**1674 Part XVII** ◆ Infectious Diseases

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| **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 *(Entamoeba histolytica)* | | | |
| 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 furoate2 | 500 mg tid PO × 10 days | 20 mg/kg/day PO in 3 doses × 10 days |
| Mild to moderate intestinal disease3 | | | |
| Drug of choice4: | Metronidazole | 500-750 mg tid PO × 7-10 days | 35-50 mg/kg/day PO in 3 doses × 7-10 days |
| *or* | Tinidazole5 | 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* | Tinidazole5 | 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 B6,7 | 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.leiterrx.com).](http://www.leiterrx.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: *Neurol 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 encephalitis 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).

**Chapter 279** ◆ Principles of Antiparasitic Therapy **1675**

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| **Table 279-1** Drugs | for Parasitic Infections—cont’d | | |
| **INFECTION** | **DRUG** | **ADULT DOSAGE** | **PEDIATRIC DOSAGE** |
| Balamuthia mandrillaris | | | |
| Drug of choice: | See footnote 9 |  |  |
| Sappinia diploidea | | | |
| Drug of choice: | See footnote 10 |  |  |
| Ancylostoma caninum (eosinophilic enterocolitis) | | | |
| Drug of choice: | Albendazole7 | 400 mg PO once | 400 mg PO once |
| *or* | Mebendazole | 100 mg PO bid × 3 days | 100 mg PO bid × 3 days |
| *or* | Pyrantel pamoate7 | 11 mg/kg PO (max 1 g) × 3 days | 11 mg/kg PO (max 1 g) × 3 days |
| *or* | Endoscopic removal |  |  |
| Ancylostoma duodenale, see Hookworm | | | |
| Angiostrongyliasis *(Angiostrongylus cantonensis, Angiostrongylus costaricensis)* | | | |
| Drug of choice: | See footnote 11 |  |  |
| Anisakiasis (*Anisakis* spp.) | | | |
| Treatment of choice12: | Surgical or endoscopic removal |  |  |
| Ascariasis (*Ascaris lumbricoides,* roundworm) | | | |
| Drug of choice: | Albendazole7 | 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* | Ivermectin7 | 150-200 μg/kg PO once | 150-200 μg/kg PO once |
| Babesiosis *(Babesia microti)* | | | |
| Drugs of choice13: | Atovaquone7 | 750 mg PO bid × 7-10 days | 20 mg/kg PO bid × 7-10 days |
|  | plus azithromycin7 | 600 mg PO daily × 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* | Clindamycin7 | 300-600 mg IV qid or 600 mg tid PO × | 20-40 mg/kg/day IV or PO in 3 or 4 doses × |
|  |  | 7-10 days | 7-10 days (max 600 mg/dose) |
|  | plus quinine7 | 650 mg tid PO × 7-10 days | 24 mg/kg/day PO in 3 doses × 7-10 days |
| Balamuthia mandrillaris, see Amebic meningoencephalitis, primary | | | |
| Balantidiasis *(Balantidium coli)* | | | |
| Drug of choice: | Tetracycline7,14 | 500 mg PO qid × 10 days | 40 mg/kg/day PO (max 2 g) in 4 doses × 10 days |
| Alternatives: | Metronidazole7 Iodoquinol7 | 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 a 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 immunosuppressed 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.

#### Continued

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| **Table 279-1** | Drugs | for Parasitic Infections—cont’d | | |
| **INFECTION** | **DRUG** | | **ADULT DOSAGE** | **PEDIATRIC DOSAGE** |
| Baylisascariasis *(Baylisascaris procyonis)* | | | | |
| Drug of choice: | See footnote 15 | |  |  |
| Blastocystis hominis infection | | | | |
| Drug of choice: | See footnote 16 | |  |  |
| Capillariasis *(Capillaria philippinensis)* | | | | |
| Drug of choice: | Mebendazole7 | | 200 mg PO bid × 20 days | 200 mg PO bid × 20 days |
| Alternatives: | Albendazole7 | | 400 mg PO daily × 10 days | 400 mg PO daily × 10 days |
| Chagas disease, see Trypanosomiasis | | | | |
| Clonorchis sinensis, see Fluke infection | | | | |
| Cryptosporidiosis *(Cryptosporidium)* | | | | |
| Immunocompetent | | | | |
| Drug of choice: | Nitazoxanide4 | | 500 mg PO bid × 3 days7 | 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 choice18: | Albendazole7 | | 400 mg PO daily × 3 days | 400 mg PO daily × 3 days |
| *or* | Ivermectin7 | | 200 μg/kg PO daily × 1-2 days | 200 μg/kg PO daily × 1-2 days |
| Alternative: | Thiabendazole | | Topically | Topically |
| Cyclosporiasis *(Cyclospora cayetanensis)* | | | | |
| Drug of choice19: | 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 *(Cystoisospora belli, formerly known as Isospora)* | | | | |
| 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 |
| Dientamoeba fragilis  infection20 | | | | |
|  | Paromomycin7 | | 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 |
| Diphyllobothrium latum, 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, Borenam 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.

**Chapter 279** ◆ Principles of Antiparasitic Therapy **1677**

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| **Table 279-1** | Drugs | for Parasitic Infections—cont’d | | |
| **INFECTION** | **DRUG** | | **ADULT DOSAGE** | **PEDIATRIC DOSAGE** |
| Dracunculus medinensis (guinea worm) infection | | | | |
| Drug of choice: | See footnote 21 | |  |  |
| Echinococcus, see Tapeworm Infection | | | | |
| Entamoeba histolytica, see Amebiasis | | | | |
| Enterobius vermicularis (pinworm) infection | | | | |
| Drug of choice22: | Albendazole7 | | 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 |
| Fasciola hepatica, see Fluke infection | | | | |
| Filariasis23 | | | | |
| Wuchereria bancrofti, Brugia malayi, Brugia timori | | | | |
| Drug of choice24: | Diethylcarbamazine | | 6 mg/kg PO in 3 doses × 14 days25 | 6 mg/kg PO in 3 doses × 14 days25 |
| Loa loa | | | | |
| Drug of choice26: | Diethylcarbamazine | | 9 mg/kg PO in 3 doses × 14 days25 | 9 mg/kg PO in 3 doses × 14 days25 |
| Mansonella ozzardi | | | | |
| Drug of choice: | See footnote 27 | |  |  |
| Mansonella perstans | | | | |
| Drug of choice: | Doxycycline7,14 | | 100 mg bid PO × 7 days | 4 mg/kg/day in 2 doses PO × 7 days |
| Mansonella streptocerca28 | | | | |
| Drug of choice: | Diethylcarbamazine Ivermectin7 | | 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 |
| Onchocerca volvulus  (river blindness) | | | | |
| Drug of choice: | Invermectin30 | | 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 (Figueredo-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* (Ottesen 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

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| **Table 279-1** Drugs | for Parasitic Infections—cont’d | | |
| **INFECTION** | **DRUG** | **ADULT DOSAGE** | **PEDIATRIC DOSAGE** |
| Clonorchis sinensis  (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* | Albendazole7 | 10 mg/kg PO × 7 days | 10 mg/kg PO × 7 days |
| Fasciola hepatica (sheep liver fluke) | | | |
| Drug of choice31: | Triclabendazole | 10 mg/kg PO once or twice32 | 10 mg/kg PO once or twice32 |
| 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 |
| Fasciolopsis buski, Heterophyes heterophyes, Metagonimus yokogawai (intestinal flukes) | | | |
| Drug of choice: | Praziquantel7 | 75 mg/kg/day PO in 3 doses × 1 day | 75 mg/kg/day PO in 3 doses × 1 day |
| Metorchis conjunctus (North American liver fluke)33 | | | |
| Drug of choice: | Praziquantel7 | 75 mg/kg/day PO in 3 doses × 1 day | 75 mg/kg/day PO in 3 doses × 1 day |
| Nanophyetus salmincola | | | |
| Drug of choice: | Praziquantel7 | 60 mg/kg/day PO in 3 doses × 1 day | 60 mg/kg/day PO in 3 doses × 1 day |
| Opisthorchis viverrini (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 |
| Paragonimus westermani (lung fluke) | | | |
| Drug of choice: | Praziquantel7 | 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 |
| Giardiasis *(Giardia duodenalis)* | | | |
| Drugs of choice: | Metronidazole7 Nitazoxanide4  Tinidazole5 | 250 mg PO tid × 5 days 500 mg PO bid × 3 days  2 g PO once | 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) |
| Alternatives35: | Paromomycin7,36 Furazolidone Quinacrine2 | 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) |
| Gnathostomiasis *(Gnathostoma spinigerum)* | | | |
| Treatment of choice37: | Albendazole7 | 400 mg PO bid × 21 days | 400 mg PO bid × 21 days |
| *or* | Ivermectin7 | 200 μg/kg/day PO × 2 days | 200 μg/kg/day PO × 2 days |
| ± | Surgical removal |  |  |
| Gongylonemiasis (*Gongylonema* sp.)38 | | | |
| Treatment of choice: | Surgical removal |  |  |
| *or* | Albendazole7 | 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;](http://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.

**Chapter 279** ◆ Principles of Antiparasitic Therapy **1679**

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| **Table 279-1** | Drugs | for Parasitic Infections—cont’d | | |
| **INFECTION** | **DRUG** | | **ADULT DOSAGE** | **PEDIATRIC DOSAGE** |
| Hookworm infection *(Ancylostoma duodenale, Necator americanus)* | | | | |
| Drug of choice: | Albendazole7 | | 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 pamoate7 | | 11 mg/kg (max 1 g) PO × 3 days | 11 mg/kg (max 1 g) PO × 3 days |
| Hydatid cyst, see Tapeworm infection | | | | |
| Hymenolepis nana, see Tapeworm infection | | | | |
| Leishmania infection | | | | |
| Visceral39, 40 | | | | |
| Drugs of choice: | Sodium stibogluconate | | 20 mg Sb/kg/day IV or IM × 28 days41 | 20 mg Sb/kg/day IV or IM × 28 days41 |
| *or* | Meglumine antimonate | | 20 mg pentavalent antimony/kg/day IV or IM × 28 days41 | 20 mg pentavalent antimony/kg/day IV or IM × 28 days41 |
| *or* | Amphotericin B7 | | 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 B42 | | 3 mg/kg/day IV (days 1-5) followed by 3 mg/kg/day on days 14 and 2143 | 3 mg/kg/day IV (days 1-5) followed by 3 mg/kg/day  on days 14 and 2143 |
| *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 |
| Alternative44: | Pentamidine7 | | 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 days41 | 20 mg Sb/kg/day IV or IM × 20 days41 |
| *or* | Meglumine antimonate | | 20 mg pentavalent antimony/kg/day IV or IM × 20 days41 | 20 mg pentavalent antimony/kg/day IV or IM × 20 days41 |
| *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 |
| Alternatives46: | Pentamidine7 | | 2-3 mg/kg IV or IM daily or every 2 days  × 4-7 doses47 | 2-3 mg/kg IV or IM daily or every 2 days × 4-7 doses47 |
| *or* | Paromomycin7,48 | | Topically 2×/day × 10-20 days | Topically 2×/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 Chakravarty, 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 cholesteryl 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).](mailto: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) braziliensis* 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.) braziliensis* 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.) braziliensis* 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

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| **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 days41 | 20 mg Sb/kg/day IV or IM × 28 days41 |
| *or* | Meglumine antimonate | | 20 mg pentavalent antimony/kg/day IV or IM × 28 days41 | 20 mg pentavalent antimony/kg/day IV or IM ×  28 days41 |
| *or* | Amphotericin B7 | | 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 *(Pediculus humanus, Pediculus capitis, Phthirus pubis)*50 | | | | |
| Drugs of choice: | 0.5% Malathion51 | | Topically | Topically |
| *or* | 1% Permethrin52 | | Topically | Topically |
| *or* | Pyrethrins with piperonyl butoxide52 | | 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* | Ivermectin7,53 | | 200 μg/kg PO × 3 doses, on days 1, 2,  and 10 | 200 μg/kg PO × 3 doses, on days 1, 2, and 10 |
| Loa loa, see Filariasis | | | | |
| Malaria, treatment of *(Plasmodium falciparum, Plasmodium ovale, Plasmodium vivax,* and *Plasmodium malariae)* | | | | |
| P. falciparum54 acquired in areas of chloroquine resistance | | | | |
| Oral55 | | | | |
| Drugs of choice: | Atovaquone/ | | 2 adult tabs PO bid58 or 4 adult tabs PO | <5 kg: not indicated |
|  | proguanil56 | | once daily × 3 days | 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 | | 650 mg PO every 8 hr × 3-7 days57 | 30 mg/kg/day PO in 3 doses × 3-7 days57 |
|  | plus | |  |  |
|  | doxycycline7,14 | | 100 mg PO bid × 7 days | 4 mg/kg/day PO in 2 doses × 7 days |
|  | or plus | |  |  |
|  | tetracycline7,14 | | 250 mg PO qid × 7 days | 6.25 mg/kg PO qid × 7 days |
|  | or plus | |  |  |
|  | clindamycin7,59 | | 20 mg/kg/day PO in 3 doses × 7 days60 | 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.

**Chapter 279** ◆ Principles of Antiparasitic Therapy **1681**

|  |  |  |  |
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| **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: | Mefloquine61,62 | 750 mg PO followed 12 hr later by 500 mg | 15 mg/kg PO followed 12 hr later by 10 mg/kg |
| P. vivax63 acquired in areas of chloroquine resistance | | | |
| Oral55 | | | |
| Drug of choice: | Quinine sulfate | 650 mg PO every 8 hr × 3-7 days57 | 30 mg/kg/day PO in 3 doses × 3-7 days57 |
|  | plus |  |  |
|  | doxycycline7,14 | 100 mg PO bid × 7 days | 4 mg/kg/day PO in 2 doses × 7 days |
|  | plus |  |  |
|  | primaquine64 | 30 mg base PO daily × 14 days | 0.5 mg/kg/day PO × 14 days |
| *or* | Mefloquine61 | 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 | 25 mg base/kg PO in 3 doses over 48 hr | 25 mg base/kg PO in 3 doses over 48 hr |
|  | plus |  |  |
|  | primaquine64 | 30 mg base PO daily × 14 days | 0.5 mg/kg/day PO × 14 days |
| All Plasmodium except chloroquine-resistant P. falciparum54 and chloroquine-resistant P. vivax63 (areas without chloroquine resistance) | | | |
| Oral55 | | | |
| Drug of choice: | Chloroquine | 1 g (600 mg base), then 500 mg (300 mg | 10 mg base/kg (max 600 mg base), then 5 mg |
|  | phosphate65 | base) 6 hr later PO, then 500 mg | base/kg 6 hr later PO, then 5 mg base/kg at 24 |
|  |  | (300 mg base) at 24 and 48 hr | and 48 hr |
| All Plasmodium | | | |
| Parenteral (severe infection; chloroquine-sensitive and resistant) | | | |
| Drugs of choice66: | Quinidine gluconate67 | 10 mg/kg IV loading dose (max 600 mg) | 10 mg/kg IV loading dose (max 600 mg) in normal |
|  |  | in normal saline over 1-2 hr, followed | saline over 1-2 hr, followed by continuous |
|  |  | by continuous infusion of 0.02 mg/kg/ | infusion of 0.02 mg/kg/min until PO therapy can |
|  |  | min until PO therapy can be started | be started |
| *or* | Quinine dihydrochloride67 | 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: | Artesunate68  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: P. vivax and P. ovale only | | | | |
| Drug of choice: | Primaquine phosphate64 | | 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 phosphate70,71 | | 500 mg (300 mg base), PO once/wk72 | 5 mg/kg base once/wk, up to adult dose of 300 mg base72 |
| Chloroquine-resistant areas54 | | | | |
| Drug of choice: | Atovaquone/ | | 1 adult tab PO q day73 | 11-20 kg: 1 pediatric tab PO/day56,73 |
|  | proguanil56,71 | |  | 21-30 kg: 2 pediatric tabs PO/day56,73 |
|  |  | |  | 31-40 kg: 3 pediatric tabs PO/day56,73 |
|  |  | |  | >40 kg: 1 adult tab PO/day56,73 |
| *or* | Mefloquine61,71,74 | | 250 mg PO once/wk72 | <9 kg: 5 mg/kg salt once/wk72 |
|  |  | |  | 9-19 kg: 14 tab once/wk72 |
|  |  | |  | 19-30 kg: 1 tab once/wk72 |
|  |  | |  |  |
|  |  | |  | 31-45 kg: 3 4 tab once/wk72 |
|  |  | |  | >45 kg: 1 tab once/wk72 |
| *or* | Doxycycline7,71 | | 100 mg PO daily75 | 2 mg/kg/day, up to 100 mg/day75 |
| Alternatives: | Primaquine7 | | 30 mg base PO daily76 | 0.6 mg/kg base daily |
| Malaria, self-presumptive treatment77 | | | | |
| Drug of choice: | Atovaquone/ | | 4 adult tabs PO daily × 3 days | <5 kg: not indicated |
|  | proguanil7,56, 78 | |  | 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 |

68Oral 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 1 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.

2

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.

