulcerations	Uncommon	Common
Perinuclear antineutrophil cytoplasmic antibody–positive	<20%	70%

Table 336-2 Extraintestinal Complications of Inflammatory Bowel Disease

MUSCULOSKELETAL	Intestinal losses • Electrolytes • Minerals • Nutrients Increased caloric needs • Inflammation • Fever
Peripheral arthritis	
Granulomatous monoarthritis	
Granulomatous synovitis	
Rheumatoid arthritis	
Sacroiliitis	
Ankylosing spondylitis	
Digital clubbing and hypertrophic osteoarthropathy	
Periostitis	
Osteoporosis, osteomalacia	
Rhabdomyolysis	
Pelvic osteomyelitis	
Recurrent multifocal osteomyelitis	
Relapsing polychondritis	
SKIN AND MUCOUS MEMBRANES	HEMATOLOGIC
Oral lesions	Anemia: iron deficiency (blood loss) Vitamin B ₁₂ (ileal disease or resection, bacterial overgrowth, folate deficiency)
Cheilitis	Anemia of chronic inflammation Anaphylactoid purpura (Crohn disease)
Aphthous stomatitis, glossitis	Hyposplenism
Granulomatous oral Crohn disease	Autoimmune hemolytic anemia
Inflammatory hyperplasia fissures and cobblestone mucosa	Coagulation abnormalities
Peristomatis vegetans	Increased activation of coagulation factors
DERMATOLOGIC	Activated fibrinolysis
Erythema nodosum	Anticardiolipin antibody
Pyoderma gangrenosum	Increased risk of arterial and venous thrombosis with cerebrovascular stroke, myocardial infarction, peripheral arterial, and venous occlusions
Sweet syndrome	
Metastatic Crohn disease	
Psoriasis	
Epidermolysis bullosa acquisita	
Perianal skin tags	
Polyarteritis nodosa	
OCULAR	RENAL AND GENITOURINARY
Conjunctivitis	Metabolic
Uveitis, iritis	• Urinary crystal formation (nephrolithiasis, uric acid, oxylate)
Episcleritis	Hypokalemic nephropathy
Scleritis	Inflammation
Retrobulbar neuritis	• Retroperitoneal abscess
Chorioretinitis with retinal detachment	• Fibrosis with ureteral obstruction
Crohn keratopathy	• Fistula formation
Posterior segment abnormalities	Glomerulitis
Retinal vascular disease	Membrane nephritis
BRONCHOPULMONARY	Renal amyloidosis, nephrotic syndrome
Chronic bronchitis with bronchiectasis	
Chronic bronchitis with neutrophilic infiltrates	PANCREATITIS
Fibrosing alveolitis	Secondary to medications (sulfasalazine, 6-mercaptopurine, azathioprine, parenteral nutrition)
Pulmonary vasculitis	Ampullary Crohn disease
Small airway disease and bronchiolitis obliterans	Granulomatous pancreatitis
Eosinophilic lung disease	Decreased pancreatic exocrine function
Granulomatous lung disease	Sclerosing cholangitis with pancreatitis
Tracheal obstruction	
CARDIAC	HEPATOBILIARY
Pleuropericarditis	Primary sclerosing cholangitis
Cardiomyopathy	Small duct primary sclerosing cholangitis (pericholangitis)
Endocarditis	Carcinoma of the bile ducts
Myocarditis	Fatty infiltration of the liver
MALNUTRITION	Cholelithiasis
Decreased intake of food	Autoimmune hepatitis
• Inflammatory bowel disease	
• Dietary restriction	ENDOCRINE AND METABOLIC
Malabsorption	Growth failure, delayed sexual maturation
• Inflammatory bowel disease	Thyroiditis
• Bowel resection	Osteoporosis, osteomalacia
• Bile salt depletion	
• Bacterial overgrowth	NEUROLOGIC
	Peripheral neuropathy
	Meningitis
	Vestibular dysfunction
	Pseudotumor cerebri
	Cerebral vasculitis
	Migraine

Modified from Kugathasan S: Diarrhea. In Kliegman RM, Greenbaum LA, Lye PS, editors: Practical strategies in pediatric diagnosis and therapy, ed 2, Philadelphia, 2004, WB Saunders, p. 285.

Table 336-4 Infectious Agents Mimicking Inflammatory Bowel Disease

AGENT	MANIFESTATIONS	DIAGNOSIS	COMMENTS
BACTERIAL			
<i>Campylobacter jejuni</i>	Acute diarrhea, fever, fecal blood, and leukocytes	Culture	Common in adolescents, may relapse
<i>Yersinia enterocolitica</i>	Acute → chronic diarrhea, right lower quadrant pain, mesenteric adenitis–pseudoappendicitis, fecal blood, and leukocytes	Culture	Common in adolescents as fever of unknown origin, weight loss, abdominal pain
<i>Clostridium difficile</i>	Extraintestinal manifestations, mimics Crohn disease Postantibiotic onset, watery → bloody diarrhea, pseudomembrane on sigmoidoscopy	Cytotoxin assay	May be nosocomial Toxic megacolon possible
<i>Escherichia coli</i> O157:H7	Colitis, fecal blood, abdominal pain	Culture and typing	Hemolytic uremic syndrome
<i>Salmonella</i>	Watery → bloody diarrhea, foodborne, fecal leukocytes, fever, pain, cramps	Culture	Usually acute
<i>Shigella</i>	Watery → bloody diarrhea, fecal leukocytes, fever, pain, cramps	Culture	Dysentery symptoms
<i>Edwardsiella tarda</i>	Bloody diarrhea, cramps	Culture	Ulceration on endoscopy
<i>Aeromonas hydrophila</i>	Cramps, diarrhea, fecal blood	Culture	May be chronic Contaminated drinking water Shellfish source
<i>Plesiomonas shigelloides</i>	Diarrhea, cramps	Culture	
Tuberculosis	Rarely bovine, now <i>Mycobacterium tuberculosis</i> Ileocecal area, fistula formation	Culture, purified protein derivative, biopsy	Can mimic Crohn disease
PARASITES			
<i>Entamoeba histolytica</i>	Acute bloody diarrhea and liver abscess, colic	Trophozoite in stool, colonic mucosal flask ulceration, serologic tests	Travel to endemic area
<i>Giardia lamblia</i>	Foul-smelling, watery diarrhea, cramps, flatulence, weight loss; no colonic involvement	"Owl"-like trophozoite and cysts in stool; rarely duodenal intubation	May be chronic
AIDS-ASSOCIATED ENTEROPATHY			
<i>Cryptosporidium</i>	Chronic diarrhea, weight loss	Stool microscopy	Mucosal findings not like inflammatory bowel disease
<i>Isospora belli</i>	As in <i>Cryptosporidium</i>		Tropical location
<i>Cytomegalovirus</i>	Colonic ulceration, pain, bloody diarrhea	Culture, biopsy	More common when on immunosuppressive medications

Table 338-10 Common Micronutrient Deficiencies in Inflammatory Bowel Disease

MICRONUTRIENT	CROHN DISEASE AND/OR ULCERATIVE COLITIS	MALABSORPTION	INTESTINAL LOSSES	INADEQUATE INTAKE
Iron	CD and UC	+ (CD)	+++	++
Vitamins A, D, E, K	CD > UC	++ (CD)		+++
Vitamin B ₁₂	CD	+++		+
Vitamin B ₁ , B ₂ , B ₆	CD > UC			++
Vitamin C, glutathione (antioxidants)	CD and UC		++	++
Folate	CD and UC	++		+
Calcium, magnesium, selenium, zinc	CD and UC	++	+++	+
Polyunsaturated fatty acids	CD	++		++

Table 336-5 Chronic Inflammatory-Like Intestinal Disorders Including Monogenetic Diseases

INFECTION (see Table 336-4)	
AIDS-Associated	
Toxin	
Immune-Inflammatory	
Severe combined immunodeficiency diseases	
Agammaglobulinemia	
Chronic granulomatous disease	
Wiskott-Aldrich syndrome	
Common variable immunodeficiency diseases	
Acquired immunodeficiency states	
Dietary protein enterocolitis	
Autoimmune polyendocrine syndrome type 1	
Behcet disease	
Lymphoid nodular hyperplasia	
Eosinophilic gastroenteritis	
Omenn syndrome	
Graft-versus-host disease	
IPEX (immune dysfunction, polyendocrinopathy, enteropathy, X-linked) syndromes	
Interleukin-10 signaling defects	
Autoimmune enteropathy*	
Microscopic colitis	
Hyperimmunoglobulin M syndrome	
Hyperimmunoglobulin E syndromes	
Mevalonate kinase deficiency	
Familial Mediterranean fever	
Phospholipase Cγ2 defects	
Familial hemophagocytic lymphohistiocytosis type 5	
X-linked lymphoproliferative syndromes types 1, 2	
Congenital neutropenias	
Leukocyte adhesion deficiency 1	
VASCULAR-ISCHEMIC DISORDERS	
Systemic vasculitis (systemic lupus erythematosus, dermatomyositis)	
Henoch-Schönlein purpura	
Hemolytic uremic syndrome	
Granulomatosis with angiitis	
OTHER	
Glycogen storage disease type 1b	
Dystrophic epidermolysis bullosa	
X-linked ectodermal dysplasia and immunodeficiency	
Dyskeratosis congenita	
ADAM-17 deficiency	
Prestenotic colitis	
Diversion colitis	
Radiation colitis	
Neonatal necrotizing enterocolitis	
Typhlitis	
Sarcoidosis	
Hirschsprung colitis	
Intestinal lymphoma	
Laxative abuse	
Endometriosis	
Hermansky-Pudlak syndrome	
Trichohepatoenteric syndrome	
PTEN hamartoma syndrome	

*May be the same as IPEX

Table 338-3 Diarrheal Diseases Appearing in the Neonatal Period

CONDITION	CLINICAL FEATURES
Microvillus inclusion disease	Secretory watery diarrhea
Tufting enteropathy	Secretory watery diarrhea
Congenital glucose-galactose malabsorption	Acidic diarrhea
Congenital lactase deficiency	Acidic diarrhea
Congenital chloride diarrhea	Hydramnion, secretory watery diarrhea Metabolic alkalosis
Congenital defective jejunal Na ⁺ -H ⁺ exchange	Hydramnion, secretory watery diarrhea
Congenital bile acid malabsorption	Steatorrhea
Congenital enterokinase deficiency	Failure to thrive, edema
Congenital trypsinogen deficiency	Failure to thrive, edema
Congenital lipase and/or colipase deficiency	Failure to thrive, oily stool
Enteric anendocrinosis (NEUROG 3 mutation)	Hyperchlormic acidosis, failure to thrive
Immunodeficiency and autoinflammatory diseases (see Table 336-5)	Failure to thrive, opportunistic infections, eczema

Table 336-7 Differential Diagnosis of Presenting Symptoms of Crohn Disease

PRIMARY PRESENTING SYMPTOM	DIAGNOSTIC CONSIDERATIONS
Right lower quadrant abdominal pain, with or without mass	Appendicitis, infection (e.g., <i>Campylobacter</i> , <i>Yersinia</i> spp.), lymphoma, intussusception, mesenteric adenitis, Meckel diverticulum, ovarian cyst
Chronic perumbilical or epigastric abdominal pain	Irritable bowel syndrome, constipation, lactose intolerance, peptic disease
Rectal bleeding, no diarrhea	Fissure, polyp, Meckel diverticulum, rectal ulcer syndrome
Bloody diarrhea	Infection, hemolytic-uremic syndrome, Henoch-Schönlein purpura, ischemic bowel, radiation colitis
Watery diarrhea	Irritable bowel syndrome, lactose intolerance, giardiasis, <i>Cryptosporidium</i> infection, sorbitol, laxatives
Perirectal disease	Fissure, hemorrhoid (rare), streptococcal infection, condyloma (rare)
Growth delay	Endocrinopathy
Anorexia, weight loss	Anorexia nervosa
Arthritis	Collagen vascular disease, infection
Liver abnormalities	Chronic hepatitis

Table 338-1 Malabsorption Disorders and Chronic Diarrhea Associated with Generalized Mucosal Defect

Mucosal disorders
Gluten-sensitive enteropathy (celiac disease)
Cow's milk and other protein-sensitive enteropathies
Eosinophilic enteropathy
Protein-losing enteropathy
Lymphangiectasia (congenital and acquired)
Disorders causing bowel mucosal inflammation, Crohn disease
Congenital bowel mucosal defects
Microvillous inclusion disease
Tufting enteropathy
Carbohydrate-deficient glycoprotein syndrome
Enterocyte heparan sulfate deficiency
Enteric anendocrinosis (NEUROG 3 mutation)
Tricho-hepatic-enteric syndrome
Immunodeficiency disorders
Congenital immunodeficiency disorders
Selective immunoglobulin A deficiency (can be associated with celiac disease)
Severe combined immunodeficiency
Agammaglobulinemia
X-linked hypogammaglobulinemia
Wiskott-Aldrich syndrome
Common variable immunodeficiency disease
Chronic granulomatous disease
Acquired immune deficiency
HIV infection
Immunosuppressive therapy and post–bone marrow transplantation
Autoimmune enteropathy
IPEX (immune dysregulation, polyendocrinopathy, enteropathy, X-linked inheritance)
IPEX-like syndromes
Autoimmune polyglandular syndrome type 1
Miscellaneous
Immunoproliferative small intestinal disease
Short bowel syndrome
Blind loop syndrome
Radiation enteritis
Protein–calorie malnutrition
Crohn disease
Pseudoobstruction

Table 338-7 Other Causes of Flat Mucosa

Autoimmune enteropathy
Tropical sprue
Giardiasis
HIV enteropathy
Bacterial overgrowth
Crohn disease
Eosinophilic gastroenteritis
Cow's milk enteropathy
Soy protein enteropathy
Primary immunodeficiency
Graft-versus-host disease
Chemotherapy and radiation
Protein energy malnutrition
Tuberculosis
Lymphoma
Nongluten food intolerances

Table 338-2 Classification of Malabsorption Disorders and Chronic Diarrhea Based on the Predominant Nutrient Malabsorbed

CARBOHYDRATE MALABSORPTION
Lactose malabsorption
Congenital lactase deficiency
Hypolactasia (adult type)
Secondary lactase deficiency
Congenital sucrase-isomaltase deficiency
Glucose galactose malabsorption
FAT MALABSORPTION
Abetalipoproteinemia
Lymphangiectasia
Homozygous hypobetalipoproteinemia
Chylomicron retention disease (Anderson disease)
Cystic fibrosis
Shwachman-Diamond syndrome
Johanson-Blizzard syndrome
Pearson syndrome
Secondary exocrine pancreatic insufficiency
Isolated enzyme deficiency
Enterokinase deficiency
Trypsinogen deficiency
Lipase/collipase deficiency
Chronic pancreatitis
Protein–calorie malnutrition
Decreased pancreatic lipase/cholecystokinin secretion
Disrupted enterohepatic circulation of bile salts
Cholestatic liver disease
Bile acid synthetic defects
Bile acid malabsorption (terminal ileal disease)
PROTEIN/AMINO ACID MALABSORPTION
Lysinuric protein intolerance (defect in dibasic amino acid transport)
Hartnup disease (defect in free neutral amino acids)
Blue diaper syndrome (isolated tryptophan malabsorption)
Oasthouse urine disease (defect in methionine absorption)
Lowe syndrome (lysine and arginine malabsorption)
Enterokinase deficiency
MINERAL AND VITAMIN MALABSORPTION
Congenital chloride diarrhea
Congenital sodium absorption defect
Acrodermatitis enteropathica (zinc malabsorption)
Menkes disease (copper malabsorption)
Vitamin D–dependent rickets
Folate malabsorption
Congenital
Secondary to mucosal damage (celiac disease)
Vitamin B ₁₂ malabsorption
Autoimmune pernicious anemia
Decreased gastric acid (H ₂ blockers or proton pump inhibitors)
Terminal ileal disease (e.g., Crohn disease) or resection
Inborn errors of vitamin B ₁₂ transport and metabolism
Primary hypomagnesemia
DRUG INDUCED
Sulfasalazine: folic acid malabsorption
Cholestyramine: calcium and fat malabsorption
Anticonvulsant drugs such as phenytoin (causing vitamin D deficiency and folic acid and calcium malabsorption)
Gastric acid suppression: vitamin B ₁₂
Methotrexate: mucosal injury

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Table 338-4 Some Clinical Manifestations of Celiac Disease in Children and Adolescents

SYSTEM	MANIFESTATION	(POSSIBLE) CAUSE
Gastrointestinal	Diarrhea	Atrophy of the small bowel mucosa Malabsorption
	Distended abdomen	
	Vomiting	
	Anorexia	
	Weight loss	
	Failure to thrive	
	Rectal prolapse	
	Aphthous stomatitis	
	Intussusception	
Hematologic	Anemia	Iron malabsorption
Skeletal	Rickets	Calcium/vitamin D malabsorption
	Osteoporosis	
	Enamel hypoplasia of the teeth	
Muscular	Atrophy	Malnutrition
Neurologic	Peripheral neuropathy	Thiamine/vitamin B ₁₂ deficiency
	Epilepsy	
	Irritability	
	Cerebral calcifications	
	Cerebellar ataxia	
Endocrinologic	Short stature	Malnutrition Calcium/vitamin D malabsorption
	Pubertas tarda	
	Secondary hyperparathyroidism	
Dermatologic	Dermatitis herpetiformis	Autoimmunity
Respiratory	Alopecia areata	
	Erythema nodosum	
	Idiopathic pulmonary hemosiderosis	

Table 338-5 Risk Groups for Celiac Disease Case-Finding

First-degree relatives
Dermatitis herpetiformis
Unexplained iron-deficiency anemia
Autoimmune thyroiditis
Type 1 diabetes
Unexplained infertility
Recurrent abortion
Dental enamel hypoplasia
Cryptic hypertransaminasemia
Autoimmune liver disease
Short stature
Delayed puberty
Down, Williams, and Turner syndromes
Irritable bowel syndrome
Unexplained osteoporosis
Sjögren syndrome
Epilepsy (poorly controlled) with occipital calcifications
Selective immunoglobulin A deficiency
Autoimmune endocrinopathies
Addison disease
Aphthous stomatitis
Ataxia
Alopecia
Polyneuropathy
Irritable bowel syndrome

Modified from Di Sabatino A, Corazza GR: Celiac disease, Lancet 373:1480–1490, 2009.

Table 338-6 Clinical Spectrum of Celiac Disease

SYMPTOMATIC
Frank malabsorption symptoms: chronic diarrhea, failure to thrive, weight loss
Extraintestinal manifestations: anemia, fatigue, hypertransaminasemia, neurologic disorders, short stature, dental enamel defects, arthralgia, aphthous stomatitis

SILENT
No apparent symptoms in spite of histologic evidence of villous atrophy

In most cases identified by serologic screening in at-risk groups (see Table 330-1)

LATENT
Subjects who have a normal histology, but at some other time, before or after, have shown a gluten-dependent enteropathy

POTENTIAL
Subjects with positive celiac disease serology but without evidence of altered jejunal histology It might or might not be symptomatic

Table 338-8 Causes of Protein-Losing Enteropathy

Mucosal inflammation
Infection
Cytomegalovirus
Bacterial overgrowth
Invasive bacterial infection
<i>Clostridium difficile</i>
<i>Helicobacter pylori</i>
<i>Giardiasis</i>
Measles
<i>Strongyloides stercoralis</i>
Gastric inflammation
Menetrier disease
Eosinophilic gastroenteropathy
Intestinal inflammation
Celiac disease
Crohn disease
Eosinophilic gastroenteropathy
Tropical sprue
Radiation enteritis
Primary intestinal lymphangiectasia
Secondary intestinal lymphangiectasia
Constrictive pericarditis
Congestive heart failure
Post-Fontan procedure
Malrotation
Lymphoma
Noonan syndrome
Sarcoidosis
Radiation therapy
Arsenic poisoning
Colonic inflammation
Inflammatory bowel diseases
Necrotizing enterocolitis
Congenital disorders of glycosylation
Enterocyte heparin sulfate deficiency

Table 338-9 Causes of Short Bowel Syndrome**CONGENITAL**

- Congenital short bowel syndrome
- Multiple atresias
- Gastroschisis

BOWEL RESECTION

- Necrotizing enterocolitis
- Volvulus with or without malrotation
- Long segment Hirschsprung disease
- Meconium peritonitis
- Crohn disease
- Trauma

Table 339-1 Causes of Intestinal Failure in Children Requiring Transplantation**SHORT BOWEL**

- Congenital disorders
- Volvulus
- Gastroschisis
- Necrotizing enterocolitis
- Intestinal atresia
- Trauma

INTESTINAL DYSMOTILITY

- Intestinal pseudoobstruction
- Intestinal aganglionosis (Hirschsprung disease)

ENTEROCYTE DYSFUNCTION

- Microvillus inclusion disease
- Tufting enteropathy
- Autoimmune disorders
- Crohn disease

TUMORS

- Familial polyposis
- Inflammatory pseudotumor

Table 340-8 Differential Diagnosis of Acute Dysentery and Inflammatory Enterocolitis**SPECIFIC INFECTIOUS PROCESSES**

- Bacillary dysentery (*Shigella dysenteriae*, *Shigella flexneri*, *Shigella sonnei*, *Shigella boydii*; invasive *Escherichia coli*)
- Campylobacteriosis (*Campylobacter jejuni*)
- Amebic dysentery (*Entamoeba histolytica*)
- Ciliary dysentery (*Balantidium coli*)
- Bilharzial dysentery (*Schistosoma japonicum*, *Schistosoma mansoni*)
- Other parasitic infections (*Trichinella spiralis*)
- Vibriosis (*Vibrio parahaemolyticus*)
- Salmonellosis (*Salmonella typhimurium*)
- Typhoid fever (*Salmonella typhi*)
- Enteric fever (*Salmonella choleraesuis*, *Salmonella paratyphi*)
- Yersiniosis (*Yersinia enterocolitica*)
- Spirillar dysentery (*Spirillum spp.*)

PROCTITIS

- Gonococcal (*Neisseria gonorrhoeae*)
- Herpetic (herpes simplex virus)
- Chlamydial (*Chlamydia trachomatis*)
- Syphilitic (*Treponema pallidum*)

OTHER SYNDROMES

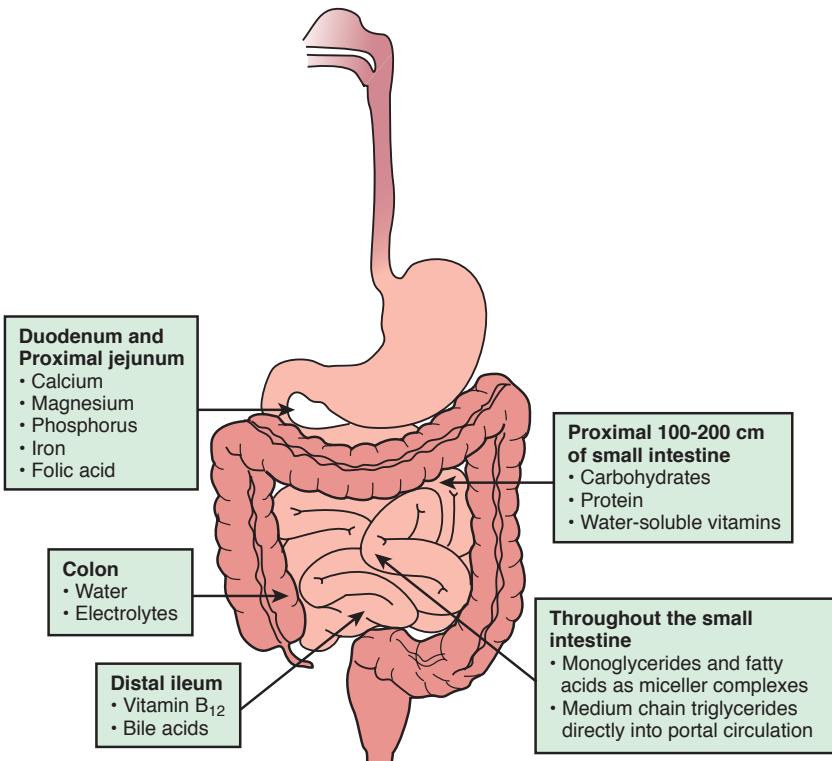
- Necrotizing enterocolitis of the newborn
- Enteritis necroticans
- Pseudomembranous enterocolitis (*Clostridium difficile*)
- Typhlitis

CHRONIC INFLAMMATORY PROCESSES

- Enteropathogenic and enteroaggregative *E. coli*
- Gastrointestinal tuberculosis
- Gastrointestinal mycosis
- Parasitic enteritis

SYNDROMES WITHOUT KNOWN INFECTIOUS CAUSE

- Idiopathic ulcerative colitis
- Crohn disease
- Radiation enteritis
- Ischemic colitis
- Allergic enteritis

**Figure 338-7** Absorption of nutrients in the small bowel varies with the region.

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Table 340-9 Extraintestinal Manifestations of Enteric Infections

MANIFESTATION	ASSOCIATED ENTERIC PATHOGEN(S)	ONSET AND PROGNOSIS
Focal infections from systemic spread of bacterial pathogens, including vulvovaginitis, urinary tract infection, endocarditis, osteomyelitis, meningitis, pneumonia, hepatitis, peritonitis, chorioamnionitis, soft-tissue infection, and septic thrombophlebitis	All major pathogens can cause such direct extraintestinal infections, including <i>Salmonella</i> , <i>Shigella</i> , <i>Yersinia</i> , <i>Campylobacter</i> , <i>Clostridium difficile</i>	Onset usually during the acute infection but can occur subsequently Prognosis depends on infection site
Reactive arthritis	<i>Salmonella</i> , <i>Shigella</i> , <i>Yersinia</i> , <i>Campylobacter</i> , <i>Cryptosporidium</i> , <i>C. difficile</i>	Typically occurs 1-3 wk after infection Relapses after reinfection can develop in 15-50% of people, but most children recover fully within 2-6 mo after the first symptoms appear
Guillain-Barré syndrome	<i>Campylobacter</i>	Usually occurs a few weeks after the original infection Prognosis is good although 15-20% may have sequelae
Glomerulonephritis	<i>Shigella</i> , <i>Campylobacter</i> , <i>Yersinia</i>	Can be of sudden onset in acute, referring to a sudden attack of inflammation, or chronic, which comes on gradually In most cases, the kidneys heal with time
Immunoglobulin A (IgA) nephropathy	<i>Campylobacter</i>	Characterized by recurrent episodes of blood in the urine, this condition results from deposits of the protein IgA in the glomeruli. IgA nephropathy can progress for years with no noticeable symptoms Men seem more likely to develop this disorder than women
Erythema nodosum	<i>Yersinia</i> , <i>Campylobacter</i> , <i>Salmonella</i>	Although painful, is usually benign and more commonly seen in adolescents Resolves with 4-6 wk
Hemolytic uremic syndrome	<i>Shigella dysenteriae</i> 1, <i>Escherichia coli</i> O157:H7, others	Sudden onset, short-term renal failure In severe cases, renal failure requires several sessions of dialysis to take over the kidney function, but most children recover without permanent damage to their health
Hemolytic anemia	<i>Campylobacter</i> , <i>Yersinia</i>	Relatively rare complication and can have a chronic course

From Centers for Disease Control and Prevention: Managing acute gastroenteritis among children, MMWR Recomm Rep 53:1-33, 2004.

Table 340-10 Symptoms Associated with Dehydration

SYMPTOM	MINIMAL OR NO DEHYDRATION (<3% LOSS OF BODY WEIGHT)	MILD TO MODERATE DEHYDRATION (3-9% LOSS OF BODY WEIGHT)	SEVERE DEHYDRATION (>9% LOSS OF BODY WEIGHT)
Mental status	Well; alert	Normal, fatigued or restless, irritable	Apathetic, lethargic, unconscious
Thirst	Drinks normally; might refuse liquids	Thirsty; eager to drink	Drinks poorly; unable to drink
Heart rate	Normal	Normal to increased	Tachycardia, with bradycardia in most severe cases
Quality of pulses	Normal	Normal to decreased	Weak, thready, or impalpable
Breathing	Normal	Normal; fast	Deep
Eyes	Normal	Slightly sunken	Deeply sunken
Tears	Present	Decreased	Absent
Mouth and tongue	Moist	Dry	Parched
Skinfold	Instant recoil	Recoil in <2 sec	Recoil in >2 sec
Capillary refill	Normal	Prolonged	Prolonged; minimal
Extremities	Warm	Cool	Cold; mottled; cyanotic
Urine output	Normal to decreased	Decreased	Minimal

Adapted from Duggan C, Santosham M, Glass RI: The management of acute diarrhea in children: oral rehydration, maintenance, and nutritional therapy, MMWR Recomm Rep 41(RR-16):1-20, 1992; and World Health Organization: The treatment of diarrhoea: a manual for physicians and other senior health workers, Geneva, 1995; World Health Organization; Centers for Disease Control and Prevention: Diagnosis and management of foodborne illnesses, MMWR 53(RR-4):1-33, 2004.

Table 340-11 Summary of Treatment Based on Degree of Dehydration

DEGREE OF DEHYDRATION	REHYDRATION THERAPY	REPLACEMENT OF LOSSES	NUTRITION
Minimal or no dehydration	Not applicable	<10 kg body weight: 60-120 mL ORS for each diarrheal stool or vomiting episode ≥10 kg body weight: 120-240 mL ORS for each diarrheal stool or vomiting episode	Continue breastfeeding or resume age-appropriate normal diet after initial hydration, including adequate caloric intake for maintenance*
Mild to moderate dehydration	ORS, 50-100 mL/kg body weight over 3-4 hr	Same	Same
Severe dehydration	Lactated Ringer solution or normal saline in 20 mL/kg body weight IV until perfusion and mental status improve; then administer 100 mL/kg body weight ORS over 4 hr or 5% dextrose normal saline IV at twice maintenance fluid rates	Same; if unable to drink, administer through nasogastric tube or administer 5% dextrose in normal saline with 20 mEq/L potassium chloride IV	Same

*Overly restricted diets should be avoided during acute diarrheal episodes. Breastfed infants should continue to nurse ad libitum even during acute rehydration. Infants too weak to eat can be given milk or formula through a nasogastric tube. Lactose-containing formulas are usually well tolerated. If lactose malabsorption appears clinically substantial, lactose-free formulas can be used. Complex carbohydrates, fresh fruits, lean meats, yogurt, and vegetables are all recommended. Carbonated drinks or commercial juices with a high concentration of simple carbohydrates should be avoided.

ORS, oral rehydration solution.

From Centers for Disease Control and Prevention: Diagnosis and management of foodborne illnesses, MMWR 53(RR-4):1-33, 2004.

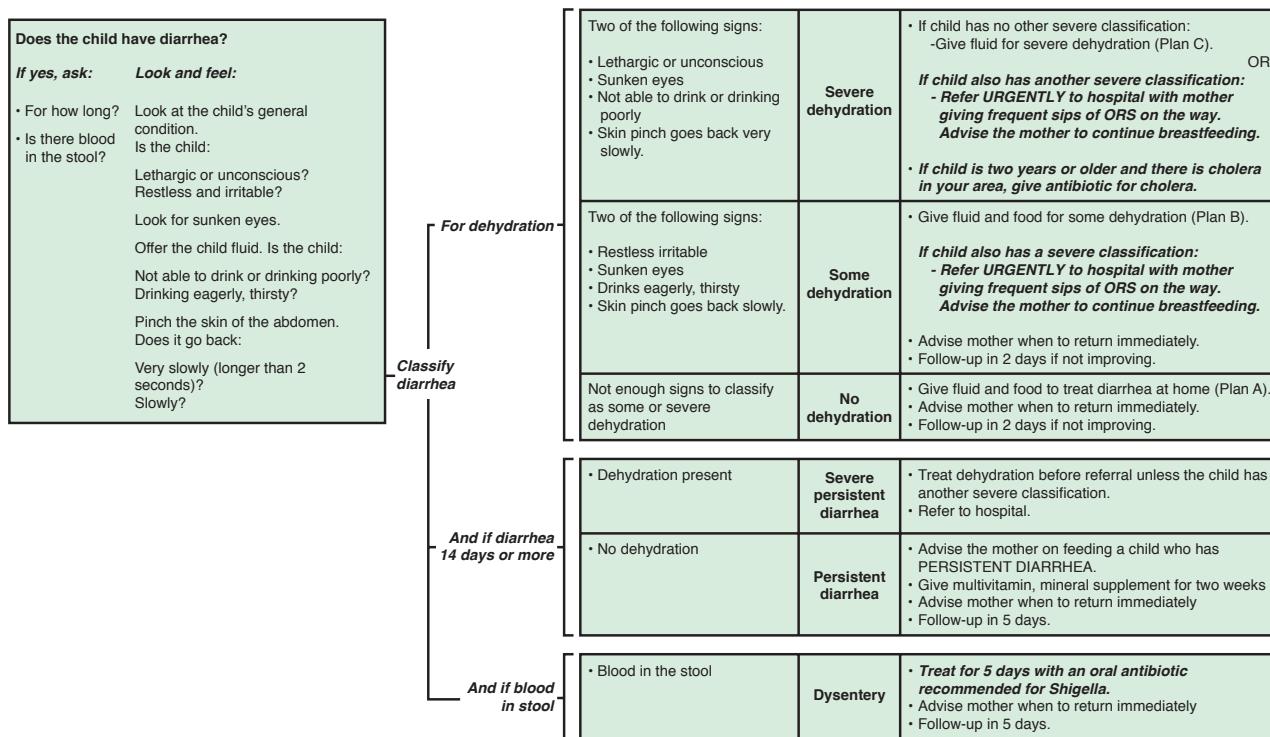


Figure 340-6 Integrated Management of Childhood Illnesses (IMCI) protocol for the recognition and management of diarrhea in developing countries. ORS, Oral rehydration solution.

