TABLE 54.36 Adverse Drug Interactions Involving Antiinfective Agents[a]—cont'd

INTERACTING DRUGS	ADVERSE EFFECT	PROBABLE MECHANISM
Desipramine	Increased desipramine effect, toxicity	Decreased metabolism
DHP CCBs	Increased DHP CCB toxicity	Decreased clearance
Doxorubicin	Increased risk of cardiotoxicity	Decreased metabolism
Elbasvir-grazoprevir	Increased grazoprevir exposure and ALT elevation	Mechanism not established
Ergot derivatives	Increased ergot toxicity	Decreased metabolism
Erythromycin	Increased erythromycin, protease effect, toxicity	Decreased metabolism
Garlic supplements	Decreased protease effect	Increased metabolism
Grapefruit juice	Decreased indinavir effect, increased saquinavir effect	Increased, decreased metabolism
H_2 receptor antagonists	Decreased indinavir effect	Decreased bioavailability
HMG-CoA reductase inhibitors	Increased statin concentrations, toxicity	Decreased metabolism
Ifosfamide	Increased ifosfamide toxicity	Decreased metabolism
Interferon alfa-2	Increased indinavir toxicity	Decreased metabolism
Isotretinoin	Increased isotretinoin effect, toxicity	Decreased metabolism
Levodopa	Increased levodopa effect, toxicity	Decreased metabolism
Lidocaine	Increased risk of lidocaine toxicity	Decreased metabolism
Loperamide	Decreased protease efficacy	Decreased bioavailability
Methadone	Decreased methadone, protease effect	Increased metabolism
Metronidazole	Increased metronidazole effect, toxicity	Decreased metabolism
Nefazodone	Increased nefazodone effect, toxicity	Decreased metabolism
Oral contraceptives	Altered efficacy of birth control possible	Increased, decreased metabolism
Oral immunosuppressants	Increased immunosuppressant effect, toxicity	Decreased metabolism
Paclitaxel	Increased effect, toxicity of paclitaxel	Decreased metabolism
Phenytoin	Decreased protease, increased phenytoin effects	Increased, decreased metabolism
Phosphodiesterase inhibitors	Increased phosphodiesterase inhibitor effect, toxicity	Decreased metabolism
Pimozide	Increased pimozide toxicity	Decreased metabolism
Primidone	Decreased protease effect	Increased metabolism
Proton pump inhibitors	Decreased effect of indinavir	Decreased bioavailability
Quinidine	Increased quinidine effect, toxicity	Decreased metabolism
Raloxifene	Possible decreased raloxifene effect with nelfinavir	Increased metabolism
Ranolazine	Increased ranolazine effect, toxicity	Decreased metabolism
Repaglinide	Increased repaglinide exposure, effects	Decreased metabolism
Rifamycins	Decreased protease effect, increased rifamycin toxicity	Increased, decreased metabolism
Risperidone	Increased risperidone toxicity	Decreased metabolism
Ritonavir	Increased protease toxicity	Decreased metabolism
SSRI antidepressants	Increased SSRI effect, toxicity	Decreased metabolism
St. John's wort	Decreased protease effect	Increased metabolism
Warfarin	Increased warfarin effect	Decreased metabolism
Zolpidem	Increased zolpidem effect, toxicity	Decreased metabolism
Pyrantel Pamoate With		
Theophylline	Increased theophylline toxicity	Decreased metabolism
Pyrazinamide With		
Cyclosporine	Decreased cyclosporine exposure	Increased metabolism
Ethionamide	Increased hepatotoxicity	Additive toxicity
Probenecid	Increased serum uric acid	Decreased uric acid excretion
Rifampin	Increased hepatotoxicity	Additive toxicity
Zidovudine	Decreased efficacy of pyrazinamide	Mechanism not established
Pyrimethamine With		
Methotrexate	Increased risk of myelosuppression	Mechanism not established

TABLE 54.36 Adverse Drug Interactions Involving Antiinfective Agents[a]—cont'd

INTERACTING DRUGS	ADVERSE EFFECT	PROBABLE MECHANISM
Trimethoprim-sulfamethoxazole	Increased risk of megaloblastic anemia and myelosuppression	Additive folate inhibition
Zidovudine	Increased risk of myelosuppression	Mechanism not established
Quinine With		
Acetazolamide	Increased quinine serum concentration; increased toxicity	Decreased clearance from increased urinary pH
Aluminum antacids	Decreased quinine serum concentration	Decreased absorption
Cimetidine	Decreased quinine clearance; increased AUC	Hepatic enzyme inhibition
Digoxin	Increased digoxin concentration	Mechanism not established
Flecainide	Increased flecainide toxicity	Decreased metabolism
Heparin	Decreased anticoagulant effect	Mechanism not established
Mefloquine	Increased cardiac events	Additive toxicity
Neuromuscular blocking agents	Potentiation of neuromuscular blocking effects	Additive toxicity
Ritonavir	Increased quinine toxicity	Decreased metabolism
Sodium bicarbonate	Increased quinine serum concentration; increased toxicity	Decreased clearance from increased urinary pH
Warfarin	Increased warfarin effect	Hepatic suppression of synthesis of vitamin K–dependent clotting factors
Quinupristin-Dalfopristin With		
Haloperidol	Increased risk of cardiotoxicity	Decreased metabolism
HMG-CoA reductase inhibitors	Increased risk of myopathy or rhabdomyolysis	Decreased metabolism
Vinca alkaloids	Increased vinca alkaloid exposure, toxicity	Decreased metabolism
Raltegravir With		
Atazanavir	Increased raltegravir exposure	Decreased metabolism
Rifamycins	Decreased raltegravir exposure	Increased metabolism
Tipranavir-ritonavir	Decreased raltegravir exposure	Increased metabolism
Ribavirin With		
Abacavir	Increased risk of lactic acidosis	Mechanism not established
Didanosine	Increased risk of lactic acidosis	Mechanism not established
Lamivudine	Increased risk of lactic acidosis	Mechanism not established
Stavudine	Increased risk of lactic acidosis	Mechanism not established
Warfarin	Decreased warfarin exposure	Mechanism not established
Zidovudine	Increased risk of lactic acidosis; in vitro retroviral antagonism	Mechanism not established; decreased phosphorylation
Rifamycins (Except Rifaximin) With		
Analgesics	Possible decreased analgesic effect	Increased metabolism
Anticoagulants, oral	Possible decreased oral anticoagulant effect	Increased metabolism
Anticonvulsants	Possible decreased anticonvulsant effect	Increased metabolism
Atovaquone	Decreased atovaquone effect	Increased metabolism
Azole antifungals	Decreased azole effect	Increased metabolism
Barbiturates	Possible decreased barbiturate effect	Increased metabolism
BCG vaccine	Negates BCG effect	Negates immune response
β-Blockers	Possible decreased β-blocker effect	Increased metabolism
Chloramphenicol	Possible decreased chloramphenicol effect	Increased metabolism
Clarithromycin	Decreased clarithromycin concentration, increased rifamycin toxicity	Increased, decreased metabolism
Clofibrate	Possible decreased clofibrate effect	Increased metabolism
Contraceptives, oral	Possible decreased oral contraceptive effect	Increased metabolism
Corticosteroids	Possible decreased corticosteroid effect	Increased metabolism
Cyclosporine	Possible decreased cyclosporine effect	Increased metabolism
Dapsone	Possible decreased dapsone effect	Increased metabolism
Delavirdine	Decreased delavirdine concentration, increased rifamycin toxicity	Increased, decreased metabolism
Diazepam	Possible decreased diazepam effect	Increased metabolism

Continued

TABLE 54.36 Adverse Drug Interactions Involving Antiinfective Agents[a]—cont'd

INTERACTING DRUGS	ADVERSE EFFECT	PROBABLE MECHANISM
Digoxin	Decreased digitoxin and digoxin effects	Increased metabolism
DHP CCBs	Decreased DHP CCB effect	Increased metabolism
Disopyramide	Possible decreased disopyramide effect	Increased metabolism
Doxycycline	Decreased doxycycline effect	Increased metabolism
Estrogens	Decreased estrogen concentrations	Hepatic enzyme induction
Ethionamide	Increased hepatotoxicity	Additive
Fluconazole	Decreased fluconazole effect	Increased metabolism
Hepatitis C direct-acting antivirals	Decreased antiviral exposure	Increased metabolism/transport
HMG-CoA reductase inhibitors	Decreased statin effect	Increased metabolism
Hypoglycemics, oral	Possible decreased oral hypoglycemic effect	Increased metabolism
Indinavir	Decreased indinavir effect; increased rifamycin exposure	Increased metabolism; decreased metabolism
Isoniazid	Possible increased hepatotoxicity	Possible increased toxic metabolites
Mexiletine	Possible decreased mexiletine effect	Increased metabolism
Narcotics	Possible decreased narcotic effect	Increased metabolism
Nelfinavir	Decreased nelfinavir effect	Increased metabolism
Nevirapine	Decreased nevirapine effect	Increased metabolism
Praziquantel	Decreased praziquantel effect	Increased metabolism
Progestins	Possible decreased progestin effect	Increased metabolism
Quinidine	Possible decreased quinidine effect	Increased metabolism
Ritonavir	Decreased ritonavir effect, increased rifamycin toxicity	Increased, decreased metabolism
Saquinavir	Decreased saquinavir effect, increased rifamycin toxicity	Increased, decreased metabolism
Tacrolimus	Decreased tacrolimus effect	Increased metabolism
Terbinafine	Decreased terbinafine effect	Increased metabolism
Theophylline	Possible decreased theophylline effect	Increased metabolism
Verapamil	Possible decreased verapamil effect	Increased metabolism
Zidovudine	Decreased zidovudine concentrations, AUCs	Mechanism not established
Rilpivirine With		
Antacids	Decreased rilpivirine exposure	Decreased absorption
Azole antifungals	Increased rilpivirine exposure	Decreased metabolism
Delavirdine	Increased rilpivirine exposure	Decreased metabolism
Efavirenz	Decreased rilpivirine exposure	Increased metabolism
Etravirine	Decreased rilpivirine exposure	Increased metabolism
H_2 receptor antagonists	Decreased rilpivirine exposure	Decreased absorption
Macrolides	Increased rilpivirine exposure	Decreased metabolism
Methadone	Decreased methadone exposure	Increased metabolism
Nevirapine	Decreased rilpivirine exposure	Increased metabolism
Ombitasvir-paritaprevir-ritonavir	Increased rilpivirine exposure	Mechanism not established
Ritonavir	Increased rilpivirine exposure	Decreased metabolism
Ritonavir, Lopinavir-Ritonavir: Same as With All Protease Inhibitors *Plus*		
Albendazole	Altered albendazole efficacy	Increased or decreased metabolism
Atovaquone	Decreased atovaquone effect	Increased phase II metabolism
Chlorpromazine	Increased ritonavir, chlorpromazine effect, toxicity	Decreased metabolism
Clozapine	Decreased clozapine effect	Increased metabolism
Codeine	Decreased analgesic effect	Decreased metabolism
Digoxin	Increased digoxin effect, toxicity	Decreased clearance
Disopyramide	Increased disopyramide effect, toxicity	Decreased metabolism
Disulfiram	Disulfiram-like reactions	Alcohol in protease dosage forms
Ethosuximide	Increased ethosuximide effect, toxicity	Decreased metabolism
Fentanyl	Increased fentanyl effect, toxicity	Decreased metabolism

TABLE 54.36 Adverse Drug Interactions Involving Antiinfective Agents[a]—cont'd

INTERACTING DRUGS	ADVERSE EFFECT	PROBABLE MECHANISM
Flecainide	Increased flecainide effect, toxicity	Decreased metabolism
Gemfibrozil	Increased ritonavir effect, toxicity	Mechanism not established
Haloperidol	Increased haloperidol effect, toxicity	Decreased metabolism
Meperidine	Increased risk of normeperidine toxicity	Increased metabolism of parent
Metoprolol	Increased metoprolol effect, toxicity	Decreased metabolism
Metronidazole	Disulfiram-like reactions	Alcohol in protease dosage forms
Mexiletine	Increased mexiletine effect, toxicity	Decreased metabolism
Morphine	Decreased morphine effect	Increased metabolism
Olanzapine	Decreased olanzapine effect	Increased metabolism
Perphenazine	Increased perphenazine, ritonavir effect, toxicity	Decreased metabolism
Prochlorperazine	Increased prochlorperazine, ritonavir effect, toxicity	Decreased metabolism
Promethazine	Increased promethazine, ritonavir effect, toxicity	Decreased metabolism
Propafenone	Increased propafenone effect, toxicity	Decreased metabolism
Quinine	Increased quinine effect, toxicity	Decreased metabolism
Tamoxifen	Increased tamoxifen effect, toxicity	Decreased metabolism
Terfenadine	Increased risk of cardiotoxicity	Decreased metabolism
Thalidomide	Increased thalidomide effect, toxicity	Decreased metabolism
Theophylline	Decreased theophylline effect	Increased metabolism
Thioridazine	Increased thioridazine, ritonavir effect, toxicity	Decreased metabolism
Timolol	Increased timolol effect, toxicity	Decreased metabolism
Tramadol	Increased tramadol effect, toxicity	Decreased metabolism
Tricyclic antidepressants	Increased tricyclic effect, toxicity	Decreased metabolism
Trifluoperazine	Increased trifluoperazine, ritonavir effect, toxicity	Decreased metabolism
Triflupromazine	Increased triflupromazine, ritonavir effect, toxicity	Decreased metabolism
Simeprevir With		
Amiodarone	Increased risk of symptomatic bradycardia	Mechanism not established
CCBs	Increased exposure of CCBs and simeprevir	Decreased metabolism
Cyclosporine	Increased cyclosporine exposure	Decreased metabolism and efflux transport
CYP3A inducers	Decreased simeprevir exposure	Increased metabolism
CYP3A inhibitors	Increased simeprevir exposure	Decreased metabolism
HMG-CoA reductase inhibitors	Increased statin exposure, toxicity	Decreased metabolism
Ledipasvir	Increased simeprevir and ledipasvir exposure	Mechanism not established
OAT1B1/3 substrates	Increased substrate exposure, toxicity	Decreased OAT1B1/3-mediated efflux
Sofosbuvir With		
Amiodarone	Increased risk of serious bradycardia	Mechanism not established
P-gp inducers	Decreased sofosbuvir exposure	Increased P-gp–mediated efflux
Rifamycins	Decreased sofosbuvir exposure	Increased P-gp–mediated efflux
Sofosbuvir-Ledipasvir: Same as Sofosbuvir *Plus*		
Antacids	Decreased ledipasvir exposure	Decreased absorption
Digoxin	Increased digoxin exposure	Decreased P-gp–mediated efflux
H_2 receptor antagonists	Decreased ledipasvir exposure	Decreased absorption
Proton pump inhibitors	Decreased ledipasvir exposure	Decreased absorption
Simeprevir	Increased ledipasvir and simeprevir exposure	Mechanism not established
Sofosbuvir-Velpatasvir: Same as Sofosbuvir *Plus*		
Antacids	Decreased velpatasvir exposure	Decreased absorption
BCRP substrates	Increased substrate exposure	Decreased BCRP-mediated efflux
Digoxin	Increased digoxin exposure	Mechanism not established
H_2 receptor antagonists	Decreased velpatasvir exposure	Decreased absorption