**Chapter 279** ◆ Principles of Antiparasitic Therapy **1683**

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| --- | --- | --- | --- | --- |
| **Table 279-1** | Drugs | for Parasitic Infections—cont’d | | |
| **INFECTION** | **DRUG** | | **ADULT DOSAGE** | **PEDIATRIC DOSAGE** |
| *or* | Quinine sulfate plus doxycycline7,14 | | 650 mg PO every 8 hr × 3-7 days57  100 mg bid PO × 7 days | 30 mg/kg/day PO in 3 doses × 3-7 days57  4 mg/kg/day in 2 PO doses × 7 days |
| *or* | Mefloquine61 | | 750 mg PO followed 12 hr later by 500 mg | 15 mg/kg followed 12 hr later by 10 mg/kg |
| Microsporidiosis | | | | |
| Ocular *(Encephalitozoon hellem, Encephalitozoon cuniculi, Vittaforma corneae [Nosema corneum])* | | | | |
| Drug of choice: | Albendazole7  plus fumagillin79 | | 400 mg PO bid |  |
| Intestinal *(Enterocytozoon bieneusi, Encephalitozoon [Septata] intestinalis)* | | | | |
| E. bieneusi 80 | | | | |
| Drug of choice: | Fumagillin | | 60 mg/day PO × 14 days in 3 divided doses |  |
| E. intestinalis | | | | |
| Drug of choice | Albendazole7 | | 400 mg PO bid × 21 days |  |
| Disseminated *(E. hellem, E. cuniculi, E. intestinalis, Pleistophora* sp., *Trachipleistophora* sp., and *Brachiola vesicularum)* | | | | |
| Drug of choice81: | Albendazole7 | | 400 mg PO bid |  |
| Mites, see Scabies | | | | |
| Moniliformis *moniliformis* infection | | | | |
| Drug of choice: | Pyrantel pamoate7 | | 11 mg/kg PO once, repeat twice, 2 wk apart | 11 mg/kg PO once, repeat twice, 2 wk apart |
| Naegleria species, see Amebic meningoencephalitis, primary | | | | |
| Necator americanus, see Hookworm infection | | | | |
| Oesophagostomum *bifurcum* | | | | |
| Drug of choice: | See footnote 82 | |  |  |
| Onchocerca volvulus, see Filariasis | | | | |
| Opisthorchis viverrini, see Fluke infection | | | | |
| Paragonimus westermani, see Fluke infection | | | | |
| Pediculus capitis, Pediculus humanus, Phthirus pubis, see Lice | | | | |
| Pinworm, see *Enterobius* | | | | |
| Pneumocystis jiroveci (formerly *Pneumocystis carinii*) 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 clindamycin7 | | 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 PO2 ≤70 mm Hg or A-aO2 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/m2, SMX 750 mg/m2 PO in 2 doses on 3 consecutive days per wk |
| Alternatives85: | Dapsone7 | | 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* | Dapsone7  plus pyrimethamine86 | | 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 *Respirgard II* nebulizer | ≥5 yr: 300 mg inhaled monthly via *Respirgard II*  nebulizer |
| *or* | Atovaquone7 | | 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 *(Sarcoptes scabiei)* | | | | |
| Drug of choice: | 5% Permethrin | | Topically, 2× at least 7 days apart87 | Topically, 2× at least 7 days apart87 |
| Alternatives88: | Ivermectin7,89 10% Crotamiton | | 200 μg/kg PO 2× at least 7 days apart 87  Topically overnight on days 1, 2, 3, 8 | 200 μg/kg PO 2× at least 7 days apart 87  Topically overnight on days 1, 2, 3, 8 |
| Schistosomiasis *(Bilharziasis)* | | | | |
| Schistosoma haematobium | | | | |
| 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 |
| Schistosoma intercalatum | | | | |
| 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 |
| Schistosoma japonicum | | | | |
| 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 × 106/L for longer than 3 mo.

85An alternative trimethoprim-sulfamethoxazole regimen is 1 DS tab 3×/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.

**Chapter 279** ◆ Principles of Antiparasitic Therapy **1685**

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| **Table 279-1** Drugs | for Parasitic Infections—cont’d | | |
| **INFECTION** | **DRUG** | **ADULT DOSAGE** | **PEDIATRIC DOSAGE** |
| Schistosoma mansoni | | | |
| 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: | Oxamniquine90 | 15 mg/kg PO once91 | 20 mg/kg/day PO in 2 doses × 1 day91 |
| Schistosoma mekongi | | | |
| 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 | | | |
| Strongyloidiasis *(Strongyloides stercoralis)* | | | |
| Drug of choice92: | Ivermectin | 200 μg/kg/day PO × 2 days | 200 μg/kg/day PO × 2 days |
| Alternative: | Albendazole7, 93 | 400 mg PO bid × 7 days | 400 mg bid PO × 7 days |
| Tapeworm infection | | | |
| Adult (intestinal stage) | | | |
| Diphyllobothrium latum (fish), Taenia saginata (beef), Taenia solium (pork), Dipylidium caninum (dog) | | | |
| Drug of choice: | Praziquantel7 | 5-10 mg/kg PO once | 5-10 mg/kg PO once |
| Alternative: | Niclosamide | 2 g PO once | 50 mg/kg PO once |
| Hymenolepis nana (dwarf tapeworm) | | | |
| Drug of choice: | Praziquantel7 | 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 days94  >34 kg: 1.5 g PO on day 1 then 1 g/d PO × 6 days94 |
| Larval (tissue stage) | | | |
| Echinococcus granulosus (hydatid cyst) | | | |
| Drug of choice95: | Albendazole | 400 mg PO bid × 1-6 mo | 15 mg/kg/day PO (max 800 mg) × 1-6 mo |
| Echinococcus multilocularis | | | |
| Treatment of choice: | See footnote 96 |  |  |
| Taenia solium (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* | Praziquantel7 | 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-reaspiration (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

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|  |  |  |  |
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| **Table 279-1** Drugs | for Parasitic Infections—cont’d | | |
| **INFECTION** | **DRUG** | **ADULT DOSAGE** | **PEDIATRIC DOSAGE** |
| Toxoplasmosis *(Toxoplasma gondii)*98 | | | |
| Drugs of choice99,100: | Pyrimethamine101  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 wk102  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 *(Trichinella spiralis)* | | | |
| Drugs of choice: | Steroids for severe symptoms  plus  Albendazole7 | Prednisone 30-60 mg PO daily × 10-15 days  400 mg PO bid × 8-14 days | 400 mg PO bid × 8-14 days |
| Alternative: | Mebendazole7 | 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 *(Trichomonas vaginalis)* | | | |
| Drug of choice103: | Metronidazole | 2 g PO once or 500 mg PO bid × 7 days | 15 mg/kg/day PO in 3 doses × 7 days |
| *or* | Tinidazole5 | 2 g PO once | 50 mg/kg PO once (max 2 g) |
| Trichostrongylus infection | | | |
| Drug of choice: | Pyrantel pamoate7 | 11 mg/kg base PO once (max 1 g) | 11 mg/kg PO once (max 1 g) |
| Alternative: | Mebendazole7 | 100 mg PO bid × 3 days | 100 mg PO bid × 3 days |
| *or* | Albendazole7 | 400 mg PO once | 400 mg PO once |
| Trichuriasis (*Trichuris trichiura,* whipworm) | | | |
| Drug of choice: | Mebendazole | 100 mg PO bid × 3 days | 100 mg PO bid × 3 days |
| Alternative: | Albendazole7 Ivermectin7 | 400 mg PO × 3 days  200 μg/kg PO × 3 days | 400 mg PO × 3 days  200 μg/kg PO × 3 days |
| Trypanosomiasis104 | | | |
| Trypanosoma cruzi  (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* | Nifurtimox105 | 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).

**Chapter 279** ◆ Principles of Antiparasitic Therapy **1687**

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| --- | --- | --- | --- | --- |
| **Table 279-1** | Drugs for Parasitic Infections—cont’d | | | |
| **INFECTION** | | **DRUG** | **ADULT DOSAGE** | **PEDIATRIC DOSAGE** |
| Trypanosoma brucei gambiense (West African trypanosomiasis, sleeping sickness) | | | | |
| Hemolymphatic stage | | | | |
| Drug of choice106: | | Pentamidine isethionate7 | 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: | | Melarsoprol107 | 2.2 mg/kg/day IV × 10 days | 2.2 mg/kg/day IV × 10 days |
| *or* | | Eflornithine108 | 400 mg/kg/day IV in 4 doses × 14 d | 400 mg/kg/day in 4 doses × 14 days |
| Trypanosoma brucei rhodesiense (East African trypanosomiasis, sleeping sickness) | | | | |
| Hemolymphatic 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: | | Melarsoprol107 | 2.2 mg/kg/day × 10 days | 2.2 mg/kg/day × 10 days |
| Visceral larva migrans109 (Toxocariasis) | | | | |
| Drugs of choice: | | Albendazole7 Mebendazole7 | 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 | | | | |
| Wuchereria bancrofti, 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.*](http://www.medicalletter.org/)

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| **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 Colitis or liver abscess: 35-50 mg/kg/day in 3 divided doses 7-10 days for 7-10 days  *or*  Tinidazole Colitis: 2 g once daily for 3 days Colitis: 50 mg/kg/day once daily for 3 days  Liver abscess: 2 g once daily for 3-5 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 Nitazoxanide  Metronidazole | | 2 g once  500 mg bid for 3 days  250 mg tid for 5-7 days | >3 yr: 50 mg/kg once  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  15 mg/kg/day in 3 divided doses for 5-7 days |
| ALTERNATIVE  Albendazole Paromomycin Quinacrine† | | 400 mg once a day for 5 days  25-35 mg/kg/day in 3 divided doses for 5-10 days  100 mg tid for 5-7 days | >6 yr: 400 mg once a day for 5 days Not recommended  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).

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| **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 |

**Chapter 288** ◆ Malaria *(Plasmodium)* **1715**

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| **Table 288-2** CDC Guidelines for Treatment of Malaria in the United States in the United States–Updated July 1, 2013) | | | (Based | on Drugs Currently Available for Use |
| (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/  *P. falciparum*  *or*  Species not identified If “species not  identified” is subsequently diagnosed as *P. vivax* or *P. ovale:* see  *P. vivax* and *P. ovale* (below) regarding treatment with primaquine | Chloroquine-resistant or unknown resistance2  (All malarious regions except those specified as chloroquine-sensitive listed in the box below) | A. Atovaquone-proguanil (Malarone)3 A. Atovaquone-proguanil (Malarone)3 Adult tab **=** 250 mg atovaquone/100 mg Adult tab **=** 250 mg atovaquone/100 mg  proguanil proguanil  4 adult tabs PO qd × 3 days 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: 1adult 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 plus 1 of the following: C. Quinine sulfate4 plus 1 of the following: doxycycline, tetracycline, or clindamycin doxycycline6, tetracycline,6 or clindamycin Quinine sulfate: 542 mg base (=650 mg Quinine sulfate: 8.3 mg base/kg (=10 mg  salt)4 PO tid × 3 or 7 days5 salt/kg) PO tid × 3 or 7 days5 Doxycycline: 100 mg PO bid × 7 days Doxycycline: 2.2 mg/kg PO every 12 hr × Tetracycline: 250 mg PO qid × 7 days 7 days  Clindamycin: 20 mg base/kg/day PO Tetracycline: 25 mg/kg/day PO divided divided tid × 7 days qid × 7 days  Clindamycin: 20 mg base/kg/day PO divided tid × 7 days  D. Mefloquine (Lariam and generics)7 D. Mefloquine (Lariam and generics)7  684 mg base (=750 mg salt) PO as 13.7 mg base/kg (=15 mg salt/kg) PO as initial dose, followed by 456 mg base initial dose, followed by 9.1 mg base/kg (=500 mg salt) PO given 6-12 hr after (=10 mg salt/kg) PO given 6-12 hr after initial dose initial dose. Total dose = 25 mg salt/kg  Total dose = 1,250 mg salt | | |
| Uncomplicated malaria/  *P. falciparum*  *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 Chloroquine phosphate (Aralen and generics)8 generics)8  600 mg base (=1,000 mg salt) PO 10 mg base/kg PO immediately, followed by immediately, followed by 300 mg base 5 mg base/kg PO at 6, 24, and 48 hr  (=500 mg salt) PO at 6, 24, and 48 hr Total dose: 25 mg base/kg Total dose: 1,500 mg base (=2,500 mg salt) *or*  *or* Hydroxychloroquine (Plaquenil and generics) Hydroxychloroquine (Plaquenil and generics) 10 mg base/kg PO immediately, followed by 620 mg base (=800 mg salt) PO immediately, 5 mg base/kg PO at 6, 24, and 48 hr  followed by 310 mg base (=400 mg salt) PO Total dose: 25 mg base/kg at 6, 24, and 48 hr  Total dose: 1,550 mg base (=2,000 mg salt) | | |

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

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| **Table 288-2** CDC Guidelines for Treatment of Malaria in the United States (Based in the United States–Updated July 1, 2013)—cont’d | | on Drugs Currently Available for Use |
| **CLINICAL** |  |  |
| **DIAGNOSIS/** |  | **RECOMMENDED DRUG AND PEDIATRIC** |
| ***PLASMODIUM*** | **REGION INFECTION RECOMMENDED DRUG** | **DOSE**1 **PEDIATRIC DOSE SHOULD *NEVER*** |
| **SPECIES** | **ACQUIRED AND ADULT DOSE**1 | **EXCEED ADULT DOSE** |
| Uncomplicated malaria/*P. malariae* or *P. knowlesi* | 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/*P. vivax* or  *P. ovale* | All regions Chloroquine phosphate8 plus primaquine  Note: for suspected phosphate9  chloroquine-resistant Chloroquine phosphate: treatment as  *P. vivax,* see row above  below Primaquine phosphate: 30 mg base PO qd  × 14 days  *or*  Hydroxychloroquine plus primaquine phosphate9  Hydroxychloroquine: treatment as above  Primaquine phosphate: 30 mg base PO qd  × 14 days | Chloroquine phosphate8 plus primaquine phosphate9  Chloroquine phosphate: treatment as above  Primaquine: 0.5 mg base/kg PO qd × 14 days  *or*  Hydroxychloroquine plus primaquine phosphate9  Hydroxychloroquine: treatment as above  Primaquine phosphate: 0.5 mg base/kg PO qd × 14 days |
| Uncomplicated malaria/*P. vivax* | Chloroquine- A. Quinine sulfate plus either doxycycline or resistant10 tetracycline plus primaquine phosphate9  (Papua New Guinea Quinine sulfate: treatment as above  and Indonesia) Doxycycline or tetracycline: Treatment as  above  Primaquine phosphate: treatment as above | A. Quinine sulfate plus either doxycycline6 or tetracycline6 plus primaquine phosphate9  Quinine sulfate: treatment as above  Doxycycline or tetracycline: treatment as above  Primaquine phosphate: treatment as above  B. Atovaquone-proguanil plus primaquine phosphate9  Atovaquone-proguanil: treatment as above  Primaquine phosphate: treatment as above  C. Mefloquine plus primaquine phosphate9 Mefloquine: treatment as above Primaquine phosphate: treatment as above |
|  | B. Atovaquone-proguanil plus primaquine phosphate9  Atovaquone-proguanil: treatment as above  Primaquine phosphate: treatment as above  C. Mefloquine plus primaquine phosphate9 Mefloquine: treatment as above Primaquine phosphate: treatment as above |
| Uncomplicated malaria: alternatives for pregnant women11-13 | Chloroquine-sensitive Chloroquine phosphate: treatment as above (See uncomplicated *or*  malaria sections Hydroxychloroquine: treatment as above above for  chloroquine-sensitive species by region)  Chloroquine-resistant Quinine sulfate plus clindamycin  (See sections above Quinine sulfate: treatment as above for regions with Clindamycin: treatment as above chloroquine-resistant *or*  *P. falciparum and* Mefloquine: treatment as above  *P. vivax*) | 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.

**Chapter 288** ◆ Malaria *(Plasmodium)* **1717**

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| **Table 288-2** CDC Guidelines for Treatment of Malaria in the United States (Based in the United States–Updated July 1, 2013)—cont’d | | | on Drugs Currently Available for Use |
| **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 malaria14-16 | All regions | Quinidine gluconate14 plus 1 of the following: doxycycline, tetracycline, or clindamycin  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  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  Tetracycline: treatment as above  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  *Investigational new drug (contact CDC for information):*  Artesunate followed by 1 of the following: atovaquone-proguanil (Malarone), doxycycline (clindamycin in pregnant women), or mefloquine | Quinidine gluconate14 plus one of the following: doxycycline4, tetracycline4, or clindamycin  Quinidine gluconate: same mg/kg dosing and recommendations as for adults  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  Tetracycline: treatment as above  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.  *Investigational new drug (contact CDC for information):* Artesunate followed by 1 of the following: atovaquone-proguanil (Malarone), clindamycin, or mefloquine |

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*](http://www.cdc.gov/malaria/resources/pdf/treatmenttable.pdf)

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| **Table 288-3** | Treatment of Uncomplicated Malaria |
| **REGIMENS** | |
| All *Plasmodium falciparum* Artemether-lumefantrine 1.5 mg/ malaria 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 *P. falciparum* Artesunate 4 mg/kg daily for 3 days malaria 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 Chloroquine 10 mg base per kg *Plasmodium vivax*‡*,* immediately, followed by 10 mg/kg *Plasmodium malariae*‡*,* at 24 hr and 5 mg/kg at 48 hr *Plasmodium ovale*‡*,*  *Plasmodium knowlesi*‡ | |

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

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| **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 | | 59 (55) | 37 (84) |
| fluid | |  |  |
| 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  Mental retardation Convulsions Spasticity and palsies  Severely impaired vision Hydrocephalus or  microcephalus Deafness Normal | | 70 PATIENTS (%) | 31 PATIENTS (%) |
| 62 (89) | 25 (81) |
| 58 (83) | 24 (77) |
| 53 (76) | 18 (58) |
| 48 (69) | 13 (42) |
| 31 (44) | 2 (6) |
| 12 (17) | 3 (10) |
| 6 (9) | 5 (16) |

†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.*

\*Intramuscular injections should be given to the anterior thigh.

* 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.

Treatment of Severe Malaria in Adults and Children

**Table 288-4**

†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.