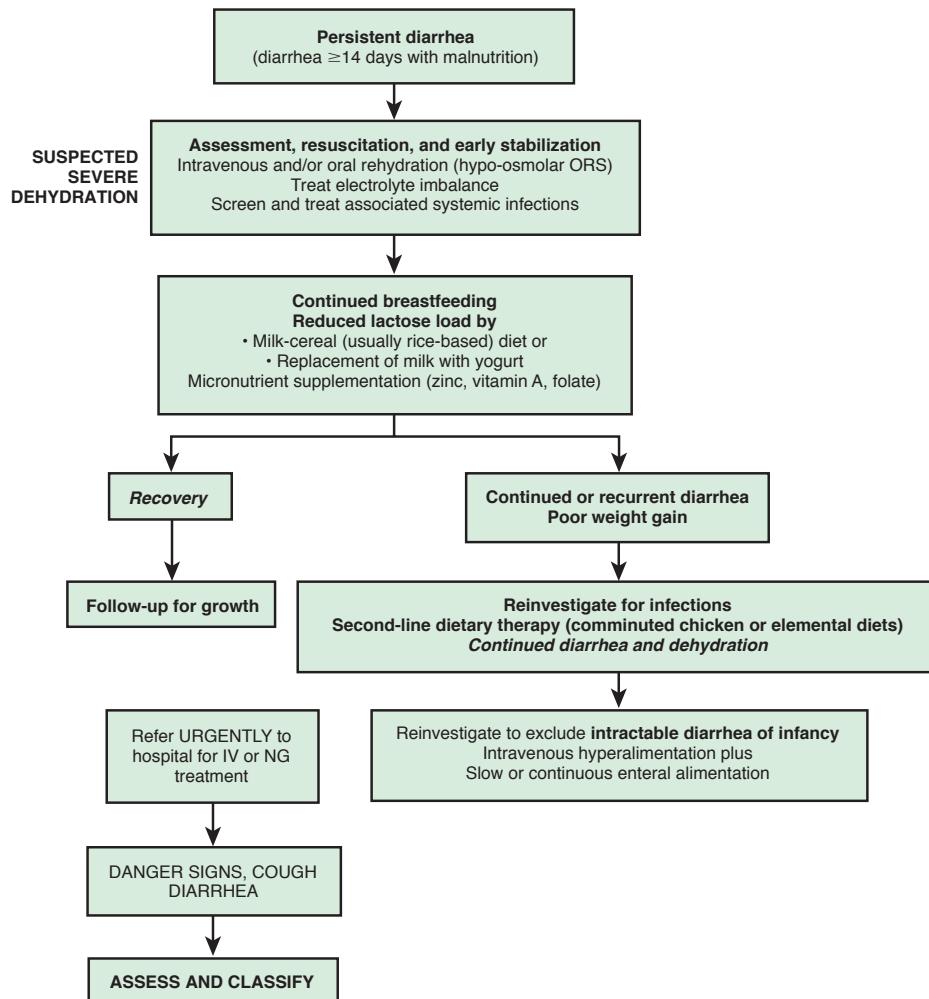


Figure 340-7 Management of persistent diarrhea. /V, Intravenous; NG, nasogastric tube; ORS, oral rehydration solution.

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Table 340-12 Antibiotic Therapy for Infectious Diarrhea

ORGANISM	DRUG OF CHOICE	DOSAGE AND DURATION OF TREATMENT
<i>Shigella</i> (severe dysentery and EIEC dysentery)	Ciprofloxacin, ampicillin, ceftriaxone, azithromycin, or TMP-SMX Most strains are resistant to several antibiotics	Ceftriaxone 50-100 mg/kg/day IV or IM, qd or bid × 7 days Ciprofloxacin 20-30 mg/kg/day PO bid × 7-10 days Ampicillin PO, IV 50-100 mg/kg/day qid × 7 days
EPEC, ETEC, EIEC	TMP-SMX or ciprofloxacin	TMP 10 mg/kg/day and SMX 50 mg/kg/day bid × 5 days Ciprofloxacin PO 20-30 mg/kg/day qid for 5-10 days
<i>Salmonella</i>	No antibiotics for uncomplicated gastroenteritis in normal hosts caused by nontyphoidal species Treatment indicated in infants younger than 3 mo, and patients with malignancy, chronic GI disease, severe colitis hemoglobinopathies, or HIV infection, and other immunocompromised patients Most strains are resistant to multiple antibiotics	See treatment of <i>Shigella</i>
<i>Aeromonas/Plesiomonas</i>	TMP-SMX Ciprofloxacin	TMP 10 mg/kg/day and SMX 50 mg/kg/day bid for 5 days Ciprofloxacin PO 20-30 mg/kg/day divided bid × 7-10 days
<i>Yersinia</i> spp.	Antibiotics are not usually required for diarrhea Deferoxamine therapy should be withheld for severe infections or associated bacteremia Treat sepsis as for immunocompromised hosts, using combination therapy with parenteral doxycycline, aminoglycoside, TMP-SMX, or fluoroquinolone	
<i>Campylobacter jejuni</i>	Erythromycin or azithromycin	Erythromycin PO 50 mg/kg/day divided tid × 5 days Azithromycin PO 5-10 mg/kg/day qid × 5 days
<i>Clostridium difficile</i>	Metronidazole (first line) Discontinue initiating antibiotic Vancomycin (second line)	PO 30 mg/kg/day divided qid × 5 days; max 2 g PO 40 mg/kg/day qid × 7 days, max 125 mg
<i>Entamoeba histolytica</i>	Metronidazole followed by iodoquinol or paromomycin	Metronidazole PO 30-40 mg/kg/day tid × 7-10 days Iodoquinol PO 30-40 mg/kg/day tid × 20 days Paromomycin PO 25-35 mg/kg/day tid × 7 days
<i>Giardia lamblia</i>	Furazolidone or metronidazole or albendazole or quinacrine	Furazolidone PO 25 mg/kg/day qid × 5-7 days Metronidazole PO 30-40 mg/kg/day tid × 7 days Albendazole PO 200 mg bid × 10 days
<i>Cryptosporidium</i> spp.	Nitazoxanide PO treatment may not be needed in normal hosts In immunocompromised, PO immunoglobulin + aggressively treat HIV, etc.	Children 1-3 yr: 100 mg bid × 3 days Children 4-11 yr: 200 mg bid
<i>Isospora</i> spp.	TMP-SMX	PO TMP 5 mg/kg/day and SMX 25 mg/kg/day, bid × 7-10 days
<i>Cyclospora</i> spp.	TMP/SMX	PO TMP 5 mg/kg/day and SMX 25 mg/kg/day bid × 7 days
<i>Blastocystis hominis</i>	Metronidazole or iodoquinol	Metronidazole PO 30-40 mg/kg/day tid × 7-10 days Iodoquinol PO 40 mg/kg/day tid × 20 days

EIEC, Enteroinvasive *Escherichia coli*; EPEC, enteropathogenic *E. coli*; ETEC, enterotoxigenic *E. coli*; GI, gastrointestinal; max, maximum; SMX, sulfamethoxazole; TMP, trimethoprim.

Table 341-2 Main Etiologies of Noninfectious Chronic Diarrhea in Children Older and Younger Than 2 Yr of Age

ETIOLOGY	YOUNGER THAN 2 YR	OLDER THAN 2 YR
Abnormal digestive processes	Shwachman-Diamond syndrome, isolated pancreatic enzyme deficiency, chronic pancreatitis, Johanson-Blizzard syndrome, Pearson syndrome. Trypsinogen and enterokinase deficiency: chronic cholestasis; use of bile acids sequestrants; primary bile acid malabsorption	Cystic fibrosis, terminal ileum resection
Nutrient malabsorption	Congenital sucrase-isomaltase deficiency; congenital lactase deficiency; glucose-galactose malabsorption; fructose malabsorption; congenital short bowel	Hypoalactasia; acquired short bowel
Immune/inflammatory	Food allergy; autoimmune enteropathy; primary and secondary immunodeficiencies; IPEX syndrome	Celiac disease; eosinophilic gastroenteritis, inflammatory bowel diseases
Structural defects	Microvillus inclusion disease, tufting enteropathy, phenotypic diarrhea, heparan-sulfate deficiency, $\alpha_2\beta_1$ and $\alpha_5\beta_4$ integrin deficiency, lymphangiectasia, enteric anendocrinosis (neurogenin-3 mutation)	Rare
Defects of electrolyte and metabolite transport	Congenital chloride diarrhea, congenital sodium diarrhea, acrodermatitis enteropathica, selective folate deficiency, abetalipoproteinemia, activating guanylate cyclase mutation	Late onset chloride diarrhea
Motility disorders	Hirschsprung disease, chronic intestinal pseudoobstruction (neurogenic and myopathic)	Thyrotoxicosis
Neoplastic diseases	Neuroendocrine hormone-secreting tumors: Apudomas such as VIPoma, Zollinger-Ellison, and mastocytosis	Neuroendocrine hormone-secreting tumors: Apudomas such as VIPoma, Zollinger-Ellison, and mastocytosis
Diarrhea associated with exogenous substances	Excessive intake of carbonated fluid, foods or drinks containing sorbitol, mannitol, or xylitol; excessive intake of antacids or laxatives containing lactulose or Mg(OH) ₂ ; excessive intake of methylxanthines-containing drinks (cola, tea, coffee)	Excessive intake of carbonated fluid, foods or drinks containing sorbitol, mannitol, or xylitol; excessive intake of antacids or laxatives containing lactulose or Mg(OH) ₂ ; excessive intake of methylxanthines-containing drinks (cola, tea, coffee)
Chronic nonspecific diarrhea	Functional diarrhea*	Irritable bowel syndrome†

*Until 4 yr of age, according to Rome III criteria.

†Older than 5 yr of age according to Rome III criteria.

IPEX, immunodysregulation polyendocrinopathy enteropathy X-linked syndrome; VIPoma, vasoactive intestinal polypeptide tumor.

Table 341-4 Degree of Malnutrition as Estimated by Visceral Protein Concentrations in Children with Chronic Diarrhea

VISCERAL PROTEIN	HALF-LIFE	NORMAL VALUES	MILD MALNUTRITION	MODERATE MALNUTRITION	SEVERE MALNUTRITION
Albumin	20 days	30-45 g/L	3.0-2.9 g/L	2.8-2.5 g/L	<2.5 g/L
Prealbumin	2 days	0.2-0.4 g/L	0.2-0.18 g/L	0.17-0.1 g/L	<0.1 g/L
Retinol binding protein	12 hr	2.6-7.6 g/L	2.5-2.0 g/L	1.9-1.5 g/L	<1 g/L
Transferrin	8 days	218-411 μ g/dL	200-150 μ g/dL	149-100 μ g/dL	<100 μ g/dL
Serum iron	11-19 hr	16-124 μ g/dL	15-13 μ g/dL	12-10 μ g/dL	<10 μ g/dL

Consider also the concentrations of the following micronutrients: calcium, zinc, magnesium, iodine, vitamin A, vitamin C, vitamin B₁.**Table 341-5** Noninvasive Tests for Intestinal Digestive-Absorptive Function and Inflammation

TEST	NORMAL VALUES	IMPLICATION
α_1 -Antitrypsin concentration	<0.9 mg/g	Increased intestinal permeability/protein loss
Steatocrit	<2.5% (older than 2 yr) fold increase over age-related values (younger than 2 yr)	Fat malabsorption
Fecal-reducing substances	Absent	Carbohydrate malabsorption
Elastase concentration	>200 μ g/g	Pancreatic function
Chymotrypsin concentration	>7.5 units/g >375 units/24 hr	Pancreatic function
Fecal occult blood	Absent	Blood loss in the stools/inflammation
Fecal calprotectin concentration	<100 μ g/g (in children to 4 yr of age) <50 μ g/g (older than 4 yr)	Intestinal inflammation
Fecal leukocytes	<5/microscopic field	Colonic inflammation
Nitric oxide in rectal dialysate	<5 μ M of NO ₂ ⁻ /NO ₃ ⁻	Rectal inflammation
Dual sugar (cellobiose/mannitol) absorption test	Urine excretion ratio: 0.010 ± 0.018	Increased intestinal permeability
Xylose oral load	25 mg/dL	Reduced intestinal surface

Table 341-3 Classification of Congenital Diarrheal Disorders Based on Their Molecular Defect and Their Inheritance

DEFECTS OF DIGESTION, ABSORPTION, AND TRANSPORT OF NUTRIENTS AND ELECTROLYTES

GENE				
DISEASE	Name	Location	TRANSMISSION AND INCIDENCE	MECHANISM
Genes Encoding Brush-Border Enzymes				
Congenital lactase deficiency (LD)	LCT	2q21.3	AR, 1 in 60,000 in Finland; lower in other ethnic groups	Osmotic
Congenital sucrase-isomaltase deficiency (SID)	SI	3q26.1	AR, 1 in 5,000; higher incidence in Greenland, Alaska, and Canada	Osmotic
Congenital maltase-glucamylase deficiency (MGD)	Not defined	—	Few cases described	Osmotic
Genes Encoding Membrane Carriers				
Glucose-galactose malabsorption (GGM)	SLC5A1	22q13.1	AR, few hundred cases described	Osmotic
Fructose malabsorption (FM)	Not defined	—	Up to 40%	Osmotic
Fanconi-Bickel syndrome (FBS)	SLC2A2	3q26.2	AR, rare, higher frequency in consanguineous	Osmotic
Acrodermatitis enteropathica (ADE)	SLC39A4	8q24.3	AR, 1 in 500,000	Osmotic
Congenital chloride diarrhea (CCD, DIAR 1)	SLC26A3	7q31.1	AR, sporadic; frequent in some ethnicities	Osmotic
Lysinuric protein intolerance (LPI)	SLC7A7	14q11.2	AR, about 1 in 60,000 in Finland and Japan; rare in other ethnic groups	Osmotic
Primary bile acid malabsorption (PBAM)	SLC10A2	13q33.1	AR	Secretory
Cystic fibrosis (CF)	CFTR	7q31.2	AR, 1 in 2,500	Osmotic
Genes Encoding Pancreatic Enzymes				
Enterokinase deficiency (EKD)	PRSS7	21q21	AR	Osmotic
Hereditary pancreatitis (HP)	PRSS1 SPINK1	7q34 5q32	AR, cases with compound mutations in different genes; SPINK1 mutations may also cause tropical pancreatitis	Osmotic
Congenital absence of pancreatic lipase (APL)	PNLIP	10q25.3	—	Osmotic
Genes Encoding Proteins of Lipoprotein Metabolism				
Abetalipoproteinemia (ALP)	MTTP	4q27	AR, about 100 cases described; higher frequency among Ashkenazi Jews	Osmotic
Hypobetalipoproteinemia (HLP)	Apo B	2p24.1	Autosomal codominant	Osmotic
Chylomicron retention disease (CRD)	SAR1B	5q31.1	AR, about 40 cases described	Osmotic
Genes Encoding Other Types of Proteins				
Congenital sodium diarrhea (CSD, DIAR 3)	SPINT2 (only syndromic CSD)	19q13.2	AR	Osmotic
Shwachman-Diamond syndrome (SDS)	SBDS	7q11	AR	Osmotic
Activating GUCY2C mutation	Guanylate cyclase-C	Unknown	AD	Secretory
Genes Encoding for Other Enzymes				
Defect in triglyceride synthesis	DGAT1	Splice variant (chromosome 8, 145541756 A G) in the splice donor site 32 of exon 8, altering the invariant GT to GC	AR	Protein-losing enteropathy
DISEASE	OMIM NUMBER		TRANSMISSION AND INCIDENCE	MECHANISM
DEFECTS OF ENTEROCYTE DIFFERENTIATION AND POLARIZATION				
Microvillus inclusion disease (MVID, DIAR 2)	251850	AR; rare; higher frequency among Navajo	Secretory	
Congenital tufting enteropathy (CTE, DIAR 5)	613217	AR; 1 in 50,000-100,000; higher among Arabians	Secretory	
Trichohepatoenteric syndrome (THE)	222470	AR; 1 in 400,000	Secretory	
DEFECTS OF ENTEROENDOCRINE CELL DIFFERENTIATION				
Congenital malabsorptive diarrhea (CMD, DIAR 4)	610370	AR; few cases described	Osmotic	
Proprotein convertase 1/3 deficiency (PCD)	600955	AR	Osmotic	
DEFECTS OF MODULATION OF INTESTINAL IMMUNE RESPONSE				
Autoimmune polyglandular syndrome type 1 (APS1)	240300	AR; AD (1 family)	Secretory	
Immune dysfunction, polyendocrinopathy, X-linked (IPEX)	601410	X-linked (autosomal cases described), very rare	Secretory	
IPEX-like syndrome	—	Not X-linked	Secretory	

AD, autosomal dominant; AR, autosomal recessive.

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Table 341-6 Stepwise Diagnostic Approach to Children with Diarrhea	
STEP 1	
<i>Intestinal Microbiology</i>	
Stool cultures	
Microscopy for parasites	
Viruses	
H ₂ breath test	
Screening Test for Celiac Disease:	
Serology according to age and level of IgA (including AGA IgA/IgG, EMA IgA/IgG, tTG IgA/IgG)	
Noninvasive Tests for:	
Intestinal function (including double sugar test, xylosemia, iron absorption test)	
Pancreatic function (amylase, lipase, fecal elastase)	
Intestinal inflammation (fecal calprotectin, rectal nitric oxide)	
Tests for Food Allergy:	
Prick/patch tests for foods	
Abdominal Ultrasounds (Scan of Last Ileal Loop)	
STEP 2	
<i>Evaluation of Intestinal Morphology:</i>	
Endoscopy and standard jejunal/colonic histology*	
Morphometry	
PAS staining	
Electron microscopy	
Imaging (upper or lower bowel series, capsule endoscopy)	
STEP 3	
<i>Special Investigations:</i>	
Intestinal immunohistochemistry	
Antienterocyte antibodies	
Serum chromogranin and catecholamines	
Autoantibodies	
⁷⁵ SeHCAT measurement	
Brush-border enzymatic activities	
Motility and electrophysiologic studies	

*The decision to perform an upper or a lower endoscopy may be supported by noninvasive tests.

AGA, antigliadin antibody; EMA, endomysial antibody; Ig, immunoglobulin; PAS, periodic acid-Schiff; ⁷⁵SeHCAT, ⁷⁵Se-homocholic acid-taurine; tTG, tissue transglutaminase.

Table 341-7 Treatment of Infectious Persistent Diarrhea				
	FACTOR	INDICATIONS	DOSAGE	DURATION
Antibiotics	Trimethoprim-sulfamethoxazole	Salmonella spp., Shigella	10-50 mg/kg/day in 2 divided doses-daily os	7 days
	Azithromycin	Shigella	1° day: 12 mg/kg/day once-daily os 2°-5° days: 6 mg/kg/day once-daily os	5 days
	Ciprofloxacin		20-30 mg/kg/day in 2 divided doses-os or iv	7 days
	Ceftriaxone		50-100 mg/kg/day once-im or iv	7 days
	Erythromycin	Campylobacter	50 mg/kg/day in 2-3 divided doses-os	7 days
	Metronidazole	Giardia, Entamoeba	20-30 mg/kg/day in 2-3 divided doses-os	7 days
				Small intestinal bacterial overgrowth
Antiparasitic	Nitazoxanide	Amebiasis, Giardiasis, Cryptosporidiosis and helminth infections	100 mg every 12 hr for children ages 12-47 mo	3 days
	Albendazole		200 mg every 12 hr for children ages 4-11 yr 500 mg every 12 hr for children older than 11 yr 400 mg once	
Probiotics	Lactobacillus GG		1-2 × 10 ¹¹ -1 × 10 ¹¹ CFU/day-os	For a minimum period of 7 days or until diarrhea stopped
	Saccharomyces boulardii		1 × 10 ¹⁰ germs live (500 mg)/day-os	For a minimum period of 7 days or till diarrhea stopped
Human serum immunoglobulin		Severe Rotavirus diarrhea	300 mg/kg single oral administration	
Antisecretory	Racecadotril	Secretory diarrhea	1.5 mg/kg every 8 hr-os	For a minimum period of 7 days or till diarrhea stopped
Adsorbents	Diosmectite		3-6 g every 12-24 hr-os	5 days

Table 342-6 Effectiveness of Treatments for Abdominal Pain in Children		
THERAPY	DEFINITION OF DISORDER	EFFECTIVENESS
Cognitive behavioral (family) therapy	Recurrent abdominal pain	Beneficial
Famotidine	Recurrent abdominal pain and dyspeptic symptoms	Inconclusive
Added dietary fiber	Recurrent abdominal pain	Unlikely to be beneficial
Lactose-free diet	Recurrent abdominal pain	Unlikely to be beneficial
Peppermint oil	Irritable bowel syndrome	Likely to be beneficial
Amitriptyline	Functional gastrointestinal disorders, irritable bowel syndrome	Inconsistent results
Lactobacillus GG	Irritable bowel syndrome using Rome III criteria	Unlikely to be beneficial

The effectiveness of analgesics, antispasmodics, sedatives, and antidepressants is currently unknown.

From Berger MY, Gieteling MJ, Benninga MA: Chronic abdominal pain in children, BMJ 334:997-1002, 2007.

Table 342-1 Recommended Clinical Definitions of Long-Standing Intermittent or Constant Abdominal Pain in Children	
DISORDER	DEFINITION
Chronic abdominal pain	Long-lasting intermittent or constant abdominal pain that is functional or organic (disease based)
Functional abdominal pain	Abdominal pain without demonstrable evidence of pathologic condition, such as anatomic metabolic, infectious, inflammatory or neoplastic disorder. Functional abdominal pain can manifest with symptoms typical of functional dyspepsia, irritable bowel syndrome, abdominal migraine or functional abdominal pain syndrome
Functional dyspepsia	Functional abdominal pain or discomfort in the upper abdomen
Irritable bowel syndrome	Functional abdominal pain associated with alteration in bowel movements
Abdominal migraine	Functional abdominal pain with features of migraine (paroxysmal abdominal pain associated with anorexia, nausea, vomiting or pallor as well as maternal history of migraine headaches)
Functional abdominal pain syndrome	Functional abdominal pain without the characteristics of dyspepsia, irritable bowel syndrome, or abdominal migraine

Adapted from Di Lorenzo C, Colletti RB, Lehmann HP, et al; American Academy of Pediatrics Subcommittee on Chronic Abdominal Pain; NASPGHAN Committee on Abdominal Pain: Chronic abdominal pain in children: a clinical report of the American Academy of Pediatrics and the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition, J Pediatr Gastroenterol Nutr 40(3):245-248, 2005.

Table 342-4 Alarm Symptoms Usually Needing Further Investigations	
Pain that wakes up the child from sleep	
Persistent right upper or right lower quadrant pain	
Significant vomiting (bilious vomiting, protracted vomiting, cyclical vomiting, or worrisome pattern to the physician)	
Unexplained fever	
Genitourinary tract symptoms	
Dysphagia	
Chronic severe diarrhea or nocturnal diarrhea	
Gastrointestinal blood loss	
Involuntary weight loss	
Deceleration of linear growth	
Delayed puberty	
Family history of inflammatory bowel disease, celiac disease, and peptic ulcer disease	

Table 342-5 Alarm Signs Usually Needing Further Investigations	
Localized tenderness in the right upper quadrant	
Localized tenderness in the right lower quadrant	
Localized fullness or mass	
Hepatomegaly	
Splenomegaly	
Jaundice	
Costovertebral angle tenderness	
Arthritis	
Spinal tenderness	
Perianal disease	
Abnormal or unexplained physical findings	
Hematochezia	
Anemia	

Table 342-2 Childhood Functional GI Disorders: Child/Adolescent (Category H)	
H1. Vomiting and aerophagia	
H1a. Adolescent rumination syndrome	
H1b. Cyclic vomiting syndrome	
H1c. Aerophagia	
H2. Abdominal pain—related functional gastrointestinal disorders	
H2a. Functional dyspepsia	
H2b. Irritable bowel syndrome	
H2c. Abdominal migraine	
H2d. Childhood functional abdominal pain	
H2d1. Childhood functional abdominal pain syndrome	
H3. Constipation and incontinence	
H3a. Functional constipation	
H3b. Nonretentive fecal incontinence	

Adapted from Rome Foundation: Rome III disorders and criteria. <http://www.romecriteria.org/criteria/>.

Table 342-3 Rome III Criteria for Childhood Functional Abdominal Pain H2d and Childhood Functional Abdominal Pain Syndrome H2d1	
H2d. CHILDHOOD FUNCTIONAL ABDOMINAL PAIN	
Diagnostic criteria* must include all of the following:	
• Episodic or continuous abdominal pain	
• Insufficient criteria for other functional gastrointestinal disorders	
• No evidence of an inflammatory, anatomic, metabolic, or neoplastic process that explains the subject's symptoms	
H2d1. CHILDHOOD FUNCTIONAL ABDOMINAL PAIN SYNDROME	
Diagnostic criteria* must satisfy criteria for childhood functional abdominal pain and have at least 25% of the time one or more of the following:	
• Some loss of daily function	
• Additional somatic symptoms such as headache, limb pain, or difficulty sleeping	

*Criteria fulfilled at least once per week for ≥2 mo prior to diagnosis.
Adapted from Rome Foundation: Rome III disorders and criteria. <http://www.romecriteria.org/criteria/>.

Table 342-7 Rome III Criteria for Child/Adolescent Irritable Bowel Syndrome H2b	
Diagnostic criteria* must include all of the following:	
1. Abdominal discomfort [†] or pain associated with 2 or more of the following at least 25% of the time:	
a. Improvement with defecation	
b. Onset associated with a change in frequency of stool	
c. Onset associated with a change in form (appearance) of stool	
2. No evidence of an inflammatory, anatomic, metabolic, or neoplastic process that explains the subject's symptoms	

*Criteria fulfilled at least once per week for at least 6 mo prior to diagnosis.

[†]"Discomfort" means an uncomfortable sensation not described as pain.
Adapted from Rome Foundation: Rome III disorders and criteria. <http://www.romecriteria.org/criteria/>

Table 346-1 Predisposing Factors for Hernias

- Prematurity
- Urogenital
 - Cryptorchidism
 - Extrophy of the bladder or cloaca
 - Ambiguous genitalia
 - Hypospadias/epispadius
- Increased peritoneal fluid
 - Ascites
 - Ventriculoperitoneal shunt
 - Peritoneal dialysis catheter
- Increased intraabdominal pressure
 - Repair of abdominal wall defects
 - Severe ascites (chylous)
 - Meconium peritonitis
- Chronic respiratory disease
 - Cystic fibrosis
- Connective tissue disorders
 - Ehlers-Danlos syndrome
 - Hunter-Hurler syndrome
 - Marfan syndrome
 - Mucopolysaccharidosis

Table 343-1 Pediatric Appendicitis Scores

FEATURE	SCORE
Fever >38°C (100.4°F)	1
Anorexia	1
Nausea/vomiting	1
Cough/percussion/hopping tenderness	2
Right lower quadrant tenderness	2
Migration of pain	1
Leukocytosis >10,000 (10 ⁹ /L)	1
Polymorphonuclear-neutrophilia >7,500 (10 ⁹ /L)	1
Total	10

From Acheson J, Banerjee J: Management of suspected appendicitis in children, Arch Dis Child Educ Pract Ed 95:9–13, 2010.

Table 350-1 Pancreatic Enzyme Replacement Therapy

Infants (up to 12 mo)	2000-4000 units lipase/120 mL breast milk or formula
12 mo-4 yr	1000 units lipase/kg/meal initially, then titrate per response
Children older than 4 yr and adults	500 units lipase/kg/meal initially, up to maximum of 2500 units lipase/kg/meal or 10,000 units lipase/kg/day or 4,000 units lipase/g fat ingested per day
PLUS: one half the standard meal dose to be given with snacks	

Table 344-1 Associated Malformations**GENITOURINARY**

- Vesicoureteric reflux
- Renal agenesis
- Renal dysplasia
- Ureteral duplication
- Cryptorchidism
- Hypospadias
- Bicornuate uterus
- Vaginal septums

VERTEBRAL

- Spinal dysraphism
- Tethered chord
- Presacral masses
- Meningocele
- Lipoma
- Dermoid
- Teratoma

CARDIOVASCULAR

- Tetralogy of Fallot
- Ventricular septal defect
- Transposition of the great vessels
- Hypoplastic left-heart syndrome

GASTROINTESTINAL

- Tracheoesophageal fistula
- Duodenal atresia
- Malrotation
- Hirschsprung disease

CENTRAL NERVOUS SYSTEM

- Spina bifida
- Tethered cord

Table 345-1 General Features of the Inherited Colorectal Cancer Syndromes

SYNDROME	POLYP DISTRIBUTION	AGE OF ONSET	RISK OF COLON CANCER	GENETIC LESION	CLINICAL MANIFESTATIONS	ASSOCIATED LESIONS
HAMARTOMATOUS POLYPS						
Juvenile polyposis	Large and small intestine, gastric polyps	1st decade	~10-50%	<i>PTEN</i> , <i>SMAD4</i> , <i>BMPR1A</i> Autosomal dominant	Possible rectal bleeding, abdominal pain, intussusception	Congenital abnormalities in 20% of the nonfamilial type, clubbing, AV malformations
Peutz-Jeghers syndrome	Small and large intestine	1st decade	Increased	<i>LKB1/STK11</i> Autosomal dominant	Possible rectal bleeding, abdominal pain, intussusception	Orocutaneous melanin pigment spots
Cowden syndrome	Colon	2nd decade	Not increased	<i>PTEN</i> gene	Macrocephaly, breast/thyroid/endometrial cancers, developmental delay	
Bannayan-Riley-Ruvalcaba syndrome	Colon	2nd decade	Not increased	<i>PTEN</i> gene	Macrocephaly, speckled penis, thyroid/breast cancers, hemangiomas, lipomas	
ADENOMATOUS POLYPS						
Familial adenomatous polyposis (FAP)	Large intestine, often >100	16 yr (range: 8-34 yr)	100%	5q (APC gene), autosomal dominant	Rectal bleeding, abdominal pain, bowel obstruction	Desmoids, CHRPE, upper GI polyps, osteoma, hepatoblastoma, thyroid cancer
Attenuated familial adenomatous polyposis (AFAP)	Colon (fewer in number)	>18 yr	Increased	APC gene	Same as FAP	Fewer associated lesions
MYH-associated polyposis	Colon	>20yr	High risk	MYH autosomal recessive	Same as FAP	May be confused with sporadic FAP or AFAP; few extraintestinal findings
Gardner syndrome	Large and small intestine	16 yr (range: 8-34 yr)	100%	5q (APC gene)	Rectal bleeding, abdominal pain, bowel obstruction	Desmoid tumors, multiple osteomas, fibromas, epidermoid cysts
Hereditary nonpolyposis colon cancer, (Lynch syndrome)	Large intestine	40 yr	30%	DNA mismatch repair genes (MMR) Autosomal dominant	Rectal bleeding, abdominal pain, bowel obstruction	Other tumors (e.g., ovary, ureter, pancreas, stomach)

AV, Arteriovenous; CHRPE, congenital hypertrophy of the retinal pigment epithelium; GI, gastrointestinal.