Continued

TABLE 54.36 Adverse Drug Interactions Involving Antiinfective Agents[a]—cont'd

INTERACTING DRUGS	ADVERSE EFFECT	PROBABLE MECHANISM
Proton pump inhibitors	Decreased velpatasvir exposure	Decreased absorption
Sofosbuvir-Velpatasvir-Voxilaprevir: Same as Sofosbuvir-Velpatasvir *Plus*		
Atazanavir	Increased voxilaprevir exposure	Mechanism not established
Cyclosporine	Increased voxilaprevir exposure	Mechanism not established
Lopinavir	Increased voxilaprevir exposure	Mechanism not established
Stavudine With		
Chloramphenicol	Increased peripheral neuropathy	Additive toxicity
Cisplatin	Increased peripheral neuropathy	Additive toxicity
Clarithromycin	Possible decreased stavudine effect	Decreased bioavailability (?)
Dapsone	Increased peripheral neuropathy	Additive toxicity
Disulfiram	Increased peripheral neuropathy	Additive toxicity
Ethionamide	Increased peripheral neuropathy	Additive toxicity
Fluconazole	Possible decreased stavudine effect	Decreased bioavailability (?)
Glutethimide	Increased peripheral neuropathy	Additive toxicity
Hydralazine	Increased peripheral neuropathy	Additive toxicity
Isoniazid	Increased peripheral neuropathy	Additive toxicity
Iodoquinol	Increased peripheral neuropathy	Additive toxicity
Methadone	Decreased stavudine effect	Decreased bioavailability
Metronidazole	Increased peripheral neuropathy	Additive toxicity
Nitrofurantoin	Increased peripheral neuropathy	Additive toxicity
Pentamidine	Increased pancreatitis	Additive toxicity
Phenytoin	Increased peripheral neuropathy	Additive toxicity
Ribavirin	Increased peripheral neuropathy	Additive toxicity
Rifabutin	Decreased stavudine effect	Decreased bioavailability (?)
Trimethoprim-sulfamethoxazole	Increased pancreatitis	Additive toxicity
Vincristine	Increased peripheral neuropathy	Additive toxicity
Sulfonamides With		
Barbiturates	Increased thiopental effect	Decreased albumin binding
Chloroprocaine	Possible antagonism of sulfonamide action	Competition for PABA site
Cyclosporine	Decreased cyclosporine effect with sulfamethazine	Possible increased metabolism
Hypoglycemics, sulfonylurea	Increased hypoglycemic effect	Mechanism not established
Lamivudine	Increased lamivudine toxicity	Competition for renal clearance
Methenamine	Crystallization of sulfonamides in the urine; precipitate of formaldehyde, sulfamethizole	Acidification of the urine
Methotrexate	Possible increased methotrexate toxicity	Decreased renal clearance and displacement from binding
Paraldehyde	Crystallization of sulfonamides in the urine	Acidification of the urine
Phenytoin	Increased phenytoin effect, except possibly with sulfisoxazole	Decreased metabolism
Procaine	Possible antagonism of sulfonamide action	Competition for PABA site
Tetracaine	Possible antagonism of sulfonamide action	Competition for PABA site
Thiopental	Increased thiopental effect; decreased dose necessary when given with sulfisoxazole	Plasma protein binding competition
Warfarin	Increased anticoagulant effect	Decreased metabolism and displacement from binding sites
Telavancin With		
Heparin	Falsely elevated aPTT results	Mechanism not established
Telbivudine With		
Peginterferon alfa-2a	Increased risk of peripheral neuropathy	Mechanism not established
Tenofovir Alafenamide Fumarate With		
Anticonvulsants	Decreased tenofovir exposure	Increased metabolism
Rifamycins	Decreased tenofovir exposure	Increased metabolism

TABLE 54.36 Adverse Drug Interactions Involving Antiinfective Agents[a]—cont'd

INTERACTING DRUGS	ADVERSE EFFECT	PROBABLE MECHANISM
Tenofovir Disoproxil Fumarate With		
Atazanavir	Decreased atazanavir, increased tenofovir exposure	Mechanism not established
Didanosine	Increased didanosine effect, toxicity	Mechanism not established
Ledipasvir	Increased tenofovir exposure	Mechanism not established
Terbinafine With		
Caffeine	Increased caffeine effect, toxicity	Decreased metabolism
Cimetidine	Increased terbinafine effect, toxicity	Decreased metabolism
Cyclosporine	Decreased cyclosporine effect	Increased metabolism
Rifamycins	Decreased terbinafine effect	Increased metabolism
Tetracyclines With		
Alcohol	Decreased doxycycline effect in alcoholics	Increased metabolism
Aminoglycosides	In vitro antagonism; no in vivo support	Mechanism not established
Antacids, oral	Decreased oral tetracycline effects	Decreased tetracycline absorption
Anticoagulants, oral	Increased anticoagulant effect	Mechanism not established
Antidepressants, tricyclic	Localized hemosiderosis with amitriptyline and minocycline	Possible synergistic toxicity
Barbiturates	Decreased doxycycline effect	Increased metabolism
Bismuth subsalicylate	Decreased tetracycline effect	Decreased absorption
CBZ	Decreased doxycycline effect	Increased metabolism
Contraceptives, oral	Decreased contraceptive effect	Possible decreased enterohepatic circulation of estrogen
Digoxin	Increased digoxin effect	Decreased gut metabolism and increased absorption
Iron, oral	Decreased tetracycline effect, but not with doxycycline; decreased iron effect	Decreased absorption
Kaolin-pectin	Decreased concentrations of tetracyclines	Decreased absorption
Lithium	Increased lithium toxicity	Decreased renal excretion
Methotrexate	Possible increased toxicity	Mechanism not established
Methoxyflurane	Increased nephrotoxicity	Displacement from binding
Penicillins	In vitro antagonism; rare in vivo support for this	Mechanism not established
Phenytoin	Decreased doxycycline effect	Increased metabolism
Rifamycins	Possible decreased doxycycline effect	Increased metabolism
Theophylline	Possible theophylline toxicity	Mechanism not established
Zinc sulfate	Decreased tetracycline effect	Decreased absorption
Tigecycline With		
Warfarin	Increased warfarin exposure without altering the INR	Mechanism not established
Tinidazole With		
Alcohol	Increased alcohol side effects	Decreased metabolism
Cholestyramine	Decreased tinidazole effect, toxicity	Decreased absorption
Cyclosporine	Increased cyclosporine effect, toxicity	Decreased metabolism
CYP3A inducers	Decreased tinidazole effect, toxicity	Increased metabolism
CYP3A inhibitors	Increased tinidazole effect, toxicity	Decreased metabolism
Disulfiram	Increased CNS toxicity	Mechanism unknown
Fluorouracil	Increased fluorouracil effect, toxicity	Decreased clearance
Lithium	Increased lithium effect, toxicity	Mechanism unknown
Phenytoin	Increased IV phenytoin effect, toxicity	Mechanism unknown
Tacrolimus	Increased tacrolimus effect, toxicity	Decreased metabolism
Warfarin	Increased anticoagulant effects	Decreased metabolism
Trimethoprim With		
Angiotensin-converting enzyme inhibitors	Hyperkalemia	Reduced potassium clearance

Continued

TABLE 54.36 Adverse Drug Interactions Involving Antiinfective Agents[a]—cont'd

INTERACTING DRUGS	ADVERSE EFFECT	PROBABLE MECHANISM
Amiloride	Trimethoprim may potentiate hyponatremia because of concomitant use of amiloride with thiazide diuretics	Additive toxicity
Azathioprine	Leukopenia	Mechanism not established
Cyclosporine	Increased nephrotoxicity	Synergistic toxicity
Dapsone	Increased dapsone toxicity	Altered clearance
Digoxin	Possible increased digoxin effect	Decreased renal excretion and possibly decreased metabolism
Methotrexate	Increased methotrexate toxicity	Decreased clearance
Phenytoin	Increased phenytoin serum concentrations—increased risk of phenytoin toxicity; increased risk of folate deficiency	Decreased metabolism; additive toxicity
Thiazide diuretics	Trimethoprim may potentiate hyponatremia because of concomitant use of amiloride with thiazide diuretics	Additive toxicity
Vancomycin With		
Aminoglycosides	Possible increased nephrotoxicity and ototoxicity	Additive toxicity
Amphotericin B	Increased nephrotoxicity	Additive toxicity
Bacitracin	Increased nephrotoxicity	Additive toxicity
Cisplatin	Increased nephrotoxicity	Additive toxicity
Digoxin	Possible decreased digoxin effect	Possibly decreased absorption
Piperacillin-tazobactam	Increased nephrotoxicity	Mechanism not established
Polymyxins	Increased nephrotoxicity	Additive toxicity
Warfarin	Increased risk of bleeding	Mechanism not established
Voriconazole With		
Amprenavir	Increased amprenavir, voriconazole effect, toxicity	Decreased metabolism
Atorvastatin	Increased atorvastatin effect, toxicity	Decreased metabolism
Barbiturates	Decreased voriconazole effect	Increased metabolism
BZDs	Increased BZD effect, toxicity	Decreased metabolism
CCBs	Increased CCB effect, toxicity	Decreased metabolism
CBZ	Decreased voriconazole effect	Increased metabolism
Ergot alkaloids	Increased ergot effect, toxicity	Decreased metabolism
HMG-CoA reductase inhibitors	Increased statin effect, toxicity	Decreased metabolism
NNRTIs	Increased NNRTI effect, toxicity	Decreased metabolism
Omeprazole	Increased omeprazole effect, toxicity	Decreased metabolism
Phenytoin	Increased phenytoin effect, toxicity; decreased voriconazole effect	Decreased, increased metabolism
Pimozide	Increased pimozide effect, toxicity	Decreased metabolism
Protease inhibitors	Increased protease inhibitor, voriconazole effect, toxicity	Decreased metabolism
Quinidine	Increased quinidine effect, toxicity	Decreased metabolism
Rifamycins	Increased rifamycin effect, toxicity; decreased voriconazole effect	Decreased, increased metabolism
Ritonavir	Increased ritonavir, voriconazole effect, toxicity	Decreased metabolism
Sirolimus	Increased sirolimus effect, toxicity	Decreased metabolism
Sulfonylureas	Increased sulfonylurea effect, toxicity	Decreased metabolism
Tacrolimus	Increased tacrolimus effect, toxicity	Decreased metabolism
Vinca alkaloids	Increased vinca effect, toxicity	Decreased metabolism
Warfarin	Increased warfarin effect, toxicity	Decreased metabolism
Zidovudine With		
Acetaminophen	Granulocytopenia	Mechanism not established
Acyclovir	Neurotoxicity	Mechanism not established
Amphotericin B	Increased risk of nephrotoxicity, hematologic toxicity	Additive toxicity
Antimycobacterials	Possible increased risk of hematologic toxicity	Decreased phase II zidovudine metabolism
Aspirin	Possible increased risk of hematologic toxicity	Decreased phase II zidovudine metabolism
Atovaquone	Possible increased risk of hematologic toxicity	Decreased phase II zidovudine metabolism
Chloramphenicol	Possible increased risk of hematologic toxicity	Decreased phase II zidovudine metabolism

TABLE 54.36 Adverse Drug Interactions Involving Antiinfective Agents[a]—cont'd

INTERACTING DRUGS	ADVERSE EFFECT	PROBABLE MECHANISM
Cimetidine	Possible increased risk of hematologic toxicity	Decreased phase II zidovudine metabolism
Clarithromycin	Decreased zidovudine concentrations and AUCs	Mechanism not established
Cytotoxic or myelosuppressive agents	Increased risk of hematologic toxicity	Additive toxicity
Dapsone	Increased neutropenia	Additive toxicity
Fluconazole	Increased risk of hematologic toxicity	Decreased phase I metabolism
Flucytosine	Increased hematologic toxicity	Additive toxicity
Ganciclovir	Decreased zidovudine effect; hematologic toxicity	Increased clearance; additive toxicity
Hydroxyurea	Increased hematologic toxicity	Additive toxicity
Indomethacin	Possible increased risk of hematologic toxicity	Mechanism not established; additive
Interferon alfa	Increased hematologic toxicity	Additive toxicity
Interferon beta	Increased hematologic toxicity	Additive toxicity
Methadone	Increased risk of hematologic toxicity	Decreased phase II zidovudine metabolism
Nephrotoxic agents	Increased risk of toxicity	Increased serum concentrations; decreased clearance
Nucleoside analogues	Increased risk of hematologic toxicity	Additive toxicity
Oral contraceptives	Increased risk of hematologic toxicity	Decreased phase II zidovudine metabolism
Oxazepam	Possible increased risk of hematologic toxicity	Decreased phase II zidovudine metabolism
Phenytoin	Increased risk of hematologic toxicity	Decreased clearance
Primaquine	Increased risk of peripheral neuropathy	Additive toxicity
Probenecid	Increased risk of hematologic toxicity	Decreased clearance, phase II metabolism
Pyrazinamide	Decreased effect of pyrazinamide	Mechanism not established
Pyrimethamine	Increased hematologic toxicity	Additive toxicity
Ribavirin	In vitro antiretroviral antagonism	Decreased phosphorylation of zidovudine
Rifamycins	Decreased zidovudine effect	Increased phase II zidovudine metabolism
Sulfadiazine	Increased hematologic toxicity	Additive toxicity
Trimethoprim	Increased risk of hematologic toxicity	Decreased zidovudine clearance
Trimethoprim-sulfamethoxazole	Increased hematologic toxicity	Additive toxicity
Valproic acid	Increased zidovudine effect, toxicity	Decreased phase II zidovudine metabolism

[a]This table includes significant adverse drug interactions and is not a comprehensive list of all potential adverse drug interactions.
ALT, Alanine aminotransferase; *aPTT,* activated partial thromboplastin time; *AUC,* area under the concentration-time curve; *BCG,* Bacillus Calmette-Guérin; *BCRP,* breast cancer resistance protein; *BZDs,* benzodiazepines; *CBZ,* carbamazepine; *CCB,* calcium channel blocker; *CNS,* central nervous system; *CYP,* cytochrome P450; *DHP CCB,* dihydropyridine calcium channel blocker; *GI,* gastrointestinal; *G6PD,* glucose-6-phosphate dehydrogenase; *HMG-CoA,* 3-hydroxy-3-methyl-glutaryl coenzyme A; *INR,* international normalized ratio; *MAO,* monoamine oxidase; *NNRTI,* nonnucleoside reverse-transcriptase inhibitor; *NSAIDs,* nonsteroidal antiinflammatory drugs; *OAT,* organic anion transporter; *PABA,* para-aminobenzoic acid; *P-gp,* P-glycoprotein; *PT,* prothrombin time; *SNRI,* serotonin and norepinephrine reuptake inhibitor; *SSRI,* selective serotonin reuptake inhibitor.