\*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: 14 tab/wk  20-30 kg: 1 tab/wk  2  31-45 kg: 3 4 tab/wk  >45 kg: 1 tab/wk (228 mg base)  2 mg/kg daily (max 100 mg)  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 | Once weekly dosing  Inexpensive  Pediatric formulation  Generally well tolerated | 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  Children going to area for <4 wk who cannot take or cannot obtain atovaquone- proguanil  Children going to malaria endemic area for <4 wk |
|  | Doxycycline‡  Atovaquone/ proguanil§ (Malarone) | Cannot give to children  <8 yr  Daily dosing  Must take with food or causes stomach upset  Photosensitivity Daily dosing Expensive  Can cause stomach upset |
| Chloroquine- susceptible area | Chloroquine phosphate  Drugs used for chloroquine-resistant areas can also be used in chloroquine- susceptible areas | 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 *Plasmodium falciparum* or *Plasmodium vivax* that is chloroquine susceptible |

\*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

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| **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 | |

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| **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 | |

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| **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 | |

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| **Table 306-4** | Differential Diagnosis of Emesis During Childhood | | |
| **INFANT** | | **CHILD** | **ADOLESCENT** |
| COMMON | |  |  |
| Gastroenteritis | | Gastroenteritis | Gastroenteritis |
| Gastroesophageal reflux | | Systemic infection | GERD |
| Overfeeding | | Gastritis | Systemic infection |
| Anatomic obstruction\* | | Toxic ingestion | Toxic ingestion |
| Systemic infection† | | Pertussis syndrome | Gastritis |
| Pertussis syndrome | | Medication | Sinusitis |
| Otitis media | | Reflux (GERD) | Inflammatory bowel disease |
|  | | Sinusitis | Appendicitis |
|  | | Otitis media | Migraine |
|  | | Anatomic obstruction\* | Pregnancy |
|  | | Eosinophilic esophagitis | Medications |
|  | |  | Ipecac abuse, bulimia |
|  | |  | Concussion |
| RARE | |  |  |
| Adrenogenital syndrome | | Reye syndrome | Reye syndrome |
| Inborn errors of metabolism | | Hepatitis | Hepatitis |
| Brain tumor (increased intracranial pressure) | | Peptic ulcer | Peptic ulcer |
| Subdural hemorrhage | | Pancreatitis | Pancreatitis |
| Food poisoning | | Brain tumor | Brain tumor |
| Rumination | | Increased intracranial pressure | Increased intracranial pressure |
| Renal tubular acidosis | | Middle ear disease | Concussion |
| Ureteropelvic junction obstruction | | Chemotherapy | Middle ear disease |
| Pseudoobstruction | | Achalasia | Chemotherapy |
|  | | Cyclic vomiting (migraine) | Cyclic vomiting (migraine) |
|  | | Esophageal stricture | Biliary colic |
|  | | Duodenal hematoma | Renal colic |
|  | | Inborn error of metabolism | Diabetic ketoacidosis |
|  | | Pseudoobstruction | Pseudoobstruction |
|  | |  | Intestinal tumor |
|  | |  | Achalasia |

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

†Meningitis, sepsis.

GERD, gastroesophageal reflux disease, inguinal hernia.

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| **Table 306-5** | Causes of Gastrointestinal Obstruction | |
| ESOPHAGUS | | Ileal atresia |
| Meconium ileus |
| *Congenital* | |
| Meckel diverticulum with volvulus or intussusception |
| Esophageal atresia | |
| Inguinal hernia |
| Vascular rings | |
| Internal hernia |
| Schatzki ring | |
| Intestinal duplication |
| Tracheobronchial remnant | |
| Pseudoobstruction |
| *Acquired* | |
| *Acquired* |
| Esophageal stricture | |
| Postsurgical adhesions |
| Foreign body | |
| Crohn disease |
| Achalasia | |
| Intussusception |
| Chagas disease | |
| Distal ileal obstruction syndrome (cystic fibrosis)  Duodenal hematoma  Superior mesenteric artery syndrome |
| Collagen vascular disease | |
| STOMACH  *Congenital* | |
| COLON  *Congenital* Meconium plug Hirschsprung disease  Colonic atresia, stenosis Imperforate anus  Rectal stenosis Pseudoobstruction Volvulus  Colonic duplication  *Acquired*  Ulcerative colitis (toxic megacolon) Chagas disease  Crohn disease  Fibrosing colonopathy (cystic fibrosis) |
| Antral webs | |
| Pyloric stenosis | |
| *Acquired* | |
| Bezoar, foreign body | |
| Pyloric stricture (ulcer) | |
| Chronic granulomatous disease of childhood | |
| Eosinophilic gastroenteritis | |
| Crohn disease | |
| Epidermolysis bullosa | |
| SMALL INTESTINE | |
| *Congenital* | |
| Duodenal atresia | |
| Annular pancreas | |
| Malrotation/volvulus | |
| Malrotation/Ladd bands | |

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| **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  Serotoninergic 5-HT3 antagonist  Phenothiazines (extrapyramidal, hematologic side effects)  Steroids Cannabinoids | | Metoclopramide  Ondansetron (Zofran) Prochlorperazine (Compazine) Chlorpromazine (Thorazine) Dexamethasone (Decadron) Tetrahydrocannabinol (Nabilone) | 0.5-1.0 mg/kg IV qid, with antihistamine prophylaxis of extrapyramidal side effects  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) |
| CYCLIC VOMITING SYNDROME  *Supportive* Analgesic Anxiolytic, sedative  Antihistamine, sedative  *Abortive*  Serotoninergic 5-HT3 antagonist  Nonsteroidal antiinflammatory agent (GI ulceration side effect)  Serotoninergic 5-HT1D 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  Antimigraine antiepileptic  Low-estrogen oral contraceptives | | Propranolol (Inderal) Cyproheptadine (Periactin) Amitriptyline (Elavil)  Phenobarbital (Luminal) Erythromycin (see above)  Consider for catamenial CVS episodes | 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  2-3 mg/kg qhs |

\*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.*

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| **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 |

**Chapter 306** ◆ Major Symptoms and Signs of Digestive Tract Disorders **1763**

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| **Table 306-9** | Supportive and Nonpharmacologic Therapies for Vomiting Episodes | |
| **DISEASE** | | **THERAPY** |
| All | | Treat cause   * Obstruction: operate * Allergy: change diet (±steroids) * Metabolic error: Rx defect * Acid peptic disease: H2RAs, PPIs, etc. |
| COMPLICATIONS  Dehydration Hematemesis Esophagitis Malnutrition Meconium ileus DIOS  Intussusception Hematemesis  Sigmoid volvulus Reflux  Psychogenic components | | IV fluids, electrolytes  Transfuse, correct coagulopathy H2RAs, PPIs  NG or NJ drip feeding useful for many chronic conditions Gastrografin enema  Gastrografin enema; balanced colonic lavage solution (e.g., GoLYTELY) Barium enema; air reduction enema  Endoscopic: injection sclerotherapy or banding of esophageal varices; injection therapy, fibrin sealant application, or heater probe electrocautery for selected upper GI tract lesions  Colonoscopic decompression  Positioning; dietary measures (infants: rice cereal, 1 tbs/oz of formula)  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.*

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| **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, toxigenic *Escherichia coli*; carcinoid, VIP, neuroblastoma, congenital chloride diarrhea, *Clostridium difficile*, 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 | *Salmonella, Shigella* infection; amebiasis; *Yersinia, Campylobacter* 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×]

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

Criteria for Cyclical Vomiting Syndrome

**Table 306-6**

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

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| **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 | Periumbilical-lower abdomen | Back | Alternating cramping (colic) and painless periods | Distention, obstipation, emesis, increased bowel sounds |
| Appendicitis | | Acute | Periumbilical, 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 | Periumbilical-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 |

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| **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 | |

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| **Table 306-15** | Differential Diagnosis of Gastrointestinal Bleeding in Childhood | | |
| **INFANT** | | **CHILD** | **ADOLESCENT** |
| COMMON  Bacterial enteritis  Milk protein allergy intolerance Intussusception  Swallowed maternal blood Anal fissure Lymphonodular hyperplasia | | Bacterial enteritis Anal fissure Colonic polyps Intussusception  Peptic ulcer/gastritis Swallowed epistaxis  Prolapse (traumatic) gastropathy secondary to emesis  Mallory-Weiss syndrome | Bacterial enteritis Inflammatory bowel disease Peptic ulcer/gastritis  Prolapse (traumatic) gastropathy secondary to emesis  Mallory-Weiss syndrome Colonic polyps  Anal fissure |
| RARE  Volvulus  Necrotizing enterocolitis Meckel diverticulum Stress ulcer, gastritis  Coagulation disorder (hemorrhagic disease of newborn)  Esophagitis | | Esophageal varices Esophagitis  Meckel diverticulum Lymphonodular hyperplasia Henoch-Schönlein purpura Foreign body  Hemangioma, arteriovenous malformation Sexual abuse  Hemolytic-uremic syndrome Inflammatory bowel disease Coagulopathy  Duplication cyst | Hemorrhoids Esophageal varices Esophagitis  Pill ulcer  Telangiectasia-angiodysplasia Graft-vs-host disease 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 Lactose intolerance  Parasite infection (especially *Giardia*) Excess fructose or sorbitol ingestion  Crohn disease Peptic ulcer  Esophagitis  Meckel diverticulum Recurrent intussusception  Internal, inguinal, or abdominal wall hernia Chronic appendicitis or appendiceal  mucocele | Hx of stool retention, evidence of constipation on examination  Symptoms may be associated with lactose ingestion; bloating, gas, cramps, and diarrhea  Bloating, gas, cramps, and diarrhea  Nonspecific abdominal pain, bloating, gas, and diarrhea  See Chapter 336  Burning or gnawing epigastric pain; worse on awakening or before meals; relieved with antacids  Epigastric pain with substernal burning Periumbilical or lower abdominal pain; may have  blood in stool (usually painless)  Paroxysmal severe cramping abdominal pain; blood may be present in stool with episode  Dull abdomen or abdominal wall pain  Recurrent RLQ pain; often incorrectly diagnosed, may be rare cause of abdominal pain | Hx and PE; plain x-ray of abdomen  Trial of lactose-free diet; lactose breath hydrogen test  Stool evaluation for O&P; specific immunoassays for *Giardia*  Large intake of apples, fruit juice, or candy or chewing gum sweetened with sorbitol  Esophagogastroduodenoscopy, upper GI contrast x-rays, or MRI enteroscopy  Esophagogastroduodenoscopy Meckel scan or enteroclysis  Identify intussusception during episode or lead point in intestine between episodes with contrast studies of GI tract  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  Other genitourinary disorders | Dull suprapubic pain, flank pain Unilateral abdominal or flank pain  Progressive, severe pain; flank to inguinal region to testicle  Suprapubic or lower abdominal pain; genitourinary symptoms | Urinalysis and urine culture; renal scan Ultrasound of kidneys  Urinalysis, ultrasound, IVP, CT  Ultrasound of kidneys and pelvis; gynecologic evaluation |
| MISCELLANEOUS CAUSES  Abdominal migraine Abdominal epilepsy  Gilbert syndrome  Familial Mediterranean fever  Sickle cell crisis Lead poisoning  Henoch-Schönlein purpura Angioneurotic edema  Acute intermittent porphyria | See text; nausea, family Hx migraine Might have seizure prodrome  Mild abdominal pain (causal or coincidental?); slightly elevated unconjugated bilirubin  Paroxysmal episodes of fever, severe abdominal pain, and tenderness with other evidence of polyserositis  Anemia  Vague abdominal pain ± constipation  Recurrent, severe crampy abdominal pain, occult blood in stool, characteristic rash, arthritis  Swelling of face or airway, crampy pain  Severe pain precipitated by drugs, fasting, or infections | Hx  EEG (can require > 1 study, including sleep-deprived EEG)  Serum bilirubin  Hx and PE during an episode, DNA diagnosis  Hematologic evaluation Serum lead level  Hx, PE, urinalysis  Hx, PE, upper GI contrast x-rays, serum C1 esterase inhibitor  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.

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| **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.*

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| **Table 315-1** | Differential Diagnosis of Oral Ulceration | |
| **CONDITION** | | **COMMENT** |
| COMMON  Aphthous (canker sore) Traumatic  Hand, foot, mouth disease Herpangina  Herpetic gingivostomatitis  Recurrent herpes labialis Chemical burns  Heat burns | | Painful, circumscribed lesions; recurrences  Accidents, chronic cheek biter, or after dental local anesthesia  Painful; lesions on tongue, anterior oral cavity, hands, and feet  Painful; lesions confined to soft palate and oropharynx  Vesicles on mucocutaneous borders; painful, febrile  Vesicles on lips; painful Alkali, acid, aspirin; painful Hot food, electrical |
| UNCOMMON  Neutrophil defects  Systemic lupus erythematosus Behçet syndrome  Necrotizing ulcerative gingivostomatitis  Syphilis  Oral Crohn disease Histoplasmosis Pemphigus  Stevens-Johnson syndrome | | Agranulocytosis, leukemia, cyclic neutropenia; painful  Recurrent, may be painless Resembles aphthous lesions;  associated with genital ulcers, uveitis  Vincent stomatitis; painful  Chancre or gumma; painless Aphthous-like; painful Lingual  May be isolated to the oral cavity May be isolated or appear initially  in the oral cavity |

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| **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 |

**Chapter 327** ◆ Ingestions **1795**

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| **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/*](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.*

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| **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.*

**1806 Part XVIII** ◆ The Digestive System

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| **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 | |

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| **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 |

\*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.*

\*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.*

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| **Table 332-3** | Suggested Medications and Dosages for Disimpaction | | |
| **MEDICATION** | | **AGE** | **DOSAGE** |
| RAPID RECTAL DISIMPACTION  Glycerin suppositories Phosphate enema  Milk of molasses enema | | Infants and toddlers  <1 yr  >1 yr  Older children | 60 mL  6 mL/kg bodyweight, up to 135 mL twice (1 : 1 milk : molasses) 200-600 mL |
| SLOW ORAL DISIMPACTION IN OLDER CHILDREN  *Over 2-3 Days*  Polyethylene glycol with electrolytes  *Over 5-7 Days*  Polyethylene without electrolytes Milk of magnesia  Mineral oil Lactulose or sorbitol | |  | 25 mL/kg bodyweight/hr, up to 1000 mL/hr until clear fluid comes from the anus  1.5 g/kg bodyweight/day for 3 days   1. mL/kg bodyweight twice/day for 7 days 2. mL/kg bodyweight twice/day for 7 days 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.*

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| **Table 332-4** | Suggested Medications and Dosages for Maintenance Therapy of Constipation | | |
| **MEDICATION** | | **AGE** | **DOSE** |
| FOR LONG-TERM TREATMENT (YEARS)  Milk of magnesia Mineral oil Lactulose or sorbitol  Polyethylene glycol 3350 (MiraLAX) | | >1 mo  >12 mo  >1 mo  >1 mo | 1-3 mL/kg bodyweight/day, divided into 1-2 doses 1-3 mL/kg bodyweight/day, divided into 1-2 doses 1-3 mL/kg bodyweight/day, divided into 1-2 doses  0.7 g/kg bodyweight/day, divided into 1-2 doses |
| FOR SHORT-TERM TREATMENT (MONTHS)  Senna (Senokot) syrup, tablets  Glycerin enemas Bisacodyl suppositories | | 1-5 yr  5-15 yr  >10 yr  >10 yr | 5 mL (1 tablet) with breakfast, max 15 mL daily  2 tablets with breakfast, maximum 3 tablets daily 20-30 mL/day ( 1 glycerin and 1 normal saline)  2 2  10 mg daily |

**1810 Part XVIII** ◆ The Digestive System

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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.*

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| **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.*

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| **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 × a day  Ranitidine 4-10 mg/kg/day Divided 2 or 3 × a day  Famotidine 1-2 mg/kg/day Divided twice a day  Nizatidine 5-10 mg/kg/day divided twice a day Older than 12 yr: 150 mg twice a day | | Syrup: 300 mg/mL  Tablets: 200, 300, 400, 800 mg Syrup: 75 mg/5 mL  Tablets: 75, 150, 300 mg Syrup: 40 mg/5 mL Tablets: 20, 40 mg  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  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  Rabeprazole 1-11 yr(weigh <15 kg): 5 mg/day  1-11 yr (weigh >15 kg): 10 mg/day  >12 yr: 20 mg tablet  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 | | Capsules: 10, 20, 40 mg  Capsules: 15, 30 mg  Powder packet: 15, 30 mg  SoluTab: 15, 30 mg  Delayed release capsule: 5, 10 mg Delayed release tablet: 20 mg  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 |

**1820 Part XVIII** ◆ The Digestive System

* 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

Montreal Classification of Extent and Severity of Ulcerative Colitis

**Table 336-3**

E, extent; S, severity.

*From Ordàs I, Eckmann L, Talamini M, et al: Ulcerative colitis,* Lancet

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| **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% |

*380:1606–1616, 2012 (Panel 2, p. 1610).*

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 gastroduodenitis

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

Etiologic Classification of Peptic Ulcers

**Table 335-1**

\*Requires search for other specific causes.