Table 351-2 Differential Diagnosis of Hyperamylasemia

PANCREATIC PATHOLOGY
Acute or chronic pancreatitis
Complications of pancreatitis (pseudocyst, ascites, abscess)
Factitious pancreatitis
SALIVARY GLAND PATHOLOGY
Parotitis (mumps, <i>Staphylococcus aureus</i> , cytomegalovirus, HIV, Epstein-Barr virus)
Sialadenitis (calculus, radiation)
Eating disorders (anorexia nervosa, bulimia)
INTRAABDOMINAL PATHOLOGY
Biliary tract disease (cholelithiasis)
Peptic ulcer perforation
Peritonitis
Intestinal obstruction
Appendicitis
SYSTEMIC DISEASES
Metabolic acidosis (diabetes mellitus, shock)
Renal insufficiency, transplantation
Burns
Pregnancy
Drugs (morphine)
Head injury
Cardiopulmonary bypass

Table 354-2 Causes of Impaired Bile Acid Metabolism and Enterohepatic Circulation

DEFECTIVE BILE ACID SYNTHESIS OR TRANSPORT
Inborn errors of bile acid synthesis (reductase deficiency, isomerase deficiency)
Progressive familial intrahepatic cholestasis (PFIC1, PFIC2, PFIC3)
Intrahepatic cholestasis (neonatal hepatitis)
Acquired defects in bile acid synthesis secondary to severe liver disease
ABNORMALITIES OF BILE ACID DELIVERY TO THE BOWEL
Celiac disease (sluggish gallbladder contraction)
Extrahepatic bile duct obstruction (e.g., biliary atresia, gallstones)
LOSS OF ENTEROHEPATIC CIRCULATION OF BILE ACIDS
External bile fistula
Cystic fibrosis
Small bowel bacterial overgrowth syndrome (with bile acid precipitation, increased jejunal absorption, and "short-circuiting")
Drug-induced entrapment of bile acids in intestinal lumen (e.g., cholestyramine)
BILE ACID MALABSORPTION
Primary bile acid malabsorption (absent or inefficient ileal active transport)
Secondary bile acid malabsorption
Ileal disease or resection
Cystic fibrosis
DEFECTIVE UPTAKE OR ALTERED INTRACELLULAR METABOLISM
Parenchymal disease (acute hepatitis, cirrhosis)
Regurgitation from cells
Portosystemic shunting
Cholestasis

Table 351-1 Etiology of Acute and Recurrent Pancreatitis in Children

DRUGS AND TOXINS	OBSTRUCTIVE
Acetaminophen overdose	Ampullary disease
Alcohol	Ascariasis
L-Asparaginase	Biliary tract malformations
Azathioprine	Choledochal cyst
Carbamazepine	Choledochocoele
Cimetidine	Cholelithiasis, microlithiasis, and choledocholithiasis (stones or sludge)
Corticosteroids	Duplication cyst
Enalapril	Endoscopic retrograde cholangiopancreatography (ERCP) complication
Erythromycin	Pancreas divisum
Estrogen	Pancreatic ductal abnormalities
Furosemide	Postoperative
Glucagon-like peptide-1 agents	Sphincter of Oddi dysfunction
Isoniazid	Tumor
Lisinopril	
6-Mercaptopurine	
Methyldopa	
Metronidazole	
Octreotide	
Organophosphate poisoning	
Pentamidine	
Retrovirals: DDC (dideoxycytidine), DDI (dideoxyinosine), tenofovir	
Sulfonamides: mesalamine, 5-aminosalicylates, sulfasalazine, trimethoprim-sulfamethoxazole	
Sulindac	
Tetracycline	
Thiazides	
Valproic acid	
Venom (spider, scorpion, Gila monster lizard)	
Vincristine	
Volatile hydrocarbons	
GENETIC	SYSTEMIC DISEASE
Cationic trypsinogen gene (<i>PRSS1</i>)	Autoimmune pancreatitis (IgG ₄ -related systemic disease)
Chymotrypsin C gene (<i>CTRC</i>)	Brain tumor
Cystic fibrosis gene (<i>CFTR</i>)	Collagen vascular diseases
Trypsin inhibitor gene (<i>SPINK1</i>)	Crohn disease
INFECTIOUS	Diabetes mellitus (ketacidosis)
Ascariasis	Head trauma
Coxsackie B virus	Hemochromatosis
Epstein-Barr virus	Hemolytic uremic syndrome
Hepatitis A, B	Hyperlipidemia: types I, IV, V
Influenza A, B	Hyperparathyroidism/hypercalcemia
Leptospirosis	Kawasaki disease
Malaria	Malnutrition
Measles	Organic academia
Mumps	Peptic ulcer
Mycoplasma	Periarteritis nodosa
Rubella	Renal failure
Rubeola	Systemic lupus erythematosus
Reye syndrome: varicella, influenza B	Transplantation: bone marrow, heart, liver, kidney, pancreas
Septic shock	Vasculitis
TRAUMATIC	
	Blunt injury
	Burns
	Child abuse
	Hypothermia
	Surgical trauma
	Total-body cast

Table 355-2 Differential Diagnosis of Unconjugated Hyperbilirubinemia**INCREASED PRODUCTION OF UNCONJUGATED BILIRUBIN FROM HEME****Hemolytic Disease (Hereditary or Acquired)**

Isoimmune hemolysis (neonatal; acute or delayed transfusion reaction; autoimmune)

- Rh incompatibility
- ABO incompatibility
- Other blood group incompatibilities

Congenital spherocytosis

Hereditary elliptocytosis

Infantile pyknocytosis

Erythrocyte enzyme defects

Hemoglobinopathy

- Sickle cell anemia
- Thalassemia
- Others

Sepsis

Microangiopathy

• Hemolytic-uremic syndrome

• Hemangioma

• Mechanical trauma (heart valve)

Ineffective erythropoiesis

Drugs

Infection

Enclosed hematoma

Polycythemia

- Diabetic mother
- Fetal transfusion (recipient)
- Delayed cord clamping

DECREASED DELIVERY OF UNCONJUGATED BILIRUBIN (IN PLASMA) TO HEPATOCYTE

Right-sided congestive heart failure

Portacaval shunt

DECREASED BILIRUBIN UPTAKE ACROSS HEPATOCYTE MEMBRANE

Presumed enzyme transporter deficiency

Competitive inhibition

- Breast milk jaundice
- Lucey-Driscoll syndrome
- Drug inhibition (radiocontrast material)

Miscellaneous

- Hypothyroidism
- Hypoxia
- Acidosis

DECREASED STORAGE OF UNCONJUGATED BILIRUBIN IN CYTOSOL (DECREASED Y AND Z PROTEINS)

Competitive inhibition

Fever

DECREASED BIOTRANSFORMATION (CONJUGATION)

Neonatal jaundice (physiologic)

Inhibition (drugs)

Hereditary (Crigler-Najjar)

- Type I (complete enzyme deficiency)
- Type II (partial deficiency)

Gilbert disease

Hepatocellular dysfunction

ENTEROHEPATIC RECIRCULATION

Breast milk jaundice

Intestinal obstruction

- Ileal atresia
- Hirschsprung disease
- Cystic fibrosis
- Pyloric stenosis

Antibiotic administration

Table 355-1 Mechanisms of Hepatomegaly**INCREASE IN THE NUMBER OR SIZE OF THE CELLS INTRINSIC TO THE LIVER****Storage**

Fat: malnutrition, obesity, diabetes mellitus, metabolic liver disease (diseases of fatty acid oxidation and Reye syndrome-like illnesses), lipid infusion (total parenteral nutrition), cystic fibrosis, medication related, pregnancy

Specific lipid storage diseases: Gaucher, Niemann-Pick, Wolman disease

Glycogen: glycogen storage diseases (multiple enzyme defects); total parenteral nutrition; infant of diabetic mother, Beckwith syndrome

Miscellaneous: α_1 -antitrypsin deficiency, Wilson disease, hypervitaminosis A, neonatal iron storage disease

Inflammation

Hepatocyte enlargement (hepatitis)

- Viral: acute and chronic
- Bacterial: sepsis, abscess, cholangitis
- Toxic: drugs
- Autoimmune
- Kupffer cell enlargement
- Sarcoidosis
- Systemic lupus erythematosus
- Macrophage activating syndrome

INFILTRATION OF CELLS**Primary Liver Tumors: Benign**

Hepatocellular

- Focal nodular hyperplasia
- Nodular regenerative hyperplasia
- Hepatocellular adenoma

Mesodermal

- Infantile hemangiobendothelioma
- Mesenchymal hamartoma

Cystic masses

- Choledochal cyst
- Hepatic cyst
- Hematoma
- Parasitic cyst
- Pyogenic or amebic abscess

Primary Liver Tumors: Malignant

Hepatocellular

- Hepatoblastoma
- Hepatocellular carcinoma

Mesodermal

- Angiosarcoma
- Undifferentiated embryonal sarcoma

Secondary or metastatic processes

- Lymphoma
- Leukemia
- Histiocytosis
- Neuroblastoma
- Wilms tumor

INCREASED SIZE OF VASCULAR SPACE

Intrahepatic obstruction to hepatic vein outflow

- Venoocclusive disease
- Hepatic vein thrombosis (Budd-Chiari syndrome)
- Hepatic vein web

Suprahepatic

- Congestive heart failure
- Pericardial disease
- Tamponade

Post-Fontan procedure

Constrictive pericarditis

Hematopoietic: sickle cell anemia, thalassemia

INCREASED SIZE OF BILIARY SPACE

Congenital hepatic fibrosis

Caroli disease

Extrahepatic obstruction

IDIOPATHIC

Various

- Riedel lobe
- Normal variant
- Downward displacement of diaphragm

Table 355-3 Differential Diagnosis of Neonatal and Infantile Cholestasis

INFECTIOUS	<ul style="list-style-type: none"> Wilson disease Neonatal iron storage disease Indian childhood cirrhosis/infantile copper overload Congenital disorders of glycosylation Mitochondrial hepatopathies Citrin deficiency
Generalized bacterial sepsis	
Viral hepatitis	
<ul style="list-style-type: none"> Hepatitis A, B, C, D, E Cytomegalovirus Rubella virus Herpesviruses: herpes simplex, human herpesvirus 6 and 7 Varicella virus Coxsackievirus Echovirus Reovirus type 3 Parvovirus B19 HIV Adenovirus 	
Others	
<ul style="list-style-type: none"> Toxoplasmosis Syphilis Tuberculosis Listeriosis Urinary tract infection 	
TOXIC	
Sepsis	
Parenteral nutrition related	
Drug, dietary supplement, herbal related	
METABOLIC	
Disorders of amino acid metabolism	
<ul style="list-style-type: none"> Tyrosinemia 	
Disorders of lipid metabolism	
<ul style="list-style-type: none"> Wolman disease Niemann-Pick disease (type C) Gaucher disease 	
Cholesterol ester storage disease	
Disorders of carbohydrate metabolism	
<ul style="list-style-type: none"> Galactosemia Fructosemia Glycogenosis IV 	
Disorders of bile acid biosynthesis	
Other metabolic defects	
<ul style="list-style-type: none"> α_1-Antitrypsin deficiency Cystic fibrosis Hypopituitarism Hypothyroidism Zellweger (cerebrohepatorenal) syndrome 	
GENETIC OR CHROMOSOMAL	
Trisomies 17, 18, 21	
INTRAHEPATIC CHOLESTASIS SYNDROMES	
"Idiopathic" neonatal hepatitis	
Alagille syndrome	
Intrahepatic cholestasis (progressive familial intrahepatic cholestasis [PFIC])	
<ul style="list-style-type: none"> FIC-1 deficiency BSEP (bile salt export pump) deficiency MDR3 deficiency 	
Familial benign recurrent cholestasis associated with lymphedema (Aagenaes syndrome)	
ARC (arthrogryposis, renal dysfunction, and cholestasis) syndrome	
Caroli disease (cystic dilation of intrahepatic ducts)	
EXTRAHEPATIC DISEASES	
Biliary atresia	
Sclerosing cholangitis	
Bile duct stricture/stenosis	
Choledochal–pancreaticoductal junction anomaly	
Spontaneous perforation of the bile duct	
Choledochal cyst	
Mass (neoplasia, stone)	
Bile/mucous plug ("inspissated bile")	
MISCELLANEOUS	
Shock and hypoperfusion	
Associated with enteritis	
Associated with intestinal obstruction	
Neonatal lupus erythematosus	
Myeloproliferative disease (trisomy 21)	
Hemophagocytic lymphohistiocytosis (HLH)	
COACH syndrome (coloboma, oligophrenia, ataxia, cerebellar vermis hypoplasia, hepatic fibrosis)	
Cholangiocyte cilia defects	

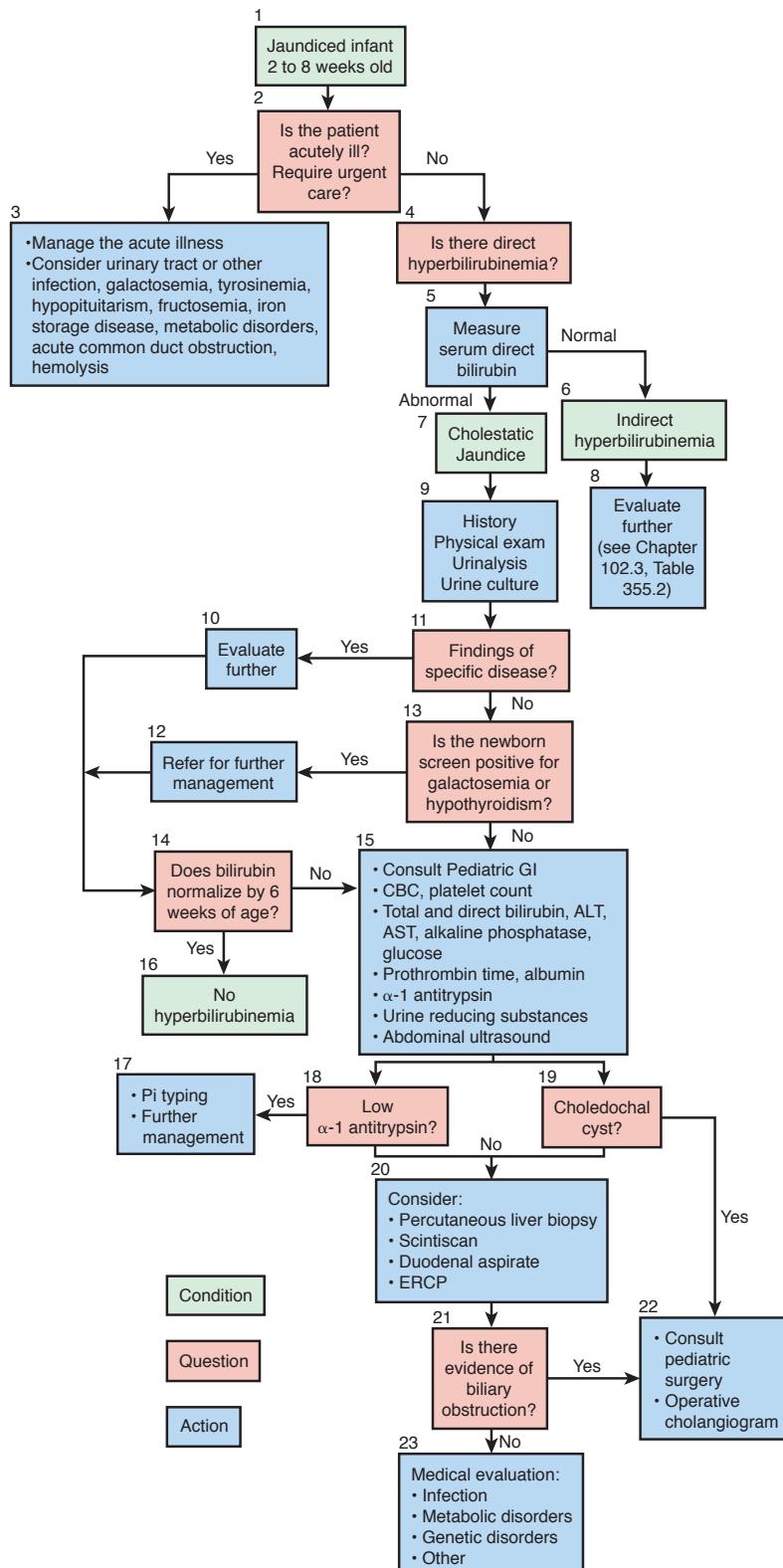


Figure 355-1 Cholestasis clinical practice guideline. Algorithm for a 2-8 wk old. ALT, alanine aminotransferase; AST, aspartate aminotransferase; ERCP, endoscopic retrograde cholangiopancreatography. (From Moyer V, Freese DK, Whitington PF, et al; North American Society for Pediatric Gastroenterology, Hepatology and Nutrition: Guideline for the evaluation of cholestatic jaundice in infants: recommendations of the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition, J Pediatr Gastroenterol Nutr 39:115-128, 2004.)

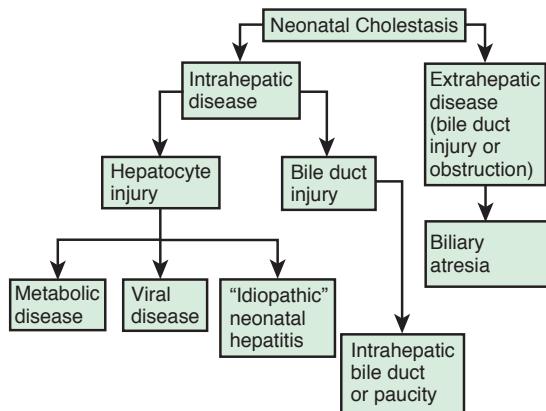


Figure 356-1 Neonatal cholestasis. Conceptual approach to the group of diseases presenting as cholestasis in the neonate. There are areas of overlap: patients with biliary atresia might have some degree of intrahepatic injury. Patients with "idiopathic" neonatal hepatitis might, in the future, be determined to have a primary metabolic or viral disease.

Table 356-1 Proposed Subtypes of Intrahepatic Cholestasis

- A. Disorders of membrane transport and secretion
 - 1. Disorders of canalicular secretion
 - a. Bile acid transport: BSEP deficiency
 - i. Persistent, progressive (PFIC type 2)
 - ii. Recurrent, benign (BRIC type 2)
 - b. Phospholipid transport: MDR3 deficiency (PFIC type 3)
 - c. Ion transport: cystic fibrosis (*CFTR*)
 - 2. Complex or multiorgan disorders
 - a. FIC1 deficiency
 - i. Persistent, progressive (PFIC type 1, Byler disease)
 - ii. Recurrent, benign (BRIC type 1)
 - b. Neonatal sclerosing cholangitis (*CLDN1*)
 - c. Arthrogryposis-renal dysfunction-cholestasis syndrome (*VPS33B*)
- B. Disorders of bile acid biosynthesis and conjugation
 - 1. 3-oxo Δ -4-steroid 5 β -reductase deficiency
 - 2. 3 β -hydroxy-5-C₂₇-steroid dehydrogenase/isomerase deficiency
 - 3. Oxysterol 7 α -hydroxylase deficiency
 - 4. Bile acid-coenzyme A (CoA) ligase deficiency
 - 5. BAAT deficiency (familial hypercholanemia)
- C. Disorders of embryogenesis
 - 1. Alagille syndrome (Jagged1 defect, syndromic bile duct paucity)
 - 2. Ductal plate malformation (ARPKD, ADPLD, Caroli disease)
- D. Unclassified (idiopathic "neonatal hepatitis"): mechanism unknown

Note: FIC1 deficiency, BSEP deficiency, and some of the disorders of bile acid biosynthesis are characterized clinically by low levels of serum GGT despite the presence of cholestasis. In all other disorders listed, the serum GGT level is elevated.

ADPLD, autosomal dominant polycystic liver disease (cysts in liver only); ARPKD, autosomal recessive polycystic kidney disease (cysts in liver and kidney); BAAT, bile acid transporter; BRIC, benign recurrent intrahepatic cholestasis; BSEP, bile salt export pump; CFT, cystic fibrosis transmembrane regulator; GGT, γ -glutamyl transpeptidase; PFIC, progressive familial intrahepatic cholestasis.

Table 356-2 Value of Specific Tests in the Evaluation of Patients with Suspected Neonatal Cholestasis

TEST	RATIONALE
Serum bilirubin fractionation (i.e., assessment of the serum level of conjugated bilirubin)	Indicates cholestasis
Assessment of stool color (does the baby have pigmented or acholic stools?)	Indicates bile flow into intestine
Urine and serum bile acids measurement	Confirms cholestasis; might indicate inborn error of bile acid biosynthesis
Hepatic synthetic function (albumin, coagulation profile)	Indicates severity of hepatic dysfunction
α_1 -Antitrypsin phenotype	Suggests (or excludes) PiZZ
Thyroxine and TSH	Suggests (or excludes) endocrinopathy
Sweat chloride and mutation analysis	Suggests (or excludes) cystic fibrosis
Urine and serum amino acids and urine reducing substances	Suggests (or excludes) metabolic liver disease
Ultrasoundography	Suggests (or excludes) choledochal cyst; might detect the triangular cord sign, suggesting biliary atresia
Hepatobiliary scintigraphy	Documents bile duct patency or obstruction
Liver biopsy	Distinguishes biliary atresia; suggests alternative diagnosis

PiZZ, protease inhibitor ZZ phenotype; TSH, thyroid-stimulating hormone

Table 356-3 Molecular Defects Causing Liver Disease

GENE	PROTEIN	FUNCTION, SUBSTRATE	DISORDER
ATP8b1	FIC1	P-type ATPase; aminophospholipid translocase that flips phosphatidylserine and phosphatidylethanolamine from the outer to the inner layer of the canalicular membrane	PFIC 1 (Byler disease), BRIC 1, GFC
ABCB11	BSEP	Canalicular protein with ATP-binding cassette (ABC family of proteins); works as a pump transporting bile acids through the canalicular domain	PFIC 2, BRIC 2
ABCB4	MDR3	Canalicular protein with ATP-binding cassette (ABC family of proteins); works as a phospholipid flippase in canalicular membrane	PFIC 3, ICP, cholelithiasis
AKR1D1	5β-reductase	3-oxoΔ-4-steroid 5β-reductase gene; regulates bile acid synthesis	BAS: neonatal cholestasis with giant cell hepatitis
HSD3B7	C27-3β-HSD	3β-hydroxy-5-C ₂₇ -steroid oxidoreductase (C27-3β-HSD) gene; regulates bile acid synthesis	BAS: chronic intrahepatic cholestasis
CYP7B1	CYP7B1	Oxysterol 7α-hydroxylase; regulates the acidic pathway of bile acid synthesis	BAS: neonatal cholestasis with giant cell hepatitis
JAG1	JAG1	Transmembrane, cell-surface proteins that interact with Notch receptors to regulate cell fate during embryogenesis	Alagille syndrome
TJP2	Tight junction protein	Belongs to the family of membrane-associated guanylate kinase homologs that are involved in the organization of epithelial and endothelial intercellular junction; regulates paracellular permeability	FHC
BAAT	BAAT	Enzyme that transfers the bile acid moiety from the acyl coenzyme A thioester to either glycine or taurine	FHC
EPHX1	Epoxide hydrolase	Microsomal epoxide hydrolase regulates the activation and detoxification of exogenous chemicals	FHC
ABCC2	MRP2	Canalicular protein with ATP-binding cassette (ABC family of proteins); regulates canalicular transport of GSH conjugates and arsenic	Dubin-Johnson syndrome
ATP7B	ATP7B	P-type ATPase; function as copper export pump	Wilson disease
CLDN1	Claudin 1	Tight junction protein	NSC
CIRH1A	Cirhin	Cell signaling?	NAICC
CFTR	CFTR	Chloride channel with ATP-binding cassette (ABC family of proteins); regulates chloride transport	Cystic fibrosis
PKHD1	Fibrocystin	Protein involved in ciliary function and tubulogenesis	ARPKD
PRKCSH	Hepatocystin	Assembles with glucosidase II α subunit in endoplasmic reticulum	ADPLD
VPS33B	Vascular Protein sorting 33	Regulates fusion of proteins to cellular membrane	ARC

ADPLD, autosomal dominant polycystic liver disease; ARC, arthrogryposis–renal dysfunction–cholestasis syndrome*; ARPKD, autosomal recessive polycystic kidney disease; ATP, adenosine triphosphate; ATPase, adenosine triphosphatase; BAAT, bile acid transporter; BAS, bile acid synthetic defect; BRIC, benign recurrent intrahepatic cholestasis; BSEP, bile salt export pump; CFTR, cystic fibrosis transmembrane conductance regulator; FHC, familial hypercholanemia; GFC, Greenland familial cholestasis; GSH, glutathione; ICP, intrahepatic cholestasis of pregnancy; NAICC, North American Indian childhood cirrhosis; NSC, neonatal sclerosing cholangitis with ichthyosis, leukocyte vacuoles, and alopecia; PFIC, progressive familial intrahepatic cholestasis*. (*Low γ-glutamyl transpeptidase [PFIC types 1 and 2, BRIC types 1 and 2, ARC].)

Table 356-4 Progressive Familial Intrahepatic Cholestasis

	PFIC 1	PFIC 2	PFIC 3
Transmission	Autosomal recessive	Autosomal recessive	Autosomal recessive
Chromosome	18q21-22	2q24	7q21
Gene	ATP8B1/F1C1	ABCB11/BSEP	ABCB4/MDR3
Protein	FIC1	BSEP	MDR3
Location	Hepatocyte, colon, intestine, pancreas; on apical membranes	Hepatocyte canalicular membrane	Hepatocyte canalicular membrane
Function	ATP-dependent aminophospholipid flippase; unknown effects on intracellular signaling	ATP-dependent bile acid transport	ATP-dependent phosphatidylcholine translocation
Phenotype	Progressive cholestasis, diarrhea, steatorrhea, growth failure, severe pruritus	Rapidly progressive cholestatic giant cell hepatitis, growth failure, pruritus	Later-onset cholestasis, portal hypertension, minimal pruritus, intraductal and gallbladder lithiasis
Histology	Initial bland cholestatic; coarse, granular canalicular bile on EM	Neonatal giant cell hepatitis, amorphous canalicular bile on EM	Proliferation of bile ductules, periportal fibrosis, eventually biliary cirrhosis
Biochemical features	Normal serum GGT; high serum, low biliary bile acid concentrations	Normal serum GGT; high serum, low biliary bile acid concentrations	Elevated serum GGT; low to absent biliary PC; absent serum LPX; normal biliary bile acid concentrations
Treatment	Biliary diversion, ileal exclusion, liver transplantation, but post-OLT diarrhea, steatorrhea, fatty liver	Biliary diversion, liver transplantation	UDCA if residual PC secretion; liver transplantation

ATP, adenosine triphosphate; BSEP, bile salt export pump; EM, electron microscopy; GGT, γ-glutamyl transpeptidase; LPX, lipoprotein X; OLT, orthotopic liver transplantation; PC, phosphatidylcholine; PFIC, progressive familial intrahepatic cholestasis; UDCA, ursodeoxycholic acid.

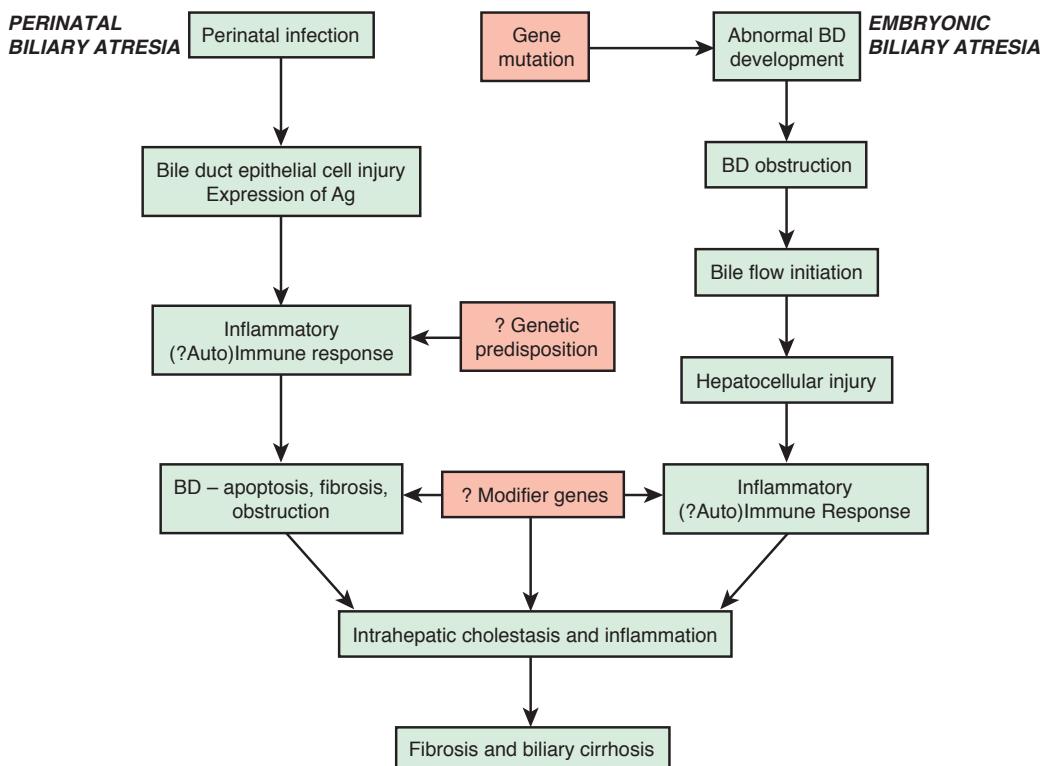


Figure 356-2 Proposed pathways for pathogenesis of 2 forms of biliary atresia (BA). Perinatal BA can develop when a perinatal insult, such as a cholangiotropic viral infection, triggers bile duct (BD) epithelial cell injury and exposure of self-antigens or neoantigens that elicit a subsequent immune response. The resulting inflammation induces apoptosis and necrosis of extrahepatic BD epithelium, resulting in fibro-obliteration of the lumen and obstruction of the BD. Intrahepatic bile ducts can also be targets in the ongoing TH1 immune (autoimmune?) attack and the cholestatic injury, resulting in progressive portal fibrosis and culminating in biliary cirrhosis. Embryonic BA may be the result of mutations in genes controlling normal bile duct formation or differentiation, which secondarily induces an inflammatory/immune response within the common bile duct and liver after the initiation of bile flow at approximately 11–13 wk of gestation. Secondary hepatocyte and intrahepatic bile duct injury ensue either as a result of cholestatic injury or as targets for the immune (autoimmune?) response that develops. The end result is intrahepatic cholestasis and portal tract fibrosis, culminating in biliary cirrhosis. Other major factors may be the role played by genetic predisposition to autoimmunity and modifier genes that determine the extent and type of cellular and immune response and the generation of fibrosis. (From Mack CL, Sokol RJ: Unraveling the pathogenesis and etiology of biliary atresia, Pediatr Res 57:87R–94R, 2005.)

Table 356-5 Suggested Medical Management of Persistent Cholestasis	
CLINICAL IMPAIRMENT	MANAGEMENT
Malnutrition resulting from malabsorption of dietary long-chain triglycerides	Replace with dietary formula or supplements containing medium-chain triglycerides
Fat-soluble vitamin malabsorption: Vitamin A deficiency (night blindness, thick skin) Vitamin E deficiency (neuromuscular degeneration) Vitamin D deficiency (metabolic bone disease)	Replace with 10,000–15,000 IU/day as Aquasol A Replace with 50–400 IU/day as oral α -tocopherol or TPGS Replace with 5,000–8,000 IU/day of D ₂ or 3–5 μ g/kg/day of 25-hydroxycholecalciferol
Vitamin K deficiency (hypoprothrombinemia)	Replace with 2.5–5.0 mg every other day as water-soluble derivative of menadione
Micronutrient deficiency	Calcium, phosphate, or zinc supplementation
Deficiency of water-soluble vitamins	Supplement with twice the recommended daily allowance
Retention of biliary constituents such as cholesterol (itch or xanthomas)	Administer choleretic bile acids (ursodeoxycholic acid, 15–30 mg/kg/day)
Progressive liver disease; portal hypertension (variceal bleeding, ascites, hypersplenism)	Interim management (control bleeding; salt restriction; spironolactone)
End-stage liver disease (liver failure)	Transplantation

TPGS, D-tocopherol polyethylene glycol 1,000 succinate.

Table 357-1 Inborn Errors of Metabolism That Affect the Liver

DISORDERS OF CARBOHYDRATE METABOLISM	
Disorders of galactose metabolism	Galactosemia (galactose-1-phosphate uridylyltransferase deficiency)
Disorders of fructose metabolism	Heredity fructose intolerance (aldolase deficiency)
	Fructose-1,6 diphosphatase deficiency
Glycogen storage diseases	Type I Von Gierke Ia (glucose-6-phosphatase deficiency) Type Ib (glucose-6-phosphatase transport defect) Type III Cori/Forbes (glycogen debrancher deficiency) Type IV Andersen (glycogen branching enzyme deficiency) Type VI Hers (liver phosphorylase deficiency)
Congenital disorders of glycosylation (multiple subtypes)	
DISORDERS OF AMINO ACID AND PROTEIN METABOLISM	
Disorders of tyrosine metabolism	Hereditary tyrosinemia type I (fumarylacetoacetate deficiency) Tyrosinemia, type II (tyrosine aminotransferase deficiency)
Inherited urea cycle enzyme defects	CPS deficiency (carbamoyl phosphate synthetase I deficiency) OTC deficiency (ornithine transcarbamoylase deficiency) Citrullinemia type I (argininosuccinate synthetase deficiency) Argininosuccinic aciduria (argininosuccinate deficiency) Argininemia (arginase deficiency)
	N-AGS deficiency (N-acetylglutamate synthetase deficiency)
Maple serum urine disease (multiple possible defects*)	
DISORDERS OF LIPID METABOLISM	
Wolman disease (lysosomal acid lipase deficiency)	
Cholesteryl ester storage disease (lysosomal acid lipase deficiency)	
Homozygous familial hypercholesterolemia (low-density lipoprotein receptor deficiency)	
Gaucher disease type I (β -glucocerebrosidase deficiency)	
Niemann-Pick type C (NPC 1 and 2 mutations)	
DISORDERS OF BILE ACID METABOLISM	
Defects in bile acid synthesis	
Zellweger syndrome—cerebrohepatorenal (multiple mutations in peroxisome biogenesis genes)	
DISORDERS OF METAL METABOLISM	
Wilson disease (ATP7B mutations)	
Hepatic copper overload	
Indian childhood cirrhosis (ICC)	
Neonatal iron storage disease	
DISORDERS OF BILIRUBIN METABOLISM	
Crigler-Najjar (bilirubin-uridine diphosphoglucuronate glucuronosyltransferase mutations)	
Type I	
Type II	
Gilbert disease (bilirubin-uridine diphosphoglucuronate glucuronosyltransferase polymorphism)	
Dubin-Johnson syndrome (multiple drug-resistant protein 2 mutation)	
Rotor syndrome	
MISCELLANEOUS	
α_1 -Antitrypsin deficiency	
Citrullinemia type II (citrin deficiency)	
Cystic fibrosis (cystic fibrosis transmembrane conductance regulator mutations)	
Erythropoietic protoporphyrria (ferrochelatase deficiency)	
Polyzystic kidney disease	

*Maple syrup urine disease can be caused by mutations in branched-chain α -keto dehydrogenase, keto acid decarboxylase, lipoamide dehydrogenase, or dihydrolipoamide dehydrogenase.

Table 358-2 Causes and Differential Diagnosis of Hepatitis in Children

INFECTIOUS	
Hepatotropic viruses	• HAV • HBV • HCV • HDV • HEV • Hepatitis non-A-E viruses
Systemic infection that can include hepatitis	• Adenovirus • Arbovirus • Coxsackievirus • Cytomegalovirus • Enterovirus • Epstein-Barr virus • "Exotic" viruses (e.g., yellow fever) • Herpes simplex virus • Human immunodeficiency virus • Paramyxovirus • Rubella • Varicella zoster
Other	
NONVIRAL LIVER INFECTIONS	
Abscess	
Amebiasis	
Bacterial sepsis	
Brucellosis	
Fitz-Hugh-Curtis syndrome	
Histoplasmosis	
Leptospirosis	
Tuberculosis	
Other	
AUTOIMMUNE	
Autoimmune hepatitis	
Sclerosing cholangitis	
Other (e.g., systemic lupus erythematosus, juvenile rheumatoid arthritis)	
METABOLIC	
α_1 -Antitrypsin deficiency	
Tyrosinemia	
Wilson disease	
Other	
TOXIC	
Iatrogenic or drug induced (e.g., acetaminophen)	
Environmental (e.g., pesticides)	
ANATOMIC	
Choledochal cyst	
Biliary atresia	
Other	
HEMODYNAMIC	
Shock	
Congestive heart failure	
Budd-Chiari syndrome	
Other	
NONALCOHOLIC FATTY LIVER DISEASE	
Idiopathic	
Reye syndrome	
Other	

Table 357-2 Clinical Manifestations That Suggest the Possibility of Metabolic Disease

Recurrent vomiting, failure to thrive, short stature
 Dysmorphic features
 Jaundice, hepatomegaly (\pm splenomegaly), fulminant hepatic failure, edema/anasarca
 Hypoglycemia, organic aciduria, lactic acidemia, hyperammonemia, bleeding (coagulopathy)
 Developmental delay/psychomotor retardation, hypotonia, progressive neuromuscular deterioration, seizures, myopathy, neuropathy
 Cardiac dysfunction/failure
 Unusual odors
 Rickets
 Cataracts

Table 358-1 Features of the Hepatotropic Viruses

VIROLOGY	HAV RNA	HBV DNA	HCV RNA	HDV RNA	HEV RNA
Incubation (days)	15-19	60-180	14-160	21-42	21-63
Transmission					
• Parenteral	Rare	Yes	Yes	Yes	No
• Fecal-oral	Yes	No	No	No	Yes
• Sexual	No	Yes	Yes	Yes	No
• Perinatal	No	Yes	Rare	Yes	No
Chronic infection	No	Yes	Yes	Yes	No
Fulminant disease	Rare	Yes	Rare	Yes	Yes

Table 358-3 Diagnostic Blood Tests: Serology and Viral PCR

HAV	HBV	HCV	HDV	HEV
ACUTE/ACTIVE INFECTION				
Anti-HAV IgM(+) Blood PCR positive*	Anti-HBc IgM(+) HBsAg(+) Anti-HBs(−) HBV DNA(+)(PCR)	Anti-HCV(+) HCV RNA(+)(PCR)	Anti-HDV IgM(+) Blood PCR positive HBsAg(+) Anti-HBs(−)	Anti-HEV IgM(+) Blood PCR positive
PAST INFECTION (RECOVERED)				
Anti-HAV IgG(+)	Anti-HBc(+) Anti-HBc IgG(+)	Anti-HCV(−) Blood PCR(−)	Anti-HDV IgG(+) Blood PCR(−)	Anti-HEV IgG(+) Blood PCR(−)
CHRONIC INFECTION				
N/A	Anti-HBc IgG(+) HBsAg(+) Anti-HBs(−) PCR (+) or (−)	Anti-HCV(+) Blood PCR(+) or (−)	Anti-HDV IgG(+) Blood PCR(−) HBsAg(+) Anti-HBs(−)	N/A
VACCINE RESPONSE				
Anti-HAV IgG(+)	Anti-HBs(+) Anti-HBc(−)	N/A	N/A	N/A

*Research tool.