This is a very important point to consider, because many clinicians will use these equations even in the face of the aforementioned contraindications, stating that "bad data are better than no data" or "everyone does it this way." We completely disagree with these premises and urge the clinician to use clinical judgement and not rely on data that he or she knows are not accurate, because this could result in serious dosing errors in a patient with resultant morbidity or mortality. In addition, the practice of "rounding serum creatinine to 1.0 mg/dL" to calculate CrCl is inaccurate and should not be done. Improvement in the estimation of kidney function is more likely to occur with the use of exogenously administered substrates (e.g., inulin, iohexol) or endogenous substrates such as cystatin C, which is less confounded by clinical variables. However, use of these novel biomarkers to guide drug dosing will be difficult to validate in the near term.

DOSAGE ADJUSTMENT FOR HEPATIC IMPAIRMENT

In theory, although hepatic impairment can impair drug clearance, accurate biomarkers of hepatic function and correlation with dosage adjustment are generally not available. Several drug labels include dose adjustment recommendations that are based on PK studies performed in patients with cirrhosis and are classified according to the three-category Child-Pugh score (A, B, or C). This scoring system was developed as a tool to predict mortality during surgery and the necessity for liver transplantation. Newer scoring systems such as the Model for End-Stage Liver Disease (MELD) have been developed as prognostic tools. However, these categoric estimates have limited clinical validity in considering dose modification. Many antiinfective agents have a high therapeutic-to-toxic ratio and therefore dosage adjustment in hepatic impairment is not necessary, even in the face of impaired body clearance. In circumstances in which narrow therapeutic-to-toxic ratios are seen, clinical judgment and appropriate treatment of infection should take precedence in drug dosage determinations.

DOSAGE ADJUSTMENT FOR BODY SIZE (OBESE AND UNDERWEIGHT)

The dosage of drugs in adults is often based on a fixed dose (with no regard to body size), weight, or body surface area (height and weight metric). Several antiinfective agents have traditionally been given on the basis of body weight (milligrams per kilogram). Although this approach may be reasonable during maturation (birth to 2 years of age), the reliability of this body size metric has been called into question because drug clearance mechanisms do not increase proportionately with weight (>2 years of age). The underlying mathematical assumptions

and dosing errors that may occur as a consequence of use of weight or an alternate body size descriptor have been recently reviewed (see Pai in Suggested Readings). In general, computing maintenance antiinfective doses on the basis of total body weight has the potential for overdose (in obese individuals) and underdose (in underweight individuals) at the extremes of the weight distribution. Over time, several alternate body size descriptors such as body surface area, ideal body weight, adjusted body weight, and lean body weight have been developed to address this problem. Adjusted body weight and lean body weight are mathematically similar to body surface area as metrics for dosages in adults. In contrast, ideal body weight is computed by sex by using height only, so this body size descriptor is conceptually equivalent to height-based dosing. As an example, if an antiinfective dose is approved at 10 mg/kg/day in an adult, then the dose will be 600 mg (60 kg) and 1200 mg (120 kg) if administered based on total body weight. If the 60-kg and 120-kg adults are male and 69 inches (175 cm) in height, then the ideal body weight is 70.7 kg and both individuals would receive the same dose of 707 mg based on ideal body weight. In contrast, the lean body weight would be 51.1 kg and 73.5 kg in the 60-kg and 120-kg adults, respectively. Therefore the doses would be 511 and 735 mg (1.4-fold difference) across this 2-fold difference in total body weight. If the antiinfective had been approved at 12 mg/kg/day based on lean body weight, the dose would be 613 mg and 882 mg in the 60- and 120-kg individuals, respectively. This last solution meets empirical observations that drug clearance typically increases by approximately 50% across this 2-fold weight distribution. Unfortunately, early-phase clinical trials, which define the dose for evaluation in phase III trials, often exclude obese and underweight participants. The resulting narrow weight distribution limits the ability to define drug-specific dose extrapolation for body size. Regrettably, consensus on a universal approach to dose extrapolation has not been reached and, therefore, specific guidance for antiinfective dosing in obese and in underweight patients should be sought on a drug-by-drug basis.

DRUG-DRUG INTERACTIONS

Drug-drug interactions are categorized into PD and PK interactions. Many interactions deemed PD are really the exposure-response effects of a PK interaction leading to greater pharmacologic effect. These PD interactions are often exploited in antiinfective therapy, and it is through this mechanism that combination therapy can demonstrate synergistic effect. Quantitation of PD interactions is at best difficult. PK interactions are somewhat more "predictable" but still show large variability in the population.

PK drug-drug interactions can occur through a number of different mechanisms. These include:

- Reduction of drug absorption by concurrent drugs: The most common absorption interactions occur by means of chelation of an antiinfective with a cation such as calcium, magnesium, or iron. A useful rule of thumb is that oral antiinfectives should not be administered within 1 hour before or 2 hours after the administration of oral divalent or trivalent cations unless a study has clearly demonstrated a lack of significant interaction with their coadministration.
- Displacement from protein-binding sites: Although this interaction in theory could enhance antiinfective tissue distribution and efficacy, homeostatic mechanisms act to increase the elimination of unbound drug, resulting in no substantial change in overall drug exposure.
- Inhibition, induction, or activation of DMEs or transporters: These drug interactions are by far the most important seen in clinical practice. Most information on drug-drug interactions is generated in a very limited number of individuals, often healthy volunteers, and may not be applicable to the general population. Some basic tenants of these drug interactions are important to remember:
  - Genetic and environmental factors, in addition to the microbiome composition, can affect the baseline activity of DMEs and transporters and thus will affect the potential for drug-drug interactions.
  - Not all patients experience a drug-drug interaction, even if this has been described in the literature. This is determined by both genetic and environmental factors.
  - Patients with low or null DMEs or transporter activity have a low chance of drug-drug interactions; however, if this low baseline activity is due to a reversible pathologic process, the potential for drug-drug interactions will increase as the pathologic process is appropriately treated.
  - Patients with normal or high DME or transporter activity have a high likelihood of drug-drug interactions.
  - Patients with a low genetic potential to make a DME or transporter (poor or intermediate metabolizers or transporters) have a small chance of an induction interaction because they do not have the genetic potential to make more of the enzyme or transporter when stimulated to do so.
  - Patients with normal or high genetic potential to make a DME or transporter are at greater risk of an induction interaction owing to the greater genetic potential to make the enzyme or transporter.
  - Patients can undergo enzyme heterocyclic activation of a DME, which increases the activity of the enzyme approximately 33%. In enzyme heterocyclic activation the peak effect occurs immediately, whereas it can take up to 2 weeks for the peak effect to be seen in induction. Heterocyclic activation is most often seen with CYP3A isozymes and CYP2B6.
  - Over the course of many infectious diseases, patients with infections (acute and chronic) have the potential to substantially change over time in terms of their risk of drug-drug interactions; thus this is not a static process.

We have provided a table of inducers, inhibitors, and substrates for important DMEs and transporters. Data on drug interactions and transporters are much more limited and less understood because specific probes and biomarkers for transporters are not well developed and validated.

Although clinicians request a specific recommendation for dosage adjustment when a drug-drug interaction is identified, it is virtually impossible to provide a specific recommendation because of the previously mentioned factors. An approach that incorporates appropriate treatment of an infection with the goals of optimizing efficacy, reducing the risk of resistance, and attempting to avoid toxicity is recommended. Familiarity with the toxic side effects of antiinfectives and how to monitor them is essential.

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Major Clinical Syndromes

II

A Fever

55 Temperature Regulation and the Pathogenesis of Fever

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SHORT VIEW SUMMARY

Terminology
- Fever is a pyrogen-mediated rise in body temperature above normal.

Clinical Thermometry
- Thermometric measurements are influenced by a host of variables, all too frequently ignored when interpreting the significance of clinical temperature readings.
- There are two basic thermal compartments worthy of special consideration: the shell and the core.
- Oral and tympanic membrane measurements differ from the core temperature as measured rectally but are adequate for the majority of uses.
- Fever may be defined as an early-morning temperature ≥37.2°C (99.0°F) or ≥37.8°C (100°F) at any time.

Thermoregulation
- The thermoregulatory system maintains a relatively constant core body temperature by functioning as a federation of relatively independent effector loops, without a single controller or set point.

The Generation of Fever
- Fever is a thermoregulatory manifestation of the innate immune response, initiated with the binding of pathogen-associated molecular patterns to pattern recognition receptors expressed by immune cells.
- The crucial step is the production of prostaglandin E_2, which crosses the blood-brain barrier and triggers fever.

Acute-Phase Response
- In addition to cytokine-mediated rise in the core temperature, numerous other physiologic reactions, collectively referred to as the acute-phase response, are mediated by members of the same group of pyrogenic cytokines that activate the thermal response of fever.

Biologic Value of Fever
- Questions concerning fever's risk-benefit quotient have generated considerable controversy, and there is as yet no consensus as to the appropriate clinical situations, if any, in which fever or its mediators should be suppressed.

Biologic Value of Fever: The Case of Sepsis
- There is evidence from human studies that suggests that fever in sepsis is associated with improved outcomes.

Biologic Value of Hypothermia
- Like fever, hypothermia is appears to be a regulated response; however, its potential value is still a matter of study and conjecture.

Antipyretic Therapy: General Considerations
- Antipyretics are commonly administered to enhance patient comfort.
- Although antipyretics can decrease postvaccination titers (in the short term) and pathogen clearance, the significance is not known.
- Antipyretics have not been shown to protect against recurrences of febrile seizures.

Antipyretic Therapy: The Case of Sepsis
- Antipyretics are of limited value in the treatment of bacterial sepsis and in critically ill patients with fever.

Antipyretic Therapy: Pharmacologic Agents
- Antipyretics can be prescribed to provide symptomatic relief in febrile patients, reduce the metabolic demands of fever in patients with underlying cardiovascular and pulmonary disorders, and possibly prevent or alleviate fever-induced mental dysfunction in older patients

Antipyretic Therapy: Physical Methods of Antipyresis
- In view of the capacity of external cooling measures to induce a cold pressor response, it is questionable whether this form of antipyretic therapy should ever be administered to febrile patients with infection.

The oldest known written reference to fever exists in Akkadian cuneiform inscriptions from the 6th century BCE, most likely derived from an ancient Sumerian pictogram of a flaming brazier used to symbolize both fever and the local warmth of inflammation.[1] Theoretical constructs of the pathogenesis of fever did not emerge until several centuries later, when Hippocratic physicians proposed that body temperature, and physiologic harmony in general, involved a delicate balance among four corporal humors: blood, phlegm, black bile, and yellow bile.[2] Fever was then believed to result from an excess of yellow bile, a concept in concert with the fact that many infections of that era caused both fever and jaundice. Galen later broadened the classification of fevers and expounded the idea that many types of fever developed from putrification of humors.[3] During the Middle Ages, demonic possession was added to the list of mechanisms thought to be responsible for fever. By the 18th century, Harvey's discovery of the circulation of blood and the birth of clinical chemistry led iatrophysicists and iatrochemists to hypothesize alternatively that body heat and fever resulted from friction associated with the flow of blood through the vascular system and that they resulted from fermentation and putrefaction occurring in the blood and intestines.[4] Ultimately, as a result of the work of Claude Bernard in the 19th century, the metabolic processes occurring within the body came to be recognized as the true source of body heat. Subsequent work established that body temperature is tightly controlled by mechanisms regulating the rate of heat production and the rate of heat dissipation (heat loss).

The origin of the practice of monitoring body temperature as an aid to diagnosis is uncertain. The oldest known references to devices used to measure temperature date to the 1st or 2nd century BCE, when Philo of Byzantium and Hero of Alexandria are believed to have invented several such devices.[5,6] The CE 10th century Persian physician Akhawaynī appears to be the first to propose and use a fever curve.[3] It is reasonably certain that Galileo manufactured a primitive (air) thermometer at about the time that he assumed the chair in mathematics at Padua in 1592.[7] However, thermometry was not fully assimilated into medical practice until 1868, when Carl Reinhold August Wunderlich published a magnum opus entitled *Das Verhalten der Eigenwärme in Krankenheiten (The Course of Temperature in Diseases)*,[8] in which he gave 37°C (98.6°F) special significance with respect to normal body temperature.[9] He described the diurnal variation of body temperature and, in the process, alerted clinicians to the fact that "normal body temperature" is actually a temperature range, rather than a specific value.

TERMINOLOGY

According to the International Union of Physiological Sciences Commission for Thermal Physiology, fever is "a state of elevated core temperature, which is often, but not necessarily, part of the defensive responses of multicellular organisms (host) to the invasion of live (microorganisms) or inanimate matter recognized as pathogenic or alien by the host."[10] The febrile response, of which the temperature rise is a component, is a complex physiologic reaction to disease, involving not only a rise in core temperature, per se, but also the generation of acute-phase reactants and the activation of numerous physiologic, endocrinologic, and immunologic systems. The active rise in body temperature during fever is to be distinguished from that occurring during episodes of passive hyperthermia. During the rising phase of fever, thermoregulation works to increase body temperature by increasing heat production (e.g., by shivering) and decreasing heat loss (e.g., by cutaneous vasoconstriction), and the work of the thermoregulation system is uncompromised. In contrast, during hyperthermia the thermoregulation system works to decrease body temperature by increasing heat loss (e.g., by sweating), and the fact that body temperature nevertheless increases equates to the system's failure. Although basic scientists often distinguish fever from hyperthermia, based on the above-mentioned argumentation, physicians often view fever as an example of hyperthermia (a state with an increased body temperature), similar to how any increase in the heart rate is considered tachycardia.[11]

In the clinical setting, fever is typically defined as a pyrogen-mediated rise in body temperature above the normal range. Although consistent with the popular perception of fever, this definition ignores the fact that a rise in body temperature is but one component of a multifaceted response. This standard clinical definition is further flawed because it implies that body temperature is a single entity, when, in fact, it is a pastiche of many different temperatures, each representative of a particular body part and each varying throughout the day in response to activities of daily living and the influence of endogenous diurnal rhythms.

CLINICAL THERMOMETRY

For more than a century the thermometer has been preeminent among clinical instruments used to distinguish health from disease and to monitor the course of illness. Unfortunately, thermometric measurements are influenced by a host of variables, all too frequently ignored when interpreting the significance of clinical temperature readings.