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| **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) | |  |

**Chapter 336** ◆ Inflammatory Bowel Disease **1821**

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| **Table 336-2** Extraintestinal Complications of Inflammatory Bowel Disease | |
| MUSCULOSKELETAL  Peripheral arthritis Granulomatous monoarthritis Granulomatous synovitis Rheumatoid arthritis Sacroiliitis  Ankylosing spondylitis  Digital clubbing and hypertrophic osteoarthropathy Periosteitis  Osteoporosis, osteomalacia Rhabdomyolysis  Pelvic osteomyelitis  Recurrent multifocal osteomyelitis Relapsing polychondritis | Intestinal losses   * Electrolytes * Minerals * Nutrients   Increased caloric needs   * Inflammation * Fever   HEMATOLOGIC  Anemia: iron deficiency (blood loss)  Vitamin B12 (ileal disease or resection, bacterial overgrowth, folate deficiency)  Anemia of chronic inflammation Anaphylactoid purpura (Crohn disease) Hyposplenism  Autoimmune hemolytic anemia Coagulation abnormalities  Increased activation of coagulation factors Activated fibrinolysis  Anticardiolipin antibody  Increased risk of arterial and venous thrombosis with cerebrovascular stroke, myocardial infarction, peripheral arterial, and venous occlusions |
| SKIN AND MUCOUS MEMBRANES  Oral lesions Cheilitis  Aphthous stomatitis, glossitis Granulomatous oral Crohn disease  Inflammatory hyperplasia fissures and cobblestone mucosa Peristomatitis vegetans |
| DERMATOLOGIC  Erythema nodosum Pyoderma gangrenosum Sweet syndrome Metastatic Crohn disease Psoriasis  Epidermolysis bullosa acquisita Perianal skin tags  Polyarteritis nodosa |
| RENAL AND GENITOURINARY  Metabolic   * Urinary crystal formation (nephrolithiasis, uric acid, oxylate) Hypokalemic nephropathy   Inflammation   * Retroperitoneal abscess * Fibrosis with ureteral obstruction * Fistula formation Glomerulitis Membrane nephritis   Renal amyloidosis, nephrotic syndrome |
| OCULAR  Conjunctivitis Uveitis, iritis Episcleritis Scleritis  Retrobulbar neuritis  Chorioretinitis with retinal detachment Crohn keratopathy  Posterior segment abnormalities Retinal vascular disease |
| PANCREATITIS  Secondary to medications (sulfasalazine, 6-mercaptopurine, azathioprine, parenteral nutrition)  Ampullary Crohn disease Granulomatous pancreatitis  Decreased pancreatic exocrine function Sclerosing cholangitis with pancreatitis |
| BRONCHOPULMONARY  Chronic bronchitis with bronchiectasis Chronic bronchitis with neutrophilic infiltrates Fibrosing alveolitis  Pulmonary vasculitis  Small airway disease and bronchiolitis obliterans Eosinophilic lung disease  Granulomatous lung disease Tracheal obstruction | HEPATOBILIARY  Primary sclerosing cholangitis  Small duct primary sclerosing cholangitis (pericholangitis) Carcinoma of the bile ducts  Fatty infiltration of the liver Cholelithiasis  Autoimmune hepatitis |
| ENDOCRINE AND METABOLIC  Growth failure, delayed sexual maturation Thyroiditis  Osteoporosis, osteomalacia |
| CARDIAC  Pleuropericarditis Cardiomyopathy Endocarditis Myocarditis |
| NEUROLOGIC  Peripheral neuropathy Meningitis  Vestibular dysfunction Pseudotumor cerebri Cerebral vasculitis Migraine |
| MALNUTRITION  Decreased intake of food   * Inflammatory bowel disease * Dietary restriction Malabsorption * Inflammatory bowel disease * Bowel resection * Bile salt depletion * Bacterial overgrowth |

*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.*

**Chapter 336** ◆ Inflammatory Bowel Disease **1823**

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| **Table 336-4** | Infectious Agents Mimicking Inflammatory Bowel Disease | | |
| **AGENT MANIFESTATIONS** | | **DIAGNOSIS** | **COMMENTS** |
| BACTERIAL  *Campylobacter jejuni* Acute diarrhea, fever, fecal blood, and leukocytes  *Yersinia enterocolitica* Acute → chronic diarrhea, right lower  quadrant pain, mesenteric adenitis– pseudoappendicitis, fecal blood, and leukocytes  Extraintestinal manifestations, mimics Crohn disease  *Clostridium difficile* Postantibiotic onset, watery → bloody  diarrhea, pseudomembrane on sigmoidoscopy  *Escherichia coli* O157:H7 Colitis, fecal blood, abdominal pain  *Salmonella* Watery → bloody diarrhea, foodborne, fecal leukocytes, fever, pain, cramps  *Shigella* Watery → bloody diarrhea, fecal leukocytes, fever, pain, cramps  *Edwardsiella tarda* Bloody diarrhea, cramps  *Aeromonas hydrophila* Cramps, diarrhea, fecal blood  *Plesiomonas* Diarrhea, cramps  *shigelloides*  Tuberculosis Rarely bovine, now *Mycobacterium tuberculosis*  Ileocecal area, fistula formation | | Culture Culture  Cytotoxin assay  Culture and typing Culture  Culture  Culture Culture  Culture  Culture, purified protein derivative, biopsy | Common in adolescents, may relapse  Common in adolescents as fever of unknown origin, weight loss, abdominal pain  May be nosocomial  Toxic megacolon possible  Hemolytic uremic syndrome Usually acute  Dysentery symptoms  Ulceration on endoscopy May be chronic Contaminated drinking water Shellfish source  Can mimic Crohn disease |
| PARASITES  *Entamoeba histolytica* Acute bloody diarrhea and liver  abscess, colic  *Giardia lamblia* Foul-smelling, watery diarrhea, cramps,  flatulence, weight loss; no colonic involvement | | Trophozoite in stool, colonic mucosal flask ulceration, serologic tests  “Owl”-like trophozoite and cysts in stool; rarely duodenal intubation | Travel to endemic area May be chronic |
| AIDS-ASSOCIATED ENTEROPATHY  *Cryptosporidium* Chronic diarrhea, weight loss  *Isospora belli* As in *Cryptosporidium Cytomegalovirus* Colonic ulceration, pain, bloody  diarrhea | | Stool microscopy  Culture, biopsy | Mucosal findings not like inflammatory bowel disease  Tropical location  More common when on immunosuppressive medications |

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| **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 B12 | | CD | +++ |  | + |
| Vitamin B1, B2, B6 | | CD > UC |  |  | ++ |
| Vitamin C, glutathione (antioxidants) | | CD and UC |  | ++ | ++ |
| Folate | | CD and UC | ++ |  | + |
| Calcium, magnesium, selenium, zinc | | CD and UC | ++ | +++ | + |
| Polyunsaturated fatty acids | | CD | ++ |  | ++ |

**1824 Part XVIII** ◆ The Digestive System

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| **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 Behçet 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 | |

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| **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) | | Hyperchloremic acidosis, failure to thrive |
| Immunodeficiency and autoinflammatory diseases (see Table 336-5) | | Failure to thrive, opportunistic infections, eczema |

\*May be the same as IPEX

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| **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., *Campylobacter, Yersinia* spp.), lymphoma, intussusception, mesenteric adenitis, Meckel diverticulum, ovarian cyst |
| Chronic periumbilical 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, *Cryptosporidium*  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 |

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 (*i*mmune dysregulation, *p*olyendocrinopathy, *e*nteropathy, *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

Malabsorption Disorders and Chronic Diarrhea Associated with Generalized Mucosal Defect

**Table 338-1**

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

Other Causes of Flat Mucosa

**Table 338-7**

**1832 Part XVIII** ◆ The Digestive System

|  |  |
| --- | --- |
| **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/colipase deficiency Chronic pancreatitis Protein–calorie malnutrition  Decreased pancreozymin/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 B12 malabsorption  Autoimmune pernicious anemia  Decreased gastric acid (H2 blockers or proton pump inhibitors) Terminal ileal disease (e.g., Crohn disease) or resection  Inborn errors of vitamin B12 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 B12 Methotrexate: mucosal injury | |

|  |  |
| --- | --- |
| **Table 338-4** | Some Clinical Manifestations of Celiac Disease in Children and Adolescents |
| **(POSSIBLE)**  **SYSTEM MANIFESTATION CAUSE** | |
| Gastrointestinal Diarrhea Atrophy of the  Distended abdomen small bowel  Vomiting mucosa  Anorexia Malabsorption Weight loss  Failure to thrive Rectal prolapse Aphthous stomatitis Intussusception | |
| Hematologic Anemia Iron malabsorption | |
| Skeletal Rickets Calcium/vitamin D Osteoporosis malabsorption Enamel hypoplasia of  the teeth | |
| Muscular Atrophy Malnutrition | |
| Neurologic Peripheral neuropathy Thiamine/vitamin  Epilepsy B12 deficiency  Irritability  Cerebral calcifications Cerebellar ataxia | |
| Endocrinologic Short stature Malnutrition  Pubertas tarda Calcium/vitamin D  Secondary malabsorption hyperparathyroidism | |
| Dermatologic Dermatitis herpetiformis Autoimmunity  Alopecia areata Erythema nodosum | |
| Respiratory Idiopathic pulmonary hemosiderosis | |

**1836 Part XVIII** ◆ The Digestive System

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

Risk Groups for Celiac Disease Case-Finding

**Table 338-5**

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

Mucosal inflammation Infection Cytomegalovirus Bacterial overgrowth

Invasive bacterial infection *Clostridium difficile Helicobacter pylori Giardiasis*

Measles

*Strongyloides stercoralis* 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

Causes of Protein-Losing Enteropathy

**Table 338-8**

|  |  |
| --- | --- |
| **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 | |

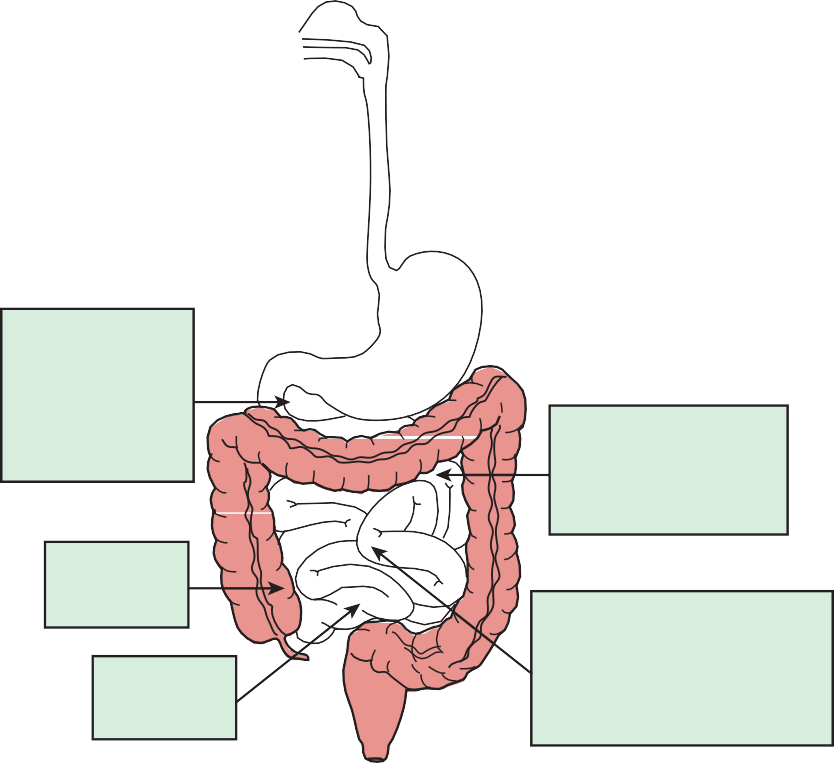
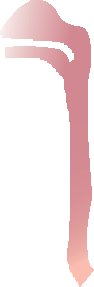
|  |  |
| --- | --- |
| **Table 340-8** | Differential Diagnosis of Acute Dysentery and Inflammatory Enterocolitis |
| SPECIFIC INFECTIOUS PROCESSES  Bacillary dysentery *(Shigella dysenteriae, Shigella flexneri, Shigella sonnei, Shigella boydii;* invasive *Escherichia coli)*  Campylobacteriosis *(Campylobacter 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 | |

|  |  |
| --- | --- |
| **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 | |

**Chapter 338** ◆ Disorders of Malabsorption **1843**

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



**Duodenum and**

**Proximal jejunum**

* Calcium
* Magnesium
* Phosphorus
* Iron
* Folic acid

**Proximal 100-200 cm**

**of small intestine**

* Carbohydrates
* Protein
* Water-soluble vitamins

**Colon**

* Water
* Electrolytes

**Distal ileum**

* + Vitamin B12
  + Bile acids

**Throughout the small**

**intestine**

* Monoglycerides and fatty acids as miceller complexes
* Medium chain triglycerides directly into portal circulation

**1870 Part XVIII** ◆ The Digestive System

|  |  |  |  |
| --- | --- | --- | --- |
| **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 Onset usually during the acute infection but can occur direct extraintestinal infections, subsequently  including *Salmonella, Shigella, Yersinia,* Prognosis depends on infection site  *Campylobacter, Clostridium difficile* | |
| Reactive arthritis | | *Salmonella, Shigella, Yersinia, Campylobacter, Cryptosporidium,*  *C. difficile* | 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 | | *Campylobacter* | Usually occurs a few weeks after the original infection Prognosis is good although 15-20% may have sequelae |
| Glomerulonephritis | | *Shigella, Campylobacter, Yersinia* | 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 | | *Campylobacter* | 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 | | *Yersinia, Campylobacter, Salmonella* | Although painful, is usually benign and more commonly seen in adolescents  Resolves with 4-6 wk |
| Hemolytic uremic syndrome | | *Shigella dysenteriae* 1, *Escherichia coli*  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 | | *Campylobacter, Yersinia* | 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.*

**Chapter 340** ◆ Acute Gastroenteritis in Children **1871**

|  |  |  |  |
| --- | --- | --- | --- |
| **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 | Continue breastfeeding or |
|  |  | for each diarrheal stool or vomiting | resume age-appropriate |
|  |  | episode >10 kg body weight: | normal diet after initial |
|  |  | 120-240 mL ORS for each diarrheal | hydration, including adequate |
|  |  | stool or vomiting episode | 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 | Same; if unable to drink, administer | Same |
|  | saline in 20 mL/kg body weight | through nasogastric tube or |  |
|  | IV until perfusion and mental | administer 5% dextrose in normal |  |
|  | status improve; then administer | saline with 20 mEq/L potassium |  |
|  | 100 mL/kg body weight ORS | chloride IV |  |
|  | over 4 hr or 5% dextrose normal |  |  |
|  | saline IV at twice maintenance |  |  |
|  | fluid rates |  |  |

\*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.*

***For dehydration ***

* For how long? Look at the child’s general

condition.

* Is there blood Is the child:

in the stool?

Lethargic or unconscious? Restless and irritable?

Look for sunken eyes.

Offer the child fluid. Is the child:

Not able to drink or drinking poorly? Drinking eagerly, thirsty?

Pinch the skin of the abdomen. Does it go back:

Very slowly (longer than 2 seconds)?

Slowly?

***Look and feel:***

***If yes, ask:***

**Does the child have diarrhea?**

|  |  |  |  |
| --- | --- | --- | --- |
|  | Two of the following signs:   * Lethargic or unconscious * Sunken eyes * Not able to drink or drinking poorly * Skin pinch goes back very slowly. | **Severe dehydration** | * If child has no other severe classification:   -Give fluid for severe dehydration (Plan C).  OR  ***If child also has another severe classification:***  ***- Refer URGENTLY to hospital with mother giving frequent sips of ORS on the way. Advise the mother to continue breastfeeding.***   * ***If child is two years or older and there is cholera in your area, give antibiotic for cholera.*** |
| Two of the following signs:   * Restless irritable * Sunken eyes * Drinks eagerly, thirsty * Skin pinch goes back slowly. | **Some dehydration** | * Give fluid and food for some dehydration (Plan B).   ***If child also has a severe classification:***  ***- Refer URGENTLY to hospital with mother giving frequent sips of ORS on the way. Advise the mother to continue breastfeeding.***   * Advise mother when to return immediately. * Follow-up in 2 days if not improving. |
| Not enough signs to classify as some or severe dehydration | **No dehydration** | * Give fluid and food to treat diarrhea at home (Plan A). * Advise mother when to return immediately. * Follow-up in 2 days if not improving. |

***Classify diarrhea***

|  |  |  |  |
| --- | --- | --- | --- |
|  | * Dehydration present | **Severe persistent diarrhea** | * Treat dehydration before referral unless the child has another severe classification. * Refer to hospital. |
| * No dehydration | **Persistent diarrhea** | * Advise the mother on feeding a child who has PERSISTENT DIARRHEA. * Give multivitamin, mineral supplement for two weeks * Advise mother when to return immediately * Follow-up in 5 days. |

***And if diarrhea 14 days or more***

***And if blood***

|  |  |  |  |
| --- | --- | --- | --- |
|  | * Blood in the stool | **Dysentery** | * ***Treat for 5 days with an oral antibiotic recommended for Shigella.*** * Advise mother when to return immediately * Follow-up in 5 days. |

***in stool***

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

**1872 Part XVIII** ◆ The Digestive System

**SUSPECTED**

**Persistent diarrhea**

(diarrhea ≥14 days with malnutrition)

**Assessment, resuscitation, and early stabilization** Intravenous and/or oral rehydration (hypo-osmolar ORS) Treat electrolyte imbalance

Screen and treat associated systemic infections

***Recovery***

**Follow-up for growth**

**Continued or recurrent diarrhea Poor weight gain**

**Continued breastfeeding Reduced lactose load by**

* Milk-cereal (usually rice-based) diet or
  + Replacement of milk with yogurt Micronutrient supplementation (zinc, vitamin A, folate)

**Reinvestigate for infections**

**Second-line dietary therapy (comminuted chicken or elemental diets)**

***Continued diarrhea and dehydration***

Reinvestigate to exclude **intractable diarrhea of infancy**

Intravenous hyperalimentation plus Slow or continuous enteral alimentation

**SEVERE DEHYDRATION**

Refer URGENTLY to hospital for IV or NG treatment

DANGER SIGNS, COUGH DIARRHEA

**ASSESS AND CLASSIFY**

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

**1874 Part XVIII** ◆ The Digestive System

|  |  |  |
| --- | --- | --- |
| **Table 340-12** Antibiotic Therapy for Infectious Diarrhea | | |
| **ORGANISM** | **DRUG OF CHOICE** | **DOSAGE AND DURATION OF TREATMENT** |
| *Shigella* (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 |
| *Salmonella* | 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 *Shigella* |
| *Aeromonas/Plesiomonas* | 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 |
| *Yersinia* 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 |  |
| *Campylobacter jejuni* | Erythromycin or azithromycin | Erythromycin PO 50 mg/kg/day divided tid × 5 days Azithromycin PO 5-10 mg/kg/day qid × 5 days |
| *Clostridium difficile* | 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 |
| *Entamoeba histolytica* | 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 |
| *Giardia lamblia* | 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 |
| *Cryptosporidium* 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 |
| *Isospora* spp. | TMP-SMX | PO TMP 5 mg/kg/day and SMX 25 mg/kg/day, bid × 7-10 days |
| *Cyclospora* spp. | TMP/SMX | PO TMP 5 mg/kg/day and SMX 25 mg/kg/day bid × 7 days |
| *Blastocystis hominis* | 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.

**Chapter 341** ◆ Chronic Diarrhea **1877**

|  |  |  |  |
| --- | --- | --- | --- |
| **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-sulphate deficiency, α2β1 and α6β4 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 | 0.2-04 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 μg/dL | 200-150 μg/dL | 149-100 μg/dL | <100 μg/dL |
| Serum iron | | 11-19 hr | 16-124 μg/dL | 15-13 μg/dL | 12-10 μg/dL | <10 μg/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** |
| α1-Antitripsin 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 μg/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 μg/g (in children to 4 yr of age)  <50 μg/g (older than 4 yr) | Intestinal inflammation |
| Fecal leukocytes | | <5/microscopic field | Colonic inflammation |
| Nitric oxide in rectal dialysate | | <5 μM of NO2−/NO3− | 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 |

**Chapter 341** ◆ Chronic Diarrhea **1879**

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

AD, autosomal dominant; AR, autosomal recessive.