HAV, hepatitis A virus; HBs, hepatitis B surface; HBsAg, hepatitis B surface antigen; Ig, immunoglobulin; PCR, polymerase chain reaction.

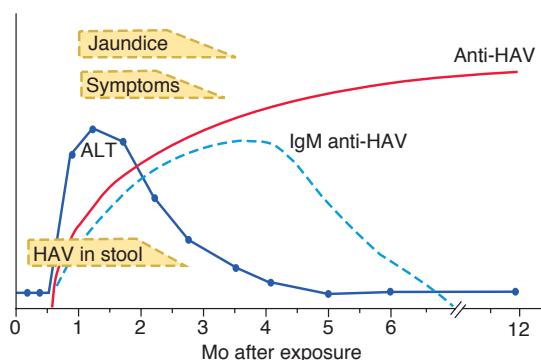
**Figure 358-1** The serologic course of acute hepatitis A. ALT, alanine aminotransferase; HAV, hepatitis A virus. (From Goldman L, Ausiello D: Cecil textbook of medicine, ed 22, Philadelphia, 2004, WB Saunders, p 913.)

Table 358-4 Hepatitis A Virus Prophylaxis

PREEXPOSURE PROPHYLAXIS (TRAVELERS TO ENDEMIC REGIONS)		
AGE	EXPECTED EXPOSURE DURATION	DOSE
<1 year of age	<3 months 3-5 months Long term (>5months)	Ig 0.02 mL/kg Ig 0.06 mL/kg Ig 0.06 mL/kg at departure and every 5 mo thereafter
≥1 year of age	Healthy host Immunocompromised host, or one with chronic liver disease or chronic health problems	HAV vaccine HAV vaccine and Ig 0.02 mL/kg
POSTEXPOSURE PROPHYLAXIS*		
EXPOSURE	RECOMMENDATIONS	
≤2 wk since exposure	<1 year-old: Ig 0.02 mL/kg Immunocompromised host, or host with chronic liver disease or chronic health problems: Ig 0.02 mL/kg and HAV vaccine >1 year and healthy host: HAV vaccine, Ig remains optional Sporadic non-household or close contact exposure: prophylaxis not indicated*	
>2 wk since exposure	None	

*Decision for prophylaxis in nonhousehold contacts should be tailored to individual exposure and risk. Ig, Immunoglobulin.

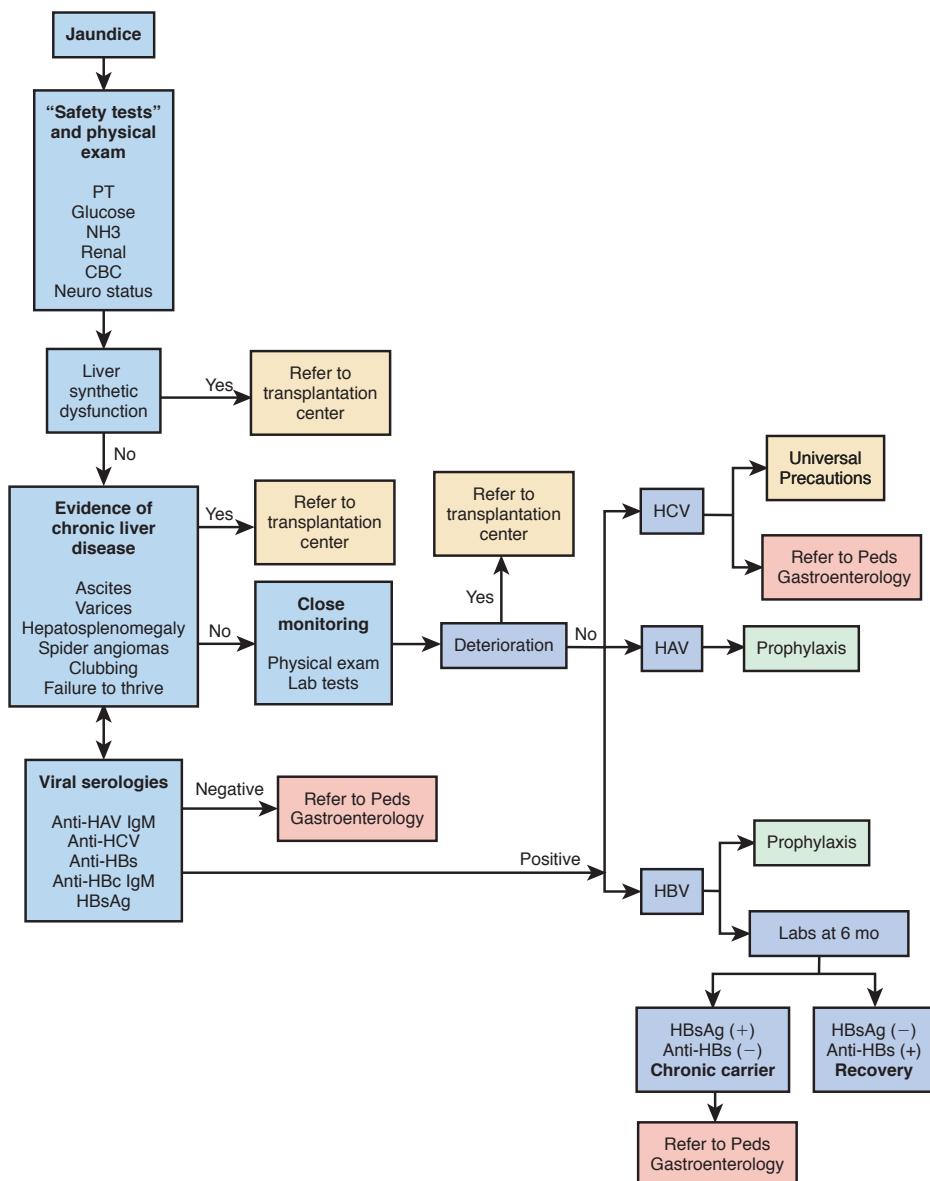


Figure 358-6 Clinical approach to viral hepatitis. CBC, complete blood count with differential; HAV, hepatitis A virus; HBs, hepatitis B surface; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; IgM, immunoglobulin M; NH₃, ammonia; PT, prothrombin time.

Table 361-2 Genotypic Classification of Primary Mitochondrial Hepatopathies and Organ Involvement

GENE	RESPIRATORY CHAIN COMPLEX	HEPATIC HISTOLOGY	OTHER ORGANS INVOLVED	CLINICAL FEATURES
Deletion	Multiple (Pearson)	Steatosis, fibrosis	Kidney, heart, CNS, muscle	Sideroblastic anemia, variable thrombocytopenia and neutropenia, persistent diarrhea
MPV17	I, III, IV	Steatosis	CNS, muscle, gastrointestinal tract	Adult-onset multisystemic involvement: myopathy, ophthalmoplegia, severe constipation, parkinsonism
DGUOK	I, III, IV	Steatosis, fibrosis	Kidneys, CNS, muscle	Nystagmus, hypotonia, renal Fanconi syndrome, acidosis
MPV17	I, III, IV	Steatosis, fibrosis	CNS, PNS	Hypotonia
SUCLG1	I, III, IV	Steatosis	Kidneys, CNS, muscle	Myopathy, sensorineural hearing loss, respiratory failure
POLG1	I, III, IV	Steatosis, fibrosis	CNS, muscle	Liver failure preceded by neurologic symptoms, intractable seizures, ataxia, psychomotor regression
C10orf2/Twinkle	I, III, IV	Steatosis	CNS, muscle	Infantile-onset spinocerebellar ataxia, loss of skills
BCS1L	III (GRACILE)		CNS ±, muscle ±, kidneys	Fanconi-type renal tubulopathy
SCO1	IV	Steatosis, fibrosis	Muscle	
TRMU	I, III, IV	Steatosis, fibrosis		Infantile liver failure with subsequent recovery
EFG1	I, III, IV	Steatosis	CNS	Severe, rapidly progressive encephalopathy
EFTu	I, III, IV	Unknown	CNS	Severe lactic acidosis, rapidly fatal encephalopathy

CNS, central nervous system; GRACILE, growth restriction, aminoaciduria, cholestasis, iron overload, lactic acidosis, and early death; PNS, peripheral nervous system.

Table 361-3 Clinical Staging of Reye Syndrome and Reye-Like Diseases

Symptoms at the time of admission:

- I. Usually quiet, **lethargic** and sleepy, vomiting, laboratory evidence of liver dysfunction
- II. Deep lethargy, **confusion**, delirium, combativeness, hyperventilation, hyperreflexia
- III. Obtunded, **light coma** ± seizures, decorticate rigidity, intact pupillary light reaction
- IV. Seizures, deepening coma, **decerebrate rigidity**, loss of oculocephalic reflexes, fixed pupils
- V. Coma, loss of deep tendon reflexes, respiratory arrest, fixed dilated pupils, **flaccidity/decerebration** (intermittent); isoelectric electroencephalogram

Table 361-4 Diseases That Present a Clinical or Pathologic Picture Resembling Reye Syndrome

Metabolic disease

- Organic aciduria
- Disorders of oxidative phosphorylation
- Urea cycle defects (carbamoyl phosphate synthetase, ornithine transcarbamylase)
- Defects in fatty acid oxidation metabolism
- Acyl-coenzyme A dehydrogenase deficiencies
- Systemic carnitine deficiency
- Hepatic carnitine palmitoyltransferase deficiency
- 3-OH, 3-methylglutaryl-coenzyme A lyase deficiency
- Fructosmia

Central nervous system infections or intoxications (meningitis), encephalitis, toxic encephalopathy

Hemorrhagic shock with encephalopathy

Drug or toxin ingestion (salicylate, valproate)

Table 361-1 Classification of Primary Mitochondrial Hepatopathies

Respiratory chain (electron transport) defects (oxidative phosphorylation)
Neonatal liver failure
Complex I deficiency
Complex IV deficiency (SCO1 mutations)
Complex III deficiency (BCS1L mutations)
Coenzyme Q deficiency
Multiple complex deficiencies (transfer and elongation factor mutations)
mtDNA depletion syndrome (DUGOK, MPV17, POLG, SUCLG1, C10orf2/Twinkle mutations)
Later-onset liver dysfunction or failure
Alpers-Huttenlocher disease (POLG mutations)
Pearson marrow-pancreas syndrome (mtDNA deletion)
Mitochondrial neurogastrointestinal encephalopathy (TYMP mutations)
Navajo neurohepatopathy (MPV17 mutations)
Fatty acid oxidation defects
Long-chain 3-hydroxyacyl-coenzyme A dehydrogenase
Carnitine palmitoyltransferases I and II deficiencies
Carnitine-acylcarnitine translocase deficiency
Urea cycle enzyme deficiencies
Electron transfer flavoprotein and electron transfer flavoprotein dehydrogenase deficiencies
Phosphoenolpyruvate carboxykinase (mitochondrial) deficiency; nonketotic hyperglycemia
Citrin deficiency; neonatal intrahepatic cholestasis caused by citrin deficiency (SLC2A13 mutations)

Table 362-1 Disorders Producing Chronic Hepatitis

Chronic viral hepatitis

- Hepatitis B
- Hepatitis C
- Hepatitis D

Autoimmune hepatitis

- Anti-actin antibody positive
- Anti-liver-kidney microsomal antibody positive
- Anti-soluble liver antigen antibody-positive
- Others (includes antibodies to liver-specific lipoproteins or asialoglycoprotein)
- Overlap syndrome with sclerosing cholangitis and autoantibodies
- Systemic lupus erythematosus
- Celiac disease

Drug-induced hepatitis

Metabolic disorders associated with chronic liver disease

- Wilson disease
- Nonalcoholic steatohepatitis
- α_1 -Antitrypsin deficiency
- Tyrosinemia
- Niemann-Pick disease type 2
- Glycogen storage disease type iv
- Cystic fibrosis
- Galactosemia
- Bile acid biosynthetic abnormalities

Table 370-1 Causes of Ascites

HEPATIC
Cirrhosis
Congenital hepatic fibrosis
Portal vein obstruction
Fulminant hepatic failure
Budd-Chiari syndrome
Lysosomal storage disease

RENAL
Nephrotic syndrome
Obstructive uropathy
Perforation of urinary tract
Peritoneal dialysis

CARDIAC
Heart failure
Constrictive pericarditis
Inferior vena cava web

INFECTIOUS
Abscess
Tuberculosis
Chlamydia
Schistosomiasis

GASTROINTESTINAL
Infarcted bowel
Perforation
Protein-losing enteropathy

NEOPLASTIC
Lymphoma
Neuroblastoma

GYNECOLOGIC
Ovarian tumors
Ovarian torsion, rupture

PANCREATIC
Pancreatitis
Ruptured pancreatic duct

MISCELLANEOUS
Systemic lupus erythematosus
Autoinflammatory recurrent fever syndromes
Ventriculoperitoneal shunt
Eosinophilic ascites
Chylous ascites
Hypothyroidism

Table 363-1 Patterns of Hepatic Drug Injury

DISEASE	DRUG
Centrilobular necrosis	Acetaminophen Halothane
Microvesicular steatosis	Valproic acid
Acute hepatitis	Isoniazid
General hypersensitivity	Sulfonamides Phenytoin
Fibrosis	Methotrexate
Cholestasis	Chlorpromazine Erythromycin Estrogens
Sinusoidal obstruction syndrome (venoocclusive disease)	Irradiation plus busulfan Cyclophosphamide
Portal and hepatic vein thrombosis	Estrogens Androgens
Biliary sludge	Ceftriaxone
Hepatic adenoma or hepatocellular carcinoma	Oral contraceptives Anabolic steroids

Table 363-2 Potentially Hepatotoxic Herbal or Dietary Supplements

Celandine
Chaparral (creosote bush, greasewood, <i>Larrea tridentata</i>)
Chinese herbs
Comfrey leaves (pyrrolizidine alkaloids)
Germander extracts (<i>Teucrium chamaedrys</i>)
Kava (Kava kava, awa, kew)
LipoKinetix (phenylpropanolamine, sodium usinate, diiodothyronine, yohimbine, caffeine)
Ma huang (<i>Ephedra</i>)
Mushroom (<i>Amanita phalloides</i> , <i>Galerina</i>)
Senecio
Valerian with skullcap

Table 367-1 Causes of Portal Hypertension**EXTRAHEPATIC PORTAL HYPERTENSION**

Portal vein agenesis, atresia, stenosis
Portal vein thrombosis or cavernous transformation
Splenic vein thrombosis
Increased portal flow
Arteriovenous fistula

INTRAHEPATIC PORTAL HYPERTENSION

Hepatocellular disease
Acute and chronic viral hepatitis
Cirrhosis
Congenital hepatic fibrosis
Wilson disease
 α_1 -Antitrypsin deficiency
Glycogen storage disease type IV
Hepatotoxicity
Methotrexate
Parenteral nutrition
Biliary tract disease
Extrahepatic biliary atresia
Cystic fibrosis
Choledochal cyst
Sclerosing cholangitis
Intrahepatic bile duct paucity
Idiopathic portal hypertension
Postsinusoidal obstruction
Budd-Chiari syndrome
Venoocclusive disease

Table 365-1 Renal Disorders Associated with Fibropolycystic Liver Diseases

FIBROPOLYCYSTIC LIVER DISEASE	ASSOCIATED RENAL DISORDER
Congenital hepatic fibrosis (CHF)	Autosomal-recessive polycystic kidney disease*
	Autosomal-dominant polycystic kidney disease
	Cystic renal dysplasia
	Nephronophthisis
	None
Caroli syndrome (CS)	Autosomal-recessive polycystic kidney disease*
	Autosomal-dominant polycystic kidney disease
	None
Caroli disease	Autosomal-recessive polycystic kidney disease
von Meyenburg complexes (isolated)	?
von Meyenburg complexes with CHF or CS	Autosomal-recessive polycystic kidney disease
von Meyenburg complexes with polycystic liver disease	Autosomal-dominant polycystic kidney disease
Polycystic liver disease	Autosomal-dominant polycystic kidney disease*
	? None

*Most common associated disorders.

Table 364-1 Stages of Hepatic Encephalopathy

	STAGES			
	I	II	III	IV
Symptoms	Periods of lethargy, euphoria; reversal of day-night sleeping; may be alert	Drowsiness, inappropriate behavior, agitation, wide mood swings, disorientation	Stupor but arousable, confused, incoherent speech	Coma IVa responds to noxious stimuli IVb no response
Signs	Trouble drawing figures, performing mental tasks	Asterixis, fetor hepaticus, incontinence	Asterixis, hyperreflexia, extensor reflexes, rigidity	Areflexia, no asterixis, flaccidity
Electroencephalogram	Normal	Generalized slowing, q waves	Markedly abnormal, triphasic waves	Markedly abnormal bilateral slowing, d waves, electric-cortical silence

Table 366-1 Conditions Associated with Hydrops of the Gallbladder

Kawasaki disease
Streptococcal pharyngitis
Staphylococcal infection
Leptospirosis
Ascariasis
Threadworm
Sickle cell crisis
Typhoid fever
Thalassemia
Total parenteral nutrition
Prolonged fasting
Viral hepatitis
Sepsis
Henoch-Schönlein purpura
Mesenteric adenitis
Necrotizing enterocolitis

Table 365-2 Syndromes Associated with Congenital Hepatic Fibrosis

SYNDROME	FEATURES
Jeune syndrome	Asphyxiating thoracic dystrophy, with cystic renal tubular dysplasia and congenital hepatic fibrosis (15q13)
Joubert syndrome	Oculo-encephalo-hepato-renal (AH11, HPHP1)
COACH syndrome	Cerebellar vermis hypoplasia, oligophrenia, congenital ataxia, ocular coloboma, and hepatic fibrosis (MKS3, CC2D2A, RPGRIP1L)
Meckel syndrome type 1	Cystic renal dysplasia abnormal bile duct development with fibrosis, posterior encephalocele, and polydactyly (13q13, 17a21, 8q24)
Carbohydrate-deficient glycoprotein syndrome type 1b	Phosphomannose isomerase 1 deficiency (PMI)
Ivemark syndrome type 2	Autosomal-recessive renal-hepatic-pancreatic dysplasia
Miscellaneous syndromes	Intestinal lymphangiectasia, enterocolitis cystic Short rib (Beemer-Langer) syndrome Osteochondrodysplasia

From Suchy FJ, Sokol RJ, Balistreri WF, editors: Liver disease in children, ed 3, New York, 2007, Cambridge University Press, p. 931.

Table 366-2 Conditions Associated with Cholelithiasis

Biliary dyskinesia
Chronic hemolytic disease (sickle cell anemia, spherocytosis, thalassemia, Gilbert disease)
Ileal resection or disease
Cystic fibrosis
Cirrhosis
Cholestasis
Crohn disease
Obesity
Insulin resistance
Prolonged parenteral nutrition
Prematurity with complicated medical or surgical course
Prolonged fasting or rapid weight reduction
Treatment of childhood cancer
Abdominal surgery
Pregnancy
Sepsis
Genetic (ABCB4, ABCG5/G8) progressive familial intrahepatic cholestasis
Cephalosporins

Respiratory System

Table 374-1 Lung Sound Nomenclature	
TYPE	SOUND
DISCONTINUOUS	
Fine (high pitch, low amplitude, short duration)	Fine crackles/rales
Coarse (low pitch, high amplitude, long duration)	Coarse crackles
CONTINUOUS	
High pitch	Wheezes
Low pitch	Rhonchi

Table 374-2 Nonpulmonary Diseases Associated with Clubbing	
CARDIAC	
Cyanotic congenital heart disease	
Subacute bacterial endocarditis	
Chronic congestive heart failure	
HEMATOLOGIC	
Thalassemia	
Congenital methemoglobinemia (rare)	
GASTROINTESTINAL	
Crohn disease	
Ulcerative colitis	
Celiac disease	
Chronic dysentery, sprue	
Polyposis coli	
Severe gastrointestinal hemorrhage	
Small bowel lymphoma	
Liver cirrhosis (including α_1 -antitrypsin deficiency)	
OTHER	
Thyroid deficiency (thyroid acropachy)	
Chronic pyelonephritis (rare)	
Toxic (e.g., arsenic, mercury, beryllium)	
Lymphomatoid granulomatosis	
Fabry disease	
Raynaud disease, scleroderma	
Familial	
UNILATERAL CLUBBING	
Vascular disorders (e.g., subclavian arterial aneurysm, brachial arteriovenous fistula)	
Subluxation of shoulder	
Median nerve injury	
Local trauma	

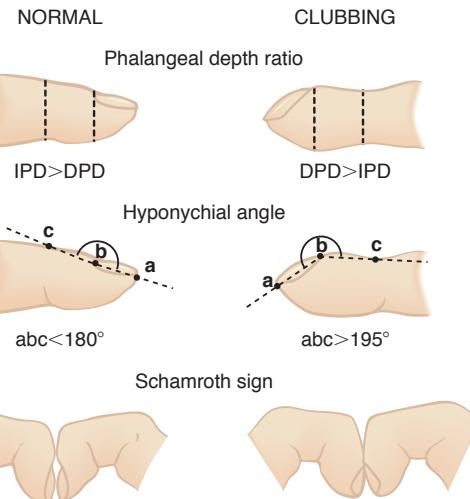


Figure 374-1 Finger clubbing can be measured in different ways. The ratio of the distal phalangeal diameter (DPD) over the interphalangeal diameter (IPD), or the phalangeal depth ratio, is <1 in normal subjects but increases to >1 with finger clubbing. The DPD/IPD can be measured with calipers or, more accurately, with finger casts. The hyponychial angle can be measured from lateral projections of the finger contour on a magnifying screen and is usually <180 degrees in normal subjects but >195 degrees in patients with finger clubbing. For bedside clinical assessment, the Schamroth sign is useful. The dorsal surfaces of the terminal phalanges of similar fingers are placed together. With clubbing, the normal diamond-shaped aperture or "window" at the bases of the nail beds disappears, and a prominent distal angle forms between the ends of the nails. In normal subjects, this angle is minimal or nonexistent. (From Pasterkamp H: The history and physical examination. In Wilmott RW, Boat TF, Bush A, et al, editors: Kendig and Chernick's disorders of the respiratory tract in children, ed 8, Philadelphia, 2012, Elsevier.)

Table 375-5 Environmental Factors Associated with Increased Risk for Sudden Infant Death Syndrome	
MATERNAL AND ANTEPARTUM RISK FACTORS	
Elevated 2nd trimester serum α -fetoprotein	
Smoking	
Alcohol use	
Drug use (cocaine, heroin)	
Nutritional deficiency	
Inadequate prenatal care	
Low socioeconomic status	
Younger age	
Lower education	
Single marital status	
Shorter interpregnancy interval	
Intrauterine hypoxia	
Fetal growth restriction	
INFANT RISK FACTORS	
Age (peak 2-4 mo, but may be decreasing)	
Male gender	
Race and ethnicity (African-American and Native American, other minorities)	
Growth failure	
No breast-feeding	
No pacifier (dummy)	
Prematurity	
Prone and side sleep position	
Recent febrile illness (mild infections)	
Inadequate immunizations	
Smoking exposure (prenatal and postnatal)	
Soft sleeping surface, soft bedding	
Bed sharing with parent(s) or other children	
Thermal stress, overheating	
Colder season, no central heating	

Table 375-1 Differential Diagnosis of Sudden Unexpected Infant Death

CAUSE OF DEATH	PRIMARY DIAGNOSTIC CRITERIA	CONFOUNDING FACTOR(S)	FREQUENCY DISTRIBUTION (%)
EXPLAINED AT AUTOPSY			
Natural infections	History, autopsy, and cultures	If minimal findings: SIDS	18-20*
Congenital anomaly	History and autopsy	If minimal findings: SIDS	35-46†
Unintentional injury	History, scene investigation, autopsy	Traumatic child abuse	14-24†
Traumatic child abuse	Autopsy and scene investigation	Unintentional injury	15*
Other natural causes	History and autopsy	If minimal findings: SIDS, or intentional suffocation	13-24*
12-17*			
UNEXPLAINED AT AUTOPSY			
SIDS	History, scene investigation, absence of explainable cause at autopsy	Intentional suffocation	80-82%
Intentional suffocation (filicide)	Perpetrator confession, absence of explainable cause at autopsy	SIDS	Unknown, but <5% of all SUID
Accidental suffocation or strangulation in bed (ASSB)	History and scene investigation, ideally including doll re-enactment	Assigned to ICD-10 code (SIDS) for U.S. vital statistics database Unexplained Undetermined	Varies with individual medical examiners and coroners

*As a percentage of all sudden unexpected infant deaths explained at autopsy.

†As a percentage of all natural causes of sudden unexpected infant deaths explained at autopsy.

ICD-10, International Classification of Diseases, Version 10; SIDS, sudden infant death syndrome; SUDI, sudden unexpected death in infancy.

Adapted from Hunt CE: *Sudden infant death syndrome and other causes of infant mortality: diagnosis, mechanisms and risk for recurrence in siblings*, Am J Respir Crit Care Med 164:346-357, 2001.

Table 375-2 Conditions That Can Cause Apparent Life-Threatening Events or Sudden Unexpected Infant Death

CENTRAL NERVOUS SYSTEM	INFECTION
Arteriovenous malformation	Sepsis
Subdural hematoma	Meningitis
Seizures	Encephalitis
Congenital central hypoventilation	Brain abscess
Neuromuscular disorders (Werdnig-Hoffmann disease)	Pyelonephritis
Chiari crisis	Bronchiolitis (respiratory syncytial virus)
Leigh syndrome	Infant botulism
Pertussis	
CARDIAC	TRAUMA
Subendocardial fibroelastosis	Child abuse
Aortic stenosis	Accidental or intentional suffocation
Anomalous coronary artery	Physical trauma
Myocarditis	Factitious syndrome (formerly Munchausen syndrome) by proxy
Cardiomyopathy	
Arrhythmias (prolonged Q-T syndrome, Wolff-Parkinson-White syndrome, congenital heart block)	
PULMONARY	POISONING (INTENTIONAL OR UNINTENTIONAL)
Pulmonary hypertension	Boric acid
Vocal cord paralysis	Carbon monoxide
Aspiration	Salicylates
Laryngotracheal disease	Barbiturates
	Ipecac
GASTROINTESTINAL	Cocaine
Diarrhea and/or dehydration	Insulin
Gastroesophageal reflux	Others
Volvulus	
ENDOCRINE-METABOLIC	
Congenital adrenal hyperplasia	
Malignant hyperpyrexia	
Long- or medium-chain acyl coenzyme A deficiency	
Hyperammonemias (urea cycle enzyme deficiencies)	
Glutaric aciduria	
Carnitine deficiency (systemic or secondary)	
Glycogen storage disease type I	
Maple syrup urine disease	
Congenital lactic acidosis	
Biotinidase deficiency	

Table 375-3 Differential Diagnosis of Recurrent Sudden Infant Death in a Sibship

IDIOPATHIC
Recurrent sudden infant death syndrome
CENTRAL NERVOUS SYSTEM
Congenital central hypoventilation
Neuromuscular disorders
Leigh syndrome
CARDIAC
Endocardial fibroelastosis
Wolff-Parkinson-White syndrome
Prolonged Q-T syndrome or other cardiac channelopathy
Congenital heart block
PULMONARY
Pulmonary hypertension
ENDOCRINE-METABOLIC
See Table 375-2
INFECTION
Disorders of immune host defense
CHILD ABUSE
Filicide or infanticide
Factitious syndrome (formerly Munchausen syndrome) by proxy

Table 375-4 Identified Genes for Which the Distribution of Polymorphisms Differs in Sudden Infant Death Syndrome Infants Compared to Control Infants

CARDIAC CHANNELOPATHIES (11)
Potassium ion channel genes (<i>KCNE2</i> , <i>KCNH2</i> , <i>KCNQ1</i> , <i>KCNJ8</i>)
Sodium ion channel gene (<i>SCN5A</i>) (long QT syndrome 3, Brugada syndrome)
<i>GPD1-L</i> -encoded connexin43 (Brugada syndrome)
<i>SCN3B</i> (Brugada syndrome)
<i>CAV3</i> (long QT syndrome 9)
<i>SCN4B</i> (long QT syndrome 10)
<i>SNTA-1</i> (long QT syndrome 11)
<i>RyR2</i> (catecholaminergic polymorphic ventricular tachycardia)
SEROTONIN (5-HT) (3)
5-HT transporter protein (5-HTT)
Intron 2 of <i>SLC6A4</i> (variable number tandem repeat [VNTR] polymorphism)
5-HT fifth Ewing variant (FEV) gene

GENES PERTINENT TO DEVELOPMENT OF AUTONOMIC NERVOUS SYSTEM (9)

Paired-like homeobox 2a (<i>PHOX2A</i>)
<i>PHOX2B</i>
Rearranged during transfection factor (<i>RET</i>)
Endothelin converting enzyme-1 (<i>ECE1</i>)
T-cell leukemia homeobox (<i>TLX3</i>)
Engrailed-1 (<i>EN1</i>)
Tyrosine hydroxylase (<i>THO1</i>)
Monamine oxidase A (<i>MAOA</i>)
Sodium/proton exchanger 3 (<i>NHE3</i>) (medullary respiratory control)

INFECTION AND INFLAMMATION (8)

Complement C4A
Complement C4B
Interleukin-1RN (gene encoding IL-1 receptor antagonist [ra]; proinflammatory)
Interleukin-6 (IL-6; proinflammatory)
Interleukin-8 (IL-8; proinflammatory; associated with prone sleeping position)
Interleukin-10 (IL-10)
Vascular endothelial growth factor (VEGF) (proinflammatory)
Tumor necrosis factor (TNF)- α (proinflammatory)

OTHER (3)

Mitochondrial DNA (mtDNA) polymorphisms (energy production)
Flavin-monooxygenase 3 (<i>FMO3</i>) (enzyme metabolizes nicotine; risk factor with smoking mothers)
Aquaporin-4 (T allele and CT/TT genotype associated with maternal smoking and with increased brain/body weight ratio in SIDS infants)

Table 377-1 Possible Causes of Epistaxis

Epistaxis digitorum (nose picking)
Rhinitis (allergic or viral)
Chronic sinusitis
Foreign bodies
Intranasal neoplasm or polyps
Irritants (e.g., cigarette smoke)
Septal deviation
Septal perforation
Trauma including child abuse
Vascular malformation or telangiectasia (hereditary hemorrhage telangiectasia)
Hemophilia
von Willebrand disease
Platelet dysfunction
Thrombocytopenia
Hypertension
Leukemia
Liver disease (e.g., cirrhosis)
Medications (e.g., aspirin, anticoagulants, nonsteroidal antiinflammatory drugs, topical corticosteroids)
Cocaine abuse

Table 381-1 Infectious Agents That Cause Pharyngitis

VIRUSES	BACTERIA
Adenovirus	<i>Streptococcus pyogenes</i> (Group A streptococcus)
Coronavirus	<i>Arcanobacterium haemolyticum</i>
Cytomegalovirus	<i>Fusobacterium necrophorum</i>
Epstein-Barr virus	<i>Corynebacterium diphtheriae</i>
Enteroviruses	<i>Neisseria gonorrhoeae</i>
Herpes simplex virus	Group C streptococci
Human immunodeficiency virus	Group G streptococci
Human metapneumovirus	<i>Francisella tularensis</i>
Influenza viruses	<i>Chlamydophila pneumoniae</i>
Measles virus	<i>Chlamydia trachomatis</i>
Parainfluenza viruses	<i>Mycoplasma pneumoniae</i>
Respiratory syncytial virus	
Rhinoviruses	

Table 379-1 Pathogens Associated with the Common Cold

ASSOCIATION	PATHOGEN	RELATIVE FREQUENCY*	OTHER COMMON SYMPTOMS AND SIGNS
Agents primarily associated with the common cold	Human rhinoviruses Coronaviruses	Frequent Occasional	Wheezing/bronchiolitis
Agents primarily associated with other clinical syndromes that also cause common cold symptoms	Respiratory syncytial viruses Human metapneumovirus Influenza viruses Parainfluenza viruses Adenoviruses Enteroviruses Coxsackievirus A Other nonpolio enteroviruses	Occasional Occasional Uncommon Uncommon Uncommon Uncommon	Bronchiolitis in children <2 yr of age Pneumonia and bronchiolitis Influenza, pneumonia, croup Croup, bronchiolitis Pharyngoconjunctival fever (palpebral conjunctivitis, watery eye discharge, pharyngeal erythema) Herpangina (fever and ulcerated papules on posterior oropharynx) Aseptic meningitis

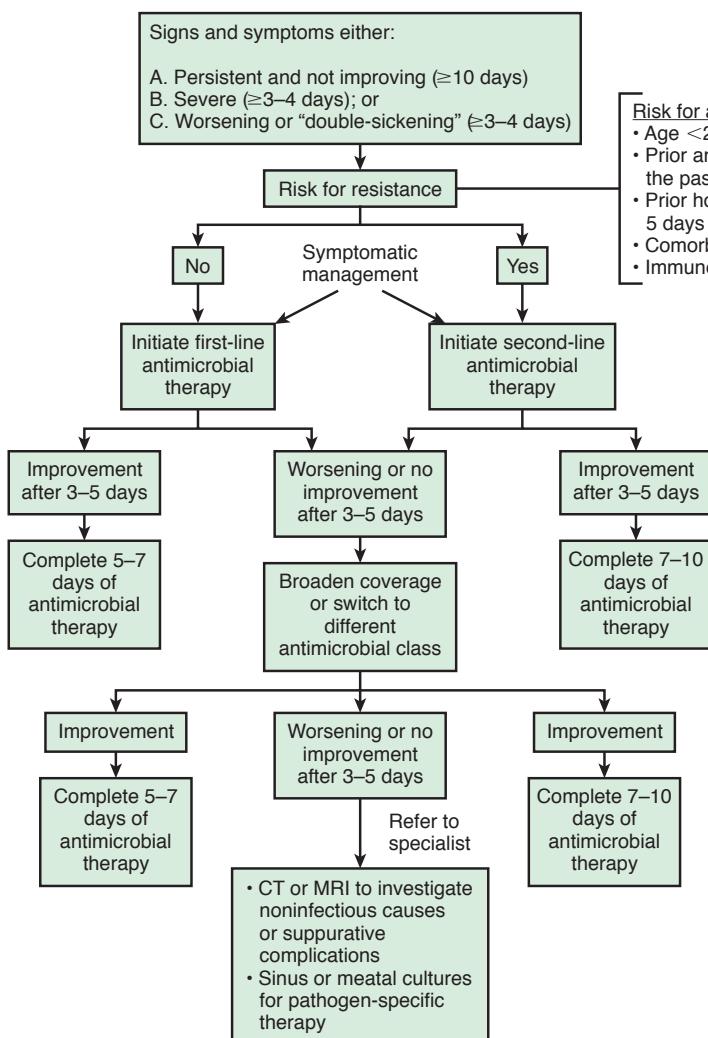


Figure 380-1 Algorithm for the management of acute bacterial rhinosinusitis. (From Chow AW, Benninger MS, Brook I, et al: Infectious Diseases Society of America. IDSA clinical practice guideline for acute bacterial rhinosinusitis in children and adults. Clin Infect Dis 54(8):e72–e112, 2012, Fig. 1.)