Anatomic Variability

Although clinicians frequently regard temperature readings from various anatomic sites as equivalent approximations of body temperature,[1] no one temperature provides a comprehensive description of the thermal status of the human body.[12] This is because the body has many different temperatures, each representative of a particular body part. Nevertheless, within the body, there are two basic thermal compartments worthy of special consideration: the shell and the core.[12,13]

The shell, which consists of mostly of skin, subcutaneous fat, and bones, insulates the core from the external environment. The core, of which the brain, thoracic viscera, and arterial and central venous blood are major components, although insulated by the shell, has temperature gradients of its own resulting from differences in the metabolic rates, blood flow patterns, and heat dissipation in the various organs contained therein. Even during baseline conditions, organs with higher metabolic rates have higher temperatures than those with lower metabolic rates and can be up to 1.3°C (2.3°F) higher than the temperature of arterial blood.[14] In addition, tissues close to the skin generally have lower temperatures than those at deeper locations.[13] Although such differences are normally small, muscle temperatures rise markedly during vigorous exercise compared with those of less metabolically active organs. During shock and under extreme environmental conditions, regional anatomic variations in temperature may also be exaggerated. Rectal measurements were once regarded as the most practical and accurate means of obtaining routine estimates of core temperature. However, rectal (and colonic) temperature readings are consistently higher than those obtained at other sites (even pulmonary artery blood), which some authorities have suggested might be caused by heat generated as a result of the metabolic activity of fecal bacteria,[13] even though an early study showed no significant decrease in the rectal temperature after a reduction in the colonic bacterial content. A significant effect on rectal temperature, however, is also exerted by that of the blood returning to the core from the lower extremities, because the internal iliac vein passes near the anorectal canal. Thus, during shock, the core area expands, the shell shrinks,[12] and perfusion of the rectum is markedly impaired, causing the rectal temperature to lag significantly behind a rapidly rising or falling core temperature.[15] For this reason, Houdas and Ring[16] have concluded that the rectal temperature provides a reliable approximation of the core temperature only if the patient is in thermal balance. In neonates and small children, even in the absence of shock, the rectal temperature measured by standard technique has been reported to correlate poorly with the core temperature as measured by a deep rectal (colonic) probe.[17,18]

The right atrium is an ideal site for measuring core temperature because it is the nexus at which venous blood from all anatomic regions joins. However, because it is relatively inaccessible, temperatures of other sites (esophageal, tympanic membrane [TM], and bladder temperature) are more often used as approximations of core temperature.[19,20]

The TM temperature is thought by some to be particularly useful in this regard because at least a portion of this membrane is perfused by a tributary of the artery that supplies the hypothalamus. The ease with which TM measurements can be obtained using modern infrared TM thermometers has made these instruments the devices of choice in many clinics and intensive care units (ICUs). There are two basic types of infrared TM thermometers. One type detects radiant energy emitted from the TM and portions of the ear canal, processes the information, and then displays a value representing tissue temperature in the ear canal (unadjusted mode). The other displays an (adjusted)

estimate of the core temperature (e.g., pulmonary arterial blood temperature) based on comparison data obtained from selected study samples. Readings obtained using the former type of TM thermometer tend to be lower than simultaneously obtained oral readings, whereas those obtained with the latter type are generally higher. Unfortunately, numerous studies of many different TM thermometers have shown that, although convenient, such instruments tend to give highly variable readings that correlate poorly with simultaneously obtained oral or rectal readings. In addition, multiple studies have demonstrated the inaccuracy of TM measurements in patients with hypothermia, hyperthermia, or fever,[21–23] and a careful study showed that there are regional variations on the TM itself.[24] Temporal artery (TA) thermometry (using similar infrared technology as TM measurements) has gained popularity in the last several years. Although some claim that this method measures core temperature, a recent meta-analysis concluded that it tends to underestimate the core and is as inaccurate as TM thermometry.[25]

Several studies have shown that monitoring the skin temperature using temperature-sensitive crystals incorporated into plastic strips placed on the forehead is an insensitive technique for detecting elevations in the core temperature. Studies have consistently demonstrated that axillary temperature measurements do not reflect core temperature,[26–28] even though axillary thermometry continues to be popular in several countries. Finally, the infrared detection of facial temperatures at airports at the present time is too inaccurate for mass screening during epidemics.[29,30]

The detection of fever in children holds its own challenges, as the use of the same sites (TM, TA, axillary) in children seems to be associated with an even greater deviation from the core temperature.[23,31,32]

Because temperatures of the rectum, mouth, and TM are related but not identical, it would be useful to have a reliable formula for converting data from one site to another. In a study of healthy young adults, Rabinowitz and associates[33] determined that, on average, rectal readings exceed concurrent oral readings by 0.4°C (0.8°F) and TM readings by 0.8°C (1.6°F), with high variability. These findings are in agreement with several earlier investigations.[34–37] However, Lorin[38] has shown TM readings to be higher than simultaneously obtained oral measurements. This discrepancy most likely reflects the fact that unadjusted-mode TM thermometers—for example, the IVAC Core—generally give lower readings than adjusted-mode TM thermometers, such as those used in earlier studies.[39]

We recommend consistency in device use, at whichever site is chosen. In addition, practitioners should be aware of the limitations of each modality (hypothermia and hyperthermia for TM readings, mucositis for oral readings), and should measure temperature by another method in those specific instances (e.g., rectal measurement in the case of hypothermia or hyperthermia, or TM measurement in those with mucositis). Currently, oral and TM measurements are the most common modalities used, at least in North America. Although these differ from the core temperature as measured rectally,[33] they are adequate for the majority of uses.

Physiologic Variables

Wunderlich and Seguin believed that "old" people have lower body temperatures than younger persons, and their views in this regard were corroborated by Howell in a report published in *Lancet* in 1948.[39a] There is also a substantial body of data suggesting that thermoregulation is impaired in older persons because of various effects of aging on the autonomic nervous system. Several studies have shown lower oral temperature measurements in the elderly.[40,41] However, core temperatures appear unchanged when comparing healthy older subjects (mean age, 80.3 years; range, 62–99 years) with healthy younger subjects. Comparisons of simultaneous oral, axillary, and rectal temperature readings from these subjects have shown lower average oral and axillary readings in older persons but comparable average rectal temperatures to those in younger subjects.

It has long been known that women exhibit increases in body temperature of about 0.5°C (0.9°F) at the time of ovulation,[16] which is used clinically to time periods of maximal fertility. Wunderlich and Seguin also maintained that women (1) have slightly higher normal temperatures than men overall and (2) often show greater and more sudden changes in temperature. Two other studies have corroborated Wunderlich and Seguin's former (but not latter) observation.[42,43] Further, in a recent study of more than 18,630 white adults age 20 to 98 years (mean, 58.3 years), women were found to have higher oral temperatures (97.5 ± 1.2°F) than men (97.2 ± 1.1°F).[40] Another study suggests that pregnancy affects the core temperature. In this study, rectal temperatures were measured during the first trimester, second trimester, third trimester, and 3 months postpartum. A core temperature of 37.1°C was noted in the first trimester, which progressively decreased and reached a nadir (36.4°C) postpartum.[43a]

Body temperature, like most physiologic functions, exhibits circadian rhythmicity, which is linked to the sleep-wake cycle.[44] Before 8 weeks of age, newborns exhibit hourly oscillations of body temperature.[45] During this time there is a decrease in the core (rectal) temperature that occurs with sleep.[46,47] The typical circadian rhythmicity of temperature seen in adults develops by 10 weeks of age.[48] During normal sleep-wake cycles (i.e., asleep during the night and awake during the day) the core temperature reaches its zenith in the late afternoon or early evening and its nadir in the early morning.[42] Adaptation to night-shift work causes a reversal of this pattern.[49] Thermoregulation has also been reported to be altered in patients with neuropsychiatric disorders, such as chronic depression.[50] Finally, there appears to be a blunting of the circadian amplitude in the elderly,[41,51] which is restored with melatonin therapy.[51] Therefore, when interpreting clinical thermometric measurements, it is important to consider not only the age of the patient, the time of the measurement, the site at which the temperature is taken, but also the sleep-wake cycle of the subject being studied.

In addition to these physiologic variables, exercise, medications (such as corticosteroids), digestion, and underlying disorders such as chronic renal failure, shock, and local inflammation at the site of the thermometric measurement (e.g., proctitis, external otitis, or stomatitis) may alter measured thermoregulatory responses, local temperature, or both. It has, for instance, been shown that the core temperature varies by as much as 3°C (from 36°C–39°C) in states ranging from sleep to moderately high levels of sustained exercise, and this continuum of body temperature is related to a continuum of activity.[52] Mucositis in cancer patients has been associated with a 0.89°C elevated oral temperature measurement compared with TM measurements.[53] Ambient temperature and humidity have been shown experimentally to affect both human sleep stages and body temperature,[54] suggesting that body temperature might also vary according to the time of year and local climate. It is pertinent in this regard that Cheng and Partridge[55] have shown that bundling and warm environments can elevate rectal temperatures of newborns to the febrile range.

"Normal Body Temperature"

A survey of physicians' perceptions of body temperature published in 1995 indicated widespread confusion regarding key features of the human body temperature.[55a] Of 268 physicians and medical students surveyed, 75% gave 37°C (98.6°F) as their definition of normal body temperature. An additional 13% defined the normal temperature as a narrow range of temperatures about a mean of 37°C (98.6°F). Only 10 (4%) subjects in the group as a whole specified a particular body site (e.g., oral or rectal) for temperature measurements in their definition. Also, 98% percent thought that the normal temperature varies during the day, with quantitative estimates of such diurnal variability ranging from 0.2°C (0.4°F) to 2.8°C (5°F). Such misconceptions are not limited to medical students and primary-care physicians. In the latest (2008) joint update from the American College of Critical Care Medicine and the Infectious Diseases Society of America (IDSA) for evaluation of new fever in critically ill adult patients, normal temperature is defined as 37°C.[19]

A 1992 descriptive analysis of 700 baseline oral temperature observations from 148 healthy men and women found a range of 35.6°C (96.0°F) to 38.2°C (100.8°F), with an overall mean of 36.8 ± 0.4°C (98.2 ± 0.7°F); 37°C (98.6°F) accounted for only 56 (8%) of the 700 oral temperature observations recorded (Fig. 55.1). The mean temperature varied diurnally, with a 6 a.m. nadir and a 4 to 6 p.m. peak (Fig. 55.2). The maximum temperature (as reflected by the 99th percentile) varied from a low of 37.2°C (98.9°F) at 6 a.m. to a high of 37.7°C (99.9°F) at 4 p.m. Age did not influence temperature within the range studied (18–40 years). Women

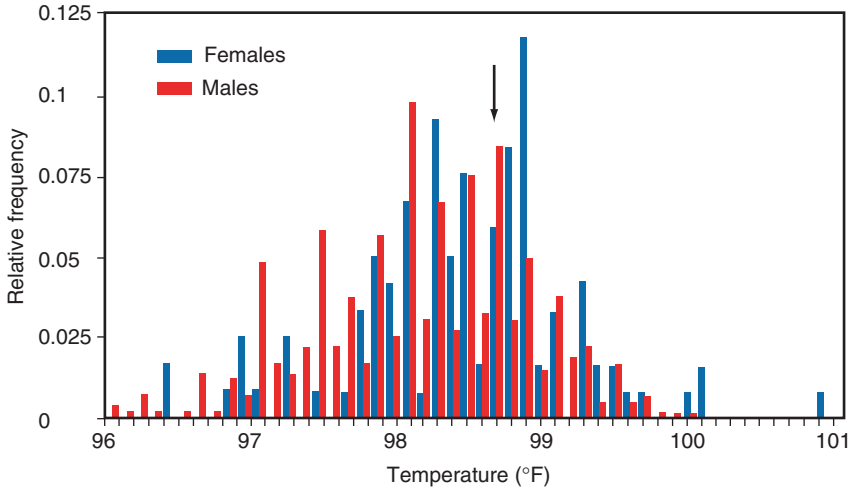

FIG. 55.1 Frequency distribution of 700 baseline oral temperatures obtained during 2 consecutive days of observation in 148 healthy young volunteers. Arrow indicates the location of 98.6°F (37°C). *(From Mackowiak PA, Wasserman SS, Levine MM. A critical appraisal of 98.6°F, the upper limit of the normal body temperature, and other legacies of Carl Reinhold August Wunderlich.* JAMA. *1992;268:1578–1580.)*

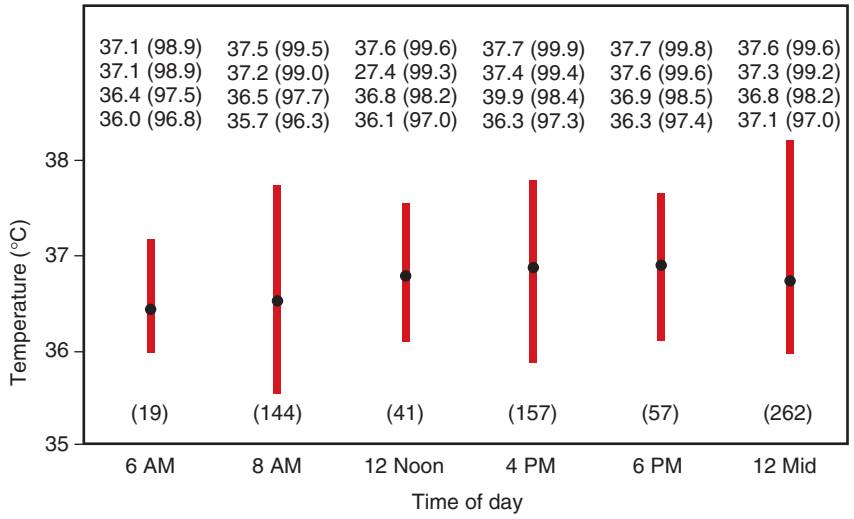

FIG. 55.2 Mean oral temperatures and temperature ranges in 148 healthy young volunteers according to time of day. The four temperatures shown at each sample time are the 99th percentile *(top)*, 95th percentile *(second)*, mean *(third)*, and 5th percentile *(bottom)* for each sample set. (The numbers in parentheses are the temperatures in degrees Fahrenheit.) The numbers in parentheses on the x-axis indicate the number of observations analyzed at each sample time. *(From Mackowiak PA, Wasserman SS, Levine MM. A critical appraisal of 98.6°F, the upper limit of the normal body temperature, and other legacies of Carl Reinhold August Wunderlich.* JAMA. *1992;268:1578–1580.)*

had a slightly higher average oral temperature than men (36.9°C [98.4°F] vs. 36.7°C [98.1°F]), with similar diurnal temperature oscillations of ~0.5°C (1.0°F). There was a linear relationship between temperature and pulse rate, with an average increase in heart rate of 4.4 beats/min for each 1°C (2.44 beats/min for each 1°F) rise in temperature over a wide range of temperatures examined.

According to Wunderlich and Seguin, "When the organism (man) is in a normal condition, the general temperature of the body maintains itself at the physiologic point: 37°C = 98.6°F."[55b] Although several subsequent investigations have recorded mean temperatures of normal adult populations closer to 36.6°C (98.0°F), Wunderlich's intimation that 37°C (98.6°F) is the most normal of temperatures persists to this day in lay thinking, although to a lessening extent in the thinking of health care workers.

Wunderlich identified 38.0°C (100.4°F) as the upper limit of normal body temperature in his patient population and therefore regarded any temperature higher than 38.0°C (100.4°F) as fever. However, the upper limit of normal body temperature varies among individuals, thereby limiting the applicability of mean values derived from population studies (even those as large as Wunderlich's) to individual subjects. However, the maximum temperature, like the mean temperature, exhibited by a population varies according to the time of day and the site at which the temperature measurement is taken. Because of such variability, no single temperature can be designated as the upper limit of normal. In the study population considered earlier, 37.2°C (98.9°F) was the maximum oral temperature (i.e., the 99th percentile) recorded at 6 a.m., whereas at 4 p.m. the maximum oral temperature observed reached 37.7°C (99.9°F). Thus these data suggest that when modern thermometers are used to monitor oral temperature in young or middle-aged adults, fever is roughly defined as an early-morning temperature of 37.2°C (99.0°F) or higher or as a temperature of 37.8°C (100°F) or higher at any time during the day. It should be noted that this definition is different than the commonly regarded dictum that fever is anything ≥38.3°C (≥101°F), which was endorsed by the IDSA for ICU patients and which is not based on any data we are aware of.