**1882 Part XVIII** ◆ The Digestive System

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| **Table 341-6** | Stepwise Diagnostic Approach to Children with Diarrhea | |
| STEP 1  *Intestinal Microbiology* Stool cultures Microscopy for parasites Viruses  H2 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  *Evaluation of Intestinal Morphology:*  Endoscopy and standard jejunal/colonic histology\* Morphometry  PAS staining Electron microscopy  Imaging (upper or lower bowel series, capsule endoscopy) |
| STEP 3  *Special Investigations:*  Intestinal immunohistochemistry Antienterocyte antibodies  Serum chromogranin and catecholamines Autoantibodies  75SeHCAT 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.

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| **Table 341-7** | Treatment of Infectious Persistent Diarrhea | | | | |
|  | | **FACTOR** | **INDICATIONS** | **DOSAGE** | **DURATION** |
| Antibiotics | | Trimethoprim- sulfamethoxazole  Azithromycin | *Salmonella* spp.,  *Shigella Shigella* | 10-50 mg/kg/day in 2 divided doses–daily os  1° day: 12 mg/kg/day once–daily os  2°-5° days: 6 mg/kg/day once–daily os  20-30 mg/kg/day in 2 divided doses–os or iv 50-100 mg/kg/day once–im or iv  50 mg/kg/day in 2-3 divided doses–os  20-30 mg/kg/day in 2-3 divided doses–os | 7 days  5 days |
|  | | Ciprofloxacin Ceftriaxone Erythromycin Metronidazole | *Campylobacter Giardia, Entamoeba* | 7 days  7 days  7 days  7 days  Small intestinal bacterial overgrowth |
| Antiparasitic | | Nitazoxanide Albendazole | *Amebiasis*, *Giardiasis*, *Cryptosporidiosis* and helminth infections | 100 mg every 12 hr for children ages 12-47 mo  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 | 3 days |
| Probiotics | | *Lactobacillus* GG  *Saccharomyces boulardii* |  | 1-2 × 1011–1 × 1011 CFU/day–os  1 × 1010 germs live (500 mg)/day–os | For a minimum period of 7 days or until diarrhea stopped  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 |

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| **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.*

**1884 Part XVIII** ◆ The Digestive System

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

Childhood Functional GI Disorders: Child/Adolescent (Category H)

**Table 342-2**

*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.*

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

Alarm Symptoms Usually Needing Further Investigations

**Table 342-4**

|  |  |  |
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| **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 Rome Foundation:* Rome III disorders and criteria*.* [*www.romecriteria.org/criteria/.*](http://www.romecriteria.org/criteria/)

|  |  |
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| **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/.*](http://www.romecriteria.org/criteria/)

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:
   1. Improvement with defecation
   2. Onset associated with a change in frequency of stool
   3. 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

Rome III Criteria for Child/Adolescent Irritable Bowel Syndrome H2b

**Table 342-7**

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

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

Alarm Signs Usually Needing Further Investigations

**Table 342-5**

†“Discomfort” means an uncomfortable sensation not described as pain.

*Adapted from Rome Foundation:* Rome III disorders and criteria*.* [*http://www.romecriteria.org/criteria/*](http://www.romecriteria.org/criteria/)

**1894 Part XVIII** ◆ The Digestive System

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| **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 (109/L) 1 | |
| Polymorphonuclear-neutrophilia >7,500 (109/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.*

Prematurity Urogenital

* Cryptorchidism
* Exstrophy 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

Predisposing Factors for Hernias

**Table 346-1**

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| **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 500 units lipase/kg/meal initially, up to  4 yr and adults 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 | |

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| **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 | |

**Chapter 345** ◆ Tumors of the Digestive Tract **1901**

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

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

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| **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, *Staphylococcus aureus*, 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 | |

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| **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 | |

**1914 Part XVIII** ◆ The Digestive System

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| **Table 351-1** Etiology of Acute and Recurrent Pancreatitis in Children | |
| DRUGS AND TOXINS  Acetaminophen overdose Alcohol  L-Asparaginase Azathioprine Carbamazepine Cimetidine Corticosteroids Enalapril Erythromycin Estrogen Furosemide  Glucagon-like peptide-1 agents Isoniazid  Lisinopril  6-Mercaptopurine Methyldopa Metronidazole Octreotide  Organophosphate poisoning Pentamidine  Retrovirals: DDC (dideoxycytidine), DDI (dideoxyinosine), tenofovir Sulfonamides: mesalamine, 5-aminosalicytates, sulfasalazine,  trimethoprim-sulfamethoxazole Sulindac  Tetracycline Thiazides Valproic acid  Venom (spider, scorpion, Gila monster lizard) Vincristine  Volatile hydrocarbons | OBSTRUCTIVE  Ampullary disease Ascariasis  Biliary tract malformations Choledochal cyst Choledochocele  Cholelithiasis, microlithiasis, and choledocholithiasis (stones or sludge) Duplication cyst  Endoscopic retrograde cholangiopancreatography (ERCP) complication  Pancreas divisum  Pancreatic ductal abnormalities Postoperative  Sphincter of Oddi dysfunction Tumor |
| SYSTEMIC DISEASE  Autoimmune pancreatitis (IgG4-related systemic disease) Brain tumor  Collagen vascular diseases Crohn disease  Diabetes mellitus (ketoacidosis) Head trauma Hemochromatosis  Hemolytic uremic syndrome Hyperlipidemia: types I, IV, V Hyperparathyroidism/hypercalcemia Kawasaki disease  Malnutrition Organic academia Peptic ulcer Periarteritis nodosa Renal failure  Systemic lupus erythematosus  Transplantation: bone marrow, heart, liver, kidney, pancreas Vasculitis |
| GENETIC  Cationic trypsinogen gene *(PRSS1)* Chymotrypsin C gene *(CTRC)* Cystic fibrosis gene *(CFTR)*  Trypsin inhibitor gene *(SPINK1)* |
| TRAUMATIC  Blunt injury Burns  Child abuse Hypothermia Surgical trauma Total-body cast |
| INFECTIOUS  Ascariasis Coxsackie B virus Epstein-Barr virus Hepatitides A, B Influenzae A, B Leptospirosis Malaria  Measles Mumps Mycoplasma Rubella Rubeola  Reye syndrome: varicella, influenza B Septic shock |

**1922 Part XVIII** ◆ The Digestive System

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| **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 | |

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| **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: α1-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 hemangioendothelioma * 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 | |

**1924 Part XVIII** ◆ The Digestive System

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| **Table 355-3** Differential Diagnosis of Neonatal and Infantile Cholestasis | |
| INFECTIOUS  Generalized bacterial sepsis Viral hepatitis   * Hepatitides 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 * Toxoplasmosis * Syphilis * Tuberculosis * Listeriosis * Urinary tract infection | * Wilson disease * Neonatal iron storage disease * Indian childhood cirrhosis/infantile copper overload * Congenital disorders of glycosylation * Mitochondrial hepatopathies * Citrin deficiency |
| GENETIC OR CHROMOSOMAL  Trisomies 17, 18, 21 |
| INTRAHEPATIC CHOLESTASIS SYNDROMES  “Idiopathic” neonatal hepatitis Alagille syndrome  Intrahepatic cholestasis (progressive familial intrahepatic cholestasis [PFIC])   * 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) |
| TOXIC  Sepsis  Parenteral nutrition related  Drug, dietary supplement, herbal related |
| 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”) |
| METABOLIC  Disorders of amino acid metabolism   * Tyrosinemia   Disorders of lipid metabolism   * Wolman disease * Niemann-Pick disease (type C) * Gaucher disease   Cholesterol ester storage disease Disorders of carbohydrate metabolism   * Galactosemia * Fructosemia * Glycogenosis IV   Disorders of bile acid biosynthesis Other metabolic defects   * α1-Antitrypsin deficiency * Cystic fibrosis * Hypopituitarism * Hypothyroidism * Zellweger (cerebrohepatorenal) syndrome |
| 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 |

**Chapter 355** ◆ Manifestations of Liver Disease **1927**

1

18

9

16

11

17

13

No

22

14

15

Normal

Does bilirubin normalize by 6 weeks of age?

Condition

Question

21

Evaluate further

* Consult pediatric surgery
* Operative cholangiogram

Measure serum direct bilirubin

Cholestatic Jaundice

* Consult Pediatric GI
* CBC, platelet count
* Total and direct bilirubin, ALT, AST, alkaline phosphatase, glucose
* Prothrombin time, albumin
* α-1 antitrypsin
* Urine reducing substances
* Abdominal ultrasound
* Pi typing
* Further management

Medical evaluation:

* Infection
* Metabolic disorders
* Genetic disorders
* Other

Is there evidence of biliary obstruction?

Yes

8

Findings of specific disease?

10

* Manage the acute illness
* Consider urinary tract or other infection, galactosemia, tyrosinemia, hypopituitarism, fructosemia, iron storage disease, metabolic disorders, acute common duct obstruction, hemolysis

Yes

Low

α-1 antitrypsin?

19

Choledochal cyst?

No

20

Refer for further management

Is there direct hyperbilirubinemia?

No hyperbilirubinemia

Jaundiced infant 2 to 8 weeks old

History Physical exam Urinalysis Urine culture

Is the patient acutely ill? Require urgent care?

12

4

5

Abnormal

7

No

No

Consider:

* Percutaneous liver biopsy
* Scintiscan
* Duodenal aspirate
* ERCP

Evaluate further

(see Chapter 102.3, Table

355.2)

Yes

6

Yes

Indirect hyperbilirubinemia

2

Yes No

3

|  |  |  |
| --- | --- | --- |
| Yes | Is the newborn screen positive for | |
|  | galactosemia or  hypothyroidism? | |
|  | |  |

Yes

23 No

Action

**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.)*

**Chapter 356** ◆ Cholestasis **1929**

Metabolic Viral “Idiopathic”

disease disease neonatal

hepatitis

Biliary

atresia

Intrahepatic

bile duct or paucity

Intrahepatic

disease

Hepatocyte Bile duct

injury injury

Neonatal Cholestasis

Extrahepatic

disease (bile duct injury or obstruction)

**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.

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.

A. Disorders of membrane transport and secretion

1. Disorders of canalicular secretion
   1. Bile acid transport: BSEP deficiency
      1. Persistent, progressive (PFIC type 2)
      2. Recurrent, benign (BRIC type 2)
   2. Phospholipid transport: MDR3 deficiency (PFIC type 3)
   3. Ion transport: cystic fibrosis *(CFTR)*
2. Complex or multiorgan disorders
   1. FIC1 deficiency
      1. Persistent, progressive (PFIC type 1, Byler disease)
      2. Recurrent, benign (BRIC type 1)
   2. Neonatal sclerosing cholangitis *(CLDN1)*
   3. Arthrogryposis-renal dysfunction-cholestasis syndrome

*(VPS33B)*

B. Disorders of bile acid biosynthesis and conjugation

1. 3-oxoΔ-4-steroid 5β-reductase deficiency
2. 3β-hydroxy-5-C27-steroid dehydrogenase/isomerase deficiency
3. Oxysterol 7α-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

Proposed Subtypes of Intrahepatic Cholestasis

**Table 356-1**

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; CFTR, 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 |
| α1-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 |
| Ultrasonography | | 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

**Chapter 356** ◆ Cholestasis **1931**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **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-C27-steroid oxidoreductase (C27-3β-HSD) gene; regulates bile acid synthesis | BAS: chronic intrahepatic cholestasis |
| *CYP7BI* | CYP7BI | | 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\*. (\*Lowγ-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.

**Chapter 356** ◆ Cholestasis **1933**

***PERINATAL BILIARY ATRESIA***

Gene mutation

Bile flow initiation

Hepatocellular injury

Inflammatory (?Auto)Immune Response

? Modifier genes

Fibrosis and biliary cirrhosis

Intrahepatic cholestasis and inflammation

BD – apoptosis, fibrosis, obstruction

Inflammatory (?Auto)Immune response

? Genetic predisposition

Perinatal infection

Bile duct epithelial cell injury Expression of Ag

BD obstruction

Abnormal BD development

***EMBRYONIC BILIARY ATRESIA***

**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)  Vitamin K deficiency (hypoprothrombinemia) | 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 D2 or 3-5 μg/kg/day of  25-hydroxycholecalciferol  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.

**Chapter 357** ◆ Metabolic Diseases of the Liver **1937**

|  |  |
| --- | --- |
| **Table 357-1** | Inborn Errors of Metabolism That Affect the Liver |
| DISORDERS OF CARBOHYDRATE METABOLISM  Disorders of galactose metabolism  Galactosemia (galactose-1-phosphate uridyltransferase deficiency) Disorders of fructose metabolism  Hereditary 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  α1-Antitrypsin deficiency Citrullinemia type II (citrin deficiency)  Cystic fibrosis (cystic fibrosis transmembrane conductance regulator mutations)  Erythropoietic protoporphyria (ferrochelatase deficiency) Polycystic kidney disease | |

|  |  |
| --- | --- |
| **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  α1-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 | |

\*Maple syrup urine disease can be caused by mutations in branched-chain

α-keto dehydrogenase, keto acid decarboxylase, lipoamide dehydrogenase, or dihydrolipoamide dehydrogenase.

**1942 Part XVIII** ◆ The Digestive System

Recurrent vomiting, failure to thrive, short stature Dysmorphic features

Jaundice, hepatomegaly (±splenomegaly), fulminant hepatic failure, edema/anasarca

Hypoglycemia, organic acidemia, lactic acidemia, hyperammonemia, bleeding (coagulopathy)

Developmental delay/psychomotor retardation, hypotonia, progressive neuromuscular deterioration, seizures, myopathy, neuropathy

Cardiac dysfunction/failure Unusual odors

Rickets Cataracts

Clinical Manifestations That Suggest the Possibility of Metabolic Disease

**Table 357-2**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **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-HBs(+) 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 (+) | 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.

Jaundice

Anti-HAV

Symptoms

ALT

IgM anti-HAV

HAV in stool

0 1 2

3 4 5

Mo after exposure

6 12

**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.)*

**Chapter 358** ◆ Viral Hepatitis **1945**

|  |
| --- |
| **Table 358-4** Hepatitis A Virus Prophylaxis |
| PREEXPOSURE PROPHYLAXIS (TRAVELERS TO ENDEMIC REGIONS) |
| **AGE EXPECTED EXPOSURE DURATION DOSE** |
| <1 year of age <3 months Ig 0.02 mL/kg  3-5 months Ig 0.06 mL/kg  Long term (>5months) Ig 0.06 mL/kg at departure and every 5 mo thereafter |
| ≥1 year of age Healthy host HAV vaccine  Immunocompromised host, or one with chronic liver disease HAV vaccine and Ig 0.02 mL/kg or chronic health problems |
| 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, Immunoglubulin.

Yes



No

**Close monitoring**

Physical exam Lab tests

Refer to Peds Gastroenterology

Prophylaxis

**Jaundice**

Yes

HAV

Universal Precautions

Deterioration

**Viral serologies**

Anti-HAV IgM Anti-HCV Anti-HBs

Anti-HBc IgM HBsAg

HBsAg (—)

Anti-HBs (+)

**Recovery**

Refer to transplantation center

Labs at 6 mo

Refer to transplantation center

HCV

Prophylaxis

Positive

HBV

Negative

**“Safety tests” and physical exam**

PT

Glucose NH3

Renal CBC

Neuro status

Refer to transplantation center

Refer to Peds Gastroenterology

Liver synthetic dysfunction

HBsAg (+)

Anti-HBs (—)

**Chronic carrier**

Refer to Peds Gastroenterology

No

|  |  |
| --- | --- |
| **Evidence of chronic liver disease**  Ascites Varices  Hepatosplenomegaly Spider angiomas Clubbing  Failure to thrive | Yes |
| No |
|  |

**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.

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
* Fructosemia

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

Hemorrhagic shock with encephalopathy Drug or toxin ingestion (salicylate, valproate)

Diseases That Present a Clinical or Pathologic Picture Resembling Reye Syndrome

**Table 361-4**

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
* α1-Antitrypsin deficiency
* Tyrosinemia
* Niemann-Pick disease type 2
* Glycogen storage disease type iv
* Cystic fibrosis
* Galactosemia
* Bile acid biosynthetic abnormalities

Disorders Producing Chronic Hepatitis

**Table 362-1**

**1958 Part XVIII** ◆ The Digestive System

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **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*.*

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 (*SLC25A13* mutations)

Symptoms at the time of admission:

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

Clinical Staging of Reye Syndrome and Reye-Like Diseases

**Table 361-3**

**Table 361-1**

Classification of Primary Mitochondrial Hepatopathies

Respiratory chain (electron transport) defects (oxidative

Celandine

Chaparral (creosote bush, greasewood, *Larrea tridentata*) Chinese herbs

Comfrey leaves (pyrrolizidine alkaloids) Germander extracts *(Teucrium chamaedrys)* Kava (*Kava kava,* awa, kew)

LipoKinetix (phenylpropanolamine, sodium usinate, diiodothyronine, yohimbine, caffeine)

Ma huang *(Ephedra)*

Mushroom *(Amanita phalloides, Galerina)*

Senecio

Valerian with skullcap

Potentially Hepatotoxic Herbal or Dietary Supplements

**Table 363-2**

|  |  |
| --- | --- |
| **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 |

|  |  |
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| **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  α1-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 | |

**Part XVIII** ◆ The Digestive System

**Chapter 365** ◆ Cystic Diseases of the Biliary Tract and Liver **1969**

|  |  |
| --- | --- |
| **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 *C*erebellar vermis hypoplasia,  *o*ligophrenia, congenital *a*taxia, ocular *c*oloboma, and *h*epatic 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 Phosphomannose isomerase 1 glycoprotein syndrome deficiency (PMI)  type 1b | |
| Ivemark syndrome type 2 Autosomal-recessive renal-hepatic-  pancreatic dysplasia | |
| Miscellaneous syndromes Intestinal lymphangiectasia,  enterocolitis cystic  Short rib (Beemer-Langer) syndrome Osteochondrodysplasia | |