Table 379-2 Conditions That Mimic the Common Cold

CONDITION	DIFFERENTIATING FEATURES
Allergic rhinitis	Prominent itching and sneezing, nasal eosinophils
Vasomotor rhinitis	May be triggered by irritants, weather changes, spicy foods, etc.
Rhinitis medicamentosa	History of nasal decongestant use
Foreign body	Unilateral, foul-smelling secretions Bloody nasal secretions
Sinusitis	Presence of fever, headache or facial pain, or periorbital edema or persistence of rhinorrhea or cough for longer than 14 days
Streptococcosis	Mucopurulent nasal discharge that excoriates the nares
Pertussis	Onset of persistent or severe paroxysmal cough
Congenital syphilis	Persistent rhinorrhea with onset in the 1st 3 mo of life

Table 381-3 Recommended Treatment for Acute Streptococcal Pharyngitis

MOST PATIENTS		WEIGHT <27 kg	WEIGHT ≥27 kg	ROUTE	DURATION
Amoxicillin		50 mg/kg once daily (maximum 1000 mg)		Oral	10 days
Penicillin V		250 mg bid	500 mg bid	Oral	10 days
Benzathine penicillin G		600,000 units	1.2 million units	IM	Once
Benzathine penicillin G + procaine penicillin G		900,000 units + 300,000 units	900,000 units + 300,000 units	IM	Once
PENICILLIN-ALLERGIC PATIENTS		ORAL DOSE		FREQUENCY	DURATION
Cephalosporins*	Varies with agent chosen				10 days
Erythromycin Ethylsuccinate	40 mg/kg/day up to 1000 mg/day		bid		10 days
Estolate	20-40 mg/kg/day up to 1000 mg/day		bid		10 days
Clarithromycin	15 mg/kg/day up to 500 mg/day		bid		10 days
Azithromycin†	12 mg/kg day 1; 6 mg/kg days 2-5		qd		5 days
Clindamycin	20 mg/kg/day up to 1.8 g/day		tid		10 days

*First-generation cephalosporins are preferred; dosage and frequency vary among agents. Do not use in patients with history of immediate (anaphylactic) hypersensitivity to penicillin or other β-lactam antibiotics.

†Maximum dose is 500 mg the 1st day, 250 mg subsequent days.

Table 383-1 Paradise Criteria for Tonsillectomy

CRITERION	DEFINITION
Minimum frequency of sore throat episodes	At least 7 episodes in the previous year, at least 5 episodes in each of the previous 2 yr, or at least 3 episodes in each of the previous 3 yr
Clinical features	Sore throat plus at least 1 of the following features qualifies as a counting episode: Temperature of greater than 38.3°C (100.9°F) Cervical adenopathy (tender lymph nodes or lymph node size >2 cm) Tonsillar exudate Culture positive for group A β-hemolytic streptococcus
Treatment	Antibiotics administered in the conventional dosage for proved or suspected streptococcal episodes
Documentation	Each episode of throat infection and its qualifying features substantiated by contemporaneous notation in a medical record If the episodes are not fully documented, subsequent observance by the physician of 2 episodes of throat infection with patterns of frequency and clinical features consistent with the initial history*

*Allows for tonsillectomy in patients who meet all but the documentation criterion. A 12 mo observation period is usually recommended before consideration of tonsillectomy.

Table 383-3 Risks and Potential Benefits of Tonsillectomy or Adenoideectomy or Both

RISKS
Cost*
Risk of anesthetic accidents
Malignant hyperthermia
Cardiac arrhythmia
Vocal cord trauma
Aspiration with resulting bronchopulmonary obstruction or infection
Risk of miscellaneous surgical or postoperative complications
Hemorrhage
Airway obstruction from edema of tongue, palate, or nasopharynx, or retropharyngeal hematoma
Central apnea
Prolonged muscular paralysis
Dehydration
Palatopharyngeal insufficiency
Otitis media
Nasopharyngeal stenosis
Refractory torticollis
Facial edema
Emotional upset
Unknown risks
POTENTIAL BENEFITS
Reduction in frequency of ear, nose, throat illness, and thus in Discomfort
Inconvenience
School absence
Parental anxiety
Work missed by parents
Costs of physician visits and drugs
Reduction in nasal obstruction with improved Respiratory function
Comfort
Sleep
Craniofacial growth and development
Appearance
Reduction in hearing impairment
Improved growth and overall well-being
Reduction in long-term parental anxiety

*Cost for tonsillectomy alone and adenoideectomy alone are somewhat lower.

Table 383-2 Comparison of American, Italian, and Scottish Guidelines for Tonsillectomy in Children and Adolescents

PARAMETER	AAO-HNS GUIDELINES	ITALIAN GUIDELINES	SCOTTISH GUIDELINES
Audience	Multidisciplinary	Multidisciplinary	Multidisciplinary
Target population	Children and adolescents 1-18 yr of age	Children and adults	Children 4-16 yr of age and adults
Scope	Treatment of children who are candidates for tonsillectomy	Appropriateness and safety of tonsillectomy	Management of sore throat and indications for tonsillectomy
Methods	Based on a priori protocol, systematic literature review, American Academy of Pediatrics scale of evidence quality	Systematic literature review, Italian National Program Guidelines scale of evidence quality	Based on a priori protocol, systematic literature review, Scottish Intercollegiate Guidelines Network scale of evidence quality
Recommendations			
Recurrent infection	Tonsillectomy is an option for children with recurrent throat infection that meets the Paradise criteria (see Table 383-1) for frequency, severity, treatment, and documentation of illness	Tonsillectomy is indicated in patients with at least 1 yr of recurrent tonsillitis (5 or more episodes per year) that is disabling and impairs normal activities, but only after an additional 6 mo of watchful waiting to assess the pattern of symptoms using a clinical diary	Tonsillectomy should be considered for recurrent, disabling sore throat caused by acute tonsillitis when the episodes are well documented, are adequately treated, and meet the Paradise criteria (see Table 383-1) for frequency of illness
Pain control	Recommendation to advocate for pain relief (e.g., provide information, prescribe) and educate caregivers about the importance of managing and reassessing pain	Recommendation for acetaminophen before and after surgery	Recommendation for adequate dose of acetaminophen for pain relief in children
Antibiotic use	Recommendation against perioperative antibiotics	Recommendation for short-term perioperative antibiotics*	NA
Steroid use	Recommendation for a single intraoperative dose of dexamethasone	Recommendation for a single intraoperative dose of dexamethasone	Recommendation for a single intraoperative dose of dexamethasone
Sleep-disordered breathing	Recommendation to counsel caregivers about tonsillectomy as a means to improve health in children with sleep-disordered breathing and comorbid conditions	Recommendation for diagnostic testing in children with suspected sleep respiratory disorders	NA
Polysomnography	Recommendation to counsel caregivers about tonsillectomy as a means to improve health in children with abnormal polysomnography	Recommendation for polysomnography when pulse oximetry results are not conclusive in agreement with Brouillette criteria	NA
Surgical technique	NA	Recommendation for "cold" technique	NA
Hemorrhage	Recommendation that the surgeon document primary and secondary hemorrhage after tonsillectomy at least annually	NA	NA
Adjunctive therapy	NA	NA	Recommendation against <i>Echinacea purpurea</i> for treatment of sore throat Recommendation for acupuncture in patients at risk of postoperative nausea and vomiting who cannot take antiemetic drugs

*Statement made prior to most recent Cochrane review.

AAO-HNS, American Academy of Otolaryngology–Head and Neck Surgery; NA, not applicable.

Adapted with permission from Baugh RF, Archer SM, Mitchell RB, et al: American Academy of Otolaryngology–Head and Neck Surgery Foundation. Clinical practice guideline: tonsillectomy in children. *Otolaryngol Head Neck Surg* 144(1 Suppl):S23, 2011, Table 9.

Table 384-3 Characteristics of Cough and Other Clinical Features and Possible Causes

SYMPOTMS AND SIGNS	POSSIBLE UNDERLYING ETIOLOGY*
Auscultatory findings (wheeze, crepitations/crackles, differential breath sounds)	Asthma, bronchitis, congenital lung disease, foreign body aspiration, airway abnormality
Cough characteristics (e.g., cough with choking, cough quality, cough starting from birth)	See text; congenital lung abnormalities
Cardiac abnormalities (including murmurs)	Any cardiac illness
Chest pain	Asthma, functional, pleuritis
Chest wall deformity	Any chronic lung disease
Daily moist or productive cough	Chronic bronchitis, suppurative lung disease
Digital clubbing	Suppurative lung disease, arteriovenous shunt
Dyspnea (exertional or at rest)	Compromised lung function of any chronic lung or cardiac disease
Failure to thrive	Compromised lung function, immunodeficiency, cystic fibrosis
Feeding difficulties (including choking and vomiting)	Compromised lung function, aspiration
Hemoptysis	Bronchitis, foreign body aspiration, suctioning trauma
Immune deficiency	Atypical and typical recurrent respiratory infections
Medications or drugs	Angiotensin-converting enzyme inhibitors, puffers, illicit drug use
Neurodevelopmental abnormality	Aspiration
Recurrent pneumonia	Immunodeficiency, congenital lung problem, airway abnormality
Symptoms of upper respiratory tract infection	Can coexist or be a trigger for an underlying problem

*This is not an exhaustive list; only the more common respiratory diseases are mentioned.

Table 384-1 Indicators of Serious Chronic Lower Respiratory Tract Disease in Children

Persistent fever
Ongoing limitation of activity
Failure to grow
Failure to gain weight appropriately
Clubbing of the digits
Persistent tachypnea and labored ventilation
Shortness of breath and exercise intolerance
Chronic purulent sputum
Persistent hyperinflation
Substantial and sustained hypoxemia
Refractory infiltrates on chest x-ray
Persistent pulmonary function abnormalities
Family history of heritable lung disease
Cyanosis and hypercarbia

Table 384-4 Clinical Clues About Cough

CHARACTERISTIC	THINK OF
Staccato, paroxysmal	Pertussis, cystic fibrosis, foreign body, <i>Chlamydia</i> spp., <i>Mycoplasma</i> spp.
Followed by "whoop"	Pertussis
All day, never during sleep	Habit cough
Barking, brassy	Croup, habit cough, tracheomalacia, tracheitis, epiglottitis
Hoarseness	Laryngeal involvement (croup, recurrent laryngeal nerve involvement)
Abrupt onset	Foreign body, pulmonary embolism
Follows exercise	Reactive airway disease
Accompanies eating, drinking	Aspiration, gastroesophageal reflux, tracheoesophageal fistula
Throat clearing	Postnasal drip, vocal tic
Productive (sputum)	Infection, cystic fibrosis, bronchiectasis
Night cough	Sinusitis, reactive airway disease, gastroesophageal reflux
Seasonal	Allergic rhinitis, reactive airway disease
Immunosuppressed patient	Bacterial pneumonia, <i>Pneumocystis jiroveci</i> , <i>Mycobacterium tuberculosis</i> , <i>Mycobacterium avium-intracellulare</i> , cytomegalovirus
Dyspnea	Hypoxia, hypercarbia
Animal exposure	<i>Chlamydia psittaci</i> (birds), <i>Yersinia pestis</i> (rodents), <i>Francisella tularensis</i> (rabbits), Q fever (sheep, cattle), hantavirus (rodents), histoplasmosis (pigeons)
Geographic	Histoplasmosis (Mississippi, Missouri, Ohio River Valley), coccidioidomycosis (Southwest), blastomycosis (North and Midwest)
Workdays with clearing on days off	Occupational exposure

Table 384-2 Differential Diagnosis of Recurrent and Persistent Cough in Children**RECURRENT COUGH**

Reactive airway disease (asthma)
Drainage from upper airways
Aspiration
Frequently recurring respiratory tract infections in immunocompetent or immunodeficient patients
Symptomatic Chiari malformation
Idiopathic pulmonary hemosiderosis
Hypersensitivity (allergic) pneumonitis

PERSISTENT COUGH

Hypersensitivity of cough receptors after infection
Reactive airway disease (asthma)
Chronic sinusitis
Chronic rhinitis (allergic or nonallergic)
Bronchitis or tracheitis caused by infection or smoke exposure
Bronchiectasis, including cystic fibrosis, primary ciliary dyskinesia, immunodeficiency
Habit cough
Foreign-body aspiration
Recurrent aspiration owing to pharyngeal incompetence, tracheolaryngoesophageal cleft, or tracheoesophageal fistula
Gastroesophageal reflux, with or without aspiration
Pertussis
Extrinsic compression of the tracheobronchial tract (vascular ring, neoplasm, lymph node, lung cyst)
Tracheomalacia, bronchomalacia
Endobronchial or endotracheal tumors
Endobronchial tuberculosis
Hypersensitivity pneumonitis
Fungal infections
Inhaled irritants, including tobacco smoke
Irritation of external auditory canal
Angiotensin-converting enzyme inhibitors

Table 384-5	Causes of Recurrent or Persistent Stridor in Children
RECURRENT	
Allergic (spasmodic) croup	
Respiratory infections in a child with otherwise asymptomatic anatomic narrowing of the large airways	
Laryngomalacia	
PERSISTENT	
Laryngeal obstruction	
• Laryngomalacia	
• Papillomas, other tumors	
• Cysts and laryngoceles	
• Laryngeal webs	
• Bilateral abductor paralysis of the cords	
• Foreign body	
Tracheobronchial disease	
• Tracheomalacia	
• Subglottic tracheal webs	
• Endobronchial, endotracheal tumors	
• Subglottic tracheal stenosis, congenital or acquired	
Extrinsic masses	
• Mediastinal masses	
• Vascular ring	
• Lobar emphysema	
• Bronchogenic cysts	
• Thyroid enlargement	
• Esophageal foreign body	
Tracheoesophageal fistula	
OTHER	
Gastroesophageal reflux	
Macroglossia, Pierre Robin syndrome	
Cri-du-chat syndrome	
Paradoxical vocal cord dysfunction	
Hypocalcemia	
Vocal cord paralysis	
Chiari crisis	
Severe neonatal episodic laryngospasm caused by SCN4A mutation	

Table 384-6	Diseases Associated with Recurrent, Persistent, or Migrating Lung Infiltrates Beyond the Neonatal Period
Aspiration	Pharyngeal incompetence (e.g., cleft palate) Laryngotracheoesophageal cleft Tracheoesophageal fistula Gastroesophageal reflux Lipid aspiration Neurologic dysphagia Developmental dysphagia Congenital anomalies Lung cysts (cystic adenomatoid malformation) Pulmonary sequestration Bronchial stenosis or aberrant bronchus Vascular ring Congenital heart disease with large left-to-right shunt Pulmonary lymphangiectasia Genetic conditions α ₁ -Antitrypsin deficiency Cystic fibrosis Primary ciliary dyskinesia (Kartagener syndrome) Sickle cell disease (acute chest syndrome) Immunodeficiency, phagocytic deficiency Humoral, cellular, combined immunodeficiency states Chronic granulomatous disease and related phagocytic defects Complement deficiency states Immunologic and autoimmune diseases Asthma Allergic bronchopulmonary aspergillosis Hypersensitivity pneumonitis Pulmonary hemosiderosis Collagen-vascular diseases Infection, congenital Cytomegalovirus Rubella Syphilis Infection, acquired Cytomegalovirus Tuberculosis HIV Other viruses Chlamydia Mycoplasma, Ureaplasma Pertussis Fungal organisms <i>Pneumocystis jiroveci</i> Visceral larva migrans Inadequately treated bacterial infection Interstitial pneumonitis and fibrosis Usual interstitial pneumonitis Lymphoid (AIDS) Genetic disorders of surfactant synthesis, secretion Desquamative Acute (Hamman-Rich) Alveolar proteinosis Drug-induced, radiation-induced inflammation and fibrosis Neoplasms and neoplastic-like conditions Primary or metastatic pulmonary tumors Leukemia Histiocytosis Eosinophilic pneumonias Other etiologies Bronchiectasis Congenital Postinfectious Sarcoidosis

Table 391-2	Pertinent Medical History in the Wheezing Infant
Did the onset of symptoms begin at birth or thereafter?	
Is the infant a noisy breather and when is it most prominent?	
Is the noisy breathing present on inspiration, expiration, or both?	
Is there a history of cough apart from wheezing?	
Was there an earlier lower respiratory tract infection?	
Is there a history of recurrent upper or lower respiratory tract infections?	
Have there been any emergency department visits, hospitalizations, or intensive care unit admissions for respiratory distress?	
Is there a history of eczema?	
Does the infant cough after crying or cough at night?	
How is the infant growing and developing?	
Is there associated failure to thrive?	
Is there a history of electrolyte abnormalities?	
Are there signs of intestinal malabsorption including frequent, greasy, or oily stools?	
Is there a maternal history of genital herpes simplex virus infection?	
What was the gestational age at delivery?	
Was the patient intubated as a neonate?	
Does the infant bottle-feed in the bed or the crib, especially in a propped position?	
Are there any feeding difficulties including choking, gagging, arching, or vomiting with feeds?	
Is there any new food exposure?	
Is there a toddler in the home or lapse in supervision in which foreign-body aspiration could have occurred?	
Change in caregivers or chance of nonaccidental trauma?	

Table 391-3 Disorders with Cough as a Prominent Finding

CATEGORY	DIAGNOSES
Inflammatory	Asthma
Chronic pulmonary processes	Bronchopulmonary dysplasia Postinfectious bronchiectasis Cystic fibrosis Tracheomalacia or bronchomalacia Ciliary abnormalities Other chronic lung diseases
Other chronic disease or congenital disorders	Laryngeal cleft Swallowing disorders Gastroesophageal reflux Airway compression (such as a vascular ring or hemangioma) Congenital heart disease
Infectious or immune disorders	Immunodeficiency Eosinophilic lung disease Tuberculosis Allergy Sinusitis Tonsillitis or adenoiditis <i>Chlamydia, Ureaplasma</i> (infants) <i>Bordetella pertussis</i> <i>Mycoplasma pneumoniae</i>
Acquired	Foreign-body aspiration, tracheal or esophageal

Table 394-1 Etiology of Bronchiolitis Obliterans

POSTINFECTION	
Adenovirus types 3, 7, and 21	
Influenza	
Parainfluenza	
Measles	
Respiratory syncytial virus	
Varicella	
<i>Mycoplasma pneumoniae</i>	
POSTTRANSPLANTATION	
Chronic rejection of lung or heart/lung transplantation	
Graft-versus-host disease associated with bone marrow transplantation	
CONNECTIVE TISSUE DISEASE	
Juvenile idiopathic arthritis	
Sjögren syndrome	
Systemic lupus erythematosus	
TOXIC FUME INHALATION	
NO ₂	
NH ₃	
Diacetyl flavorings (microwave popcorn)	
CHRONIC HYPERSENSITIVITY PNEUMONITIS	
Avian antigens	
Mold	
ASPIRATION	
Stomach contents: gastroesophageal reflux	
Foreign bodies	
DRUGS	
Penicillamine	
Cocaine	
STEVENS-JOHNSON SYNDROME	
Idiopathic	
Drug induced	
Infection related	

Table 391-1 Differential Diagnosis of Wheezing in Infancy

INFECTION	
<i>Viral</i>	Respiratory syncytial virus Human metapneumovirus Parainfluenza Adenovirus Influenza Rhinovirus Bocavirus Coronavirus Enterovirus
<i>Other</i>	<i>Chlamydia trachomatis</i> Tuberculosis Histoplasmosis Papillomatosis
ASTHMA	
	Transient wheezer (resolved by 6 yr of age) • Initial risk factor is primarily diminished lung size
	Persistent wheezers (persists beyond 6 yr of age) • Initial risk factors include parental asthma history, atopic dermatitis, allergen sensitization, peripheral eosinophilia (>4%) and wheezing unrelated to colds in the 1st yr of life
	• At increased risk of developing clinical asthma
	Late-onset wheezer (symptoms begin after age 3 yr and persist)
ANATOMIC ABNORMALITIES	
	Central Airway Abnormalities Malacia of the larynx, trachea, and/or bronchi Laryngeal or tracheal web Tracheoesophageal fistula (specifically H-type fistula) Laryngeal cleft (resulting in aspiration)
	Extrinsic Airway Anomalies Resulting in Airway Compression Vascular ring or sling Mediastinal lymphadenopathy from infection or tumor Mediastinal mass or tumor Esophageal foreign body
	Intrinsic Airway Anomalies Airway hemangioma, other tumor Cystic adenomatoid malformation Bronchial or lung cyst Congenital lobar emphysema Aberrant tracheal bronchus Sequestration Congenital heart disease with left-to-right shunt (increased pulmonary edema) Foreign body
	Immunodeficiency States Immunoglobulin A deficiency B-cell deficiencies AIDS Bronchiectasis
MUCOCILIARY CLEARANCE DISORDERS	
	Cystic fibrosis Primary ciliary dyskinesia Bronchiectasis
ASPIRATION SYNDROMES	
	Gastroesophageal reflux disease Pharyngeal/swallow dysfunction
OTHER	
	Bronchopulmonary dysplasia Interstitial lung disease, including bronchiolitis obliterans Heart failure Anaphylaxis Inhalation injury—burns

Table 398-1 Conditions Predisposing to Aspiration Lung Injury in Children**ANATOMICAL AND MECHANICAL**

- Tracheoesophageal fistula
- Laryngeal cleft
- Vascular ring
- Cleft palate
- Micrognathia
- Macroglossia
- Cysts, tumors
- Achalasia
- Esophageal foreign body
- Tracheostomy
- Endotracheal tube
- Nasal or oral feeding tube
- Collagen vascular disease (scleroderma, dermatomyositis)
- Gastroesophageal reflux disease
- Obesity

NEUROMUSCULAR

- Altered consciousness

Immaturity of swallowing/Prematurity

Dysautonomia

Increased intracranial pressure

Hydrocephalus

Vocal cord paralysis

Cerebral palsy

Muscular dystrophy

Hypotonia

Myasthenia gravis

Guillain-Barré syndrome

Spinal muscular atrophy

Ataxia-telangiectasia

Cerebral vascular accident

MISCELLANEOUS

Poor oral hygiene

Gingivitis

Prolonged hospitalization

Gastric outlet or intestinal obstruction

Poor feeding techniques (bottle propping, overfeeding, inappropriate foods for toddlers)

Bronchopulmonary dysplasia

Viral infection/bronchiolitis

Table 396-1 Etiology of Pulmonary Edema**INCREASED PULMONARY CAPILLARY PRESSURE**

Cardiogenic, such as left ventricular failure

Noncardiogenic, as in pulmonary venoocclusive disease, pulmonary venous fibrosis, mediastinal tumors

INCREASED CAPILLARY PERMEABILITY

Bacterial and viral pneumonia

Acute respiratory distress syndrome

Inhaled toxic agents

Circulating toxins

Vasoactive substances such as histamine, leukotrienes, thromboxanes

Diffuse capillary leak syndrome, as in sepsis

Immunologic reactions, such as transfusion reactions

Smoke inhalation

Aspiration pneumonia/pneumonitis

Drowning and near drowning

Radiation pneumonia

Uremia

LYMPHATIC INSUFFICIENCY

Congenital and acquired

DECREASED ONCOTIC PRESSURE

Hypoalbuminemia, as in renal and hepatic diseases, protein-losing states, and malnutrition

INCREASED NEGATIVE INTERSTITIAL PRESSURE

Upper airway obstructive lesions, such as croup and epiglottitis

Reexpansion pulmonary edema

MIXED OR UNKNOWN CAUSES

Neurogenic pulmonary edema

High-altitude pulmonary edema

Eclampsia

Pancreatitis

Pulmonary embolism

Heroin (narcotic) pulmonary edema

Table 396-2 Radiographic Features That May Help Differentiate Cardiogenic from Noncardiogenic Pulmonary Edema

RADIOGRAPHIC FEATURE	CARDIOGENIC EDEMA	NONCARDIOGENIC EDEMA
Heart size	Normal or greater than normal	Usually normal
Width of the vascular pedicle*	Normal or greater than normal	Usually normal or less than normal
Vascular distribution	Balanced or inverted	Normal or balanced
Distribution of edema	Even or central	Patchy or peripheral
Pleural effusions	Present	Not usually present
Peribronchial cuffing	Present	Not usually present
Septal lines	Present	Not usually present
Air bronchograms	Not usually present	Usually present

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Table 398-2 | Summary of Diagnostic Tests of Aspiration

EVALUATION	BENEFITS	LIMITATIONS
Chest radiograph	Inexpensive and widely available Assesses accumulation of injury over time	Insensitive to early subtle changes of lung injury
High-resolution CT	Sensitive in detecting lung injury, such as bronchiectasis, tree-in-bud opacities, and bronchial thickening Less radiation than conventional CT Assesses accumulation of injury over time	More radiation exposure than plain radiograph Expensive
Video swallow study	Evaluates all phases of swallowing Evaluates multiple consistencies Feeding recommendations made at time of study	Information limited if child consumes only small quantities Difficult to perform in child who has not been feeding by mouth Radiation exposure proportional to study duration Cannot be performed at bedside Limited evaluation of anatomy Evaluates 1 moment in time Expensive
FEES/with sensory testing	Ability to thoroughly evaluate functional anatomy Evaluates multiple consistencies Can assess risk of aspiration in non-orally feeding child; airway protective reflexes can be assessed Feeding recommendations made at time of study Visual feedback for caregivers Can be performed at bedside No radiation exposure	Blind to esophageal phase and actual swallow Invasive and may not represent physiological swallowing conditions Evaluates 1 moment in time Not widely available Expensive
BAL	Evaluates anatomy of entire upper and lower airways Samples the end-organ of damage Sample available for multiple cytological and microbiologic tests Widely available	Uncertainty regarding interpretation of lipid-laden macrophage index Index cumbersome to calculate Requires sedation or anesthesia Invasive Expensive
Esophageal pH monitoring	Current gold standard for diagnosis of Acid gastroesophageal reflux Established normative data in children	Blind to majority of reflux (nonacid) events Difficult to establish causal relationship between gastroesophageal reflux and aspiration Somewhat invasive Evaluates short time interval
Esophageal impedance monitoring	Likely gold standard for diagnosis of GERD with supraesophageal manifestations Able to detect acid and nonacid reflux events Detects proximal reflux events Able to evaluate for GERD without stopping medications	Lack of normative data for children Somewhat invasive Expensive and cumbersome to interpret Not widely available Evaluates short time interval
Gastroesophageal scintigraphy	Performed under physiologic conditions Low radiation exposure	Poor sensitivity May not differentiate between aspiration from dysphagia or GERD
Radionuclide salivagram	Child does not have to be challenged with food bolus Low radiation exposure	Unknown sensitivity Unknown relationship to disease outcomes Evaluates 1 moment in time
Dye studies	Can be constructed as screening test or confirmatory test Can evaluate aspiration of secretions or feeds Repeating over time allows for broader evaluation	Uncertainty in interpretation owing to variability of technique Can only be performed in children with tracheostomies
Other biomarkers (pepsin, bile acids) milk protein	Theoretical high specificity and sensitivity	Limited availability and standardization Variable results to date

BAL, bronchoalveolar lavage; FEES, fiberoptic-endoscopic evaluation of swallowing; GERD, gastroesophageal reflux disease.

Modified from Boesch RP, Daines C, Willging JP, et al: Advances in the diagnosis and management of chronic pulmonary aspiration in children, Eur Respir J 28:847-861, 2006; and Tutor JD, Gosa MM: Dysphagia and aspiration in children, Pediatr Pulmonol 47(4):321-337, 2012.

Table 399-1 Antigen Sources Associated with Specific Causes of Hypersensitivity Pneumonitis

HYPERSENSITIVITY PNEUMONITIS	ANTIGEN SOURCE	HYPERSENSITIVITY PNEUMONITIS	ANTIGEN SOURCE
Bagassosis (mold on pressed sugar cane)	<i>Thermoactinomyces sacchari</i> <i>Thermoactinomyces vulgaris</i>	Miller's lung (dust-contaminated grain)	<i>Sitophilus granarius</i> (i.e., wheat weevil)
Bat lung (bat droppings)	Bat serum protein	Moldy hay, grain, silage (farmer's lung)	Thermophilic actinomycetes Fungi (e.g., <i>Aspergillus umbrosus</i>)
Bible printer's lung	Moldy typesetting water	Mollusk shell hypersensitivity pneumonitis	Sea-snail shell
Bird fancier's lung (parakeets, budgerigars, pigeons)	Droppings, feathers, serum proteins	Mushroom worker's lung	Mushroom spores Thermophilic actinomycetes
Byssinosis ("brown lung") (unclear if a true cause of hypersensitivity pneumonitis; asthma is common)	Cotton mill dust (carding and spinning areas of cotton, flax, and soft-hemp)	Paprika slicer's lung (moldy paprika pods)	<i>Mucor stolonifer</i>
Canary fancier's lung	Serum proteins	Pauli's reagent alveolitis	Sodium diazobenzene sulfate
Cheese washer's lung (moldy cheese)	<i>Penicillium casei</i> <i>Aspergillus clavatus</i>	Pearl oyster shell pneumonitis	Oyster shells
Chemical hypersensitivity pneumonitis	Diphenylmethane diisocyanate (MDI) Toluene diisocyanate (TDI)	Pituitary snuff taker's disease	Dried, powdered cattle or pig pituitary proteins
Coffee worker's lung	Coffee-bean dust	Potato riddler's lung (moldy hay around potatoes)	Thermophilic actinomycetes <i>T. vulgaris</i> <i>Faenia rectivirgula</i> <i>Aspergillus</i> spp.
Composter's lung	<i>T. vulgaris</i> <i>Aspergillus</i> species	Poultry worker's lung (feather plucker's disease)	Serum proteins (chicken products)
Contaminated basement (sewage) pneumonitis	<i>Cephalosporium</i>	Pyrethrum (pesticide)	Pyrethrum
Coptic lung (mummy handler's lung)	Cloth wrappings of mummies	Sauna taker's lung	<i>Aureobasidium</i> spp., other sources
Detergent worker's lung (washing powder lung)	<i>Bacillus subtilis</i> enzymes	Sequoiosis (moldy wood dust)	<i>Graphium</i> <i>Pullularia</i> <i>Trichoderma</i> spp. <i>Aureobasidium pullulans</i>
Dry rot lung	<i>Merulius lacrymans</i>	Suberosis (moldy cork dust)	<i>Thermoactinomyces viridis</i> <i>Penicillium glabrum</i> <i>Aspergillus</i> conidia
Duck fever	Feathers, serum proteins	Summer-type pneumonitis	<i>Trichosporon cutaneum</i>
Epoxy resin lung	Phthalic anhydride (heated epoxy resin)	Tea grower's lung	Tea plants
Esparto dust (mold in plaster dust)	<i>Aspergillus fumigatus</i> Thermophilic actinomycetes	Thatched-roof lung (huts in New Guinea)	<i>Saccharomonospora viridis</i> (dead grasses and leaves)
Fish meal worker's lung	Fish meal	Tobacco grower's lung	<i>Aspergillus</i> spp. <i>Scopulariopsis brevicaulis</i>
Furrier's lung (sewing furs; animal fur dust)	Animal pelts	Turkey handling disease	Serum proteins (turkey products)
Grain measurer's lung	Cereal grain (<i>Sporobolomyces</i>) Grain dust (mixture of dust, silica, fungi, insects, and mites)	Unventilated shower	<i>Epicoccum nigrum</i>
Hot-tub lung (mists; mold on ceiling and around tub)	<i>Cladosporium</i> spp. <i>Mycobacterium avium</i> complex	Upholstery fabric (nylon filament, cotton/polyester, and latex adhesive)	Aflatoxin-producing fungus, <i>Fusarium</i> spp.
Humidifier fever	<i>Thermoactinomyces</i> (<i>T. vulgaris</i> , <i>T. sacchari</i> , <i>T. candidus</i>) <i>Klebsiella oxytoca</i> <i>Naegleria gruberi</i> <i>Acanthamoeba polyphaga</i> <i>Acanthamoeba castellani</i>	Velvet worker's lung	Unknown (? nylon velvet fiber, tannic acid, potato starch)
Laboratory worker's lung (rats, gerbils)	Urine, serum, pelts, proteins	Vineyard sprayer's lung	Copper sulfate (bordeaux mixture)
Lifeguard lung	Aerosolized endotoxin from pool-water sprays and fountains	Wine maker's lung (mold on grapes)	<i>Botrytis cinerea</i>
Lycoperdonosis (Lycoperdon puffballs)	Puffball spores	Wood dust pneumonitis (oak, cedar, and mahogany dust, pine and spruce pulp)	<i>Alternaria</i> spp. <i>Bacillus subtilis</i>
Machine operator's lung	<i>Pseudomonas fluorescens</i> Aerosolized metal working fluid	Wood pulp worker's disease (oak and maple trees)	<i>Penicillium</i> spp.
Malt worker's disease (moldy barley)	<i>Aspergillus fumigatus</i> , <i>Aspergillus clavatus</i>	Wood trimmer's disease (contaminated wood trimmings)	<i>Rhizopus</i> spp., <i>Mucor</i> spp.
Maple bark disease (moldy maple bark)	<i>Cryptostroma corticale</i>		