Wunderlich wrote in 1868 that "[temperature] oscillates even in healthy persons according to time of day by 0.5°C = 0.9°F." The next year, Wunderlich and Reeve wrote, "The lowest point is reached in the morning hours between two and eight, and the highest in the afternoon between four and nine."[55c] Modern authorities have generally concurred with these observations. However, Tauber[56] has suggested that the amplitude of diurnal variation might be as high as 1°C (1.8°F).

Nevertheless, the subjects examined in that study exhibited considerable individual variability, with some having daily temperature oscillations as wide as 1.3°C (2.4°F) and others having oscillations as narrow as 0.1°C (0.2°F). A more recent study that used a "temperature holter," a device that measures 24-hour TM and axillary temperature, demonstrated an increase in temperature amplitude in the circadian rhythm of patients with fever, particularly those with tuberculosis.[56a]

THERMOREGULATION

Although the core is only relatively homogeneous, as described earlier, it is reasonable to consider that the thermoregulatory system regulates core (deep) body temperature. This is achieved by use of multiple effector responses, both behavioral and physiologic, that can be activated from multiple thermosensors located within the shell (mostly in the skin) and the core (most importantly in the brain). Thermoregulatory behaviors include heat or cold avoidance and seeking, as well as many others—from simple postural changes, to selecting clothes appropriate for the weather, to complex multiperson operations such as building houses with the desired thermal environment. The principal physiologic cold-defense responses are shivering and sympathetically driven skin vasoconstriction and nonshivering thermogenesis in brown adipose tissue (BAT), the latter two being autonomic responses. Although laboratory rodents, such as rats and mice, exhibit robust shivering responses if core temperature falls, nonshivering thermogenesis is a more important mechanism for heat production in rodents.[57] Conversely, although humans have significant BAT deposits,[58] shivering is thought to be a primary mechanism for heat production in humans.[59] Of interest, BAT also has been shown to be present in adult humans and found to contribute to thermogenesis, especially on a long time scale, such as in cases of cold adaptation, and to affect body mass.[60–64] This highly specialized form of adipose tissue is characterized by its brownish color (due to an abundance of mitochondria) and a profuse vascular supply. In humans multiple small depots of BAT are located in the neck and chest (near the clavicles, along the spinal column, and in other locations). Physiologic (autonomic) heat defenses include cutaneous vasodilation and species-specific responses aimed at evaporating water from the skin or respiratory tract, such as thermoregulatory salivation in rats, panting in dogs, and sweating (and perhaps also hyperpnea[65]) in humans.

How the multisensor, multieffector thermoregulatory system is functionally organized remains a subject of debate. Previously, it was widely believed that the thermoregulation system is unified and fully integrated, as an engineered system for temperature control would be. It was thought that thermoreceptors in different parts of the body detect local temperatures, code them into electric signals, and send these signals to the preoptic anterior hypothalamus (POA). The POA was believed to integrate these temperatures into some functionally meaningful "mean body temperature," to compare this integrated mean temperature with some set point and to recruit the corresponding thermoeffector responses in a coordinated fashion. One of the popular descriptions of such a unified thermoregulatory system with a single set point was given by Hammell.[66] However, no neuronal networks for computing a mean body temperature, computing the set point, comparing the mean temperature with the set point, or coordinating effector responses have been identified, at least not definitively.

A different concept has emerged over the last decade.[18,67,68] This concept is based on the idea that, similar to other physiologic systems,[69] the thermoregulatory system functions as a federation of relatively independent effector loops,[70] without a single controller and without a single set point or its equivalent.[71] Each thermoeffector loop includes a unique efferent neural pathway driving the corresponding effector response,[72,73] and each loop uses negative feedback from the main control variable, core temperature, and feedback (either negative or positive) from the auxiliary (additional) variable, skin temperature.[67] The auxiliary feedback control is similar to the feedforward control in that it allows the body to anticipate thermal disturbances coming from the environment and to maintain the core temperature at a more stable level. By the same token, each thermoeffector is sensitive to a unique combination of shell and core temperatures,[74–78] and each therefore defends a different level of differently distributed body temperatures.[12,79,80] However, the individual activities of each thermoeffector affect the core body temperature, which plays, therefore, a coordinating role for thermoeffector responses.[12] In fact, coordination through the common control variable is probably sufficient to explain all examples of coordinated recruitment of thermoeffectors in a response. This coordination serves as a fundamental unifying force in the thermoregulation system. Of importance, the new concept requires no neural networks for computation of an integrated mean temperature, comparing this temperature with an obvious or hidden set point in a unified system, or for coordinating different thermoeffectors responses with each other. By acting on the thermoreceptive elements of a thermosensitive neuron, a local temperature (whether skin or brain) can change the activity of that neuron and, sequentially, of the entire thermoeffector pathway synaptically linked to that neuron. As explained by Kobayashi,[81,82] a thermosensitive neuron does not code its local temperature into an electric signal to be processed by the central control network. Instead, it generates an effector-driving signal when the local temperature reaches that neuron's threshold; this signal then spreads by a neural pathway and triggers the effector response. (An engineering term for such an element would be "thermostat," not "sensor.") This concept emphasizes the significance of the thermoreceptive elements of thermosensory neurons and gives these elements a principal role in determining whether a thermoeffector response will be triggered. Some of these thermoreceptive elements, especially those located in the skin, are likely to be thermosensitive transient receptor potential channels,[67] whereas the nature of other, especially central, thermoreceptors is largely unknown. The thermoregulatory system also overlaps, or "meshes," with other control systems in multiple ways. Behavioral thermoregulatory responses also involve elements of feedforward control that use nonthermal signals, for instance, selecting weather-appropriate clothes based on a weather forecast.[67] A schematic of thermoregulation by independent effector loops is given in Fig. 55.3. For more information on how the thermoregulation system works, see the recent review by Romanovsky.[82a]

THE GENERATION OF FEVER

Historically, various substances have been shown to raise core temperature and cause fever. They were divided into two general categories: those that originate outside the body (exogenous pyrogens, such as bacterial endotoxin [lipopolysaccharide, LPS]), and those that are derived from host cells (endogenous pyrogens). Endogenous pyrogens are now known as pyrogenic cytokines.[83]

Today, fever is viewed as a thermoregulatory manifestation of the innate immune response.[84] It is initiated with the binding of pathogen-associated molecular patterns, such as LPS, viral RNA, and fungal sugars, to pattern recognition receptors (PRRs) expressed by these immune cell populations.[85] This binding results in the activation of gene expression and synthesis of a broad range of molecules, which, in addition to pyrogenic cytokines, include chemokines, cell adhesion molecules, and immunoreceptors, as well as various enzymes and lipid mediators.[84]

Undoubtedly, LPS is the best-studied example of an exogenous pyrogen. In small laboratory animals (mice, rats, and rabbits), intravenous (IV) injection of LPS produces a monophasic fever (one body temperature peak) at low doses and polyphasic (at least biphasic) fevers, that is, several subsequent body temperature rises, at higher doses.[86–88] Very high doses of LPS (1 mg/kg and higher) often cause hypothermia and shock[89,90]; body temperature is dynamic in these species and dependent on LPS dose and ambient temperature.[11,91] Similarly, low doses of LPS cause monophasic fever in humans, with a single peak in body temperature occurring 3 to 6 hours after injection,[92–94] although there may be a second peak as well.[83,95] High doses of LPS, especially those that cause hypothermia and shock, have not been studied in humans.

The list of pyrogenic cytokines includes interleukin (IL)-1α, IL-1β, IL-6, tumor necrosis factor (TNF)-α, ciliary neurotropic factor, interferon (IFN)-δ, and possibly others.[96–104] Most pyrogenic cytokines have monomeric molecular masses ranging from 17 to 30 kilodaltons. Undetectable under basal conditions in healthy subjects, they are produced by many different tissues in response to appropriate stimuli. Once released, pyrogenic cytokines have short intravascular half-lives. They are pleiotropic, in that they interact with receptors present on many different host cells. They are active in picomolar quantities, induce maximal cellular responses even at low receptor occupancy, and exert

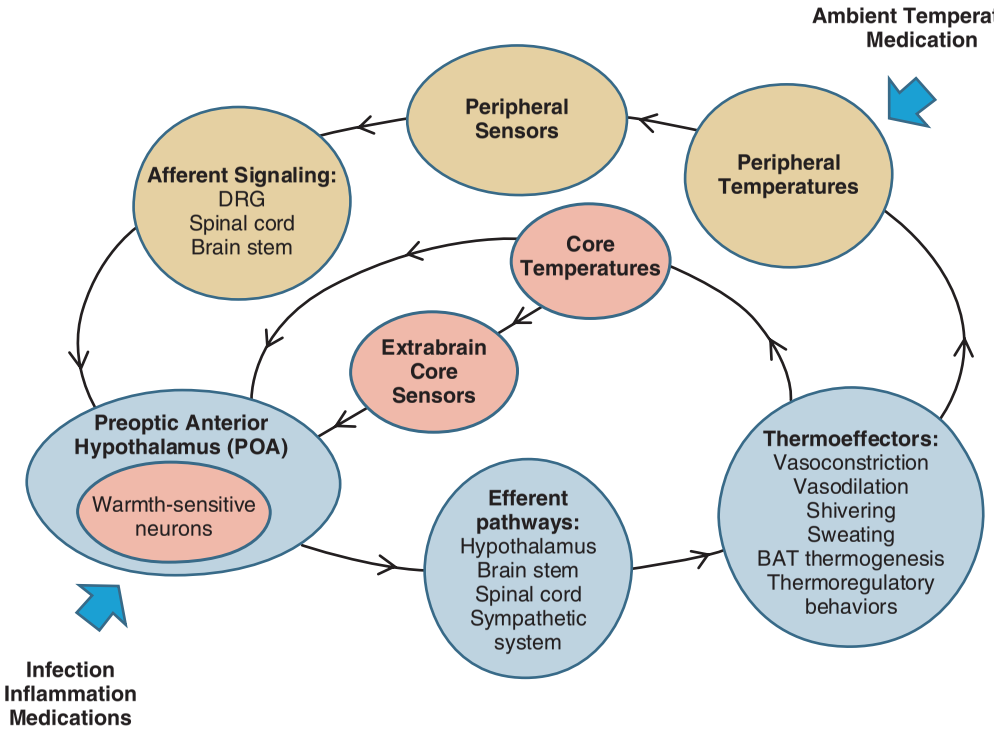

FIG. 55.3 Thermoregulation. Body temperature is regulated by a set of relatively independent thermoeffector control loops. All loops follow the general flow, as outlined in the figure by black arrows. In reality, however, every loop shown in the figure consists of multiple loops, each including only one thermoeffector element and one or more thermoreceptors. Thermoreceptors in the shell and core are activated by changes in peripheral (primarily skin) and core (in the hypothalamus and outside the brain) temperatures, respectively. The resultant signals, through efferent portions of the loops, drive thermoeffector responses. The thermoeffector responses change both core and shell temperatures, thus closing control loops. *BAT,* Brown adipose tissue.

local (autocrine-paracrine) as well as systemic (endocrine) effects.[105] Among the pyrogenic cytokines, complex context-specific relationships exist, with certain members upregulating or downregulating the expression of other members or their receptors.[105] Infusion of pyrogenic cytokines into animals and humans causes fevers.[83]

The crucial step for fever generation by LPS and most other pyrogens is the production of prostaglandin E_2 (PGE_2). For example, in humans, LPS-induced fever can occur even when IL-1 or TNF-α signaling is blocked,[93,95,106] but the vast majority of clinical fevers[107] and all phases of LPS-induced fevers in laboratory animals[108–110] are blocked by pharmacologic or genetic inactivation of cyclooxygenase (COX)-2, an enzyme within the PGE_2-synthesizing cascade; this is how aspirin works.

Binding of LPS to Toll-like receptor 4 (TLR4), one of the PRRs, on pulmonary and hepatic macrophages[111,112] causes massive, rapid induction of COX-2 and microsomal PGE synthase (mPGES)-1 (one of terminal PGE_2 synthases) in the LPS-processing organs, such as the liver and lungs, thus resulting in a rise of PGE_2 concentration in the blood.[112–114] Although PGE_2 is rapidly catabolized in the same organs (liver and lungs), the upsurge in the synthesis is so massive that large amounts of circulating PGE_2 escape the catabolism, and PGE_2 concentration increases even in the aortic blood, that is, immediately downstream of the pulmonary circulation.[154] This peripheral synthesis occurs very early, before body temperature starts rising.[113] The circulating PGE_2, which is bound in the blood to albumin, crosses the blood-brain barrier, probably with the help of a transporter, and triggers fever.[11] Hence the first febrile phase is caused exclusively by the PGE_2 synthesized in the periphery. As the febrile response progresses, PGE_2 synthesis becomes upregulated in the brain as well. For example, during LPS fever in rats the second phase involves the robust upregulation of phospholipaseA_2 (PLA_2; an early enzyme of the PGE_2 cascade), COX-2, and mPGES-1.[113] In the brain PGE_2 is produced by COX-2 in perivascular and endothelial cells.[115–117] Low doses of LPS upregulate COX-2 expression in perivascular cells, whereas higher doses also increase COX-2 in endothelial cells, primarily along small venules.[117,118] However, only endothelial cells have been found to produce mPGES-1 in the adult brain,[119] indicating that they are the source of PGE_2 in the later phases of fever.

This general pattern of febrile pathogenesis, that is, mediation of early phases of fever by peripherally produced PGE_2 and mediation of later phases by both peripheral and central PGE_2, reflects a consensus opinion.[85,120,121] Other authors favor alternative mechanisms, that is, transport of pyrogenic cytokines across the blood-brain barrier, their synthesis in the circumventricular organs (that lack a blood-brain barrier), and neural (via the vagus nerve) signaling by pyrogenic cytokines and PGE_2 from the periphery.[122] The proposed pathways of passage of peripheral pyrogenic signals across the blood-brain barrier are schematically depicted in Fig. 55.4.