\*Most common associated disorders.

|  |  |  |
| --- | --- | --- |
| **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 |

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

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **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 |

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

Conditions Associated with Hydrops of the Gallbladder

**Table 366-1**

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

Conditions Associated with Cholelithiasis

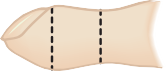
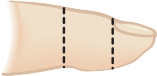
**Table 366-2**

# Respiratory System

**1994 Part XIX** ◆ Respiratory System

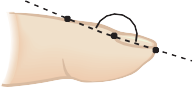
NORMAL CLUBBING

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

Phalangeal depth ratio

IPD>DPD DPD>IPD

Hyponychial angle



**c**

**b**

**a**

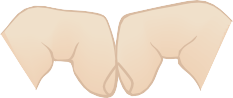
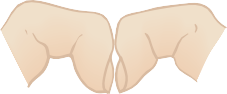


**b c**

**a**

abc<180° abc>195°

|  |  |
| --- | --- |
| **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 α1-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 | |

Schamroth sign

**Figure 374-1** Finger clubbing can be measured in different ways. The ratio of the distal phalangeal diameter (DPD) over the interphalan- geal 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, Phila- delphia, 2012, Elsevier.)*

|  |  |
| --- | --- |
| **Table 375-5** | Environmental Factors Associated with Increased Risk for Sudden Infant Death Syndrome |
| MATERNAL AND ANTENATAL 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 | |

**Chapter 375** ◆ Sudden Infant Death Syndrome **1999**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **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 Congenital anomaly  Unintentional injury Traumatic child abuse Other natural causes | | History, autopsy, and cultures History and autopsy  History, scene investigation, autopsy Autopsy and scene investigation History and autopsy | If minimal findings: SIDS If minimal findings: SIDS Traumatic child abuse Unintentional injury  If minimal findings: SIDS, or intentional suffocation | 18-20\*  35-46†  14-24†  15\*  13-24\*  12-17\* |
| UNEXPLAINED AT AUTOPSY  SIDS  Intentional suffocation (filicide)  Accidental suffocation or strangulation in bed (ASSB) | | History, scene investigation, absence of explainable cause at autopsy  Perpetrator confession, absence of explainable cause at autopsy  History and scene investigation, ideally including doll re-enactment | Intentional suffocation  SIDS  Assigned to ICD-10 code (SIDS) for U.S. vital statistics database  Unexplained Undetermined | 80-82%  Unknown, but <5% of all SUID  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 | |
|  |
| Subendocardial fibroelastosis | | TRAUMA |
| Aortic stenosis | | Child abuse |
| Anomalous coronary artery | | Accidental or intentional suffocation |
| Myocarditis | | Physical trauma |
| Cardiomyopathy | | Factitious syndrome (formerly Munchausen syndrome) by proxy |
| Arrhythmias (prolonged Q-T syndrome, Wolff-Parkinson-White | |
| POISONING (INTENTIONAL OR UNINTENTIONAL)  Boric acid  Carbon monoxide Salicylates Barbiturates Ipecac  Cocaine Insulin Others |
| syndrome, congenital heart block) | |
| PULMONARY | |
| Pulmonary hypertension | |
| Vocal cord paralysis | |
| Aspiration | |
| Laryngotracheal disease | |
| GASTROINTESTINAL | |
| Diarrhea and/or dehydration | |
| Gastroesophageal reflux | |
| 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 | |

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

Possible Causes of Epistaxis

**Table 377-1**

|  |  |
| --- | --- |
| **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 | |

|  |  |
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| **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 *(KCNE2, KCNH2, KCNQ1, KCNJ8)*  Sodium ion channel gene *(SCN5A)* (long QT syndrome 3, Brugada syndrome)  *GPD1-L-encoded connexin43* (Brugada syndrome)  *SCN3B* (Brugada syndrome) *CAV3* (long QT syndrome 9) *SCN4B* (long QT syndrome 10) *SNTA-1* (long QT syndrome 11)  *RyR2* (catecholaminergic polymorphic ventricular tachycardia) | |
| SEROTONIN (5-HT) (3)  5-HT transporter protein *(5-HTT)*  Intron 2 of *SLC6A4* (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 *(PHOX2A) PHOX2B*  Rearranged during transfection factor *(RET)*  Endothelin converting enzyme-1 *(ECE1)* T-cell leukemia homeobox *(TLX3)* Engrailed-1 *(EN1)*  Tyrosine hydroxylase *(THO1)*  Monamine oxidase A *(MAOA)*  Sodium/proton exchanger 3 *(NHE3)* (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 (*FMO3*) (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) | |

**2000 Part XIX** ◆ Respiratory System

|  |  |
| --- | --- |
| **Table 381-1** | Infectious Agents That Cause Pharyngitis |
| **VIRUSES BACTERIA** | |
| Adenovirus *Streptococcus pyogenes*  Coronavirus (Group A streptococcus)  Cytomegalovirus *Arcanobacterium haemolyticum*  Epstein-Barr virus *Fusobacterium necrophorum*  Enteroviruses *Corynebacterium diphtheriae*  Herpes simplex virus *Neisseria gonorrhoeae* Human immunodeficiency virus Group C streptococci Human metapneumovirus Group G streptococci Influenza viruses *Francisella tularensis*  Measles virus *Chlamydophila pneumoniae*  Parainfluenza viruses *Chlamydia trachomatis* Respiratory syncytial virus *Mycoplasma pneumoniae* Rhinoviruses | |

**2012 Part XIX** ◆ Respiratory System

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **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 | Occasional Occasional 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 |
|  | | Enteroviruses Coxsackievirus A  Other nonpolio enteroviruses | Uncommon |

Risk for resistance

Symptomatic management

No

Risk for antibiotic resistance

* Age <2 or >65, daycare

Signs and symptoms either:

1. Persistent and not improving (≥10 days)
2. Severe (≥3–4 days); or
3. Worsening or “double-sickening” (≥3–4 days)

* Prior antibiotics within

the past month

* Prior hospitalization past 5 days
* Comorbidities

Yes

* Immunocompromised

Initiate first-line antimicrobial therapy

Initiate second-line antimicrobial therapy

Improvement after 3–5 days

Complete 5–7 days of antimicrobial therapy

Worsening or no improvement after 3–5 days

Broaden coverage or switch to different antimicrobial class

Improvement after 3–5 days

Complete 7–10 days of antimicrobial therapy

Improvement

Complete 5–7 days of antimicrobial therapy

Worsening or no improvement after 3–5 days

Refer to specialist

* CT or MRI to investigate noninfectious causes

or suppurative complications

* Sinus or meatal cultures for pathogen-specific therapy

Improvement

Complete 7–10 days of antimicrobial therapy

|  |  |
| --- | --- |
| **Table 379-2** | Conditions That Can 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 | |

**Figure 380-1** Algorithm for the manage- ment 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.)*

**2020 Part XIX** ◆ Respiratory System

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| --- | --- | --- | --- | --- |
| **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 Estolate  Clarithromycin | | 40 mg/kg/day up to 1000 mg/day bid  20-40 mg/kg/day up to 1000 mg/day bid |  | 10 days  10 days |
| 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.

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| **Table 383-3** | Risks and Potential Benefits of Tonsillectomy or Adenoidectomy 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 | |

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| **Table 383-1** | Paradise Criteria for Tonsillectomy |
| **CRITERION DEFINITION** | |
| Minimum frequency At least 7 episodes in the previous year, at of sore throat least 5 episodes in each of the previous episodes 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.

\*Cost for tonsillectomy alone and adenoidectomy alone are somewhat lower.

**Chapter 383** ◆ Tonsils and Adenoids **2025**

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| **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  Pain control  Antibiotic use Steroid use  Sleep-disordered breathing  Polysomnography  Surgical technique Hemorrhage | 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  Recommendation to advocate for pain relief (e.g., provide information, prescribe) and educate caregivers about the importance of managing and reassessing pain  Recommendation against perioperative antibiotics  Recommendation for a single intraoperative dose of dexamethasone  Recommendation to counsel caregivers about tonsillectomy as a means to improve health in children with sleep-disordered breathing and comorbid conditions  Recommendation to counsel caregivers about tonsillectomy as a means to improve health in children with abnormal polysomnography  NA  Recommendation that the surgeon document primary and secondary hemorrhage after tonsillectomy at least annually | 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  Recommendation for acetaminophen before and after surgery  Recommendation for short-term perioperative antibiotics\*  Recommendation for a single intraoperative dose of dexamethasone  Recommendation for diagnostic testing in children with suspected sleep respiratory disorders  Recommendation for polysomnography when pulse oximetry results are not conclusive in agreement with Brouillette criteria  Recommendation for “cold” technique  NA | 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  Recommendation for adequate dose of acetaminophen for pain relief in children  NA  Recommendation for a single intraoperative dose of dexamethasone  NA  NA  NA NA |
| Adjunctive therapy | NA | NA | Recommendation against *Echinacea purpurea* 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.*

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| **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 | |

**2028 Part XIX** ◆ Respiratory System

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

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| **Table 384-4** | Clinical Clues About Cough | |
| **CHARACTERISTIC** | | **THINK OF** |
| Staccato, paroxysmal | | Pertussis, cystic fibrosis, foreign body,  *Chlamydia* spp., *Mycoplasma* 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, *Pneumocystis jiroveci, Mycobacterium tuberculosis, Mycobacterium avium-intracellulare,* cytomegalovirus |
| Dyspnea | | Hypoxia, hypercarbia |
| Animal exposure | | *Chlamydia psittaci* (birds), *Yersinia pestis* (rodents), *Francisella tularensis* (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 |

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

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

Indicators of Serious Chronic Lower Respiratory Tract Disease in Children

**Table 384-1**

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

α1-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

*Pneumocystis jiroveci*

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

Diseases Associated with Recurrent, Persistent, or Migrating Lung Infiltrates Beyond the Neonatal Period

**Table 384-6**

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?

Pertinent Medical History in the Wheezing Infant

**Table 391-2**

**2030 Part XIX** ◆ Respiratory System

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| **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 | |

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| **Table 391-3** | Disorders with Cough as a Prominent Finding |
| **CATEGORY DIAGNOSES** | |
| Inflammatory Asthma | |
| Chronic pulmonary Bronchopulmonary dysplasia processes Postinfectious bronchiectasis  Cystic fibrosis  Tracheomalacia or bronchomalacia Ciliary abnormalities  Other chronic lung diseases | |
| Other chronic disease or Laryngeal cleft congenital disorders Swallowing disorders  Gastroesophageal reflux  Airway compression (such as a vascular ring or hemangioma)  Congenital heart disease | |
| Infectious or immune Immunodeficiency disorders Eosinophilic lung disease  Tuberculosis Allergy Sinusitis  Tonsillitis or adenoiditis *Chlamydia, Ureaplasma* (infants) *Bordetella pertussis Mycoplasma pneumoniae* | |
| Acquired Foreign-body aspiration, tracheal or esophageal | |

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| **Table 391-1** | Differential Diagnosis of Wheezing in Infancy |
| INFECTION  *Viral*  Respiratory syncytial virus Human metapneumovirus Parainfluenza  Adenovirus Influenza Rhinovirus Bocavirus Coronavirus Enterovirus *Other*  *Chlamydia trachomatis* 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 | |

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| **Table 394-1** | Etiology of Bronchiolitis Obliterans |
| POSTINFECTION  Adenovirus types 3, 7, and 21 Influenza  Parainfluenza Measles  Respiratory syncytial virus Varicella  *Mycoplasma pneumoniae* | |
| 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  NO2 NH3  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 | |

**Chapter 391** ◆ Wheezing, Bronchiolitis, and Bronchitis **2045**

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| **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 | |

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| **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, dermatomyositises) 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 | |

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| **Table 396-2** | Radiographic Features That May Help Differentiate Cardiogenic from Noncardiogenic Pulmonary Edema |
| **RADIOGRAPHIC CARDIOGENIC NONCARDIOGENIC FEATURE EDEMA EDEMA** | |
| Heart size Normal or greater Usually normal than normal | |
| Width of the vascular Normal or greater Usually normal or less pedicle\* than normal than normal | |
| Vascular distribution Balanced or Normal or balanced  inverted | |
| Distribution of Even or central Patchy or peripheral edema | |
| 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 | |

**Chapter 396** ◆ Pulmonary Edema **2061**

**2066 Part XIX** ◆ Respiratory System

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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.*

**2068 Part XIX** ◆ Respiratory System

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

**Chapter 399** ◆ Immune and Inflammatory Lung Disease **2069**

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)

1. 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
2. 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)
3. 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

Criteria Used in the Diagnosis of Hypersensitivity Pneumonitis

**Table 399-2**

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)

Clinical History Clues Leading to a Diagnosis of Hypersensitivity Pneumonitis

**Table 399-3**

**2072 Part XIX** ◆ Respiratory System

|  |  |  |  |
| --- | --- | --- | --- |
| **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  Bakery Lactalbumin  Butcher Cow bone dust, pig, goat dander  Cook Raw beef  Dairy industry Lactoserum, lactalbumin  Egg producer Egg protein  Farmer Deer dander, mink urine  Frog catcher Frog  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 | | ACARIANS  Apple grower  Citrus farmer Farmer  Flour handler Grain-store worker Horticulturist Poultry worker Vine grower | Fruit tree red spider mite *(Panonychus ulmi)*  Citrus red mite *(Panonychus citri)*  Barn mite, two-spotted spider mite  *(Tetranychus urticae)*, grain mite Mites and parasites  Grain mite *Amblyseius cucumeris* Fowl mite  McDaniel spider mite *(Tetranychus mcdanieli)* |
| MOLDS  Agriculture Baker  Beet sugar worker Coal miner Coffee maker Laborer  Logging worker Plywood factory worker Sausage processing Sawmill worker  Stucco worker Technician | *Plasmopara viticola*  *Alternaria, Aspergillus* (unspecified)  *Aspergillus* (unspecified) *Rhizopus nigricans Chrysonilia sitophila*  Sooty molds (*Ascomycetes*, deuteromycetes)  *Chrysonilia sitophila Neurospora*  *Penicillium nalgiovense Trichoderma koningii*  *Mucor* spp. (contaminating esparto fibers)  *Dictyostelium discoideum* (mold),  *Aspergillus niger* |
| CRUSTACEANS, SEAFOOD, FISH  Canning factory Octopus  Diet product Shark cartilage  Fish food factory Gammarus shrimp  Fish processor Clam, shrimp, crab, prawn, salmon, trout, lobster, turbot, various fishes  Fisherman Red soft coral, cuttlefish  Jewelry polisher Cuttlefish bone  Laboratory grinder Marine sponge  Oyster farm Hoya (oyster farm prawn or sea-squirt) Restaurant seafood handler Scallop and shrimp  Scallop plant processor King scallop and queen scallop Technician Shrimp meal *(Artemia salina)* | |
| MUSHROOMS  Agriculture Baker  Greenhouse worker Hotel manager Mushroom producer  Mushroom soup processor Office worker  Seller | *Agaricus bisporus* (white mushroom)  Baker’s yeast *(Saccharomyces cerevisiae), Boletus edulis* Sweet pea *(Lathyrus odoratus)*  *Boletus edulis Pleurotus cornucopiae* Mushroom unspecified *Boletus edulis*  *Pleurotus ostreatus* (spores of white spongy rot) |
| ARTHROPODS  Agronomist Bottling  Chicken breeder  Engineer at electric power plant  Entomologist  Farmer  Fish bait handler | *Bruchus lentis*  Ground bug  Herring worm *(Anisakis simplex)*  Caddis flies *(Phryganeidae)*  Lesser mealworm (*Alphitobius diaperinus* Panzer), moth, butterfly  Grain pests (*Eurygaster* and *Pyrale*) Insect larvae *(Galleria mellonella)*,  mealworm larvae *(Tenebrio molitor)*, green bottle fly larvae *(Lucila caesar)*, daphnia, fish-feed Echinodorus larva *(Echinodorus plasmosus)*, Chiromids midge *(Chironomus thummi thummi)*  Herring worm *(Anisakis simplex)*  Screw worm fly *(Cochliomyia hominivorax)*  Honeybee  Cricket, fruit fly, grasshopper *(Locusta migratoria)*, locust  Confused flour beetle *(Tribolium confusum)*  Beetles (Coleoptera)  Mexican bean weevil *(Zabrotes subfasciatus)*  Silkworm, larva of silkworm Sewer fly *(Psychoda alternata)* Arthropods *(Chrysoperla carnea,*  *Leptinotarsa decemlineata, Ostrinia nubilalis, and Ephestia kuehniella),* sheep blowfly *(Lucilia cuprina)*  *Dermestidae* spp. |
| ALGAE  Pharmacist Thalassotherapist | Chlorella  Algae (species unspecified) |
| FLOURS  Animal fodder Baker | Marigold flour *(Tagetes erecta)*  Wheat, rye, soya, and buckwheat flour; Konjac flour; white pea flour *(Lathyrus sativus)*  White Lupin flour *(Lupinus albus)* |
| Fish processing Flight crew  Honey processors Laboratory worker | Food processing |
| POLLENS  Florist Gardener | Cyclamen, rose  Canary island date palm *(Phoenix canariensis)*, Bell of Ireland *(Moluccella laevis)*, Bell pepper, chrysanthemum, eggplant *(Solanum melongena)*, *Brassica oleracea* (cauliflower and broccoli)  Sunflower (*Helianthus* spp.), thale cress  *(Arabidopsis thaliana)* White mustard *(Sinapis alba) Helianthus annuus* |
| Mechanic in a rye plant |  |
| Museum curator Seed house | Laboratory worker |
| Sericulture  Sewage plant worker Technician | Olive farmers Processing worker |
| Wool worker |  |