Table 399-2 Criteria Used in the Diagnosis of Hypersensitivity Pneumonitis

1. Identified exposure to offending antigen(s) by:
 - Medical history of exposure to suspected antigen in the patient's living environment
 - Investigations of the environment confirm the presence of an inciting antigen
 - Identification of specific immune responses (immunoglobulin G serum precipitin antibodies against the identified antigen) are suggestive of the potential etiology but are insufficient in isolation to confirm a diagnosis
2. Clinical, radiographic, or physiologic findings compatible with hypersensitivity pneumonitis:
 - Respiratory and often constitutional signs and symptoms
 - Crackles on auscultation of the chest
 - Weight loss
 - Cough
 - Breathlessness
 - Episodic fever
 - Wheezing
 - Fatigue
 - NOTE: These findings are especially suggestive of hypersensitivity pneumonitis when they appear or worsen several hours after antigen exposure.
 - A reticular, nodular, or ground glass opacities on chest radiograph or high-resolution CT
 - Abnormalities in the following pulmonary function tests
 - Spirometry (restrictive, obstructive, or mixed patterns)
 - Lung volumes (low or high)
 - Reduced diffusion capacity by carbon monoxide
 - Altered gas exchange either at rest or with exercise (reduced partial pressure of arterial oxygen by blood gas or pulse oximeter testing)
3. Bronchoalveolar lavage with lymphocytosis:
 - Usually with low CD4:CD8 ratio (i.e., CD8 is higher than normal)
 - Lymphocyte stimulation by offending antigen results in proliferation and cytokine production
4. Abnormal response to inhalation challenge testing to the offending antigen:
 - Reexposure to the environment
 - Inhalation challenge to the suspected antigen (rarely done any longer because of the risk of exacerbation of the disease)
5. Histopathology showing compatible changes with hypersensitivity pneumonitis by 1 of these findings:
 - Poorly formed, noncaseating granulomas (most often found closer to the respiratory epithelium where deposition of the offending antigen occurs)
 - Mononuclear cell infiltrate in the pulmonary interstitium

Table 399-3 Clinical History Clues Leading to a Diagnosis of Hypersensitivity Pneumonitis

- Recurrent pneumonia
- Pneumonia after repeat exposures (week, season, situation)
- Cough, fever, and chest symptoms after making a job change or home change
- Cough, fever, wheezing after return to school or only at school
- Pet exposure (especially birds that shed dust such as pigeons, canaries, cockatiels, cockatoos)
- Bird contaminant exposure (e.g., pigeon infestation)
- Farm exposure to birds and hay
- History of water damage despite typical cleaning
- Use of hot tub, sauna, swimming pool
- Other family members or workers with similar recurrent symptoms
- Improvement after temporary environment change (e.g., vacation)

Table 399-5 High Molecular Weight Antigens Known to Induce Occupational or Environmental Asthma

OCCUPATION OR ENVIRONMENT	SOURCE	OCCUPATION OR ENVIRONMENT	SOURCE
ANIMAL-DERIVED ANTIGENS			
Agricultural worker	Cow dander	ACARIANS	Fruit tree red spider mite (<i>Panonychus ulmi</i>)
Bakery	Lactalbumin	Citrus farmer	Citrus red mite (<i>Panonychus citri</i>)
Butcher	Cow bone dust, pig, goat dander	Farmer	Barn mite, two-spotted spider mite (<i>Tetranychus urticae</i>), grain mite
Cook	Raw beef	Flour handler	Mites and parasites
Dairy industry	Lactosерum, lactalbumin	Grain-store worker	Grain mite
Egg producer	Egg protein	Horticulturist	<i>Amblyseius cucumeris</i>
Farmer	Deer dander, mink urine	Poultry worker	Fowl mite
Frog catcher	Frog	Vine grower	McDaniel spider mite (<i>Tetranychus mcdanieli</i>)
Hairdresser	Sericin		
Ivory worker	Ivory dust		
Laboratory technician	Bovine serum albumin, laboratory animal, monkey dander		
Nacre buttons	Nacre dust		
Pharmacist	Endocrine glands		
Pork producer	Pig gut (vapor from soaking water)		
Poultry worker	Chicken		
Tanner	Casein (cow's milk)		
Various	Bat guano		
Veterinarian	Goat dander		
Zookeeper	Birds		
CRUSTACEANS, SEAFOOD, FISH			
Canning factory	Octopus	MOLDS	<i>Plasmopara viticola</i>
Diet product	Shark cartilage	Baker	<i>Alternaria</i> , <i>Aspergillus</i> (unspecified)
Fish food factory	Gammarus shrimp	Beet sugar worker	<i>Aspergillus</i> (unspecified)
Fish processor	Clam, shrimp, crab, prawn, salmon, trout, lobster, turbot, various fishes	Coal miner	<i>Rhizopus nigricans</i>
Fisherman	Red soft coral, cuttlefish	Coffee maker	<i>Chrysotilus sitophila</i>
Jewelry polisher	Cuttlefish bone	Laborer	Sooty molds (Ascomycetes, deuteromycetes)
Laboratory grinder	Marine sponge	Logging worker	<i>Chrysotilus sitophila</i>
Oyster farm	Hoya (oyster farm prawn or sea-squirt)	Plywood factory worker	<i>Neurospora</i>
Restaurant seafood handler	Scallop and shrimp	Sausage processing	<i>Penicillium nalgiovense</i>
Scallop plant processor	King scallop and queen scallop	Sawmill worker	<i>Trichoderma koningii</i>
Technician	Shrimp meal (<i>Artemia salina</i>)	Stucco worker	<i>Mucor</i> spp. (contaminating esparto fibers)
ARTHROPODS			
Agronomist	<i>Bruchus latus</i>	Technician	<i>Dictyostelium discoideum</i> (mold), <i>Aspergillus niger</i>
Bottling	Ground bug		
Chicken breeder	Herring worm (<i>Anisakis simplex</i>)		
Engineer at electric power plant	Caddis flies (<i>Phryganeidae</i>)		
Entomologist	Lesser mealworm (<i>Alphitobius diaperinus</i> Panzer), moth, butterfly		
Farmer	Grain pests (<i>Eurygaster</i> and <i>Pyrale</i>)		
Fish bait handler	Insect larvae (<i>Galleria mellonella</i>), mealworm larvae (<i>Tenebrio molitor</i>), green bottle fly larvae (<i>Lucilia caesar</i>), daphnia, fish-feed Echinodorus larva (<i>Echinodorus plasmosus</i>), Chironomids midge (<i>Chironomus thummi</i> <i>thummi</i>)		
Fish processing	Herring worm (<i>Anisakis simplex</i>)		
Flight crew	Screw worm fly (<i>Cochliomyia hominivorax</i>)		
Honey processors	Honeybee		
Laboratory worker	Cricket, fruit fly, grasshopper (<i>Locusta migratoria</i>), locust		
Mechanic in a rye plant	Confused flour beetle (<i>Tribolium confusum</i>)		
Museum curator	Beetles (Coleoptera)		
Seed house	Mexican bean weevil (<i>Zabrotes subfasciatus</i>)		
Sericulture	Silkworm, larva of silkworm		
Sewage plant worker	Sewer fly (<i>Psychoda alternata</i>)		
Technician	Arthropods (<i>Chrysoperla carnea</i> , <i>Leptinotarsa decemlineata</i> , <i>Ostrinia nubilalis</i> , and <i>Ephestia kuhniella</i>), sheep blowfly (<i>Lucilia cuprina</i>)		
Wool worker	Dermestidae spp.		
MOLDS			
Agriculture			
Baker			
Beet sugar worker			
Coal miner			
Coffee maker			
Laborer			
Logging worker			
Plywood factory worker			
Sausage processing			
Sawmill worker			
Stucco worker			
Technician			
MUSHROOMS			
Agriculture			
Baker			
Greenhouse worker			
Hotel manager			
Mushroom producer			
Mushroom soup processor			
Office worker			
Seller			
ALGAE			
Pharmacist			
Thalassotherapist			
FLOURS			
Animal fodder			
Baker			
Food processing			
FLOORS			
Marigold flour (<i>Tagetes erecta</i>)			
Wheat, rye, soya, and buckwheat flour; Konjac flour; white pea flour (<i>Lathyrus sativus</i>)			
White Lupin flour (<i>Lupinus albus</i>)			
POLLENS			
Florist			
Gardener			
Laboratory worker			
Olive farmers			
Processing worker			
CYCLAMEN, ROSE			
Canary island date palm (<i>Phoenix canariensis</i>)			
Bell of Ireland (<i>Moluccella laevis</i>)			
Bell pepper, chrysanthemum, eggplant (<i>Solanum melongena</i>), <i>Brassica oleracea</i> (cauliflower and broccoli)			
Sunflower (<i>Helianthus</i> spp.), thale cress (<i>Arabidopsis thaliana</i>)			
White mustard (<i>Sinapis alba</i>)			
<i>Helianthus annuus</i>			

Table 399-5 High Molecular Weight Antigens Known to Induce Occupational or Environmental Asthma—cont'd

OCCUPATION OR ENVIRONMENT	SOURCE	OCCUPATION OR ENVIRONMENT	SOURCE
PLANTS			
Brewery chemist	Hops	Laborer	Citrus food handling (<i>dl</i> -limonene, <i>l</i> -citronellol, and dichlorophen)
Brush-makers	Tampico fiber in agave leaves	Oil industry	Castor bean, olive oilcake
Butcher	Aromatic herb	Pharmaceutical	Rose hip, passion flower (<i>Passiflora alata</i>), cascara sagrada (<i>Rhamnus purshiana</i>)
Chemist	Linseed oilcake, <i>Voacanga africana</i> seed dust	Powder	Lycopodium powder
Cosmetics	Dusts from seeds of Sacha Inchi (<i>Plukenetia volubilis</i>), chamomile (unspecified)	Sewer	Kapok
Decorator	Cacoon seed (<i>Entage gigas</i>)	Sheller	Almond shell dust
Floral worker	Decorative flower, safflower (<i>Carthamus tinctorius</i>) and yarrow (<i>Achillea millefolium</i>), spate flower, statice (<i>Limonium tataricum</i>), baby's breath (<i>Gypsophila paniculata</i>), ivy (<i>Hedera helix</i>), flower (various), sea lavender (<i>Limonium sinuatum</i>)	Stucco handler	Esparto (<i>Stipa tenacissima</i> and <i>Lygeum spartum</i>)
Food industry	Aniseed, fenugreek, peach, garlic dust, asparagus, coffee bean, sesame seed, grain dust, carrot (<i>Daucus carota L.</i>), green bean (<i>Phaseolus multiflorus</i>), lima bean (<i>Phaseolus lunatus</i>), onion, potato, swiss chard (<i>Beta vulgaris L.</i>), courgette, carob bean, spinach powder, cauliflower, cabbage, chicory, fennel seed, onion seeds (<i>Allium cepa</i> , red onion), rice, saffron (<i>Crocus sativus</i>), spices, grain dust	Tobacco manufacturer	Tobacco leaf
Gardener	Copperleaf (<i>Acalypha wilkesiana</i>), grass juice, weeping fig (<i>Ficus benjamina</i>), umbrella tree (<i>Schefflera spp.</i>), amaryllis (<i>Hippeastrum spp.</i>), Madagascar jasmine sap (<i>Stephanotis floribunda</i>), vetch (<i>Vicia sativa</i>)		
Hairdresser	Henna (unspecified)		
Herbal tea processor	Herbal tea, sarsaparilla root, sanyak (<i>Dioscorea batatas</i>), Korean ginseng (<i>Panax ginseng</i>), tea plant dust (<i>Camellia sinensis</i>), chamomile (unspecified)		
Herbalist	Liquorice roots (<i>Glycyrrhiza spp.</i>), wonji (<i>Polygala tenuifolia</i>), herb material		
Horticulture	Freesia (<i>Freesia hybrida</i>), paprika (<i>Capsicum annum</i>), Brazil ginseng (<i>Pfaffia paniculata</i>)		

Table 399-6 Low Molecular Weight Chemicals Known to Induce Occupational or Environmental Asthma

CHEMICALS	OCCUPATION OR ENVIRONMENT SOURCE	CHEMICALS	OCCUPATION OR ENVIRONMENT SOURCE
Diisocyanates		Metals	Metal work
• Diphenylmethane	Polyurethane	• Chromic acid	• Plating
• Hexamethylene	Roofing materials	• Potassium dichromate	• Welding
• Naphthalene	Insulations	• Nickel sulfate	
• Toluene	Paint	• Vanadium	
Anhydrides	Manufacturers or users	• Platinum salts	
• Trimellitic	• Paint	Drugs	Exposure to drugs in environment
• Phthalic	• Plastics	• β -Lactams	• Pharmaceutical workers
	• Epoxy resins	• Opioids	• Farmers
Dyes	Personal or business use of dyes	• Other	• Healthcare workers
• Anthraquinone	• Hair dye	Chemicals	Exposure in the healthcare field
• Carmine	• Fur dye	• Formaldehyde	• Laboratory work
• Henna	• Fabric dye	• Glutaraldehyde	• Healthcare professionals
Persulfate		• Ethylene oxide	
Glue or resin	Plastic	Wood dust	Workers/hobbyists
• Methacrylate	• Manufacturers	• Western red cedar (plicatic acid)	• Sawmill
• Acrylates	• Healthcare professionals	• Exotic woods	• Carpentry
• Epoxy	• Orthopedic specialists	• Maple	• Woodworking
		• Oak	

Table 399-8

Key Elements in the Medical History and Physical Exam to Raise Clinical Suspicion for Diagnostic Testing to Confirm Eosinophilic Lung Disease

Medical history and examination

- Drug exposure (especially antibiotics, NSAIDs, antiepileptics, antileukotriene modifiers in EGPA)
- Environmental inhalation exposures to dust or inhaled chemicals
- New onset of smoking cigarettes
- Travel or immigration status from areas endemic with various parasites or coccidiomycosis
- Asthma (may be severe or poorly controlled with ABPA, CSS, or is relatively new in onset with IAEP)
- ABPA concurrent in 7-10% of patients with cystic fibrosis
- Extrapulmonary symptoms suggestive of vasculitis, neuropathy, heart failure, or neoplasm
- Rash (creeping eruption in visceral larval migrans disease or ulceration in EGPA)

Diagnostic imaging and testing

- Radiography helpful in AEP, CEP, and ABPA
- Radiography not diagnostic in EGPA or drug-induced eosinophilic disease of the lung
- Simple chest radiography findings
 - Nonlobar infiltrate
 - Classic description as mirror image of pulmonary edema with peripheral infiltrates
 - Bilateral pleural effusion in AEP
 - Central bronchiectasis in ABPA
- High-resolution computerized tomography of the chest
 - Middle and upper lobe nonlobar infiltrates with areas of ground-glass appearance
 - Mucous plugging in ABPA
 - Central bronchiectasis in ABPA (confused with cystic fibrosis)
- Blood eosinophil count
 - Elevated in many eosinophilic lung diseases
 - Magnitude of eosinophil blood count does not distinguish different pulmonary diseases
 - Usually not elevated in AEP (eosinophilic disease compartmentalized to lungs)
 - May occasionally not be elevated in CEP or after use of corticosteroids
- Total serum IgE elevated in ABPA but not always in patients with cystic fibrosis with ABPA
- Serology for helminthic infections or parasites may be diagnostic but are usually not available acutely
- P-ANCA (MPO ANCA) is positive in 40-70% of EGPA (CSS)
- BAL eosinophil percentage
 - ≥25% eosinophils diagnostic in AEP
 - ≥40% eosinophils diagnostic in CEP or tropical pulmonary eosinophilia
 - Eosinophil percentages below these criteria may require lung biopsy
 - <25% eosinophils seen in connective tissue disease, sarcoid, drug-induced disease, histiocytosis X of pulmonary Langerhans cells, and interstitial pulmonary fibrosis
- Lung biopsy
 - Open lung biopsy or video-assisted thorascopic surgery when BAL nondiagnostic
 - Transbronchial biopsy is usually insufficient with peripheral infiltrative disease
 - Histology with alveolar and interstitial infiltrates of eosinophils, non-necrotizing non-granulomatous vasculitis, multinucleated giant cells without granuloma
 - EGPA shows eosinophil rich small to medium vessel, necrotizing, granulomatous vasculitis

ABPA, allergic bronchopulmonary aspergillosis; AEP, acute eosinophilic pneumonia; BAL, bronchoalveolar lavage; CEP, chronic eosinophilic pneumonia; CSS, Churg-Strauss syndrome; EGPA, eosinophilic granulomatosis with polyangiitis; IAEP, idiopathic acute eosinophilic pneumonia; MPO ANCA, myeloperoxidase antineutrophil cytoplasmic antibody; NSAID, nonsteroidal antiinflammatory drug; P-ANCA, perinuclear antineutrophil cytoplasmic antibody.

Table 399-7

Criteria for the Diagnosis of Reactive Airways Disease Syndrome

- Absence of previous documented respiratory symptom
- Onset of symptoms most often occur after a single specific exposure
- Exposure is most often to a high concentration of gas, smoke, fume, or vapor with irritant qualities
- Symptoms occur within 24 hr of exposure and persist for 3 mo or longer
- Symptoms mimic asthma with cough, wheezing, shortness of breath, and/or dyspnea
- Pulmonary function tests may demonstrate airflow obstruction but not always
- Bronchial hyperresponsiveness is documented by methacholine challenge
- Alternative pulmonary diseases are not able to be found

Table 399-10

Criteria for the Diagnosis of Allergic Bronchopulmonary Aspergillosis

Allergic bronchopulmonary aspergillosis—central bronchiectasis

- Medical history of asthma*
- Immediate skin prick test reaction to *Aspergillus* antigens*
- Precipitating (IgG) serum antibodies to *Aspergillus fumigatus**
- Total IgE concentration >417 IU/mL (>1000 ng/mL)*
- Central bronchiectasis on chest CT*
- Peripheral blood eosinophilia >500/mm³
- Lung infiltrates on chest x-ray or chest HRCT
- Elevated specific serum IgE and IgG to *A. fumigatus*

Allergic bronchopulmonary aspergillosis seropositive†

- Medical history of asthma†
- Immediate skin prick test reaction to *A. fumigatus* antigens†
- Precipitating (IgG) serum antibodies to *A. fumigatus*†
- Total IgE concentration >417 IU/mL (>1000 ng/mL)†

Staging of allergic bronchopulmonary aspergillosis

Stage 1	Acute	Upper and middle lob infiltration	High IgE
Stage 2	Remission	No infiltrate off steroids >6 mo	Normal to high IgE
Stage 3	Exacerbation	Upper and middle lobe infiltrations	High IgE
Stage 4	CSD asthma	Minimal infiltrate	Normal to high IgE
Stage 5	End stage	Fibrosis and/or bullae	Normal

*The criteria required for diagnosis of ABPA with central bronchiectasis.

†The first 4 criteria are required for a diagnosis of seropositive ABPA. CSD, corticosteroid dependent.

Table 399-9

The Classification of the Eosinophilic Lung Diseases

IDIOPATHIC	KNOWN ETIOLOGY
Acute eosinophilic pneumonia	Drug-induced eosinophilic pneumonia
Chronic eosinophilic pneumonia	Infectious causes
Eosinophilic granulomatosis with polyangiitis	<ul style="list-style-type: none"> • Ascariasis (Löffler syndrome)*
Hypereosinophilic syndromes	<ul style="list-style-type: none"> • <i>Toxocara (canis or cati)</i>
<ul style="list-style-type: none"> • Myeloproliferative variant • Lymphocytic variant 	<ul style="list-style-type: none"> • Filarial (tropical filarial eosinophilic pneumonia) • <i>Strongyloides stercoralis</i> Allergic bronchopulmonary aspergillosis
	<ul style="list-style-type: none"> • Toxic <ul style="list-style-type: none"> • L-Tryptophan (eosinophilia myalgia syndrome) • Toxic oil syndrome • Illicit drug use (cocaine, heroin, cannabis)

*Note: Löffler eosinophilic pneumonia has transient symptoms and is often classified as neither an acute or chronic eosinophilic pneumonia.

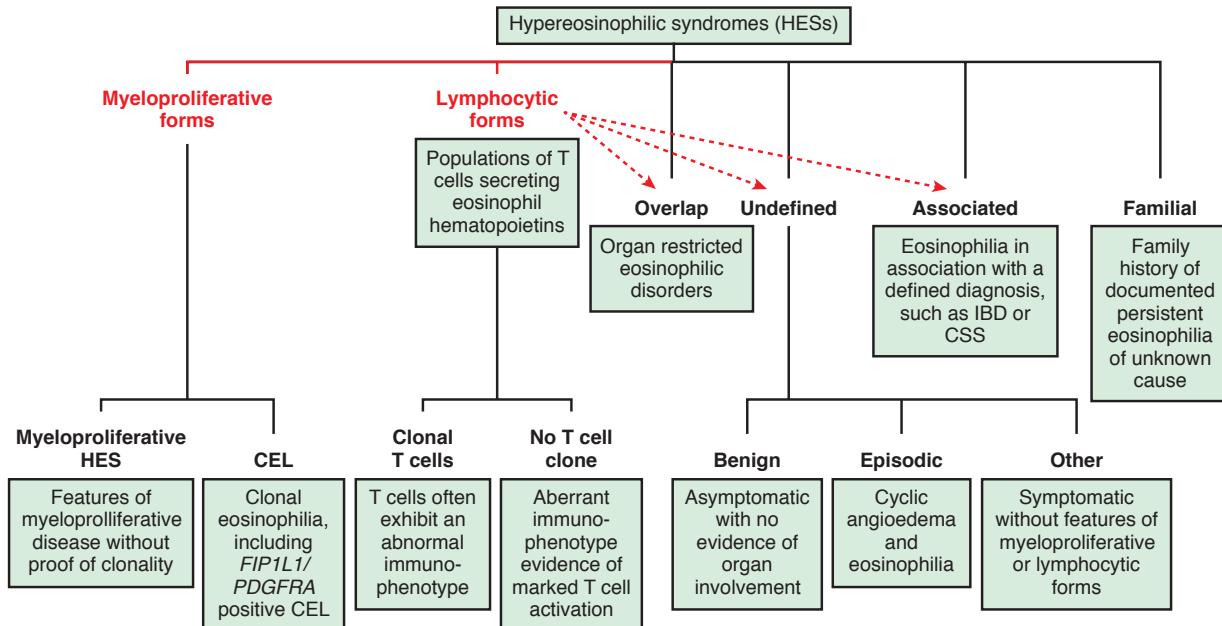


Figure 399-7 A revised classification of hypereosinophilic syndrome (HES). Changes from the previous classification are indicated in red. Dashed arrows identify HES forms for which at least some patients have T-cell–driven disease. Classification of myeloproliferative forms has been simplified, and patients with HES and eosinophil hematopoietin-producing T cells in the absence of a T-cell clone are included in the lymphocytic forms of HES. CSS, Churg-Strauss syndrome; IBD, inflammatory bowel disease. (From Simon H, Rothenberg ME, Bochner BS, et al. Refining the definition of hypereosinophilic syndrome. J Allergy Clin Immunol 126:45–49, 2010, Fig. 1.)

Table 400-3 Etiologic Agents Grouped by Age of the Patient	
AGE GROUP	FREQUENT PATHOGENS (IN ORDER OF FREQUENCY)
Neonates (<3 wk)	Group B streptococcus, <i>Escherichia coli</i> , other Gram-negative bacilli, <i>Streptococcus pneumoniae</i> , <i>Haemophilus influenzae</i> (type b,* nontypeable)
3 wk-3 mo	Respiratory syncytial virus, other respiratory viruses (rhinoviruses, parainfluenza viruses, influenza viruses, adenovirus), <i>S. pneumoniae</i> , <i>H. influenzae</i> (type b,* nontypeable); if patient is afebrile, consider <i>Chlamydia trachomatis</i>
4 mo-4 yr	Respiratory syncytial virus, other respiratory viruses (rhinoviruses, parainfluenza viruses, influenza viruses, adenovirus), <i>S. pneumoniae</i> , <i>H. influenzae</i> (type b,* nontypeable), <i>Mycoplasma pneumoniae</i> , group A streptococcus
≥5 yr	<i>M. pneumoniae</i> , <i>S. pneumoniae</i> , <i>Chlamydophila pneumoniae</i> , <i>H. influenzae</i> (type b,* nontypeable), influenza viruses, adenovirus, other respiratory viruses, <i>Legionella pneumophila</i>

**H. influenzae* type b is uncommon with routine *H. influenzae* type b immunization.

Table 399-11 Hypereosinophilic Syndrome Variants	
Myeloproliferative	Nonclonal or Clonal-F1P1L1/PDGFR α -positive chronic eosinophilic leukemia
Lymphocytic	Nonclonal T cells or Clonal T-cell expansion with T-cell activation
Overlap	Organ restricted
Familial	Family history of eosinophilia without known cause
Associated	Eosinophilia in chronic disease like inflammatory bowel disease or EGPA (Churg-Strauss syndrome)
Undefined	Asymptomatic or Cyclic angioedema with eosinophilia (Gleich syndrome) or Symptomatic without myeloproliferation or lymphocytic form

EGPA, eosinophilic granulomatosis with polyangiitis; PDGFR α , platelet-derived growth factor receptor- α .

Table 400-2 Causes of Infectious Pneumonia

BACTERIAL	
Common	
<i>Streptococcus pneumoniae</i>	Consolidation, empyema
Group B streptococci	Neonates
Group A streptococci	Empyema
<i>Mycoplasma pneumoniae*</i>	Adolescents; summer-fall epidemics
<i>Chlamydophila pneumoniae*</i>	Adolescents
<i>Chlamydia trachomatis</i>	Infants
Mixed anaerobes	Aspiration pneumonia
Gram-negative enterics	Nosocomial pneumonia
Uncommon	
<i>Haemophilus influenzae</i> type b	Unimmunized
<i>Staphylococcus aureus</i>	Pneumatoceles, empyema; infants
<i>Moraxella catarrhalis</i>	
<i>Neisseria meningitidis</i>	
<i>Francisella tularensis</i>	
<i>Nocardia</i> species	Animal, tick, fly contact; bioterrorism
<i>Chlamydophila psittaci*</i>	Immunosuppressed persons
<i>Yersinia pestis</i>	Bird contact (especially parakeets)
<i>Legionella</i> species*	Plague; rat contact; bioterrorism
<i>Coxiella burnetii*</i>	Exposure to contaminated water; nosocomial
	Q fever; animal (goat, sheep, cattle) exposure
VIRAL	
Common	
Respiratory syncytial virus	Bronchiolitis
Parainfluenza types 1-3	Croup
Influenzas A, B	High fever; winter months
Adenovirus	Can be severe; often occurs between January and April
Human metapneumovirus	Similar to respiratory syncytial virus
Uncommon	
Rhinovirus	Rhinorrhea
Enterovirus	Neonates
Herpes simplex	Neonates
Cytomegalovirus	Infants, immunosuppressed persons
Measles	Rash, coryza, conjunctivitis
Varicella	Adolescents or unimmunized
Hantavirus	Southwestern United States, rodents
Coronavirus (severe acute respiratory syndrome, Middle East respiratory syndrome [MERS])	Asia, Arabian peninsula
FUNGAL	
<i>Histoplasma capsulatum</i>	Ohio/Mississippi River valley; bird, bat contact
<i>Blastomyces dermatitidis</i>	Ohio/Mississippi River valley
<i>Coccidioides immitis</i>	Southwest United States
<i>Cryptococcus neoformans</i>	Bird contact
Aspergillus species	Immunosuppressed persons; nodular lung infection
Mucormycosis	Immunosuppressed persons
<i>Pneumocystis jiroveci</i>	Immunosuppressed, steroids
RICKETTSIAL	
<i>Rickettsia rickettsiae</i>	Tick bite
MYCOBACTERIAL	
<i>Mycobacterium tuberculosis</i>	Travel to endemic region; exposure to high-risk persons
<i>Mycobacterium avium</i> complex	Immunosuppressed persons
PARASITIC	
Various parasites (e.g., <i>Ascaris</i> , <i>Strongyloides</i> species)	Eosinophilic pneumonia

*Atypical pneumonia syndrome; may have extrapulmonary manifestations, low-grade fever, patchy diffuse infiltrates, poor response to β -lactam antibiotics, and negative sputum Gram stain.

From Kliegman RM, Greenbaum LA, Lye PS: Practical strategies in pediatric diagnosis & therapy, ed 2, Philadelphia, 2004, Elsevier, p. 29.

Table 399-12 The Pediatric Interstitial Lung Diseases

AGE-RELATED ILDS IN INFANCY AND EARLY CHILDHOOD
Diffuse developmental disorders
• Acinar dysplasia
• Congenital alveolar dysplasia
• Alveolar capillary dysplasia with misalignment of pulmonary veins (some due to <i>FOXF1</i> mutation)
Growth abnormalities reflecting deficient alveolarization
• Pulmonary hypoplasia
• Chronic neonatal lung disease
• Chromosomal disorders
• Congenital heart disease
Neuroendocrine cell hyperplasia of infancy
Pulmonary interstitial glycogenesis (infantile cellular interstitial pneumonia)
Surfactant dysfunction disorders (pulmonary alveolar proteinosis)
• Surfactant protein-B mutation
• Surfactant protein-C mutation
• ABCA3 mutation
• Granulocyte-macrophage colony-stimulating factor receptor (<i>CSF2RA</i>) mutation
ILD DISORDERS WITH KNOWN ASSOCIATIONS
Infectious/postinfectious processes
• Adenovirus viruses
• Influenza viruses
• <i>Chlamydia pneumoniae</i>
• <i>Mycoplasma pneumoniae</i>
Environmental agents
• Hypersensitivity pneumonitis
• Toxic inhalation
Aspiration syndromes
PULMONARY DISEASES ASSOCIATED WITH PRIMARY AND SECONDARY IMMUNE DEFICIENCY
Opportunistic infections
Granulomatous lymphocytic ILD associated with common variable immunodeficiency syndrome
Lymphoid intestinal pneumonia (HIV infection)
Therapeutic interventions: chemotherapy, radiation, transplantation, and rejection
IDIOPATHIC ILDS
Usual interstitial pneumonitis
Desquamative interstitial pneumonitis
Lymphocytic interstitial pneumonitis and related disorders
Nonspecific interstitial pneumonitis (cellular/fibrotic)
Eosinophilic pneumonia
Bronchiolitis obliterans syndrome
Pulmonary hemosiderosis and acute idiopathic pulmonary hemorrhage of infancy
Pulmonary alveolar proteinosis
Pulmonary vascular disorders
Pulmonary lymphatic disorders
Pulmonary microlithiasis
Persistent tachypnea of infancy
Brain-thyroid-lung syndrome
SYSTEMIC DISORDERS WITH PULMONARY MANIFESTATIONS
Goodpasture disease
Gaucher disease and other storage diseases
Malignant infiltrates
Hemophagocytic lymphohistiocytosis
Langerhans cell histiocytosis
Sarcoidosis
Systemic sclerosis
Polymyositis/dermatomyositis
Systemic lupus erythematosus
Rheumatoid arthritis
Lymphangioleiomyomatosis
Pulmonary hemangiomatosis
Neurocutaneous syndromes
Hermansky-Pudlak syndrome

Modified from Deutsch GH, Young LR, Deterding RR, et al; ChILD Research Co-operative: Diffuse lung disease in young children: application of a novel classification scheme, Am J Respir Crit Care Med 176:1120-1128, 2007.

Table 400-4 Differential Diagnosis of Recurrent Pneumonia

HEREDITARY DISORDERS	
Cystic fibrosis	
Sickle cell disease	
DISORDERS OF IMMUNITY	
HIV/AIDS	
Bruton agammaglobulinemia	
Selective immunoglobulin G subclass deficiencies	
Common variable immunodeficiency syndrome	
Severe combined immunodeficiency syndrome	
Chronic granulomatous disease	
Hyperimmunoglobulin E syndromes	
Leukocyte adhesion defect	
DISORDERS OF CLIA	
Immotive cilia syndrome	
Kartagener syndrome	
ANATOMIC DISORDERS	
Pulmonary sequestration	
Lobar emphysema	
Gastroesophageal reflux	
Foreign body	
Tracheoesophageal fistula (H type)	
Bronchiectasis	
Aspiration (oropharyngeal incoordination)	
Aberrant bronchus	

Table 400-5 Factors Suggesting Need for Hospitalization of Children with Pneumonia

Age <6 mo
Sickle cell anemia with acute chest syndrome
Multiple lobe involvement
Immunocompromised state
Toxic appearance
Moderate to severe respiratory distress
Requirement for supplemental oxygen
Complicated pneumonia*
Dehydration
Vomiting or inability to tolerate oral fluids or medications
No response to appropriate oral antibiotic therapy
Social factors (e.g., inability of caregivers to administer medications at home or follow-up appropriately)

*Pleural effusion, empyema, abscess, bronchopleural fistula, necrotizing pneumonia, acute respiratory distress syndrome, extrapulmonary infection (meningitis, arthritis, pericarditis, osteomyelitis, endocarditis), hemolytic uremic syndrome, sepsis.

Table 400-6 Differentiation of Pleural Fluid

	TRANSUDATE	EMPYEMA
Appearance	Clear	Cloudy or purulent
Cell count (per mm ³)	<1,000	Often >50,000 (cell count has limited predictive value)
Cell type	Lymphocytes, monocytes	Polymorphonuclear leukocytes (neutrophils)
Lactate dehydrogenase	<200 U/L	More than two-thirds upper limit of normal for serum lactate dehydrogenase (LDH)
Pleural fluid:serum LDH ratio	<0.6	>0.6
Protein >3 g	Unusual	Common
Pleural fluid:serum protein ratio	<0.5	>0.5
Glucose*	Normal	Low (<40 mg/dL)
pH*	Normal (7.40-7.60)	<7.10
Gram stain	Negative	Occasionally positive (less than one-third of cases)
Cholesterol		>55 mg/dL
Pleural cholesterol:serum cholesterol ratio	<0.3	>0.3

*Low glucose or pH may be seen in malignant effusion, tuberculosis, esophageal rupture, pancreatitis (positive pleural amylase), and rheumatologic diseases (e.g., systemic lupus erythematosus).