When PGE_2, either synthesized in the periphery and transported across the blood-brain barrier to the POA or synthesized locally, gains access to neurons within autonomic thermoeffector loops, it triggers cold-defense responses, thus causing fever. The neurons that are believed to be responsible for fever initiation are located in the median preoptic nucleus (one of the POA nuclei) and express the EP3 receptor to PGE_2.[123–125] They are likely to be γ-aminobutyric acid–ergic warmth-sensitive neurons that tonically inhibit thermogenesis and skin vasoconstriction; PGE_2 removes inhibition from these thermoeffectors, and body temperature rises.[11] Of interest, thermoregulatory behaviors involved in fever do not depend on the POA, and rats with ablated POA develop appropriate fevers when allowed to regulate body temperature by selecting their thermal environment.[126]

ACUTE-PHASE RESPONSE

As noted, a cytokine-mediated rise in the core temperature is but one of many features of the febrile response. Numerous other physiologic reactions, collectively referred to as the acute-phase response, are mediated by members of the same group of pyrogenic cytokines that activate the thermal response of fever. Such reactions include a host of behavioral, physiologic, biochemical, and nutritional alterations (Table 55.1).[127] Stimuli capable of inducing an acute-phase response include bacterial and, to a lesser extent, viral infections, trauma, malignant neoplasms, burns, tissue infarction, immunologically mediated and crystal-induced inflammatory states, strenuous exercise, and childbirth.[128,129] There is also evidence that major depression,[130]

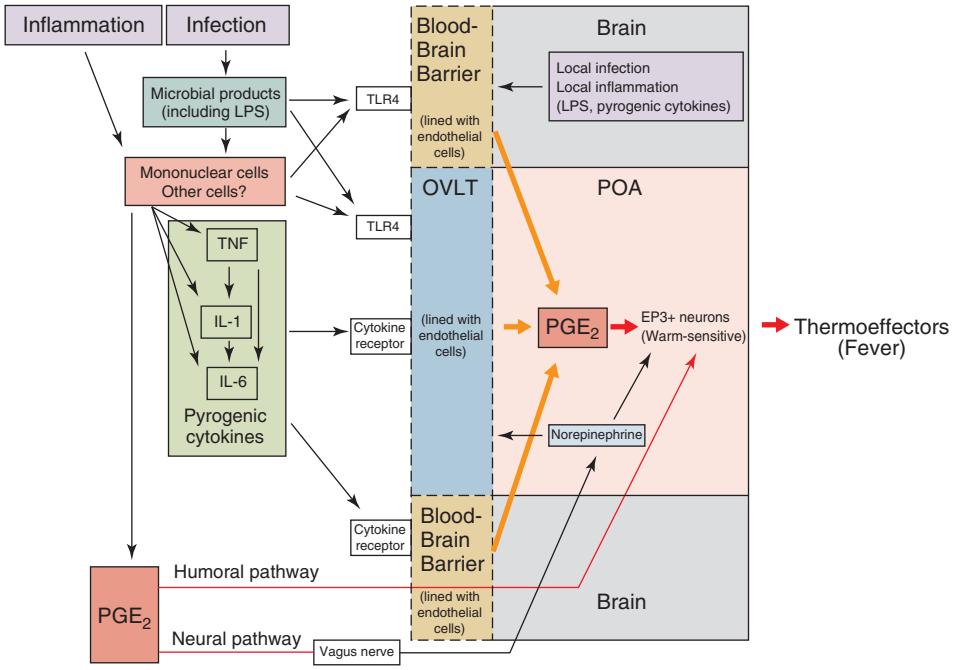

FIG. 55.4 Model for the febrile response. Fever can be initiated by microbial products, which directly or indirectly (through pyrogenic cytokines) activate the production of prostaglandin E_2 *(PGE_2)* in the periphery and in the brain. PGE_2 reaches the γ-aminobutyric acid–ergic, warmth-sensitive neurons in the preoptic anterior hypothalamus *(POA),* specifically, in the median preoptic nucleus. By acting on the *EP3* receptor on these neurons, PGE_2 disinhibits cold defenses such as skin vasoconstriction and non-shivering and shivering thermogenesis. The increased heat conservation and heat production results in a body temperature rise (fever). *EP3,* Subtype of prostaglandin E_2; *IL,* interleukin; *LPS,* lipopolysaccharide; *OVLT,* organum vasculosum laminae terminalis; *TLR4,* Toll-like receptor 4; *TNF,* tumor necrosis factor.

TABLE 55.1 Acute-Phase Physiologic Reactions

Neuroendocrine Changes

Fever, somnolence, and anorexia
Increased secretion of corticotropin-releasing hormone, corticotropin, and cortisol
Increased secretion of arginine vasopressin
Decreased production of insulin-like growth factor-1
Increased adrenal secretion of catecholamines

Hematopoietic Changes

Anemia of chronic disease
Leukocytosis
Thrombocytosis

Metabolic Changes

Loss of muscle and negative nitrogen balance
Decreased gluconeogenesis
Osteoporosis
Increased hepatic lipogenesis
Increased lipolysis in adipose tissue
Decreased lipoprotein lipase activity in muscle and adipose tissue
Cachexia

Hepatic Changes

Increased metallothionein, inducible nitric oxide synthase, heme oxygenase, manganese superoxide dismutase, and tissue inhibitor of metalloproteinase-1
Decreased phosphoenolpyruvate carboxykinase activity

Changes in Nonprotein Plasma Constituents

Hypozincemia, hypoferremia, and hypercupremia
Decreased plasma retinol concentrations
Increased plasma glutathione concentrations

From Gabay C, Kushner I. Acute-phase proteins and other systemic responses to inflammation. N Engl J Med. *1999;340:448–454. Copyright © 1999 Massachusetts Medical Society. All rights reserved.*

schizophrenia,[131] and psychological stress[132] are capable of inducing an acute-phase response.

Traditionally, the term *acute-phase response* has been used to denote changes in plasma concentrations of a number of secretory proteins derived from hepatocytes. The acute-phase response is part of the innate immune response triggered through PRRs (such as TLRs). Acute-phase proteins, of which there are many (Table 55.2), exhibit increased synthesis (positive acute-phase proteins) or decreased synthesis (negative acute-phase proteins) during the acute-phase response. IL-6 is the chief stimulator of the production of most acute-phase proteins. Other pyrogenic cytokines, however, also influence the production of various subgroups of these proteins.

Many of the acute-phase proteins are believed to modulate inflammation and tissue repair.[133] A major function of C-reactive protein (CRP), for example, is presumed to involve the binding of phosphocholine on pathogenic microorganisms, as well as phospholipid constituents on damaged or necrotic host cells. Through such binding, CRP might activate the complement system and promote phagocyte adherence, thereby initiating the process whereby pathogenic microbes or necrotic cells are cleared from the host. Such activities are most likely potentiated by CRP-induced production of inflammatory cytokines[134] and tissue factor[135] by monocytes. Nevertheless, the ultimate function of CRP is uncertain, in that several in vivo studies have shown it to have antiinflammatory properties.[136–138]

Another major human acute-phase protein, serum amyloid A, has been reported to potentiate adhesiveness and chemotaxis of phagocytic cells and lymphocytes.[139] There is also evidence that macrophages bear specific receptors for serum amyloid A; serum amyloid A—rich, high-density lipoproteins mediate the transfer of cholesterol to macrophages at sites of inflammation[140]; and serum amyloid A enhances low-density lipoprotein oxidation in arterial walls.[141]

TABLE 55.2 Human Acute-Phase Proteins

Proteins Whose Plasma Concentrations Increase

Complement System

C3
C4
C5
C9
Mycobacterium avium complex
Factor B
C1 inhibitor
C4b-binding protein
Mannose-binding lectin

Coagulation and Fibrinolytic System

Fibrinogen
Plasminogen
Tissue plasminogen activator
Urokinase
Protein S
Vitronectin
Plasminogen-activator inhibitor-1
Kininogen

Antiproteases

α_1-Protease inhibitor
α_1-Antichymotrypsin
Pancreatic secretory trypsin inhibitor
Inter–α-trypsin inhibitors

Transport Proteins

Ceruloplasmin
Haptoglobin
Hemopexin

Participants in Inflammatory Responses

Secreted phospholipase A_2
Lipopolysaccharide-binding protein
Interleukin-1 receptor antagonist
Granulocyte colony-stimulating factor

Others

C-reactive protein
Serum amyloid A
α_1-Acid glycoprotein
Fibronectin
Ferritin
Angiotensinogen

Proteins Whose Plasma Concentrations Decrease

Albumin
Transferrin
Transthyretin
α_2-HS glycoprotein
α-Fetoprotein
Thyroxine-binding globulin
Insulin-like growth factor-1
Factor XII
Retinol-binding protein

HS, Heremans-Schmid.
Modified from Gabay C, Kushner I. Acute-phase proteins and other systemic responses to inflammation. N Engl J Med. *1999;340:448–454. Copyright © 1999 Massachusetts Medical Society. All rights reserved.*

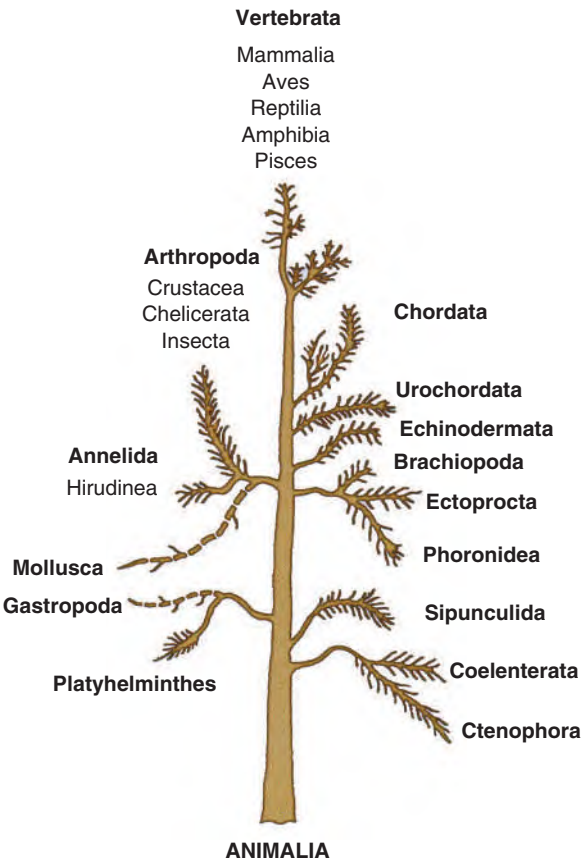

FIG. 55.5 Evolutionary tree of animals. A febrile response has been documented in the Vertebrata, Arthropoda, and Annelida. These observations suggest that the febrile response evolved more than 400,000,000 years ago at about the time that evolutionary lines leading to arthropods and annelids diverged.

Complement components, many of which are acute-phase reactants, induce pyrogenic cytokines and PGE_2; modulate chemotaxis, opsonization, vascular permeability, and vascular dilation; and have cytotoxic effects. Haptoglobin, hemopexin, and ceruloplasmin are all antioxidants and are thought to attenuate infection by binding their respective metals. It is therefore reasonable to assume that, like the antiproteases α_1-antichymotrypsin, and C1-esterase inhibitor, they play important roles in modulating inflammation. However, the functional capacity of such proteins is broad. There is also a growing literature concerned with the acute-phase protein LPS-binding protein, which appears both to enhance and neutralize the biologic activity of LPS through its interaction with the CD14 receptor on macrophages.

Although closely associated with fever, the acute-phase response is not an invariable component of the febrile response. Some febrile patients (e.g., those with certain viral infections) have normal blood levels of CRP. Moreover, patients with elevated blood levels of CRP are not always febrile. Nutritional fatty acids (typically elevated in obesity) can act as TLR4 ligands, generating a chronic acute-phase response.

The acute-phase response, like the febrile response, is a complex response consisting of numerous, separately regulated components. The particular components expressed in response to a given disease process more than likely reflect the specific cytokines induced by the disease.

BIOLOGIC VALUE OF FEVER

Questions concerning fever's risk-benefit quotient have generated considerable controversy. The controversy arises because of data indicating both potentiating and inhibitory effects of the response on resistance to infection. As a result, there is as yet no consensus as to the appropriate clinical situations, if any, in which fever or its mediators should be suppressed. In general the febrile response can be viewed as an adaptive response that has arisen evolutionarily to stymie myriad infectious challenges. Such responses, arising from noninfectious causes (tissue injury from cerebrovascular accidents or myocardial infarction), constitute a separate category that are not dealt with in this chapter; however, mounting evidence points to these being maladaptive responses, harmful to the host, and responding to lowering core and body temperature.[142–144]

Evidence illustrating fever's beneficial effects originates from several sources. Studies of the phylogeny of fever have shown the response to be widespread within the animal kingdom. With few exceptions, mammals, reptiles, amphibians, and fish, as well as several invertebrate species, have been shown to elevate their core temperature after challenge with microorganisms or other known pyrogens (Fig. 55.5). It has been assumed, although not established conclusively, that such elevations in

temperature are the poikilothermic corollary of fever. The prevalence of such febrile responses has been offered as some of the strongest theoretical evidence that fever is an adaptive host defense response, based on the argument that the metabolically expensive increase in body temperature that accompanies the febrile response would not have evolved and been so faithfully preserved in the animal kingdom unless fever had some net benefit to the host.

Further evidence of fever's beneficial effects can be found in numerous investigations demonstrating enhanced resistance of animals to infection with increases in body temperature within the physiologic range. In classic studies involving experimental infection of the reptile *Dipsosaurus dorsalis* with *Aeromonas hydrophila*, Kluger and associates demonstrated a direct correlation between body temperature and survival.[144a] They also showed in their model that suppression of the febrile response with sodium salicylate was associated with a substantial increase in mortality. Covert and Reynolds corroborated these findings in an experimental model involving goldfish.[144b]

In experimental mammalian models, increasing the body temperature by artificial means has been reported to enhance the resistance of mice to herpes simplex virus,[145] poliovirus,[146] coxsackie B virus,[147] rabies virus,[148] *Klebsiella pneumoniae,*[149] and *Cryptococcus neoformans*[150] but to decrease resistance to *Streptococcus pneumoniae.*[151] Increased resistance of rabbits to *S. pneumoniae*[152] and *C. neoformans,*[153] dogs to herpesvirus,[154] piglets to gastroenteritis virus,[155] and ferrets to influenza virus[156] has also been observed after the induction of artificial fever. Unfortunately, because raising the body temperature by artificial means does not duplicate the physiologic alterations that occur during fever in homeotherms, and indeed, entails a number of opposite physiologic responses,[157] evidence obtained using mammalian experimental models must be interpreted with caution when used to understand the febrile response.

Clinical data supporting an adaptive role for fever have accumulated slowly. Like animal data, clinical data include evidence of the beneficial effects of fever and adverse effects of antipyretics on the outcome of infections. In an examination of factors influencing the prognosis of spontaneous bacterial peritonitis, Weinstein and coworkers identified a positive correlation between a temperature reading higher than 38°C (100.4°F) and survival.[157a] In studies of elderly patients with community-acquired pneumonia, those without a fever had higher mortality. In another study, ICU patients with invasive *Candida* infections and temperatures less than 36.5°C had a higher mortality than those with temperatures greater than 38.2°C.[157b]

All data reviewed earlier are subject to interpretation and do not prove a causal relationship between fever and improved prognosis during infection. Nevertheless, they are consistent with such a relationship and, when considered in concert with the phylogeny of the febrile response and the animal data summarized earlier, constitute strong circumstantial evidence that fever is an adaptive response in most situations.

Whereas many of the foregoing investigations examined the relationship between elevation of the core temperature and outcome of infection, others have considered the endogenous mediators of the febrile response. In such studies, all the principal pyrogenic cytokines have been shown to have immune-potentiating capabilities, which might theoretically enhance resistance to infection; many of these capabilities have been shown to be enhanced by elevated body temperature. In vitro and in vivo investigations of these cytokines have provided evidence of a protective effect of IFN, TNF-α, or IL-1, or all of these, against *Plasmodium, Toxoplasma gondii, Leishmania major, Trypanosoma cruzi,* and *Cryptosporidium.*

Several reports have also shown enhancement of resistance to viral and bacterial infections by pyrogenic cytokines. Treatment of normal and granulocytopenic animals with IL-1 has been shown to prevent death in some gram-positive and gram-negative bacterial infections. However, IL-1 is effective only if administered an appreciable time (e.g., 24 hours) before the initiation of infections having rapidly fatal courses. In less acute infections, IL-1 administration can be delayed until shortly after the infectious challenge. Such observations suggest that those physiologic effects of the febrile response that enhance resistance to infection might be limited to localized infections or systemic infections of only mild-to-moderate severity. They may also indicate that the beneficial actions of IL-1 and/or fever are programmed for specific stages in the progression of an infection.