**Chapter 399** ◆ Immune and Inflammatory Lung Disease **2073**

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| --- | --- | --- | --- | --- |
| **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 | |  | Laborer  Oil industry Pharmaceutical  Powder Sewer Sheller  Stucco handler  Tobacco manufacturer | Citrus food handling (*dl*-limonene,  *l*-citronellol, and dichlorophen) Castor bean, olive oilcake  Rose hip, passion flower *(Passiflora alata)*, cascara sagrada *(Rhamnus purshiana)*  Lycopodium powder Kapok  Almond shell dust  Esparto (*Stipa tenacissima* and *Lygeum spartum*)  Tobacco leaf |
| Brewery chemist | | Hops |
| Brush-makers | | Tampico fiber in agave leaves |
| Butcher | | Aromatic herb |
| Chemist | | Linseed oilcake, *Voacanga africana* seed |
|  | | dust |
| Cosmetics | | Dusts from seeds of Sacha Inchi |
|  | | *(Plukenetia volubilis)*, chamomile |
|  | | (unspecified) |
| Decorator | | Cacoon seed (Entage gigas) |
| Floral worker | | Decorative flower, safflower *(Carthamus* |
|  | | *tinctorius)* and yarrow *(Achillea* |
|  | | *millefolium)*, spathe flower, statice |
| PLANT-DERIVED NATURAL PRODUCTS  Baker Gluten, soybean lecithin  Candy maker Pectin  Glove manufacturer Latex  Health professional Latex  Rose extraction Rose oil | |
|  | | *(Limonium tataricum)*, baby’s breath |
|  | | *(Gypsophila paniculata)*, ivy *(Hedera* |
|  | | *helix)*, flower (various), sea lavender |
|  | | *(Limonium sinuatum)* |
| Food industry | | Aniseed, fenugreek, peach, garlic dust, |
|  | | asparagus, coffee bean, sesame seed, |
| BIOLOGIC ENZYMES  Baker  Cheese producer  Detergent industry Factory worker Fruit processor Hospital personnel Laboratory worker Pharmaceutical  Plastic | Fungal amylase, fungal amyloglucosidase and hemicellulase  Various enzymes in rennet production (proteases, pepsine, chymosins)  Esterase, *Bacillus subtilis Bacillus subtilis* Pectinase and glucanase Empynase (pronase B)  Xylanase, phytase from *Aspergillus niger* Bromelin, flaviastase, lactase, pancreatin, papain, pepsin, serratia peptidase, and  lysozyme chloride; egg lysozyme, trypsin  Trypsin |
|  | | grain dust, carrot *(Daucus carota L.)*, |
|  | | green bean *(Phaseolus multiflorus)*, |
|  | | lima bean *(Phaseolus lunatus),* onion, |
|  | | potato, swiss chard *(Beta vulgaris L.)*, |
|  | | courgette, carob bean, spinach |
|  | | powder, cauliflower, cabbage, chicory, |
|  | | fennel seed, onion seeds (*Allium cepa*, |
|  | | red onion), rice, saffron *(Crocus* |
|  | | *sativus),* spices, grain dust |
| Gardener | | Copperleaf *(Acalypha wilkesiana),* grass |
|  | | juice, weeping fig *(Ficus benjamina),* |
|  | | umbrella tree (*Schefflera* spp.), |
|  | | amaryllis (*Hippeastrum* spp.), |
|  | | Madagascar jasmine sap *(Stephanotis* |
|  | | *floribunda)*, vetch *(Vicia sativa)* |
| Hairdresser  Herbal tea processor | | Henna (unspecified)  Herbal tea, sarsaparilla root, sanyak *(Dioscorea batatas),* Korean ginseng *(Panax ginseng),* tea plant dust *(Camellia sinensis)*, chamomile |
| VEGETABLE GUMS  Carpet manufacturing Dental hygienist  Gum importer | Guar  *Gutta-percha*  Tragacanth |
| Hairdresser | Karaya |
|  | | (unspecified) |
| Printer | Acacia |
| Herbalist | | Liquorice roots (*Glycyrrhiza* spp.), wonji |
|  | | *(Polygala tenuifolia)*, herb material |  |  |
| Horticulture | | Freesia (Freesia hybrida), paprika |  |  |
|  | | *(Capsicum annuum)*, Brazil ginseng |  |  |
|  | | *(Pfaffia paniculata)* |  |  |

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

**2080 Part XIX** ◆ Respiratory System

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

Criteria for the Diagnosis of Reactive Airways Disease Syndrome

**Table 399-7**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **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 in filtrations | High IgE |
| Stage 4 | CSD asthma | | Minimal infiltrate | Normal to high IgE |
| Stage 5 | End stage | | Fibrosis and/or bullae | Normal |

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.

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

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

**Table 399-8**

\*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 | | * Ascariasis (Löffler syndrome)\* |
| Hypereosinophilic syndromes | | * *Toxocara* (*canis* or *cati*) |
| * Myeloproliferative variant | | * Filarial (tropical filarial eosinophilic pneumonia) |
| * Lymphocytic variant | | * *Strongyloides stercoralis*   Allergic bronchopulmonary aspergillosis  Toxic   * 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.

**2084 Part XIX** ◆ Respiratory System

**Myeloproliferative**

**Myeloproliferative**

**forms**

**Lymphocytic**

**forms**

**Overlap Undefined**

**Associated**

**Familial**

Populations of T cells secreting eosinophil hematopoietins

Hypereosinophilic syndromes (HESs)

Family history of documented persistent eosinophilia of unknown cause

Eosinophilia in association with a defined diagnosis, such as IBD or CSS

Organ restricted eosinophilic disorders

**HES CEL**

**Clonal T cells**

**No T cell clone**

**Benign Episodic Other**

|  |  |
| --- | --- |
| Features of | Clonal |
| myeloprolliferative | eosinophilia, |
| disease without | including |
| proof of clonality | *FIP1L1/* |
|  | *PDGFRA* |
|  |
| positive CEL |

T cells often exhibit an abnormal immuno- phenotype

Aberrant immuno- phenotype evidence of marked T cell activation

Asymptomatic with no evidence of organ involvement

Cyclic angioedema and eosinophilia

Symptomatic without features of myeloproliferative or lymphocytic forms

**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 simpli- fied, 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, *Escherichia coli,* other Gram-negative bacilli, *Streptococcus pneumoniae, Haemophilus influenzae* (type b,\* nontypeable) |
| 3 wk-3 mo | Respiratory syncytial virus, other respiratory viruses (rhinoviruses, parainfluenza viruses, influenza viruses, adenovirus), *S. pneumoniae, H. influenzae* (type b,\* nontypeable); if patient is afebrile, consider *Chlamydia trachomatis* |
| 4 mo-4 yr | Respiratory syncytial virus, other respiratory viruses (rhinoviruses, parainfluenza viruses, influenza viruses, adenovirus), *S. pneumoniae, H. influenzae* (type b,\* nontypeable), *Mycoplasma pneumoniae,* group A streptococcus |
| ≥5 yr | *M. pneumoniae, S. pneumoniae, Chlamydophila pneumoniae, H. influenzae* (type b,\* nontypeable), influenza viruses, adenovirus, other respiratory viruses, *Legionella pneumophila* |

|  |  |  |
| --- | --- | --- |
| **Table 399-11** | Hypereosinophilic Syndrome Variants | |
| Myeloproliferative | | Nonclonal  Clonal–F1P1L1/PDGFRA-positive chronic eosinophilic leukemia |
| Lymphocytic | | Nonclonal T cells  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  Cyclic angioedema with eosinophilia (Gleich syndrome)  Symptomatic without myeloproliferation or lymphocytic form |

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

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

**2086 Part XIX** ◆ Respiratory System

|  |  |  |
| --- | --- | --- |
| **Table 400-2** | Causes of Infectious Pneumonia | |
| BACTERIAL  *Common*  *Streptococcus pneumoniae* Group B streptococci Group A streptococci *Mycoplasma pneumoniae\**  *Chlamydophila pneumoniae\* Chlamydia trachomatis* Mixed anaerobes  Gram-negative enterics  *Uncommon*  *Haemophilus influenzae* type b *Staphylococcus aureus Moraxella catarrhalis*  *Neisseria meningitidis Francisella tularensis*  *Nocardia* species *Chlamydophila psittaci\* Yersinia pestis Legionella* species\*  *Coxiella burnetii*\* | | Consolidation, empyema Neonates  Empyema  Adolescents; summer-fall epidemics  Adolescents Infants  Aspiration pneumonia Nosocomial pneumonia  Unimmunized  Pneumatoceles, empyema; infants  Animal, tick, fly contact; bioterrorism  Immunosuppressed persons  Bird contact (especially parakeets) Plague; rat contact; bioterrorism Exposure to contaminated water;  nosocomial  Q fever; animal (goat, sheep, cattle) exposure |
| VIRAL  *Common*  Respiratory syncytial virus Parainfluenza types 1-3 Influenzas A, B Adenovirus  Human metapneumovirus  *Uncommon* Rhinovirus Enterovirus Herpes simplex Cytomegalovirus  Measles Varicella *Hantavirus*  Coronavirus (severe acute respiratory syndrome, Middle East respiratory syndrome [MERS]) | | Bronchiolitis Croup  High fever; winter months Can be severe; often occurs  between January and April Similar to respiratory syncytial  virus  Rhinorrhea Neonates Neonates  Infants, immunosuppressed persons  Rash, coryza, conjunctivitis Adolescents or unimmunized Southwestern United States,  rodents  Asia, Arabian peninsula |
| FUNGAL  *Histoplasma capsulatum*  *Blastomyces dermatitidis Coccidioides immitis Cryptococcus neoformans Aspergillus* species  Mucormycosis  *Pneumocystis jiroveci* | | Ohio/Mississippi River valley; bird, bat contact  Ohio/Mississippi River valley Southwest United States Bird contact Immunosuppressed persons;  nodular lung infection Immunosuppressed persons Immunosuppressed, steroids |
| RICKETTSIAL  *Rickettsia rickettsiae* | | Tick bite |
| MYCOBACTERIAL  *Mycobacterium tuberculosis*  *Mycobacterium avium* complex | | Travel to endemic region; exposure to high-risk persons  Immunosuppressed persons |
| PARASITIC  Various parasites (e.g., Ascaris,  *Strongyloides* species) | | Eosinophilic pneumonia |

|  |  |
| --- | --- |
| **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 *FOXF1* mutation)   Growth abnormalities reflecting deficient alveolarization   * Pulmonary hypoplasia * Chronic neonatal lung disease * Chromosomal disorders * Congenital heart disease Neuroendocrine cell hyperplasia of infancy   Pulmonary interstitial glycogenosis (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 (*CSF2RA*) mutation | |
| ILD DISORDERS WITH KNOWN ASSOCIATIONS  Infectious/postinfectious processes   * Adenovirus viruses * Influenza viruses * *Chlamydia pneumoniae* * *Mycoplasma pneumoniae*   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 | |

\*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.*

*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.*

**Chapter 400** ◆ Community-Acquired Pneumonia **2091**

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)

Factors Suggesting Need for Hospitalization of Children with Pneumonia

**Table 400-5**

|  |  |
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| **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 CILIA  Immotile cilia syndrome Kartagener syndrome | |
| ANATOMIC DISORDERS  Pulmonary sequestration Lobar emphysema Gastroesophageal reflux Foreign body  Tracheoesophageal fistula (H type) Bronchiectasis  Aspiration (oropharyngeal incoordination) Aberrant bronchus | |

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

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| **Table 400-6** | Differentiation | of | Pleural Fluid | |
|  | | **TRANSUDATE** | | **EMPYEMA** |
| Appearance | | Clear | | Cloudy or purulent |
| Cell count (per mm3) | | <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).

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| **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 | |

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

Diagnostic Criteria for Cystic Fibrosis (CF)

**Table 403-3**

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| **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) | |

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| **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 | |

**2104 Part XIX** ◆ Respiratory System

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| **Table 403-7** | Antimicrobial Agents for Cystic Fibrosis Lung Infection | | | |
| **ROUTE** | **ORGANISMS** | **AGENTS** | **DOSAGE (mg/kg/24 hr)** | **NO. DOSES/24 hr** |
| Oral | *Staphylococcus aureus* | Dicloxacillin Linezolid Cephalexin Clindamycin  Amoxicillin-clavulanate Amoxicillin Ciprofloxacin Trimethoprim-  sulfamethoxazole Azithromycin Erythromycin | 25-50 | 4 |
|  |  | 20 | 2 |
|  |  | 50 | 4 |
|  |  | 10-30 | 3-4 |
|  |  | 25-45 | 2-3 |
|  | *Haemophilus influenzae* | 50-100 | 2-3 |
|  | *Pseudomonas aeruginosa* | 20-30 | 2-3 |
|  | *Burkholderia cepacia* | 8-10\* | 2-4 |
|  | Empirical | 10, day 1; 5, days 2-5  30-50 | 1  3-4 |
| Intravenous | *S. aureus* | Nafcillin | 100-200 | 4-6 |
|  |  | Vancomycin | 40 | 3-4 |
|  | *P. aeruginosa* | 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 |
|  |  | Meropenem | 60-120 | 3 |
|  |  | Imipenem-cilastatin | 45-100 | 3-4 |
|  |  | Ceftazidime | 150 | 3 |
|  |  | Aztreonam | 150-200 | 4 |
|  | *B. cepacia* | Chloramphenicol Meropenem | 50-100  60-120 | 4  3 |
| Aerosol |  | Tobramycin (inhaled) Aztreonam (inhaled) | 300§  75 | 2  3 |

\*Quantity of trimethoprim.

†Quantity of ticarcillin.

‡Quantity of piperacillin.

§In mg per dose.

**Chapter 403** ◆ Cystic Fibrosis **2107**

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| **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 | |

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| **Table 403-6** | Complications of Therapy for Cystic Fibrosis\* | |
| **COMPLICATION** | | **AGENT** |
| Gastrointestinal bleeding | | Ibuprofen |
| Hyperglycemia | | Corticosteroids (systemic) |
| Growth retardation  Renal dysfunction: Tubular  Interstitial nephritis | | Corticosteroids (systemic, inhaled)  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.

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| **Table 404-2** | Electron Microscopic Findings in Primary Ciliary Dyskinesia vs Acquired Cilia Abnormality | |
| **PCD** | | **ACQUIRED DEFECTS** |
| EM ultrastructure Dynein arm deficiency  Outer arms | | Compound cilia Added peripheral  tubules  Deleted peripheral tubules  Added central pairs Translocation of central  tubules  Few or absent cilia (patchy) |
| Inner arms | |
| Both Translocation of  central tubules Few or absent cilia  (generalized) | |
| 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.

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| **Table 404-1** | Clinical Manifestations of Primary Ciliary Dyskinesia | |
| RESPIRATORY TRACT  *Lung*  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 polyposis | | GENITOURINARY TRACT  Male and female infertility |
| LEFT-RIGHT ORIENTATION DEFECTS  Situs inversus Heterotaxy  Congenital heart disease |
| CENTRAL NERVOUS SYSTEM  Hydrocephalus Retinitis pigmentosa |

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| **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 | |

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

**Chapter 405** ◆ Diffuse Lung Diseases in Childhood **2117**

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| **Table 405-1** | Comparison of Surfactant Deficiency Syndromes | | | | |
|  | | **SP-B DEFICIENCY** | **SP-C DISEASE** | **ABCA3 DEFICIENCY** | **TTF-1 DEFICIENCY** |
| Gene name | | *SFTPB* | *SFTPC* | *ABCA3* | *NKX2-1* |
| 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)*  Genetic *(DNA)*  Ultrastructural *(lung biopsy–electron microscopy)* | | Absence of SP-B and presence of proSP-C  Sequence *SFTPB*  Disorganized lamellar bodies | None  Sequence *SFTPC*  Not specific; may have dense aggregates | None  Sequence *ABCA3*  Small dense lamellar bodies with eccentrically placed dense cores | None  Sequence *NKX2-1;*  deletion analysis 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

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| **Table 406-1** | Diffuse Alveolar Hemorrhage Syndromes |
| **CLASSIFICATION SYNDROME** | |
| Disorders with Idiopathic pulmonary capillaritis 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 Idiopathic pulmonary hemosiderosis causes 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)  Cardiovascular causes Mitral stenosis  Pulmonary venoocclusive disease Arteriovenous malformations Pulmonary lymphangioleiomyomatosis Pulmonary hypertension  Pulmonary capillary hemangiomatosis Chronic heart failure  Vascular thrombosis with infarction | |

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| **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  Hyperhomocysteinanemia (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) | |

**Chapter 408** ◆ Atelectasis **2129**

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| **Table 408-1** | Anatomic Causes of Atelectasis |
| **CAUSE CLINICAL EXAMPLES** | |
| External compression on the Pleural effusion, pneumothorax, pulmonary parenchyma intrathoracic tumors,  diaphragmatic hernia | |
| Endobronchial obstruction Enlarged lymph node, tumor, completely obstructing the cardiac enlargement, foreign ingress of air body, mucoid plug,  broncholithiasis | |
| Intraluminal obstruction of a Foreign body, asthma, bronchus 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 Neuromuscular abnormalities, paralysis osseous deformities, overly  restrictive casts and surgical dressings, defective movement of the diaphragm, or restriction of respiratory effort | |

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| **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.

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| **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 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 | |

**2148 Part XIX** ◆ Respiratory System

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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.*

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| **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

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| **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  Upper gastrointestinal tract bleeding | Posterior flow of bleeding causes appearance of pulmonary origin  Hematemesis mimics hemoptysis | History and physical findings suggest nasal source; normal chest examination, and chest radiography  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 |

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| **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 |

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| **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 H2O* | | Evaluate PFTs every 6 mo CXR and polysomnography  every year |
| *If vital capacity <60% predicted or maximal respiratory pressures*  *<60 cm H2O* | | 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.