Table 401-1 Conditions That Predispose to Bronchiectasis in Children

PROXIMAL AIRWAY NARROWING
Airway wall compression (i.e., vascular ring, adenopathy impinging on airways)
Airway intraluminal obstruction (e.g., inhaled foreign body, granulation tissue)
Airway stenosis and malacia
AIRWAY INJURY
Bronchiolitis obliterans (e.g., postviral, after lung transplantation)
Recurrent pneumonitis or pneumonia (e.g., pneumococcal pneumonia, aspiration pneumonia)
ALTERED PULMONARY HOST DEFENSES
Cystic fibrosis
Ciliary dyskinesia
Impaired cough (e.g., neuromuscular weakness conditions)
ALTERED IMMUNE STATES
Primary abnormalities (e.g., hypogammaglobulinemia)
Secondary abnormalities (e.g., HIV infection, immunosuppressive agents)
OTHER
Allergic bronchopulmonary aspergillosis
Plastic bronchitis

Table 403-1 Complications of Cystic Fibrosis**RESPIRATORY**

Bronchiectasis, bronchitis, bronchiolitis, pneumonia
Atelectasis
Hemoptysis
Pneumothorax
Nasal polyps
Sinusitis
Reactive airway disease
Cor pulmonale
Respiratory failure
Mucoid impaction of the bronchi
Allergic bronchopulmonary aspergillosis

GASTROINTESTINAL

Meconium ileus, meconium plug (neonate)
Meconium peritonitis (neonate)
Distal intestinal obstruction syndrome (non-neonatal obstruction)
Rectal prolapse
Intussusception
Volvulus
Fibrosing colonopathy (strictures)
Appendicitis
Intestinal atresia
Pancreatitis
Biliary cirrhosis (portal hypertension: esophageal varices, hypersplenism)
Neonatal obstructive jaundice
Hepatic steatosis
Gastroesophageal reflux
Cholelithiasis
Inguinal hernia
Growth failure (malabsorption)
Vitamin deficiency states (vitamins A, K, E, D)
Insulin deficiency, symptomatic hyperglycemia, diabetes
Malignancy (rare)

OTHER

Infertility
Delayed puberty
Edema-hypoproteinemia
Dehydration-heat exhaustion
Hypertrophic osteoarthropathy-arthritis
Clubbing
Amyloidosis
Diabetes mellitus
Aquagenic palmoplantar keratoderma (skin wrinkling)

Table 403-4 Conditions Associated with False-Positive and False-Negative Sweat Test Results**WITH FALSE-POSITIVE RESULTS**

Eczema (atopic dermatitis)
Ectodermal dysplasia
Malnutrition/failure to thrive/deprivation
Anorexia nervosa
Congenital adrenal hyperplasia
Adrenal insufficiency
Glucose-6-phosphatase deficiency
Mauriac syndrome
Fucosidosis
Familial hypoparathyroidism
Hypothyroidism
Nephrogenic diabetes insipidus
Pseudohypoaldosteronism
Klinefelter syndrome
Familial cholestasis syndrome
Autonomic dysfunction
Prostaglandin E infusions
Munchausen syndrome by proxy

WITH FALSE-NEGATIVE RESULTS

Dilution
Malnutrition
Edema
Insufficient sweat quantity
Hyponatremia
Cystic fibrosis transmembrane conductance regulator mutations with preserved sweat duct function

Table 403-3 Diagnostic Criteria for Cystic Fibrosis (CF)

Presence of typical clinical features (respiratory, gastrointestinal, or genitourinary)
or
A history of CF in a sibling
or
A positive newborn screening test
plus
Laboratory evidence for CFTR (CF transmembrane regulator) dysfunction:
Two elevated sweat chloride concentrations obtained on separate days
or
Identification of two CF mutations
or
An abnormal nasal potential difference measurement

Table 403-7 Antimicrobial Agents for Cystic Fibrosis Lung Infection

ROUTE	ORGANISMS	AGENTS	DOSAGE (mg/kg/24 hr)	NO. DOSES/24 hr
Oral	<i>Staphylococcus aureus</i>	Dicloxacillin	25-50	4
		Linezolid	20	2
		Cephalexin	50	4
		Clindamycin	10-30	3-4
	<i>Haemophilus influenzae</i> <i>Pseudomonas aeruginosa</i> <i>Burkholderia cepacia</i>	Amoxicillin-clavulanate	25-45	2-3
		Amoxicillin	50-100	2-3
		Ciprofloxacin	20-30	2-3
		Trimethoprim-sulfamethoxazole	8-10*	2-4
	Empirical	Azithromycin	10, day 1; 5, days 2-5	1
		Erythromycin	30-50	3-4
Intravenous	<i>S. aureus</i>	Nafcillin	100-200	4-6
		Vancomycin	40	3-4
	<i>P. aeruginosa</i>	Tobramycin	8-12	1-3
		Amikacin	15-30	2-3
		Ticarcillin	400	4
		Piperacillin	300-400	4
		Ticarcillin-clavulanate	400†	4
		Piperacillin-tazobactam	240-400‡	3
	<i>B. cepacia</i>	Meropenem	60-120	3
		Imipenem-cilastatin	45-100	3-4
		Ceftazidime	150	3
		Aztreonam	150-200	4
		Chloramphenicol	50-100	4
		Meropenem	60-120	3
Aerosol		Tobramycin (inhaled)	300§	2
		Aztreonam (inhaled)	75	3

*Quantity of trimethoprim.

†Quantity of ticarcillin.

‡Quantity of piperacillin.

§In mg per dose.

Table 403-5 Symptoms and Signs Associated with Exacerbation of Pulmonary Infection in Patients with Cystic Fibrosis

SYMPTOMS	
Increased frequency and duration of cough	
Increased sputum production	
Change in appearance of sputum	
Increased shortness of breath	
Decreased exercise tolerance	
Decreased appetite	
Feeling of increased congestion in the chest	
SIGNS	
Increased respiratory rate	
Use of accessory muscles for breathing	
Intercostal retractions	
Change in results of auscultatory examination of chest	
Decline in measures of pulmonary function consistent with the presence of obstructive airway disease	
Fever and leukocytosis	
Weight loss	
New infiltrate on chest radiograph	

Table 404-1 Clinical Manifestations of Primary Ciliary Dyskinesia

RESPIRATORY TRACT	GENITOURINARY TRACT
Lung	Male and female infertility
Neonatal respiratory distress	
Chronic cough	
Recurrent pneumonia	
Bronchiectasis	
Middle Ear	
Chronic otitis media	
Conductive hearing loss	
Paranasal Sinuses	
Neonatal rhinitis	
Chronic mucopurulent rhinitis	
Chronic pansinusitis	
Nasal polypsis	
LEFT-RIGHT ORIENTATION DEFECTS	
Situs inversus	
Heterotaxy	
Congenital heart disease	
CENTRAL NERVOUS SYSTEM	
Hydrocephalus	
Retinitis pigmentosa	

Table 407-2 Etiology of Pulmonary Hemorrhage (Hemoptysis)*

FOCAL HEMORRHAGE		
Bronchitis and bronchiectasis (especially cystic fibrosis-related)		
Infection (acute or chronic), pneumonia, abscess		
Tuberculosis		
Trauma		
Pulmonary arteriovenous malformation		
Foreign body (chronic)		
Neoplasm including hemangioma		
Pulmonary embolus with or without infarction		
Bronchogenic cysts		
DIFFUSE HEMORRHAGE		
Idiopathic of infancy		
Congenital heart disease (including pulmonary hypertension, venoocclusive disease, congestive heart failure)		
Prematurity		
Cow's milk hyperreactivity (Heiner syndrome)		
Goodpasture syndrome		
Collagen vascular diseases (systemic lupus erythematosus, rheumatoid arthritis)		
Henoch-Schönlein purpura and vasculitic disorders		
Granulomatous disease (granulomatosis with polyangiitis)		
Celiac disease		
Coagulopathy (congenital or acquired)		
Malignancy		
Immunodeficiency		
Exogenous toxins		
Hyperammonemia		
Pulmonary hypertension		
Pulmonary alveolar proteinosis		
Idiopathic pulmonary hemosiderosis		
Tuberous sclerosis		
Lymphangiomyomatosis or lymphangioleiomyomatosis		
Physical injury or abuse		
Catamenial		

Table 403-6 Complications of Therapy for Cystic Fibrosis*

COMPLICATION	AGENT
Gastrointestinal bleeding	Ibuprofen
Hyperglycemia	Corticosteroids (systemic)
Growth retardation	Corticosteroids (systemic, inhaled)
Renal dysfunction: Tubular Interstitial nephritis	Aminoglycosides Semisynthetic penicillins, nonsteroidal antiinflammatory drugs
Hearing loss, vestibular dysfunction	Aminoglycosides
Peripheral neuropathy or optic atrophy	Chloramphenicol (prolonged course)
Hypomagnesemia	Aminoglycosides
Hyperuricemia, colonic stricture	Pancreatic extracts (very large doses)
Goiter	Iodine-containing expectorants
Gynecomastia	Spironolactone
Enamel hypoplasia or staining	Tetracyclines (used in 1st 8 yr of life)

*Common hypersensitivity reactions to drugs are not included.

Table 404-2 Electron Microscopic Findings in Primary Ciliary Dyskinesia vs Acquired Cilia Abnormality

PCD	ACQUIRED DEFECTS	
EM ultrastructure	Dynein arm deficiency Outer arms Inner arms Both Translocation of central tubules Few or absent cilia (generalized)	Compound cilia Added peripheral tubules Deleted peripheral tubules Added central pairs Translocation of central tubules Few or absent cilia (patchy)
Beat frequency	Hyperkinetic, slow or absent	May be normal or reduced
Wave form	Abnormal	May be normal or abnormal

EM, electron microscopy; PCD, primary ciliary dyskinesia.

From Stillwell PC, Wartchow EP, Sagel SD. Primary ciliary dyskinesia in children

Table 405-1 Comparison of Surfactant Deficiency Syndromes

	SP-B DEFICIENCY	SP-C DISEASE	ABCA3 DEFICIENCY	TTF-1 DEFICIENCY
Gene name	<i>SFTPB</i>	<i>SFTPC</i>	<i>ABCA3</i>	<i>NKX2-1</i>
Age of onset	Birth	Birth–adulthood	Birth–childhood	Birth–childhood
Inheritance	Recessive	Dominant/sporadic	Recessive	Sporadic/dominant
Mechanism	Loss of function	Gain of toxic function or dominant negative	Loss of function	Loss of function ?Gain of function
Natural history	Lethal	Variable	Generally lethal, may be chronic	Variable
Diagnosis:				
Biochemical (tracheal aspirate)	Absence of SP-B and presence of proSP-C	None	None	None
Genetic (DNA)	Sequence <i>SFTPB</i>	Sequence <i>SFTPC</i>	Sequence <i>ABCA3</i>	Sequence <i>NKX2-1</i> ; deletion analysis
Ultrastructural (lung biopsy–electron microscopy)	Disorganized lamellar bodies	Not specific; may have dense aggregates	Small dense lamellar bodies with eccentrically placed dense cores	Variable
Treatment	Lung transplantation or compassionate care	Supportive care, lung transplantation if progressing	Consider lung transplantation	Supportive care; treat coexisting conditions (hypothyroidism)

SP, surfactant protein

Table 406-1 Diffuse Alveolar Hemorrhage Syndromes

CLASSIFICATION	SYNDROME
Disorders with pulmonary capillaritis	Idiopathic pulmonary capillaritis Granulomatosis with polyangiitis (Wegener granulomatosis) Microscopic polyangiitis Systemic lupus erythematosus Goodpasture syndrome Antiphospholipid antibody syndrome Henoch-Schönlein purpura Immunoglobulin A nephropathy Behçet syndrome Cryoglobulinemia Drug-induced capillaritis (hypersensitivity) Idiopathic pulmonary-renal syndrome Eosinophilic granulomatosis angiitis (Churg-Strauss syndrome)
Disorders without pulmonary capillaritis: Noncardiovascular causes	Idiopathic pulmonary hemosiderosis Heiner syndrome Acute idiopathic pulmonary hemorrhage of infancy Bone marrow transplantation Immunodeficiency Coagulation disorders Hemolytic uremic syndromes Celiac disease (Lane-Hamilton syndrome) Infanticide (child abuse) Infection (HIV, cryptococcosis, Legionnaires disease) Mitral stenosis
Cardiovascular causes	Pulmonary venoocclusive disease Arteriovenous malformations Pulmonary lymphangioleiomyomatosis Pulmonary hypertension Pulmonary capillary hemangiomatosis Chronic heart failure Vascular thrombosis with infarction

Table 407-1 Risk Factors for Pulmonary Embolism

ENVIRONMENTAL
Long-haul air travel
Obesity
Cigarette smoking
Hypertension
Immobility
WOMEN'S HEALTH
Oral contraceptives, including progesterone-only and, especially, third-generation pills
Pregnancy
Hormone replacement therapy
Septic abortion
MEDICAL ILLNESS
Previous pulmonary embolism or deep venous thrombosis
Cancer
Heart failure
Chronic obstructive pulmonary disease
Diabetes mellitus
Inflammatory bowel disease
Antipsychotic drug use
Long-term indwelling central venous catheter
Permanent pacemaker
Internal cardiac defibrillator
Stroke with limb paresis
Spinal cord injury
Nursing home confinement or current or repeated hospital admission
SURGICAL
Trauma
Orthopedic surgery
General surgery
Neurosurgery, especially craniotomy for brain tumor
THROMBOPHILIA
Factor V Leiden mutation
Prothrombin gene mutation
Hyperhomocysteinemias (including mutation in methylenetetrahydrofolate reductase)
Antiphospholipid antibody syndrome
Deficiency of antithrombin III, protein C, or protein S
High concentrations of factor VIII or XI
Increased lipoprotein (a)
NONTHROMBOTIC
Air
Foreign particles (e.g., hair, talc, as a consequence of intravenous drug misuse)
Amniotic fluid
Bone fragments, bone marrow
Fat
Tumors (Wilms tumor)

Table 408-1 Anatomic Causes of Atelectasis

CAUSE	CLINICAL EXAMPLES
External compression on the pulmonary parenchyma	Pleural effusion, pneumothorax, intrathoracic tumors, diaphragmatic hernia
Endobronchial obstruction completely obstructing the ingress of air	Enlarged lymph node, tumor, cardiac enlargement, foreign body, mucoid plug, broncholithiasis
Intraluminal obstruction of a bronchus	Foreign body, asthma, granulomatous tissue, tumor, secretions including mucous plugs, bronchiectasis, pulmonary abscess, chronic bronchitis, acute laryngotracheobronchitis, plastic bronchitis
Intrabronchiolar obstruction	Bronchiolitis, interstitial pneumonitis, asthma
Respiratory compromise or paralysis	Neuromuscular abnormalities, osseous deformities, overly restrictive casts and surgical dressings, defective movement of the diaphragm, or restriction of respiratory effort

Table 408-2 Benefit of Airway Clearance Therapies in Pediatric Conditions

CLEAR AND PROVEN BENEFIT
Cystic fibrosis
PROBABLE BENEFIT
Neuromuscular disease
Cerebral palsy
Atelectasis in children undergoing mechanical ventilation
POSSIBLE BENEFIT
Prevention of postextubation atelectasis in neonates
MINIMAL TO NO BENEFIT
Acute asthma
Bronchiolitis
Hyaline membrane disease
Respiratory failure without atelectasis
Prevention of atelectasis immediately following surgery

Table 411-1 Causes of Pneumothorax in Children

SPONTANEOUS
Primary idiopathic—usually resulting from ruptured subpleural blebs
Secondary blebs
Congenital lung disease:
Congenital cystic adenomatoid malformation
Bronchogenic cysts
Pulmonary hypoplasia*
Birt-Hogg-Dube syndrome
Conditions associated with increased intrathoracic pressure:
Asthma
Bronchiolitis
Air-block syndrome in neonates
Cystic fibrosis
Airway foreign body
Smoking (cigarettes, marijuana, crack cocaine)
Infection:
Pneumatocele
Lung abscess
Echinococcosis
Bronchopleural fistula
Diffuse lung disease:
Langerhans cell histiocytosis
Tuberous sclerosis
Marfan syndrome
Ehlers-Danlos syndrome
Metastatic neoplasm—usually osteosarcoma (rare)
Pulmonary blastoma

TRAUMATIC

Noniatrogenic
Penetrating trauma
Blunt trauma
High-flow therapy
Loud music (air pressure)
Iatrogenic
Thoracotomy
Thoracoscopy, thoracentesis
Tracheostomy
Tube or needle puncture
Mechanical ventilation

*Associated with renal agenesis, diaphragmatic hernia, amniotic fluid leaks.

Table 416-1 Forms of Bronchopulmonary Dysplasia

FEATURES OF ALL BPD	ADDITIONAL FEATURES OF MILD BPD	ADDITIONAL FEATURES OF MODERATE BPD	ADDITIONAL FEATURES OF SEVERE BPD
<32 wk PMA Oxygen requirement 1st 28 days	Breathing room air at 36 wk PMA	<30% Supplemental oxygen at 36 wk PMA	>30% Supplemental oxygen at 36 wk PMA and mechanical support, CPAP, or ventilation
>32 wk PMA Oxygen requirement 1st 28 days of life	Breathing room air at 56 days of life	<30% Supplemental oxygen at 56 days of life	>30% Supplemental oxygen at 56 days of life and mechanical support, CPAP, or ventilation

BPD, bronchopulmonary dysplasia; CPAP, continuous positive airway pressure; PMA, postmenstrual age.

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Table 418-2 Clinical Classification of Spinal Muscular Atrophy

SMA TYPE	AGE OF ONSET	HIGHEST FUNCTION	NATURAL AGE OF DEATH
Type 1 (severe)	0-6 mo	Never sits	<2 yr
Type 2 (intermediate)	7-18 mo	Never stands	<2 yr
Type 3 (mild)	Older than 18 mo	Stands and walks	Adult
Type 4 (adult)	Second or third decade	Walks during adult years	Adult

From Wang CH, Finkel RS, Bertini ES, et al: Consensus statement for standard of care in spinal muscular atrophy, *J Child Neurol* 22:1027–1049, 2007.

Table 419-1 Respiratory Signs and Symptoms Originating from Outside the Respiratory Tract

SIGN OR SYMPTOM	NONRESPIRATORY CAUSE(S)	PATHOPHYSIOLOGY	CLUES TO DIAGNOSIS
Chest pain	Cardiac disease	Inflammation (pericarditis), ischemia (anomalous coronary artery, vascular disease)	Precordial pain, friction rub on examination; exertional pain, radiation to arm or neck
Chest pain	Gastroesophageal reflux disease	Esophageal inflammation and/or spasm	Heartburn, abdominal pain
Cyanosis	Congenital heart disease Methemoglobinemia	Right-to-left shunt Increased levels of methemoglobin interfere with delivery of oxygen to tissues	Neonatal onset, lack of response to oxygen Drug or toxin exposure, lack of response to oxygen
Dyspnea	Toxin exposure, drug side effect, or overdose Anxiety, panic disorder	Variable, but often metabolic acidosis Increased respiratory drive and increased perception of respiratory efforts	Drug or toxin exposure confirmed by history or toxicology screen, normal oxygen saturation measured by pulse oximetry Occurs during stressful situation, other symptoms of anxiety or depression

Continued

Table 419-1 Respiratory Signs and Symptoms Originating from Outside the Respiratory Tract—cont'd

SIGN OR SYMPTOM	NONRESPIRATORY CAUSE(S)	PATHOPHYSIOLOGY	CLUES TO DIAGNOSIS
Exercise intolerance	Anemia	Inadequate oxygen delivery to tissues	Pallor, tachycardia, history of bleeding, history of inadequate diet
Exercise intolerance	Deconditioning	Self-explanatory	History of inactivity, obesity
Hemoptysis	Nasal bleeding	Posterior flow of bleeding causes appearance of pulmonary origin	History and physical findings suggest nasal source; normal chest examination, and chest radiography
	Upper gastrointestinal tract bleeding	Hematemesis mimics hemoptysis	History and physical examination suggest gastrointestinal source, normal chest examination and chest radiography
Wheezing, cough, dyspnea	Congenital or acquired cardiac disease	Pulmonary overcirculation (atrioseptal defect, ventriculoseptal defect, patent ductus arteriosus), left ventricular dysfunction	Murmur Refractory to bronchodilators Radiographic changes (prominent pulmonary vasculature, pulmonary edema)
Wheezing, cough	Gastroesophageal reflux disease	Laryngeal and bronchial response to stomach contents Vagally mediated bronchoconstriction	Emesis, pain, heartburn Refractory to bronchodilators

Table 419-2 Disorders with Frequent Respiratory Tract Complications

UNDERLYING DISORDER(S)	RESPIRATORY COMPLICATIONS	DIAGNOSTIC TESTS
Autoimmune disorders	Pulmonary vascular disease, restrictive lung disease, pleural effusion (especially systemic lupus erythematosus), upper airway disease (Wegener granulomatosis)	Spirometry, lung volume determination, oximetry, diffusing capacity of the lung for carbon monoxide, chest radiography, upper airway endoscopy, and/or CT
Central nervous system disease (static or progressive)	Aspiration of oral or gastric contents	Chest radiography, videofluoroscopic swallowing study, esophageal pH probe, fiberoptic bronchoscopy
Immunodeficiency	Infection, bronchiectasis	Chest radiography, fiberoptic bronchoscopy, chest CT
Liver disease	Pleural effusion, hepatopulmonary syndrome	Chest radiography, assessment of orthodeoxia
Malignancy and its therapies	Infiltration, metastasis, malignant or infectious effusion, parenchymal infection, graft-versus-host disease (bone marrow transplant)	Chest radiography, chest CT, fiberoptic bronchoscopy, lung biopsy
Neuromuscular disease	Hypoventilation, atelectasis, pneumonia	Spirometry, lung volume determination, respiratory muscle force measurements
Obesity	Restrictive lung disease, obstructive sleep apnea syndrome, asthma	Spirometry, lung volume determination, nocturnal polysomnography

Table 422-1 Differential Diagnosis of Chest Pain in Pediatric Patients

MUSCULOSKELETAL (COMMON)
Trauma (accidental, abuse)
Exercise, overuse injury (strain, bursitis)
Costochondritis (Tietze syndrome)
Herpes zoster (cutaneous)
Pleurodynia
Fibrosis
Slipping rib
Precordial catch
Sickle cell anemia vasoocclusive crisis
Osteomyelitis (rare)
Primary or metastatic tumor (rare)
PULMONARY (COMMON)
Pneumonia
Pleurisy
Asthma
Chronic cough
Pneumothorax
Infarction (sickle cell anemia)
Foreign body
Embolism (rare)
Pulmonary hypertension (rare)
Tumor (rare)
Bronchiectasis
GASTROINTESTINAL (LESS COMMON)
Esophagitis (gastroesophageal reflux, infectious, pill)
Esophageal foreign body
Esophageal spasm
Cholecystitis
Subdiaphragmatic abscess
Perihepatitis (Fitz-Hugh-Curtis syndrome)
Peptic ulcer disease
Pancreatitis
CARDIAC (LESS COMMON)
Pericarditis
Postpericardiectomy syndrome
Endocarditis
Cardiomyopathy
Mitral valve prolapse
Aortic or subaortic stenosis
Arrhythmias
Marfan syndrome (dissecting aortic aneurysm)
Kawasaki disease
Cocaine, sympathomimetic ingestion
Angina (familial hypercholesterolemia, anomalous coronary artery)
IDIOPATHIC (COMMON)
Anxiety, hyperventilation
Panic disorder
OTHER (LESS COMMON)
Spinal cord or nerve root compression
Breast-related pathologic condition (mastalgia)
Castleman disease (lymph node neoplasm)

Table 418-1 Proposed Guidelines for Initial Evaluation and Follow-Up of Patients with Neuromuscular Disease

INITIAL EVALUATION	BASIC INTERVENTION/ TRAINING
History/physical/anthropometrics	Nutritional consultation and guidance
Lung function and maximal respiratory pressures (PFTs)	Regular chest physiotherapy
Arterial blood gases	Use of percussive devices
Polysomnography*	Respiratory muscle training
Exercise testing (in selected cases)	Annual influenza vaccine
If vital capacity >60% predicted or maximal respiratory pressures >60 cm H ₂ O	Evaluate PFTs every 6 mo CXR and polysomnography every year
If vital capacity <60% predicted or maximal respiratory pressures <60 cm H ₂ O	Evaluate PFTs every 3-4 mo CXR, MIP/MEP every 6 mo Polysomnography every 6 mo to year

*Please note that if polysomnography is not readily available, multichannel recordings including oronasal airflow, nocturnal oximetry, and end-tidal carbon dioxide levels may provide an adequate alternative.

CXR, chest x-ray; MEP, maximal expiratory pressure; MIP, maximal inspiratory pressure; PFT, pulmonary function test.

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Table 422-2

Congenital Malformation Syndromes Associated with Congenital Heart Disease

SYNDROME	FEATURES
CHROMOSOMAL DISORDERS	
Trisomy 21 (Down syndrome)	Endocardial cushion defect, VSD, ASD
Trisomy 21p (cat eye syndrome)	Miscellaneous, total anomalous pulmonary venous return
Trisomy 18	VSD, ASD, PDA, coarctation of aorta, bicuspid aortic or pulmonary valve
Trisomy 13	VSD, ASD, PDA, coarctation of aorta, bicuspid aortic or pulmonary valve
Trisomy 9	Miscellaneous
XXXXY	PDA, ASD
Penta X	PDA, VSD
Triploidy	VSD, ASD, PDA
XO (Turner syndrome)	Bicuspid aortic valve, coarctation of aorta
Fragile X	Mitral valve prolapse, aortic root dilatation
Duplication 3q2	Miscellaneous
Deletion 4p	VSD, PDA, aortic stenosis
Deletion 9p	Miscellaneous
Deletion 5p (cri du chat syndrome)	VSD, PDA, ASD
Deletion 10q	VSD, TOF, conotruncal lesions*
Deletion 13q	VSD
Deletion 18q	VSD
SYNDROME COMPLEXES	
CHARGE association (coloboma, heart, atresia choanae, retardation, genital, and ear anomalies)	VSD, ASD, PDA, TOF, endocardial cushion defect
DiGeorge sequence, CATCH 22 (cardiac defects, abnormal facies, thymic aplasia, cleft palate, and hypocalcemia)	Aortic arch anomalies, conotruncal anomalies
Alagille syndrome (arteriohepatic dysplasia)	Peripheral pulmonic stenosis, PS, TOF
VATER association (vertebral, anal, tracheoesophageal, radial, and renal anomalies)	VSD, TOF, ASD, PDA
FAVS (facioauriculovertebral spectrum)	TOF, VSD
CHILD (congenital hemidysplasia with ichthyosiform erythroderma, limb defects)	Miscellaneous
Mulibrey nanism (muscle, liver, brain, eye)	Pericardial thickening, constrictive pericarditis
Asplenia syndrome	Complex cyanotic heart lesions with decreased pulmonary blood flow, transposition of great arteries, anomalous pulmonary venous return, dextrocardia, single ventricle, single atrioventricular valve
Polysplenia syndrome	Acyanotic lesions with increased pulmonary blood flow, azygous continuation of inferior vena cava, partial anomalous pulmonary venous return, dextrocardia, single ventricle, common atrioventricular valve
PHACE syndrome (posterior brain fossa anomalies, facial hemangiomas, arterial anomalies, cardiac anomalies and aortic coarctation, eye anomalies)	VSD, PDA, coarctation of aorta, arterial aneurysms
TERATOGENIC AGENTS	
Congenital rubella	PDA, peripheral pulmonic stenosis
Fetal hydantoin syndrome	VSD, ASD, coarctation of aorta, PDA
Fetal alcohol syndrome	ASD, VSD
Fetal valproate effects	Coarctation of aorta, hypoplastic left side of heart, aortic stenosis, pulmonary atresia, VSD
Maternal phenylketonuria	VSD, ASD, PDA, coarctation of aorta
Retinoic acid embryopathy	Conotruncal anomalies
OTHERS	
Apert syndrome	VSD
Autosomal dominant polycystic kidney disease	Mitral valve prolapse
Carpenter syndrome	PDA
Conradi syndrome	VSD, PDA
Crouzon disease	PDA, coarctation of aorta
Cutis laxa	Pulmonary hypertension, pulmonic stenosis
de Lange syndrome	VSD
Ellis-van Creveld syndrome	Single atrium, VSD
Holt-Oram syndrome	ASD, VSD, 1st-degree heart block
Infant of diabetic mother	Hypertrophic cardiomyopathy, VSD, conotruncal anomalies
Kartagener syndrome	Dextrocardia
Meckel-Gruber syndrome	ASD, VSD
Noonan syndrome	Pulmonic stenosis, ASD, cardiomyopathy
Pallister-Hall syndrome	Endocardial cushion defect
Rubinstein-Taybi syndrome	VSD
Scimitar syndrome	Hypoplasia of right lung, anomalous pulmonary venous return to inferior vena cava
Smith-Lemli-Opitz syndrome	VSD, PDA
TAR syndrome (thrombocytopenia and absent radius)	ASD, TOF
Treacher Collins syndrome	VSD, ASD, PDA
Williams syndrome	Supravalvular aortic stenosis, peripheral pulmonic stenosis

ASD, atrial septal defect; AV, aortic valve; PDA, patent ductus arteriosus; PS, pulmonary stenosis; TOF, tetralogy of Fallot; VSD, ventricular septal defect.

*Conotruncal includes TOF, pulmonary atresia, truncus arteriosus, and transposition of great arteries.

Table 422-3 Cardiac Manifestations of Systemic Diseases

SYSTEMIC DISEASE	CARDIAC COMPLICATIONS
INFLAMMATORY DISORDERS	
Sepsis	Hypotension, myocardial dysfunction, pericardial effusion, pulmonary hypertension
Juvenile idiopathic arthritis	Pericarditis, rarely myocarditis
Systemic lupus erythematosus	Pericarditis, Libman-Sacks endocarditis, coronary arteritis, coronary atherosclerosis (with steroids), congenital heart block
Scleroderma	Pulmonary hypertension, myocardial fibrosis, cardiomyopathy
Dermatomyositis	Cardiomyopathy, arrhythmias, heart block
Kawasaki disease	Coronary artery aneurysm and thrombosis, myocardial infarction, myocarditis, valvular insufficiency
Sarcoidosis	Granuloma, fibrosis, amyloidosis, biventricular hypertrophy, arrhythmias
Lyme disease	Arrhythmias, myocarditis
Löffler hypereosinophilic syndrome	Endomyocardial disease
INBORN ERRORS OF METABOLISM	
Refsum disease	Arrhythmia, sudden death
Hunter or Hurler syndrome	Valvular insufficiency, heart failure, hypertension
Fabry disease	Mitral insufficiency, coronary artery disease with myocardial infarction
Glycogen storage disease IIa (Pompe disease)	Short P-R interval, cardiomegaly, heart failure, arrhythmias
Carnitine deficiency	Heart failure, cardiomyopathy
Gaucher disease	Pericarditis
Homocystinuria	Coronary thrombosis
Alkaptonuria	Atherosclerosis, valvular disease
Morquio-Ullrich syndrome	Aortic incompetence
Scheie syndrome	Aortic incompetence
CONNECTIVE TISSUE DISORDERS	
Arterial calcification of infancy	Calcinosis of coronary arteries, aorta
Marfan syndrome	Aortic and mitral insufficiency, dissecting aortic aneurysm, mitral valve prolapse
Congenital contractual arachnodactyly	Mitral insufficiency or prolapse
Ehlers-Danlos syndrome	Mitral valve prolapse, dilated aortic root
Osteogenesis imperfecta	Aortic incompetence
Pseudoxanthoma elasticum	Peripheral arterial disease
NEUROMUSCULAR DISORDERS	
Friedreich ataxia	Cardiomyopathy
Duchenne dystrophy	Cardiomyopathy, heart failure
Tuberous sclerosis	Cardiac rhabdomyoma
Familial deafness	Occasionally arrhythmia, sudden death
Neurofibromatosis	Pulmonic stenosis, pheochromocytoma, coarctation of aorta
Riley-Day syndrome	Episodic hypertension, postural hypotension
Von Hippel-Lindau disease	Hemangiomas, pheochromocytomas
ENDOCRINE-METABOLIC DISORDERS	
Graves disease	Tachycardia, arrhythmias, heart failure
Hypothyroidism	Bradycardia, pericardial effusion, cardiomyopathy, low-voltage electrocardiogram
Pheochromocytoma	Hypertension, myocardial ischemia, myocardial fibrosis, cardiomyopathy
Carcinoid	Right-sided endocardial fibrosis
HEMATOLOGIC DISORDERS	
Sickle cell anemia	High-output heart failure, cardiomyopathy, pulmonary hypertension
Thalassemia major	High-output heart failure, hemochromatosis
Hemochromatosis (1° or 2°)	Cardiomyopathy
OTHERS	
Appetite suppressants (fenfluramine and dexfenfluramine)	Cardiac valvulopathy, pulmonary hypertension
Cockayne syndrome	Atherosclerosis
Familial dwarfism and nevi	Cardiomyopathy
Jervell and Lange-Nielsen syndrome	Prolonged QT interval, sudden death
Kearns-Sayre syndrome	Heart block
LEOPARD syndrome (lentiginosis)	Pulmonic stenosis, prolonged Q-T interval
Progeria	Accelerated atherosclerosis
Osler-Weber-Rendu disease	Arteriovenous fistula (lung, liver, mucous membrane)
Romano-Ward syndrome	Prolonged Q-T interval, sudden death
Weill-Marchesani syndrome	Patent ductus arteriosus
Werner syndrome	Vascular sclerosis, cardiomyopathy

LEOPARD, multiple lentigines, electrocardiographic conduction abnormalities, ocular hypertelorism, pulmonary stenosis, abnormal genitalia, retardation of growth, sensorineural deafness.