BIOLOGIC VALUE OF FEVER: THE CASE OF SEPSIS

The febrile response's potential for harm was reflected in multiple reports, suggesting that IL-1, TNF-α, IL-6, and IFN mediate the physiologic abnormalities of certain infections. Although proof of an adverse effect of fever on the clinical outcome of these infections has yet to be established, the implication is that if pyrogenic cytokines contribute to the pathophysiologic burden of infections, both the mediators themselves and the febrile response are potentially deleterious. The most persuasive evidence in this regard derives from studies of gram-negative bacterial sepsis.[158] Sepsis is a defined as systemic inflammation due to infection, often resulting in life-threatening organ dysfunction, whereas septic shock is a subset of sepsis, which is accompanied by shock and has higher mortality.[159]

It has long been suspected that bacterial LPS is involved in the pathophysiology of sepsis. Purified LPS induces a spectrum of physiologic abnormalities similar to those occurring in patients with gram-negative bacterial sepsis. In experimental animals, challenge with LPS causes TNF-α and IL-1 to be released into the bloodstream coincident with the appearance of signs of sepsis. Furthermore, patients with sepsis may have detectable levels of circulatory TNF-α, IL-1, and IL-6 independent of culture-documented infection, and these levels correlate inversely with survival.[160] IL-1, alone or in combination with other cytokines, induces many of the same physiologic abnormalities (e.g., fever, hypoglycemia, shock, and death) seen after the administration of purified LPS.[161] In a murine experimental model for septic shock, IFN administered before or as long as 4 hours after LPS challenge increases mortality, whereas pretreatment with anti-IFN antibody significantly reduces mortality.[162] In several investigations, the adverse effects of gram-negative bacterial sepsis, LPS injections, or both, have been attenuated by pretreating experimental animals with IL-1 antagonists[163,164] and monoclonal antibodies directed against TNF-α.[165,166] Furthermore, animals rendered tolerant to TNF-α by repeated injections of the recombinant cytokine are protected against the hypotension, hypothermia, and lethality of gram-negative bacterial sepsis.[167]

The theory derived from these observations—that death from sepsis is the consequence of cytokine-mediated overstimulation of the immune system—unfortunately correlates only loosely with the clinical picture in humans, most likely because the studies cited used large doses of endotoxin or bacteria that induced levels of circulating pyrogenic cytokines exponentially higher than those detected in patients with sepsis. Thus the "cytokine storm" created in such animals most likely has only limited relevance for human sepsis. This perhaps explains why, in clinical trials, inhibition of pyrogenic cytokines in septic patients has had only modest success, improving outcome in patients with a high risk for death but not those with a low risk. Another explanation is that, in the laboratory, experimental sepsis and aseptic systemic inflammation are typically studied in young animals, whereas the majority of human patients with sepsis are elderly, and the clinical course of sepsis and its resistance to therapy is likely to change with age (see reference 168).

There is evidence from human studies suggesting that fever in sepsis is associated with improved outcomes. The first study to show this was a retrospective analysis of 218 patients with gram-negative bacteremia, in which Bryant and associates reported a positive correlation between maximum temperatures on the day bacteremia was diagnosed and survival.[168a] A similar relationship has been observed in patients with polymicrobial sepsis and mild (but not severe) underlying diseases. Another study, by Lee and colleagues,[169] did not show a higher mortality in septic patients with fever, but the results are likewise difficult to interpret due to most of the measurements being taking via the axillary route. A study by Laupland and colleagues[170] showed an association of increased mortality in ICU patients with fever; however, this study is uninterpretable as they did not distinguish those with and without infection in the analysis, even though they had collected the microbiologic data. Two recent studies by Young and colleagues[171,172] did show an association of early peak temperatures (>39°C in one study and >37.5°C

in another study) in septic patients with infection as being associated with improved outcomes. The major problem of all the studies just cited is that they were either retrospective or had limitations related to temperature measurements (e.g., temperature was not recorded or did not reflect core temperature). These problems were addressed in a prospective study measuring core temperatures in patients with severe infection in the ICU.[173] Henriksen and colleagues[173] were able to demonstrate that temperature >38°C was associated with reduced mortality, whereas temperature <36°C was associated with increased mortality.

Hence it appears that fevers in sepsis due to infections appears to be associated with improved outcomes. It should be noted that the development of fever may lead to earlier initiation of antibiotics and hence better outcomes, and this is one additional potential confounding factor that needs to be addressed in future studies. Nevertheless, it is reasonable to assume that the benefits of a febrile response are due to known inhibitory effects of elevated temperature on growth and pathogenesis of bacteria, along with potential benefits from cytokines and other acute-phase reactants involved in the fever response. However, it is also known that cytokines are involved in shock and death, thus separating and stymieing the effects of one (cytokines) and amplifying the effects of the other (elevated temperature) could be a future strategy for improved outcomes. Finally, fever is only one thermoregulatory response to systemic inflammation; the other is hypothermia. While this chapter was in preparation, a comprehensive review on these two thermoregulatory responses was released.[173a]

BIOLOGIC VALUE OF HYPOTHERMIA

Both humans and experimental animals respond to most severe forms of systemic inflammation with hypothermia. Moreover, this response is regulated. For example, it has been established that rats with severe systemic inflammation actively seek a cold environment and that this cold-seeking behavior promotes hypothermia.[79,89,126] Similar to fever, hypothermia in systemic inflammation is an evolutionarily developed response and has an adaptive value when the energy cost of fever exceeds its benefits.[174] Experimental support for this hypothesis has been produced in rats with aseptic systemic inflammation caused by LPS[175,176] or with acute *Escherichia coli* infection.[176] In these studies rats challenged with high doses of LPS or *E. coli* were either allowed to develop hypothermia in a mildly cool environment, which they preferred, or were "forced" to develop fever in a warm environment. Development of hypothermia instead of fever resulted in diminished organ damage and decreased mortality. Similar results have been obtained in mice injected with LPS at a high dose.[177] The mechanisms behind the protection aided by hypothermia in severe forms of systemic inflammation are still poorly understood. However, the metabolic suppression that drives hypothermia occurs concurrently with the earliest decrease in cardiac output in endotoxic shock, so that the balance between oxygen delivery and consumption is maintained and tissue hypoxia does not occur.[178] Tissue hypoxia in this model occurs only when the hypothermic response is prevented.

In contrast with these studies in laboratory animals is the prevailing clinical perception that hypothermia is a dysregulated, detrimental phenomenon in sepsis.[179,180] This perception is rooted in observational studies, which we described earlier in detail, and which identified hypothermia as a poor prognostic factor in septic patients.[181–184] However, the prognostic value of hypothermia does not imply that it is the hypothermia itself that worsens the outcome; those patients who develop hypothermia are usually sicker than those who do not.[173,185–187]

ANTIPYRETIC THERAPY: GENERAL CONSIDERATIONS

Although clinicians have long had at their disposal effective means of lowering the core temperature in febrile patients, the actual benefit of such reductions in temperature is still uncertain. Moreover, it has yet to be shown in humans that increases in the core temperature encountered during fever are actually harmful. Certainly, during the course of heat stroke and other forms of hyperthermia, the core temperature can, and frequently does, rise to levels that are inherently harmful. However, such levels are almost never reached during a febrile rise in temperature, which rarely exceeds 41°C (105.8°F) in humans.[188] Nevertheless, whereas healthy volunteers have been reported to withstand core temperatures of 42°C (107.6°F) for periods as long as 4 hours without apparent ill effects, the possibility remains that in certain patients, even the relatively modest increases in core temperature encountered during fever are deleterious and should therefore be suppressed.

Antipyretic therapy is also commonly administered to enhance patient comfort. General experience with antipyretic drugs, which are usually also analgesic agents, seems to support this notion. However, carefully controlled efficacy studies have not yet established the validity of this contention, and any potential short-term gains must be compared with potential longer-term effects. It has been reported that children with chickenpox who are treated with acetaminophen have a longer time to total crusting of lesions than placebo-treated controls. Stanley and colleagues have reported that adults infected with rhinovirus exhibit more nasal viral shedding when they receive aspirin than when given placebo.[188a] Furthermore, Graham and colleagues have reported a trend toward a longer duration of rhinovirus shedding in association with antipyretic therapy and have shown that the use of aspirin or acetaminophen is associated with suppression of the serum-neutralizing antibody response and with increased nasal symptoms and signs.[188b] A more recent retrospective observational analysis of studies of human volunteers infected with influenza A has found a relationship between antipyretic therapy and prolonged illness, although this was not seen in another study.[188c,188d] In an investigation of children infected with *Plasmodium falciparum*, paracetamol prolonged the parasite clearance time. Of interest, plasma concentrations of TNF and IL-6 in children not receiving paracetamol were no different from those receiving paracetamol, suggesting that elevated temperature itself was responsible for the accelerated parasite clearance. One case-control study showed an increase risk of empyema in children treated with nonsterioidal antiinflammatory drugs (NSAIDs) for acute viral infections.[189] Finally, it should be noted that one recent study and a meta-analysis did not find any adverse effects of adjunctive corticosteroids in the treatment of pneumonia, although both showed a reduction in fever and/or clinical symptoms.[190,191] Corticosteroids are known to have wide-ranging actions, and thus caution and more studies will be needed to determine if these are indeed safe and effective.

In the past several years there have been a number of studies linking certain antipyretics to decreased vaccine responses. In a study by Prymula and colleagues[192] that was designed to study the efficacy of paracetamol on febrile reactions, the authors vaccinated children against *Streptococcus pneumococcus, Haemophilus influenzae, Clostridium tetani, Corynebacterium diphtheriae, Bordetella pertussis,* poliovirus, hepatitis B virus, and rotavrius. Children who had received prophylactic paracetamol (starting at the time of vaccination) had lower opsonophagocytic antibodies against *S. pneumococcus* and lower antibody titers against *S. pneumococcus, H. influenzae, C. tetani, C. diphtheriae, B. pertussis,* and hepatitis B virus. In a follow-up paper from the same group, the investigators showed a trend toward a lower percentage of subjects colonized in the nasopharynx by pneumococcal vaccine serotypes, *H. influenzae,* and nontypeable *H. influenzae* in children who had received paracetamol prophylactically compared with those who did not.[192] A further study with reboosting the same children with *H. influenzae* vaccine showed a trend toward lower antibody titers but no difference in opsonic activity or memory responses, leading the authors to conclude that any changes due to paracetamol therapy are transient.[193] Another study of infants receiving vaccination for *S. pneumococcus, H. influenzae, C. tetani, C. diphtheriae, B. pertussis,* poliovirus, and hepatitis B virus showed that prophylactic paracetamol, started at the time of vaccination, resulted in recipients with lower levels of serotype-specific pneumococcal anticapsular immunoglobulin G than control subjects, whereas ibuprofen recipients had reduced antibody responses to pertussis and tetanus antigens.[194] Like the previous study, these differences did not last, with no difference noted after the dose at 13 months of age. Another recent study in children showed reduced antibody levels to the vaccine antigens within paracetamol- or ibuprofen-treated groups, validating the findings in the previous studies, but of interest, this was not seen if the prophylaxis was started in the booster phase.[195] Finally, a study in adults vaccinated with hepatitis B vaccine demonstrated lower titers of anti-HBs antibodies

if paracetamol was given prophylactically (at the time of vaccination), but not when given therapeutically (6 hours after vaccination).[196] Taken together, until more studies are carried out, antipyretics should be given sparingly during vaccination, especially during the primary series, as decreased levels can have implications for herd immunity.

Another category of patients in whom fever suppression has been studied includes children at risk for febrile seizures, primarily those between the ages of 3 months and 5 years. In such children seizures have been reported to occur during episodes of fever at a frequency as high as 14% in select populations. Although most children with febrile seizures have temperatures of 39°C (102.2°F) or higher at the time of their seizure, many tolerate even higher fevers at later dates without convulsing. Unfortunately, antipyretic therapy has not been shown to protect against recurrences of febrile seizures in the few controlled trials conducted thus far. Camfield and colleagues have conducted a randomized double-blind study comparing a single daily dose of phenobarbital plus antipyretic instruction with placebo plus antipyretic instruction to prevent recurrent seizure after an initial simple febrile seizure.[196a] In children treated with phenobarbital and antipyretics, the febrile seizure recurrence rate was 5%, whereas in those given placebo with antipyretics, the rate was 25%, suggesting that a single daily 5-mg/kg dose of phenobarbital is more effective than counseling parents about antipyretic therapy in preventing recurrent febrile seizures. Acetaminophen has been given to children with fever as prophylaxis against febrile seizure recurrences. Whether given in moderate dosage (10 mg/kg dose four times daily) or in relatively high doses (15–20 mg/kg dose every 4 hours), acetaminophen failed to reduce the rate of febrile seizure recurrence.

Antipyretic therapy is also occasionally given to reverse fever-induced mental dysfunction in frail elderly patients. Beisel and coworkers have shown that aspirin, in combination with propoxyphene, ameliorates fever-induced decrements in mental work performance in young volunteers infected with sand fly fever virus, even in the face of only partial relief of the fever or other symptoms of the illness.[196b] In view of these observations, antipyretic therapy might be expected to have a beneficial effect on fever-induced mental dysfunction in frail elderly patients. However, studies designed to test this hypothesis have not yet been reported.

One of the reasons commonly given to justify suppressing fever is that the metabolic cost of fever exceeds its clinical benefit.[197] Such energy demands are particularly high during the chill phase if shivering is present, as evidenced by increases in the sympathetic tone,[157] oxygen consumption, respiratory minute volume, and respiratory quotient.[198] Because of the potential adverse consequences of these metabolic effects on cardiovascular and pulmonary function, fever has been attacked with particular vigor in patients with underlying cardiovascular and pulmonary diseases.[200] Although antipyretic therapy has theoretical merit in this regard, if it does not induce shivering,[201] the detrimental effects of fever and the salutary effects of antipyretic therapy have yet to be critically evaluated.

External cooling, which is widely used in critically ill patients to suppress fevers unresponsive to antipyretic drugs, has been shown to decrease oxygen consumption by as much as 20% if shivering is prevented by therapeutic paralysis.[201] If shivering is not inhibited, external cooling causes a rise, rather than a fall, in oxygen consumption, which increases energy demand and may exacerbate hypoxemia.[201] Perhaps more important to febrile patients with underlying cardiovascular disease, external cooling has the capacity to cause vasospasm of diseased coronary arteries by inducing a cold pressor response.[202,203]

Finally, we turn to the use of antipyretics for distinguishing serious from nonserious infections, and infections from cancer. Numerous investigators have observed a direct correlation between the height of fevers and the rate of serious bacterial infections in children, with the maximal incidence of such infections at temperatures in excess of 40°C (104°F).[204–207] It has also been suggested that the response of a fever to antipyretic therapy might have diagnostic implications, in that a drop in temperature, improvement in the appearance of a febrile child, or both generally indicates that the fever is not the result of a serious illness. This conclusion, however, is not supported by numerous investigations comparing the temperature response of bacteremic and nonbacteremic infections with antipyretic therapy in children.