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| **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 Fibrositis 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 Postpericardiotomy 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) | |

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

**T**he **c**ardiova**sc**ular **Sys**tem

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| **Table 422-2** Congenital Malformation Syndromes Associated with Congenital Heart Disease | |
| **SYNDROME** | **FEATURES** |
| CHROMOSOMAL DISORDERS  Trisomy 21 (Down syndrome) Trisomy 21p (cat eye syndrome) Trisomy 18  Trisomy 13  Trisomy 9 XXXXY  Penta X Triploidy  XO (Turner syndrome) Fragile X  Duplication 3q2 Deletion 4p Deletion 9p  Deletion 5p (cri du chat syndrome) Deletion 10q  Deletion 13q Deletion 18q | Endocardial cushion defect, VSD, ASD  Miscellaneous, total anomalous pulmonary venous return  VSD, ASD, PDA, coarctation of aorta, bicuspid aortic or pulmonary valve VSD, ASD, PDA, coarctation of aorta, bicuspid aortic or pulmonary valve Miscellaneous  PDA, ASD PDA, VSD  VSD, ASD, PDA  Bicuspid aortic valve, coarctation of aorta Mitral valve prolapse, aortic root dilatation Miscellaneous  VSD, PDA, aortic stenosis Miscellaneous  VSD, PDA, ASD  VSD, TOF, conotruncal lesions\* VSD  VSD |
| SYNDROME COMPLEXES  CHARGE association (*c*oloboma, *h*eart, *a*tresia choanae, *r*etardation, *g*enital, and *e*ar anomalies)  DiGeorge sequence, CATCH 22 (*c*ardiac defects, *a*bnormal facies,  *t*hymic aplasia, *c*left palate, and *h*ypocalcemia) Alagille syndrome (arteriohepatic dysplasia)  VATER association (*v*ertebral, *a*nal, *t*racheo*e*sophageal, *r*adial, and  *r*enal anomalies)  FAVS (*f*acio*a*uriculo*v*ertebral *s*pectrum)  CHILD (congenital hemidysplasia with ichthyosiform erythroderma, limb defects)  Mulibrey nanism (muscle, liver, brain, eye) Asplenia syndrome  Polysplenia syndrome  PHACE syndrome (*p*osterior brain fossa anomalies, facial *h*emangiomas, *a*rterial anomalies, *c*ardiac anomalies and aortic coarctation, *e*ye anomalies) | VSD, ASD, PDA, TOF, endocardial cushion defect Aortic arch anomalies, conotruncal anomalies  Peripheral pulmonic stenosis, PS, TOF VSD, TOF, ASD, PDA  TOF, VSD  Miscellaneous  Pericardial thickening, constrictive pericarditis  Complex cyanotic heart lesions with decreased pulmonary blood flow, transposition of great arteries, anomalous pulmonary venous return, dextrocardia, single ventricle, single atrioventricular valve  Acyanotic lesions with increased pulmonary blood flow, azygos continuation of inferior vena cava, partial anomalous pulmonary venous return, dextrocardia, single ventricle, common atrioventricular valve  VSD, PDA, coarctation of aorta, arterial aneurysms |
| TERATOGENIC AGENTS  Congenital rubella  Fetal hydantoin syndrome Fetal alcohol syndrome Fetal valproate effects  Maternal phenylketonuria Retinoic acid embryopathy | PDA, peripheral pulmonic stenosis VSD, ASD, coarctation of aorta, PDA ASD, VSD  Coarctation of aorta, hypoplastic left side of heart, aortic stenosis, pulmonary atresia, VSD  VSD, ASD, PDA, coarctation of aorta Conotruncal anomalies |
| OTHERS  Apert syndrome  Autosomal dominant polycystic kidney disease Carpenter syndrome  Conradi syndrome Crouzon disease Cutis laxa  de Lange syndrome Ellis–van Creveld syndrome Holt-Oram syndrome  Infant of diabetic mother Kartagener syndrome Meckel-Gruber syndrome Noonan syndrome Pallister-Hall syndrome  Rubinstein-Taybi syndrome Scimitar syndrome  Smith-Lemli-Opitz syndrome  TAR syndrome (thrombocytopenia and absent radius) Treacher Collins syndrome  Williams syndrome | VSD  Mitral valve prolapse PDA  VSD, PDA  PDA, coarctation of aorta  Pulmonary hypertension, pulmonic stenosis VSD  Single atrium, VSD  ASD, VSD, 1st-degree heart block  Hypertrophic cardiomyopathy, VSD, conotruncal anomalies Dextrocardia  ASD, VSD  Pulmonic stenosis, ASD, cardiomyopathy Endocardial cushion defect  VSD  Hypoplasia of right lung, anomalous pulmonary venous return to inferior vena cava  VSD, PDA ASD, TOF  VSD, ASD, PDA  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.

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| **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 contractural arachnodactyly | Mitral insufficiency or prolapse |
| Ehlers-Danlos syndrome | Mitral valve prolapse, dilatated 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 *l*entigines, *e*lectrocardiographic conduction abnormalities, *o*cular hypertelorism, *p*ulmonary stenosis, *a*bnormal genitals, *r*etardation of growth, sensorineural *d*eafness.

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115

110

105

Systolic BP

100

95

90

85

80

75

70

65

75

70

Diastolic BP (K4)

65

60

55

50

95th 90th

75th 50th

0 1 2 3 4 5 6 7 8 9 10 11 12

Mo

95th 90th

75th 50th

115

110

105

Systolic BP

100

95

90

85

80

75

70

65

75

70

Diastolic BP (K4)

65

60

55

50

95th 90th

75th 50th

0 1 2 3 4 5 6 7 8 9 10 11 12

Mo

95th 90th

75th 50th

45

90th Perc Sys BP

0 1 2 3 4 5 6 7 8 9 10 11 12

Mo

87 101 106 106 106 105 105 105 105 105 105 105 105

45

90th Perc Sys BP

0 1 2 3 4 5 6 7 8 9 10 11 12

Mo

76 98 101 104 105 106 106 106 106 106 106 105 105

Dias BP Ht cm

Wt kg

## A

130

125

120

Systolic BP

115

110

105

100

95

90

Diastolic BP (K4)

68 65 63

51 59 63

4 4 5

63 63

66 68

5 6

65 66 67

70 72 73

7 8 9

68 68

74 76

9 10

69 69

77 78

10 11

69

80

11

95th 90th

75th 50th

Dias BP 68

Ht cm 54

Wt kg 4

## B

130

125

120

Systolic BP

115

110

105

100

95

90

65 64 64

55 56 58

4 4 5

65 65

61 63

5 6

66 66

66 68

7 8

66 67 67 67

70 72 74 75

9 9 10 10

67

77

11

95th 90th

75th 50th

90th Perc

1 2 3 4 5 6 7 8 9 10 11 12 13

Yr

85 95th

80 90th

Diastolic BP (K4)

75 75th

70

50th

65

60

55

50

1 2 3 4 5 6 7 8 9 10 11 12 13

Yr

90th Perc

1 2 3 4 5 6 7 8 9 10 11 12 13

Yr

85

80

75

70

65

60

55

50

1 2 3 4 5 6 7 8 9 10 11 12 13

Yr

95th 90th

75th 50th

Sys BP

105 106 107 108 109 111 112 114 115 117 119 121 124

Sys BP

105 105 106 107 109 111 112 114 115 117 119 122 124

Dias BP

69 68 68

69 69

70 71 73

74 75

76 77 79

Dias BP

67 69

69 69

69 70 71

72 74

75 77

78 80

Ht cm

80 91 100 108 115 122 129 135 141 147 153 159 165

Ht cm

77 89

98 107 115 122 129 135 142 148 154 160 165

Wt kg

## C

11 14 16

18 22

25 29 34

39 44

50 55 62

Wt kg

## D

11 13

15 18

22 25 30

35 40 45

51 58 63

**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.)*

Systolic BP

Systolic BP

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**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 mea- surements 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.)*

140

135

130

125

120

115

110

105

95th

90th

75th

140

135

130

125

120

115

110

105

95th

90th

50th

75th

50th

13 14

15 16

Years

17

18

13

14

15

16

17

18

Years

90

85

95th

90th

90

85

80 75th

80

95th

90th

75

75

75th

50th

70

70

50th

65

65

60 60

13 14 15 16 17 18 13 14 15 16 17 18

90th

Perc Sys BP Dias BP Ht cm Wt kg

Years

124

77

165

62

126

78

172

68

129

79

178

74

131

81

182

80

134

83

184

84

136

84

184

86

90th

Perc Sys BP Dias BP Ht cm Wt kg

Years

124

78

165

63

126

81

168

67

126

82

169

70

127

81

170

72

127

80

170

73

127

80

170

74

A

B

Diastolic BP (K5)

Diastolic BP (K5)

|  |  |  |  |
| --- | --- | --- | --- |
| **Table 422-4** | Pulse Rates at Rest | | |
| **LOWER LIMITS**  **OF NORMAL AVERAGE**  **AGE (beats/min) (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** | | **GIRLS** | **BOYS** |
| 12 yr 70 65 90 85 | | 110 | 105 |
| 14 yr 65 60 85 80 | | 105 | 100 |
| 16 yr 60 55 80 75 | | 100 | 95 |
| 18 yr 55 50 75 70 | | 95 | 90 |

|  |  |  |
| --- | --- | --- |
| **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 |

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| **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.

**Chapter 424** ◆ Epidemiology and Genetic Basis of Congenital Heart Disease **2185**

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| **Table 424-3** | Genetics of Isolated Congenital Heart Disease (Nonsyndromic) | |
| **GENE IMPLICATED\* PROTEIN ENCODED** | | **CARDIAC DEFECTS** |
| GENES ENCODING TRANSCRIPTION FACTORS  *ANKRD1* Ankyrin repeat domain  *CITED2* cAMP responsive element-binding protein  *FOG2/ZFPM2* Friend of GATA  *GATA6* GATA6 transcription factor  *HAND2* Helix-loop-helix transcription factor  *IRX4* Iroquois homeobox 4  *MED13L* Mediator complex subunit 13-like  *NKX2-5/NKX2.5* Homeobox containing transcription factor  *TBX20* T-Box 20 transcription factor  *ZIC3* Zinc finger transcription factor | | TAPVR ASD, VSD TOF  ASD, VSD, TOF, PS, AVSD, PDA TOF  VSD TGA  ASD, VSD, TOF, HLHS, CoA, TGA, IAA  ASD, VSD, mitral stenosis  TGA, PS, TAPVR, HLHS, ASD, VSD |
| GENES ENCODING RECEPTORS AND SIGNALING MOLECULES  *ACVR1/ALK2* BMP receptor  *ACVR2B* Activin receptor  *ALDH1A2* Retinaldehyde dehydrogenase  *CFC1/CRYPTIC* Cryptic protein  *CRELD1* Epidermal growth factor-related proteins  *FOXH1* Forkhead activin signal transducer  *GDF1* Growth differentiation factor-1  *GJA1* Connexin 43  *LEFTY2* Left-right determination factor  *NODAL* Nodal homolog (TGF-β superfamily)  *NOTCH1* NOTCH1 (Ligand of JAG1)  *PDGFRA* Platelet-derived growth factor receptor α  *SMAD6* MAD-related protein  *TAB2* TGF-β activated kinase  *TDGF1* Teratocarcinoma-derived growth factor 1  *VEGF* Vascular endothelial growth factor | | AVSD  PS, DORV, TGA TOF  TOF, TGA, AVSD, ASD, VSD, IAA, DORV ASD; AVSD  TOF, TGA  TOF, TGA, DORV, heterotaxy ASD, HLHS, TAPVR  TGA, AVSD, IAA, CoA  TGA, PA, TOF, DORV, TAPVR, AVSD  Bicuspid aortic valve, AS, CoA, HLHS TAPVR  Bicuspid aortic valve, CoA, AS Outflow tract defects  TOF, VSD  CoA, outflow tract defects |
| GENES ENCODING STRUCTURAL PROTEINS  *ACTC* α Cardiac actin  *MYH11* Myosin heavy chain 11  *MYH6* α-Myosin heavy chain  *MYH7* β-Myosin heavy chain | | ASD  PDA, aortic aneurysm ASD, TA, AS, TGA  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 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.

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| **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 azygos 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 |

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| **Table 424-4** | Genetics of Cardiomyopathies | | |
| Hypertrophic cardiomyopathy | | 14q1  15q2 | β-Myosin heavy chain  α-Tropomyosin |
|  | | 1q31 | Troponin T |
|  | | 19p13.2-19q13.2 | Troponin I |
|  | | 11p13-q13 | Myosin-binding protein C |
|  | | 12q23 | Cardiac slow myosin regulatory light chain |
|  | | 13p21 | Ventricular slow myosin essential light chain |
|  | | 2q31 | Titin |
|  | | 3p25 | Caveolin-3 |
|  | | Mitochondrial DNA | tRNA-glycine |
|  | | Mitochondrial DNA | tRNA-isoleucine |
| Hypertrophic cardiomyopathy with Wolff-Parkinson- White syndrome | | 7q36.1 | AMP-activated protein kinase |
| Other genetic diseases causing cardiac hypertrophy Familial amyloid disease  Noonan syndrome | | 18q12.1  12q24.1, 2p22.1, 3p25,12p12.1 | Transthyretin (TTR)  Protein tyrosine phosphatase 11 (PTPN11), son of sevenless homologue 1 (SOS1), RAF1 protooncogene, GTPase KRAS  α-Galactoside A (GLA)  Lysosomal-associated membrane protein 2 (LAMP2) Hereditary hemochromatosis protein (HFE)  Acid α-glucosidase (GAA) |
| Fabry disease Danon disease  Hereditary hemochromatosis Pompe disease | | Xq22 Xq24 6p21.3  17q25 |
| Dilated cardiomyopathy X-linked  Autosomal recessive | | Xp21 Xp28  19p13.2-19q13.2 | Dystrophin Tafazzin 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 KATP channel); and lamin A/C.

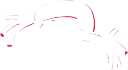
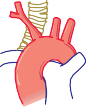
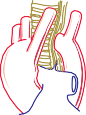
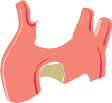
Isolated noncompaction of the left ventricle: autosomal dominant, autosomal recessive, X-linked, and mitochondrial inheritance patterns have been reported. Genes that have been implicated include: α-dystrobrevin, Cypher/ZASP, lamin A/C, Tafazzin, MIB1, and LIM domain-binding protein 3 (LDB3).

*Partially adapted from Dunn KE, Caleshu C, Cirino AL, et al. A clinical approach to inherited hypertrophy: 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) LQT2 (autosomal dominant) LQT3 (autosomal dominant) LQT4 (autosomal dominant) LQT5 (autosomal dominant) LQT6  Jervell and Lange-Nielsen syndrome (autosomal recessive, congenital deafness)  LQT8-13 | | 11p15.5  7q35  3p21  4q25-27  21q22-q22  21q22.1  11p15.5  Unknown | *KVLQT1* (K+ channel) *HERG* (K+ channel) *SCN5A* (Na+ channel) Not known  *KCNE1* (K+ channel) *KCNE2* (K+ channel) *KVLQT1* (K+ channel)  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-β3* (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 | | 3p21-p24 *SCN5A* (Na+ channel) | |
| elevation, unexpected sudden death) | | 3p22-p24 *GPD-1L* (glycerol-3-phosphate dehydrogenase) | |
| Catecholaminergic polymorphic ventricular tachycardia | | * *RYR2* (autosomal dominant) * *CASQ2* (autosomal recessive) | |

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|  |  |  |
| --- | --- | --- |
| **Table 431-1** | Total Anomalous Pulmonary Venous Return | |
| **SITE OF CONNECTION (% OF CASES)** | | **% WITH SIGNIFICANT OBSTRUCTION** |
| Supracardiac (50) | |  |
| Left superior vena | | 40 |
| cava (40) | |  |
| Right superior vena cava (10) | | 75 |
| Cardiac (25) | |  |
| Coronary sinus (20) | | 10 |
| Right atrium (5) | | 5 |
| Infracardiac (20) | | 95-100 |
| Mixed (5) | | |



**Table 432-1** Vascular Rings

**LESION**

DOUBLE ARCH

**SYMPTOMS**

**PLAIN FILM**

**BARIUM MRI**

**SWALLOW BRONCHOSCOPY ECHOCARDIOGRAPHY TREATMENT**

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 AP—tracheal

distress deviation to

Swallowing left (right

dysfunction 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 Normal swallowing

dysfunction

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.*

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|  |  |
| --- | --- |
| **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 | |

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

Revised World Health Organization Classification of Pulmonary Hypertension

**Table 433-1**

|  |  |  |  |
| --- | --- | --- | --- |
| **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 [PGI2], 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 PGI2) | | 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 PGI2) | | 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 1 dose for 1st mo  2  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 1 final target dose to  2  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.

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Rhythm disorder Supraventricular tachycardia Right bundle branch block Heart block

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)

Congenital Heart Defects Associated with Survival into Adulthood Without Surgery or Interventional Cardiac Catheterization

**Table 434-2**

Risks in Adults Who Have Congenital Heart Disease

**Table 434-4**

Ventricular tachycardia Sudden death Coarctation of aorta Essential hypertension Recoarctation Aneurysm formation

Residual lesions (shunts)

Ventral septal defect Atrial septal defect Patent ductus arteriosus Acquired lesions

Subacute bacterial endocarditis Subvalvular stenosis Supravalvular stenosis

Valvular insufficiency Valvular restenosis Eisenmenger complex

Pregnancy risk (see Table 434-5)

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

Most Common Congenital Heart Defects Surviving to Adulthood After Surgery or Interventional Catheterization

**Table 434-3**

|  |  |
| --- | --- |
| **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.

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

Issues That Require Coordination of Care Between the Cardiologist and the Primary Care Physician

**Table 434-6**

**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.*

Serum ferritin ≤15 µg/L Transferrin saturation ≤15%

Serum ferritin ≥15 µg/L Transferrin saturation ≥15%

**Patient iron-deficient**

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

**Patient iron-replete**

No symptoms of hyperviscosity

**Patient iron-replete**

Symptoms of hyperviscosity

Reassess symptoms

Repeat laboratory tests

Consider cessation of iron supplementation when iron replete (serum ferritin ≥15 µg/L

and transferrin saturation ≥15%)

Some patients will require chronic iron supplementation for steady-state erythrocytosis

Regularly reassess symptoms and laboratory tests

Assess for other causes

of symptoms and treat accordingly: e.g., Hypovolaemia

Gout

Brain abscess Hypothyroidism Depression

Resolution of

symptoms Patient remains iron-replete

Persistent moderate-

severe hyperviscosity symptoms

Packed cell volume

>65%

Reassess every

6-12 months

Trial of phlebotomy

with fluid replacement

**Assess annually**

Anemia history\*

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