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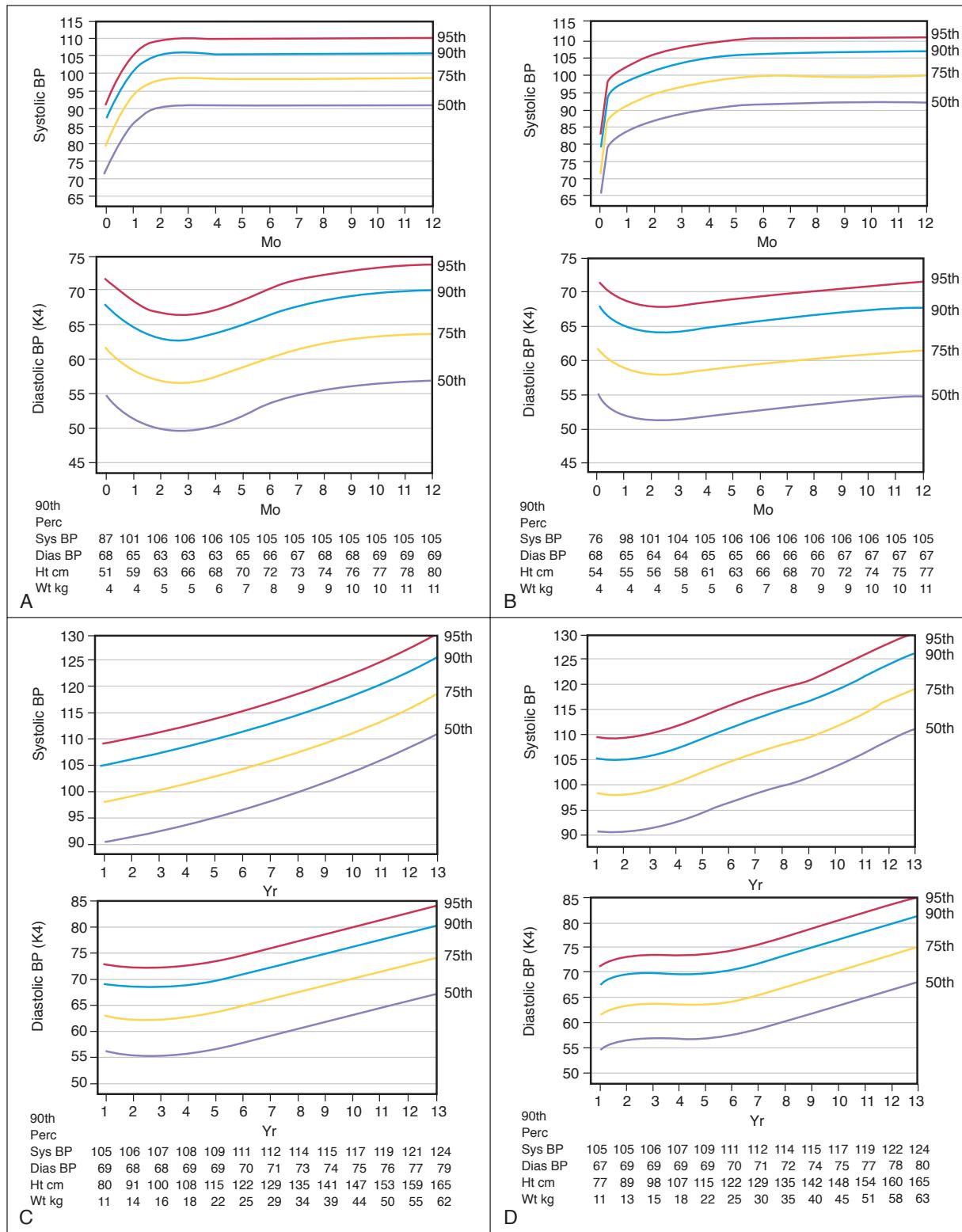


Figure 422-1 A, Age-specific percentiles of blood pressure (BP) measurements in boys from birth to 12 mo of age. B, Age-specific percentiles of BP measurements in girls from birth to 12 mo of age. C, Age-specific percentiles of BP measurements in boys 1-13 yr of age. D, Age-specific percentiles of BP measurements in girls 1-13 yr of age; Korotkoff phase IV (K4) used for diastolic BP. Dias, diastolic; Ht, height; Perc, percentile; Sys, systolic; Wt, weight. (From Report of the Second Task Force on Blood Pressure Control in Children—1987. National Heart, Lung, and Blood Institute, Bethesda, MD, Pediatrics 79:1-25, 1987. Copyright 1987 by the American Academy of Pediatrics.)

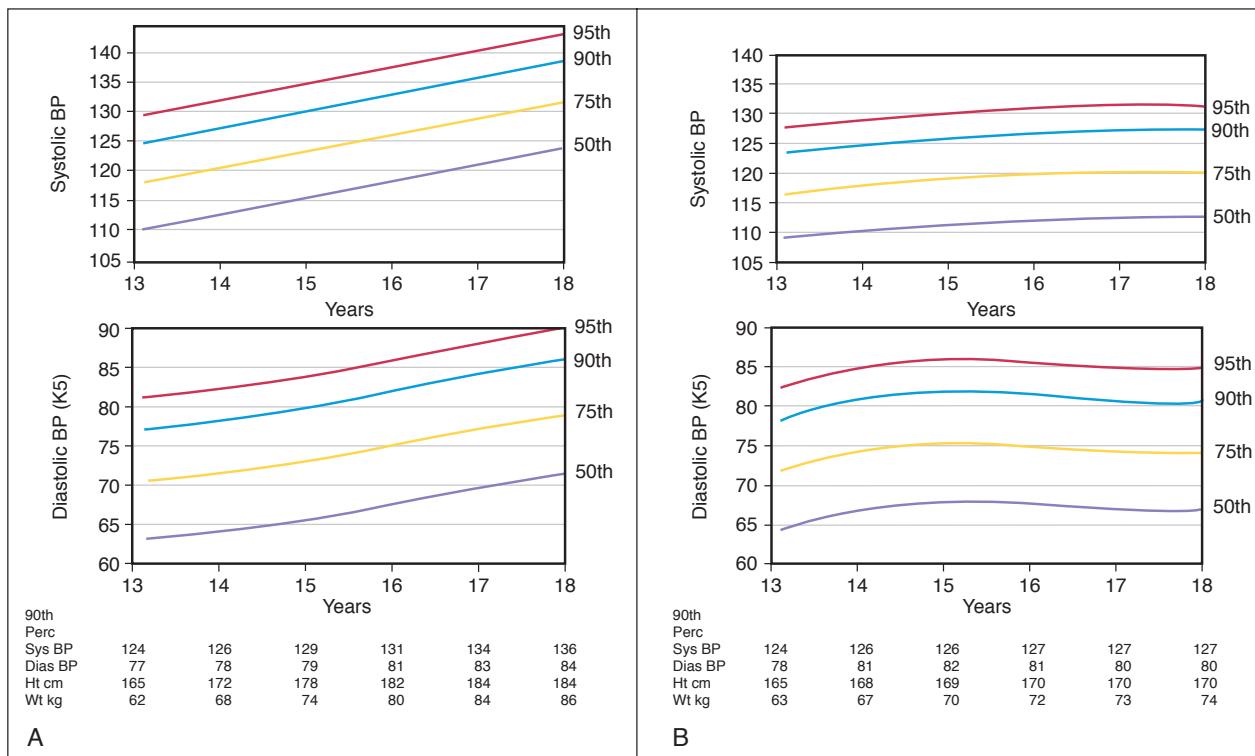


Figure 422-2 A, Age-specific percentiles of blood pressure (BP) measurements in boys 13-18 yr of age. B, Age-specific percentiles of BP measurements in girls 13-18 yr of age; Korotkoff phase V (K5) used for diastolic BP. Dias, diastolic; Ht, height; Perc, percentile; Sys, systolic; Wt, weight. (From Report of the Second Task Force on Blood Pressure Control in Children—1987, National Heart, Lung, and Blood Institute, Bethesda, MD, Pediatrics 79:1-25, 1987. Copyright 1987 by the American Academy of Pediatrics.)

Table 422-4 Pulse Rates at Rest

AGE	LOWER LIMITS OF NORMAL (beats/min)	AVERAGE (beats/min)	UPPER LIMITS OF NORMAL (beats/min)
Newborn	70	125	190
1-11 mo	80	120	160
2 yr	80	110	130
4 yr	80	100	120
6 yr	75	100	115
8 yr	70	90	110
10 yr	70	90	110
GIRLS	BOYS	GIRLS	BOYS
12 yr	70	65	90
14 yr	65	60	85
16 yr	60	55	80
18 yr	55	50	75
GIRLS	BOYS	GIRLS	BOYS
12 yr	70	85	110
14 yr	65	80	105
16 yr	60	75	100
18 yr	55	70	95

Table 424-1 Relative Frequency of Major Congenital Heart Lesions*

LESION	% OF ALL LESIONS
Ventricular septal defect	35-30
Atrial septal defect (secundum)	6-8
Patent ductus arteriosus	6-8
Coarctation of aorta	5-7
Tetralogy of Fallot	5-7
Pulmonary valve stenosis	5-7
Aortic valve stenosis	4-7
D-Transposition of great arteries	3-5
Hypoplastic left ventricle	1-3
Hypoplastic right ventricle	1-3
Truncus arteriosus	1-2
Total anomalous pulmonary venous return	1-2
Tricuspid atresia	1-2
Single ventricle	1-2
Double-outlet right ventricle	1-2
Others	5-10

Table 424-2 Genetics of Congenital Heart Disease: Defects Associated with Syndromes

CARDIOVASCULAR DISEASE	CHROMOSOMAL LOCATION	GENE(S) IMPLICATED*	COMMON CARDIAC DEFECTS
DiGeorge syndrome, velocardiofacial syndrome	22q11.2, 11p13p14	TBX1	TOF, IAA, TA, VSD
Familial ASD with heart block	5q35	NKX2.5	ASD, heart block
Familial ASD without heart block	8p22-23	GATA4	ASD
Alagille syndrome (bile duct hypoplasia, right-sided cardiac lesions)	20p12, 1p12	JAGGED1, NOTCH2	Peripheral pulmonary hypoplasia, PS, TOF
Holt-Oram syndrome (limb defects, ASD)	12q24	TBX5	ASD, VSD, PDA
Trisomy 21 (Down syndrome)	21q22	Not known	AVSD
Isolated familial AV septal defect (without trisomy 21)	1p31-p21, 3p25	CRELD1	AVSD
Familial TAPVR	4p13-q12	Not known	TAPVR
Noonan syndrome (PS, ASD, hypertrophic cardiomyopathy)	12q24, 12p1.21, 2p212, 3p25.2, 7q34, 15q22.31, 11p15.5, 1p13.2, 10q25.2, 11q23.3, 17q11.2	PTPN11, KRAS, SOS1, RAF1, BRAF, MEK1, HRAS, NRAS, SHOC2, CBL, NF1	PS, ASD, VSD, PDA, cardiomyopathy
Ellis-van Creveld syndrome (polydactyly, ASD)	4p16	EVC, EVC2	ASD, common atrium
Char syndrome (craniofacial, limb defects, PDA)	6p12-21.1	TFAP2B	PDA
Williams-Beuren syndrome (supravalvular AS, branch PS, hypercalcemia)	7q11.23	ELN (Elastin)	Supravalvar AS, peripheral PS
Marfan syndrome (connective tissue weakness, aortic root dilation)	15q21	Fibrillin	Aortic aneurysm, mitral valve disease
Familial laterality abnormalities	Xq24-2q7, 1q42, 9p13-21	ZIC3, DNAI1	Situs inversus, complex congenital heart disease
Turner	X	Not known	Coarctation of the aorta, Aortic stenosis
Trisomy 13 (Patau syndrome)	13	Not known	ASD, VSD, PDA, valve abnormalities
Trisomy 18 (Edwards syndrome)	18	Not known	ASD, VSD, PDA, Valve abnormalities
Cri du chat	5p15.2	CTNND2	ASD, VSD, PDA, TOF
Cat eye	22q11	Not known	TAPVR, TOF
Jacobsen	11q23	JAM-3	HLHS
Costello	11p15.5	HRAS	PS, hypertrophic cardiomyopathy, arrhythmias
CHARGE	8p12, 7q21.11	CHD7, SEMA3E	ASD, VSD, TOF
Kabuki syndrome	12q13.12	MLL2	ASD, VSD, TOF, coarctation, TGA
Carney syndrome	2p16	PRKAR1A	Atrial and ventricular myxomas

AS, aortic stenosis; ASD, atrial septal defect; AV, atrioventricular; AVSD, atrioventricular septal defect; HLHS, hypoplastic left-heart syndrome; IAA, interrupted aortic arch; PDA, patent ductus arteriosus; PS, pulmonic stenosis; TA, truncus arteriosus; TAPVR, total anomalous pulmonary venous return; TGA, transposition of great arteries; TOF, tetralogy of Fallot; VSD, ventricular septal defect.

*In many cases, mutation of a single gene has been closely linked to a specific cardiovascular disease, for example, by finding a high incidence of mutations or deletions of that gene in a large group of patients. These findings are often confirmed by studies in mice in which deletion or alteration of the gene induces a similar cardiac phenotype to the human disease. In others, mutation of a gene may increase the risk of cardiovascular disease, but with decreased penetrance, suggesting that modifier genes or environmental factors play a role. Finally, in some cases, gene mutations have only been identified in a small number of pedigrees, and confirmation awaits screening of larger numbers of patients.

Table 424-3 Genetics of Isolated Congenital Heart Disease (Nonsyndromic)		
GENE IMPLICATED*	PROTEIN ENCODED	CARDIAC DEFECTS
GENES ENCODING TRANSCRIPTION FACTORS		
ANKRD1	Ankyrin repeat domain	TAPVR
CITED2	cAMP responsive element-binding protein	ASD, VSD
FOG2/ZFPFM2	Friend of GATA	TOF
GATA6	GATA6 transcription factor	ASD, VSD, TOF, PS, AVSD, PDA
HAND2	Helix-loop-helix transcription factor	TOF
IRX4	Iroquois homeobox 4	VSD
MED13L	Mediator complex subunit 13-like	TGA
NKX2-5/NKX2.5	Homeobox containing transcription factor	ASD, VSD, TOF, HLHS, CoA, TGA, IAA
TBX20	T-Box 20 transcription factor	ASD, VSD, mitral stenosis
ZIC3	Zinc finger transcription factor	TGA, PS, TAPVR, HLHS, ASD, VSD
GENES ENCODING RECEPTORS AND SIGNALING MOLECULES		
ACVR1/ALK2	BMP receptor	AVSD
ACVR2B	Activin receptor	PS, DORV, TGA
ALDH1A2	Retinaldehyde dehydrogenase	TOF
CFC1/CRYPTIC	Cryptic protein	TOF, TGA, AVSD, ASD, VSD, IAA, DORV
CRELD1	Epidermal growth factor-related proteins	ASD; AVSD
FOXH1	Forkhead activin signal transducer	TOF, TGA
GDF1	Growth differentiation factor-1	TOF, TGA, DORV, heterotaxy
GJA1	Connexin 43	ASD, HLHS, TAPVR
LEFTY2	Left-right determination factor	TGA, AVSD, IAA, CoA
NODAL	Nodal homolog (TGF-β superfamily)	TGA, PA, TOF, DORV, TAPVR, AVSD
NOTCH1	NOTCH1 (Ligand of JAG1)	Bicuspid aortic valve, AS, CoA, HLHS
PDGFRA	Platelet-derived growth factor receptor α	TAPVR
SMAD6	MAD-related protein	Bicuspid aortic valve, CoA, AS
TAB2	TGF-β activated kinase	Outflow tract defects
TDGF1	Teratocarcinoma-derived growth factor 1	TOF, VSD
VEGF	Vascular endothelial growth factor	CoA, outflow tract defects
GENES ENCODING STRUCTURAL PROTEINS		
ACTC	α Cardiac actin	ASD
MYH11	Myosin heavy chain 11	PDA, aortic aneurysm
MYH6	α-Myosin heavy chain	ASD, TA, AS, TGA
MYH7	β-Myosin heavy chain	Ebstein anomaly, ASD

AS, aortic stenosis; ASD, atrial septal defect; AVSD, atrioventricular septal defect; cAMP, cyclic adenosine monophosphate; CoA, coarctation of the aorta; DORV, double-outlet right ventricle; HLHS, hypoplastic left heart syndrome; IAA, interrupted aortic arch; PA, pulmonary artery; PDA, patent ductus arteriosus; PS, pulmonic stenosis; TA, truncus arteriosus; TAPVR, total anomalous pulmonary venous return; TGA, transposition of the great arteries; TGF, transforming growth factor; TOF, tetralogy of Fallot; VSD, ventricular septal defect.

*In many cases, mutation of single gene has been closely linked to a specific cardiovascular disease, for example, by finding a high incidence of mutations or deletions of that gene in a large group of patients. These findings are often confirmed by studies in mice in which deletion or alteration of the gene induces a similar cardiac phenotype to the human disease. In others, mutation of a gene may increase the risk of cardiovascular disease, but with decreased penetrance, suggesting that modifier genes or environmental factors play a role. Finally, in some cases, gene mutations have only been identified in a small number of pedigrees, and confirmation awaits screening of larger numbers of patients.

Table 431-2 Comparison of Cardiosplenic Heterotaxy Syndromes		
FEATURE	ASPLENIA (RIGHT ISOMERISM)	POLYSPLENIA (LEFT ISOMERISM)
Spleen	Absent	Multiple
Sidedness (isomerism)	Bilateral right	Bilateral left
Lungs	Bilateral trilobar with eparterial bronchi	Bilateral bilobar with hyparterial bronchi
Sex	Male (65%)	Female ≥ male
Right-sided stomach	Yes	Less common
Symmetric liver	Yes	Yes
Partial intestinal rotation	Yes	Yes
Dextrocardia (%)	30-40	30-40
Pulmonary blood flow	Decreased (usually)	Increased (usually)
Severe cyanosis	Yes	No
Transposition of great arteries (%)	60-75	15
Total anomalous pulmonary venous return (%)	70-80	Rare
Common atrioventricular valve (%)	80-90	20-40
Single ventricle (%)	40-50	10-15
Absent inferior vena cava with azygous continuation	No	Characteristic
Bilateral superior vena cava	Yes	Yes
Other common defects	PA, PS	Partial anomalous pulmonary venous return, ventricular septal defect, double-outlet right ventricle
Risk of pneumococcal sepsis	Yes	Yes
Howell-Jolly and Heinz bodies, pitted erythrocytes	Yes	No
Risk of nosocomial infection	Yes	Yes
Absent gallbladder; biliary atresia	No	Yes

Table 424-4 Genetics of Cardiomyopathies

Hypertrophic cardiomyopathy	14q1 15q2 1q31 19p13.2-19q13.2 11p13-q13 12q23 13p21 2q31 3p25 Mitochondrial DNA Mitochondrial DNA	β -Myosin heavy chain α -Tropomyosin Troponin T Troponin I Myosin-binding protein C Cardiac slow myosin regulatory light chain Ventricular slow myosin essential light chain Titin Caveolin-3 tRNA-glycine tRNA-isoleucine
Hypertrophic cardiomyopathy with Wolff-Parkinson-White syndrome	7q36.1	AMP-activated protein kinase
Other genetic diseases causing cardiac hypertrophy		
Familial amyloid disease	18q12.1	Transthyretin (TTR)
Noonan syndrome	12q24.1, 2p22.1, 3p25, 12p12.1	Protein tyrosine phosphatase 11 (PTPN11), son of sevenless homologue 1 (SOS1), RAF1 protooncogene, GTPase KRAS
Fabry disease	Xq22	α -Galactosidase A (GLA)
Danon disease	Xq24	Lysosomal-associated membrane protein 2 (LAMP2)
Hereditary hemochromatosis	6p21.3	Hereditary hemochromatosis protein (HFE)
Pompe disease	17q25	Acid α -glucosidase (GAA)
Dilated cardiomyopathy		
X-linked	Xp21 Xp28	Dystrophin Tafazzin
Autosomal recessive	19p13.2-19q13.2	Troponin I

Autosomal dominant: genes encoding multiple proteins have been identified, including cardiac actin; desmin; δ -sarcoglycan; β -myosin heavy chain; cardiac troponin C and T; α -tropomyosin; titin; metavinculin; myosin-binding protein C; muscle LIM protein; α -actinin-2; phospholamban; Cypher/LIM binding domain 3; α -myosin heavy chain; SUR2A (regulatory subunit of K_{ATP} channel); and lamin A/C.

Isolated noncompaction of the left ventricle: autosomal dominant, autosomal recessive, X-linked, and mitochondrial inheritance patterns have been reported. Genes that have been implicated include: α -dystrobrevin, Cypher/ZASP, lamin A/C, Tafazzin, MIB1, and LIM domain-binding protein 3 (LDB3).

Partially adapted from Dunn KE, Caleshu C, Cirino AL, et al. A clinical approach to inherited hypertension: the use of family history in diagnosis, risk assessment, and management. Circ Cardiovasc Genet 6:118-131, 2013.

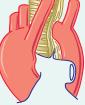
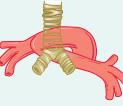
Table 424-5 Genetics of Arrhythmias

Complete heart block	19q13	Not known
Long Q-T syndrome		
LQT1 (autosomal dominant)	11p15.5	KVLQT1 (K ⁺ channel)
LQT2 (autosomal dominant)	7q35	HERG (K ⁺ channel)
LQT3 (autosomal dominant)	3p21	SCN5A (Na ⁺ channel)
LQT4 (autosomal dominant)	4q25-27	Not known
LQT5 (autosomal dominant)	21q22-q22	KCNE1 (K ⁺ channel)
LQT6	21q22.1	KCNE2 (K ⁺ channel)
Jervell and Lange-Nielsen syndrome (autosomal recessive, congenital deafness)	11p15.5	KVLQT1 (K ⁺ channel)
LQT8-13	Unknown	Private mutations (rare)
Arrhythmogenic RV dysplasia: There are now 11 genes associated with arrhythmogenic right ventricular dysplasia (ARVD1 through 11) usually with autosomal dominant inheritance, but with variable penetrance. These genes are: TGF- β ₃ (transforming growth factor β), RyR2 (ryanodine receptor), LAMR1 (laminin receptor-1), PTPLA (protein tyrosine phosphatase), DSP (desmoplakin), PKP2 (plakophilin-2), DSG2 (desmoglein), and DSC2 (desmocollin).		
Familial atrial fibrillation (autosomal dominant)	10q22-q24, 6q14-16 11p15.5 11p15.5 21q22 17q23.1-q24.2 7q35-q36	Not known KVLQT1 (K ⁺ channel) KCNQ1 (K ⁺ channel) KCNE2 (K ⁺ channel) KCNJ2 (K ⁺ channel) KCNH2 (K ⁺ channel)
Brugada syndrome (right bundle-branch block, ST segment elevation, unexpected sudden death)	3p21-p24 3p22-p24	SCN5A (Na ⁺ channel) GPD-1L (glycerol-3-phosphate dehydrogenase)
Catecholaminergic polymorphic ventricular tachycardia	— —	RYR2 (autosomal dominant) CASQ2 (autosomal recessive)

Table 431-1 Total Anomalous Pulmonary Venous Return

SITE OF CONNECTION (% OF CASES)	% WITH SIGNIFICANT OBSTRUCTION
Supracardiac (50) Left superior vena cava (40) Right superior vena cava (10)	40 75
Cardiac (25) Coronary sinus (20) Right atrium (5)	10 5
Infracardiac (20)	95-100
Mixed (5)	

Table 432-1 Vascular Rings

LESION	SYMPTOMS	PLAIN FILM	BARIUM SWALLOW	BRONCHOSCOPY	MRI ECHOCARDIOGRAPHY	TREATMENT	
DOUBLE ARCH		Stridor Respiratory distress Swallowing dysfunction Reflex apnea	AP—wider base of heart Lat.—narrowed trachea displaced forward at C3-C4	Bilateral indentation of esophagus	Bilateral tracheal compression—both pulsatile	Diagnostic	Ligate and divide smaller arch (usually left)
RIGHT ARCH AND LIGAMENTUM/DUCTUS		Respiratory distress Swallowing dysfunction	AP—tracheal deviation to left (right arch)	Bilateral indentation of esophagus R > L	Bilateral tracheal compression—r. pulsatile	Diagnostic	Ligate ligamentum or ductus
ANOMALOUS INNOMINATE		Cough Stridor Reflex apnea	AP—normal Lat.—anterior tracheal compression	Normal	Pulsatile anterior tracheal compression	Unnecessary	Conservative apnea, then suspend
ABERRANT RIGHT SUBCLAVIAN		Occasional swallowing dysfunction	Normal	AP—oblique defect upward to right Lat.—small defect on right posterior wall	Usually normal	Diagnostic	Ligate artery
PULMONARY SLING		Expiratory stridor Respiratory distress	AP—low L. hilum, r. emphysema/atelectasis Lat.—anterior bowing of right bronchus and trachea	±Anterior indentation above carina between esophagus and trachea	Tracheal displacement to left Compression of right main bronchus	Diagnostic	Detach and reanastomose to main pulmonary artery in front of trachea

AP, anteroposterior; L and I., left; Lat., lateral; MRI, magnetic resonance imaging; R and r., right.

From Kliegman RM, Greenbaum LA, Lye PS: Practical strategies in pediatric diagnosis and therapy, ed 2, Philadelphia, 2004, Elsevier, p. 88.

Table 432-2
Congenital Anomalies of Coronary Arteries Unassociated with Congenital Heart Disease
Anomalous Aortic Origin

- Eccentric ostium within an aortic sinus
- Ectopic ostium above an aortic sinus
- Conus artery from the right aortic sinus
- Circumflex coronary artery from the right aortic sinus or from the right coronary artery
- Origin of left anterior descending and circumflex coronary arteries from separate ostia in the left aortic sinus (absence of left main coronary artery)
- Atresia of the left main coronary artery
- Origin of the left anterior descending coronary artery from the right aortic sinus or from the right coronary artery
- Origin of the right coronary artery from the left aortic sinus, from posterior aortic sinus, or from left coronary artery
- Origin of a single coronary artery from the right or left aortic sinus
- Anomalous origin from a noncardiac systemic artery

Anomalous Aortic Origin with Anomalous Proximal Course

- Acute proximal angulation
- Ectopic right coronary artery passing between aorta and pulmonary trunk
 - Ectopic left main coronary artery:
 - Between aorta and pulmonary trunk
 - Anterior to the pulmonary trunk
 - Posterior to the aorta
- Within the ventricular septum (intramyocardial)
- Ectopic left anterior descending coronary artery that is anterior, posterior, or between the aorta and pulmonary trunk

Anomalous Origin of a Coronary Artery from the Pulmonary Trunk

- Left main coronary artery
- Left anterior descending coronary artery
- Right coronary artery
- Both right and left coronary arteries
- Circumflex coronary artery
- Accessory coronary artery

Table 433-1
Revised World Health Organization Classification of Pulmonary Hypertension

1. Pulmonary arterial hypertension (PAH)
 - 1.1. Idiopathic (IPAH)
 - 1.2. Familial (FPAH)
 - 1.3. Associated with (APAH):
 - 1.3.1. Connective tissue disorder
 - 1.3.2. Congenital systemic-to-pulmonary shunts
 - 1.3.3. Portal hypertension
 - 1.3.4. HIV infection
 - 1.3.5. Drugs and toxins
 - 1.3.6. Other (thyroid disorders, glycogen storage disease, Gaucher disease, hereditary hemorrhagic telangiectasia, hemoglobinopathies, chronic myeloproliferative disorders, splenectomy)
 - 1.4. Associated with significant venous or capillary involvement
 - 1.4.1. Pulmonary venoocclusive disease (PVOD)
 - 1.4.2. Pulmonary capillary hemangiomatosis (PCH)
 - 1.5. Persistent pulmonary hypertension of the newborn
2. Pulmonary hypertension with left-heart disease
 - 2.1. Left-sided atrial or ventricular heart disease
 - 2.2. Left-sided valvular heart disease
3. Pulmonary hypertension associated with lung diseases and/or hypoxemia
 - 3.1. Chronic obstructive pulmonary disease
 - 3.2. Interstitial lung disease
 - 3.3. Sleep disordered breathing
 - 3.4. Alveolar hypoventilation disorders
 - 3.5. Chronic exposure to high altitude
 - 3.6. Developmental abnormalities
4. Pulmonary hypertension due to chronic thrombotic and/or embolic disease (CTEPH)
 - 4.1. Thromboembolic obstruction of proximal pulmonary arteries
 - 4.2. Thromboembolic obstruction of distal pulmonary arteries
 - 4.3. Nonthrombotic pulmonary embolism (tumor, parasites, foreign material)
5. Miscellaneous: sarcoidosis, histiocytosis X, lymphangiomatosis, compression of pulmonary vessels (adenopathy, tumor, fibrosis, mediastinitis)

Table 433-2
Summary of Drugs Used to Treat Pulmonary Hypertension*

DRUG AND MECHANISM OF ACTION	DOSES USED IN PEDIATRIC STUDIES	COMMON SIDE EFFECTS
Epoprostenol (prostacyclin [PGI ₂], a potent vasodilator; also inhibits platelet aggregation)	1 ng/kg/min initially. Increase based on clinical course and tolerance to 5-50 ng/kg/min. Some patients may require even higher doses. Must be given by continuous infusion that is not interrupted	Flushing, headache, nausea, diarrhea, hypotension, chest pain, jaw pain
Iloprost (synthetic analog of PGI ₂)	2.5-5.0 µg 6-9 times daily (not more frequently than every 2 hr) via inhalation	Flushing, headache, diarrhea, hypotension, jaw pain, exacerbation of pulmonary symptoms (cough, wheezing)
Treprostinil (synthetic analog of PGI ₂)	1 ng/kg/min initially. Target dose ranges from 20-80 ng/kg/min. Given either IV or SC via continuous infusion. Longer half-life than epoprostenol	Flushing, headache, diarrhea, hypotension, jaw pain. Pain at infusion site when given SC
Bosentan, ambrisentan, (endothelin receptor EtA and EtB antagonist)	2 mg/kg/dose bid. Use ½ dose for 1st mo and check for liver function test abnormalities prior to up-titrating	Flushing, headache, diarrhea, hypotension, fluid retention, exacerbation of heart failure, anemia, elevated liver function tests, palpitations
Sildenafil (inhibitor of cyclic guanosine monophosphate-specific phosphodiesterase 5)	1 mg/kg/dose given 3-4 times daily. Initial dosing should be ½ final target dose to evaluate for hypotension	Flushing, headache, diarrhea, myalgia, hypotension, priapism, visual disturbance (blue coloration)
Calcium channel blockers (amlodipine, diltiazem, nifedipine)	Previously widely used. Now indicated only for patients who show a strong response to nitric oxide during cardiac catheterization	Flushing, headache, edema, arrhythmia, headache, hypotension, rash, nausea, constipation, elevated liver function tests

*These medications should only be administered under the direction of a specialist in pulmonary hypertension.

Table 434-2 Congenital Heart Defects Associated with Survival into Adulthood Without Surgery or Interventional Cardiac Catheterization

- Mild pulmonary valve stenosis
- Bicuspid aortic valve
- Small to moderate size atrial septal defect
- Small ventricular septal defect
- Small patent ductus arteriosus
- Mitral valve prolapse
- Partial atrioventricular canal (ostium primum atrial septal defect and cleft mitral valve)
- Marfan syndrome
- Ebstein anomaly
- Congenitally corrected transposition (atrioventricular and ventriculoarterial discordance)

Table 434-3 Most Common Congenital Heart Defects Surviving to Adulthood After Surgery or Interventional Catheterization

- Aortic valve disease following balloon valvuloplasty or surgical valvotomy
- Pulmonary valve stenosis following balloon valvuloplasty or surgical valvotomy
- Tetralogy of Fallot
- Ventricular septal defect
- Complete atrioventricular canal defect
- Transposition of the great arteries
- Coarctation of the aorta
- Complex single ventricles after the modified Fontan procedure

Table 434-6 Issues That Require Coordination of Care Between the Cardiologist and the Primary Care Physician

- Antibiotic prophylaxis for endocarditis
- Medications and drug interactions
- Anticoagulation with prosthetic valves
- Exercise and sports participation
- Educational and vocational planning
- Contraception and pregnancy
- Drug, alcohol, and tobacco use
- Noncardiac surgical planning
- Anesthetic issues
- New symptoms or acute illnesses
- Coexistent medical conditions
- Travel

Table 434-4 Risks in Adults Who Have Congenital Heart Disease

Rhythm disorder	Ventricular septal defect
Supraventricular tachycardia	Atrial septal defect
Right bundle branch block	Patent ductus arteriosus
Heart block	Acquired lesions
Ventricular tachycardia	Subacute bacterial endocarditis
Sudden death	Subvalvular stenosis
Coarctation of aorta	Supravalvular stenosis
Essential hypertension	Valvular insufficiency
Recoarctation	Valvular restenosis
Aneurysm formation	Eisenmenger complex
Residual lesions (shunts)	Pregnancy risk (see Table 434-5)

Table 434-5 Lesion Specific Risks of Maternal and Neonatal Complications of Pregnancy

No additional risk	Small septal defects Surgically closed ASD, VSD, PDA Mild to moderate aortic regurgitation Mild to moderate pulmonary stenosis
Slightly increased risk	Postoperative repair of tetralogy of Fallot Transposition of the great arteries, s/p arterial switch procedure
Moderate risk	Transposition of the great arteries, s/p atrial switch procedure Congenitally corrected transposition of the great arteries Single ventricle physiology, s/p Fontan procedure
Severe risk	Cyanotic congenital heart disease, unoperated or palliated Marfan syndrome Prosthetic valves Obstructive lesions including coarctation
Pregnancy contraindicated	Severe pulmonary hypertension Severe obstructive lesions Marfan syndrome, aortic root >40 mm

ASD, atrial septal defect; PDA, patent ductus arteriosus; s/p, status post (after); VSD, ventricular septal defect.

Assess annually

- Anemia history*
- Symptoms of hyperviscosity†
- Measure oxygen saturation‡
- Laboratory measures:
haemoglobin, packed cell volume, red-cell indices, serum ferritin, transferrin saturation

Serum ferritin $\leq 15 \mu\text{g/L}$
Transferrin saturation $\leq 15\%$

Patient iron-deficient
Iron supplementation
Address other causes of iron deficiency as identified from history

Reassess symptoms
Repeat laboratory tests
Consider cessation of iron supplementation when iron replete (serum ferritin $\geq 15 \mu\text{g/L}$ and transferrin saturation $\geq 15\%$)
Some patients will require chronic iron supplementation for steady-state erythrocytosis
Regularly reassess symptoms and laboratory tests

Serum ferritin $\geq 15 \mu\text{g/L}$
Transferrin saturation $\geq 15\%$

Patient iron-replete
No symptoms of hyperviscosity
Patient iron-replete
Symptoms of hyperviscosity

Assess for other causes of symptoms and treat accordingly: e.g.,
Hypovolaemia
Gout
Brain abscess
Hypothyroidism
Depression

Resolution of symptoms
Patient remains iron-replete
Reassess every 6–12 months

Persistent moderate-severe hyperviscosity symptoms
Packed cell volume $>65\%$
Trial of phlebotomy with fluid replacement

Figure 434-1 Important issues that are crucial to address at time of transition. (From Spence MS, Balaratnam MS, Gatzoulis MA: Clinical update: cyanotic adult congenital heart disease, Lancet 370:1530–1532, 2007, p. 1531.)