Several studies have suggested that an antipyretic response to NSAIDs can distinguish fevers of infectious origin from those caused by cancer by virtue of the fact that the latter fevers are more readily suppressed by such agents. Naproxen was the first such agent to be studied in this regard. Subsequent randomized comparisons have shown naproxen, indomethacin, and diclofenac to be equally effective in inhibiting cancer-induced fever, although the sensitivity and specificity of the naproxen test for differentiating neoplastic from infectious fevers are not yet known. Moreover, there is no physiologic rationale to explain why NSAIDs might be more effective in reducing fever caused by cancer than that caused by infection.

ANTIPYRETIC THERAPY: THE CASE OF SEPSIS

As noted earlier, nowhere are the decisions to be made regarding antipyretic therapy more urgent than in the patient with sepsis. On the one hand, it appears that the presence of fever is associated with better outcomes, although some of its mediators are known to be responsible for the mortality seen in this condition. However, even an association of fever with improved outcomes in sepsis does not necessarily mean that fever should not be treated because the mortality still remains high.

The use of antipyretics in the ICU setting is common, with one recent study showing 64% of patients received at least 1 g of paracetamol.[208] However, data regarding its risks and benefits are just starting to accumulate. Retrospective and observational studies have not been able to answer the question of whether antipyretics in sepsis lower mortality, either showing increased mortality,[169] no benefit,[209] or decreased mortality.[208,210] The first placebo-controlled study to look at this was conducted by Bernard and colleagues,[211] who performed a double-blind placebo-controlled trial to evaluate ibuprofen in patients with sepsis. They did not find any difference in mortality between the two groups, although the placebo group was tainted by the fact that 44% were treated with acetaminophen, making the entire results uninterpretable. Two recent randomized placebo–controlled studies have shown no improvement in mortality with acetaminophen treatment compared with placebo.[212,213] A study by Schortgen and colleagues[214] showed external cooling and sedation improved 14-day, but not longer, outcomes. A recent meta-analysis that analyzed observational and randomized studies has also found that antipyretic therapy does not improve 28-day mortality. Thus antipyretic agents have been shown to be of only limited value for the treatment of bacterial sepsis and critically ill patients with fever.

ANTIPYRETIC THERAPY: PHARMACOLOGIC AGENTS

Although clinicians have long resorted to various forms of antipyretic therapy, there is a dearth of scientific data concerning the actual benefits and relative risks of such treatment. Nevertheless, several tentative conclusions regarding antipyretic therapy seem warranted in light of the limited data available. It is clear, for example, that short courses of approved doses of standard antipyretic drugs carry a low risk for toxicity. Most of these drugs have analgesic as well as antipyretic properties. Therefore, if not otherwise contraindicated (e.g., aspirin in young children because of the risk for Reye syndrome), such drugs can be prescribed to provide symptomatic relief in febrile patients, reduce the metabolic demands of fever in patients with underlying cardiovascular and pulmonary disorders, and possibly prevent or alleviate fever-induced mental dysfunction in older patients. To minimize antipyretic-induced fluctuations in temperature, as well as the risk for recurrent shivering with its associated increased metabolic demands, antipyretic agents should be administered to febrile patients at regular intervals that preclude abrupt recurrences of sweating, chills, and fever, rather than as needed for temperatures above some arbitrary level. Whenever such medications are prescribed, it should also be recognized that each carries its own risk for toxicity and might prolong the course of the illness responsible for the fever while reducing the intensity of its symptoms.

Antipyretic drugs can be grouped into three general categories on the basis of their mechanisms of action. These include corticosteroids, aspirin and the other NSAIDs, and acetaminophen. Each exerts its effects at different points in the febrile response pathway.

Although not generally used for antipyresis, corticosteroids suppress fever through direct and indirect mechanisms. They block the transcription of pyrogenic cytokines and inducible COX via interactions involving the glucocorticoid receptor. They downregulate the synthesis of cytokine receptors and, by inducing lipocortin-1, they secondarily inhibit the activity of PLA_2, a critical enzyme in the PGE_2 synthetic pathway, which leads to fever suppression.

Acetaminophen and aspirin and the other NSAIDs all inhibit COX-mediated synthesis of inflammatory thromboxanes and PGs from arachidonic acid. COX has several distinct isoforms, of which COX-1 and COX-2 are the best studied. The former was long regarded as a constitutively expressed cellular enzyme involved in various housekeeping functions, whereas the latter was touted as an inducible enzyme responsible for hypothalamus-mediated fever and produced as part of the inflammatory process by various cell lines, including macrophages, synoviocytes, and endothelial cells. However, this dichotomous concept of a constitutive COX-1 and an inducible proinflammatory COX-2 has proved to be oversimplified. Not only do some cells express COX-2 constitutively but, under certain conditions, COX-2 has also been shown to promote healing of mucosal lesions and resolution of inflammation. Whereas COX-2 mediates fever, COX-1 mediates hypothermia in experimental systemic inflammation.[215]

The distinctive affinities of the various categories of antipyretic drugs for the different COX variants are thought to determine their relative antipyretic and analgesic potencies. NSAIDS are inhibitors of COX-1 and COX-2, and depending on the individual drug, they are predominantly COX-1 selective (low-dose aspirin and ketorolac), COX-2 selective (rofecoxib, lumiracoxib), or nonselective (ibuprofen, naproxyn sodium, high-dose aspirin). Only aspirin irreversibly inhibits COX via acetylation within the active site of the enzyme. Other NSAIDs and acetaminophen inhibit COX reversibly. Acetaminophen has traditionally been considered a weak inhibitor of COX-1 and COX-2. With the discovery of COX-3,[216] a close relative of COX-1, it was believed that the mechanism for the antipyretic action of acetaminophen was also uncovered. However, it appears that these enzymes vary considerably across mammalian species and that acetaminophen in humans does not reduce fever through COX-3. More recently, one study has shown that acetaminophen is a potent COX-2 inhibitor in humans, thus challenging earlier work.[217] Although the antipyretic activity of NSAIDs through inhibition of COX-2 conforms to current models of fever generation[114] (also see Fig. 55.4), our current understanding of the antipyretic activity of acetaminophen is limited. Studies have shown that aspirin and the NSAIDs also have COX-independent antipyretic activity. Aspirin induces cytochrome P450, which might augment its antipyretic effect by shifting arachidonic acid metabolism toward cytochrome P450–mediated production of antipyretic epoxyeicosanoids. In addition, acetylation of COX-2 by aspirin increases the production of 15R-hydroxyeicosatetraenoic acid, which neutrophils use to form aspirin-triggered lipoxins. These lipoxins have potent antiinflammatory activity independent of aspirin. Heat shock proteins have been shown to reduce the transcription of IL-1β in vitro, and therapeutic doses of aspirin and certain NSAIDs increase heat shock factor 1 concentration in vitro. These same drugs also diminish the activity of transcriptional activator nuclear factor kappa B, which is involved in the transcription of pyrogenic cytokines, adhesion molecules, inducible nitric oxide synthase, and COX-2 in certain cell lines, as well as in fever generation.[154] Production of adenosine, an antiinflammatory mediator produced by leukocytes, is enhanced by aspirin and NSAIDs. The clinical implications of these alternative antipyretic pathways remain to be determined.

Unfortunately, certain antipyretic drugs also appear to cause coronary vasoconstriction in patients with coronary artery disease. Friedman and associates[218] observed significant increases in the mean arterial pressure, coronary vascular resistance, and myocardial arteriovenous oxygen difference after IV indomethacin (0.5 mg/kg) in such patients. Coronary blood flow simultaneously decreased substantially.[218] Thus, in this investigation, myocardial oxygen demand increased in the face of a fall in coronary blood flow after indomethacin administration. The authors believe that indomethacin's vasoconstrictor effect most likely derives from to its capacity to block the synthesis of vasodilatory prostaglandins. Perhaps even more disturbing are reports suggesting that, compared with other NSAIDs, COX-2–selective NSAIDs seem to increase the risk for cardiovascular thrombotic events in patients not taking aspirin. In view of indomethacin's capacity to cause coronary vasoconstriction in patients with coronary artery disease and the possible increased risk for cardiovascular thrombotic events associated with COX-2–selective NSAIDs, it should be used cautiously to suppress fever in such patients.

Although the side-effect profiles of these drugs are well known, there are also recent reports of the association of NSAIDS with inflammatory bowel disease, renal cell carcinoma, and *Clostridioides difficile* (formerly *Clostridium difficile*) colitis.[219–221] Researchers have also noted an association between acetaminophen and development of asthma, although this was not seen in a recent prospective, randomized, double-blind study.[222] Moreover, the relative cost of such symptomatic relief, in terms of drug toxicity and adverse effects of antipyretic agents on the course of the illness responsible for the fever, has rarely been studied.

ANTIPYRETIC THERAPY: PHYSICAL METHODS OF ANTIPYRESIS

In view of the capacity of external cooling measures to induce a cold pressor response, it is questionable whether this form of antipyretic therapy should ever be administered to febrile patients with infection, much less to ICU patients, for whom it is so frequently prescribed, unless future studies can show a clear benefit. If external cooling is used to treat fever, care must be taken to prevent shivering because of its associated increased oxygen consumption. Unfortunately, even if shivering is prevented, there is no guarantee that a cold pressor response will be averted.

Various physical techniques are used to cool febrile patients. These include sponging with various solutions (e.g., tepid water or alcohol), the application of ice packs or cooling blankets, and exposure to circulating fans (most often in conjunction with sponging). With the latter method, Helox (80% helium, 20% oxygen) has been shown to be superior to air in lowering core temperature, at least in experimental animals, because of the greater thermal conductivity of helium compared with that of nitrogen. In contrast to antipyretic drugs, external cooling lowers the temperature of febrile patients by overwhelming effector mechanisms that have been evoked by pyrogens. Therefore, unless concomitant antipyretic agents are used or shivering is inhibited by other pharmacologic means, external cooling is vigorously opposed in the febrile patient by thermoregulatory mechanisms endeavoring to maintain the elevated body temperature. In patients undergoing therapeutic body temperature modulation, shivering can also be prevented by skin warming, similar to how radiative heating from the sun makes people comfortable when exposed to even severe ambient cooling (the so-called Arctic sun).

Physical methods of antipyresis promote heat loss by conduction, convection, and evaporation. Evaporative methods have traditionally been touted as the most effective physical means of promoting heat loss in febrile patients because these methods are deemed to be least likely to induce shivering. However, carefully designed comparative trials have not yet established any one physical method of antipyresis as superior.

Similarly, direct comparisons of pharmacologic and physical methods of antipyresis are all but nonexistent. In the only extant controlled study, Wenzel and Werner reported that salicylates reduced the second phase of endotoxin-induced fever in rabbits, whereas abdominal cooling increased heat production and did not lower the core temperature unless the animals were simultaneously exposed to environmental hyperthermia.[223] Neither antipyretic modality abolished the initial febrile response.

The few available clinical studies of the efficacy of physical methods of antipyresis have differed in their conclusions. Interpretation of the results of these studies has been difficult, because pharmacologic agents have almost invariably been administered concomitantly with external cooling. Steele and coworkers found acetaminophen (in age-adjusted dosages ranging from 80–320 mg) and sponging to be equally effective in lowering fever in children admitted to a pediatric hospital because of fever.[224] However, when combined, the two modalities produced more rapid cooling than either alone. Similar results were obtained by

Aksoylar and colleagues who found that sponging was more effective than medication in the first 30 minutes, after which medications provided more relief.[225] O'Donnell and colleagues have concluded that in adults, although hypothermia blanket therapy adds little to the action of pharmacologic agents in lowering temperature, it induces wider temperature fluctuations and more episodes of rebound hypothermia.[226] For these reasons we believe that cooling blankets and ice water baths should generally be avoided in treating fevers due to infections but not with hyperthermia or fevers due to noninfectious causes, and that wet sponges with tepid water can be used in combination with pharmacologic therapy to make febrile patients comfortable.

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We dedicate this chapter to Dr. Philip Mackowiak, a superb clinician and researcher, who has worked in this field for many decades, and whose insights are instrumental to our current understanding of the clinical definition of fever. Dr. Mackowiak wrote earlier editions of this chapter, upon which the current chapter is based.

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56 Fever of Unknown Origin

William F. Wright

SHORT VIEW SUMMARY

Definition
- Occurrence of several occasions of fever higher than 38.3°C (100.9°F) with a duration greater than at least 3 weeks despite 1 week of hospital evaluation is still recognized as the classic definition for fever of unknown origin (FUO).
- The advent of improved diagnostic testing modalities coupled with an increasing number of immunocompromised patients led to a revised definition in which cases of FUO are currently codified into four distinct subclasses: classic FUO, health care–associated FUO, immune-deficient FUO, and human immunodeficiency virus–related FUO.

Etiology and Epidemiology
- Infections, neoplasms, connective tissue diseases, miscellaneous causes, and undiagnosed fevers remain the most common causes of classic FUO.
- The frequency with which infections and neoplasms have been identified as the causes of classic FUO has decreased steadily, whereas the proportion of miscellaneous causes and undiagnosed conditions has risen in recent years.

Diagnosis
- A comprehensive medical history with verification of fever and a detailed physical examination are essential in directing formal laboratory testing. Focal inflammatory and infectious processes can readily and more quickly be detected by advanced imaging and biomarker analysis techniques, such as ^{18}F-fluorodeoxyglucose–positron emission tomography (FDG-PET) or diffusion-weighted magnetic resonance imaging.

Therapy
- Empirical therapeutic trials of antimicrobial agents continue to have a limited role in the management of patients with FUO.
- Owing to the relatively high prevalence of serious bacterial infections responsible for fevers in patients with neutropenia, such patients should receive broad-spectrum antipseudomonal therapy immediately after samples for appropriate cultures have been obtained.

Prognosis
- Although the prognosis of a FUO is determined by its etiology and underlying diseases, most patients with prolonged undiagnosed FUO generally have a favorable outcome.

Most episodes of fever in humans are short lived and do not require diagnostic investigation or specific therapy. Some are manifestations of more serious illnesses, most of which can be readily diagnosed and effectively treated. However, small but important subgroups of fevers are both persistent and difficult to diagnose. Such puzzling fevers have fascinated and frustrated clinicians since the earliest days of clinical thermometry,[1] resulting in a welter of clinical publications. The two most important of these, from a historical perspective, are the classic text *Prolonged and Perplexing Fevers,* by Keefer and Leard (published in 1955),[2] and the paper *"Fever of unexplained origin: report on 100 cases,"* by Petersdorf and Beeson (published in 1961).[3]

TERMINOLOGY AND DEFINITIONS

In the United States, the term *fever of unknown origin* (FUO) is generally used.[4] In other countries an alternative term, *pyrexia of unknown origin* (PUO), is often used.[5]

The first formal definition of FUO to gain broad acceptance was proposed by Petersdorf and Beeson nearly six decades ago: "fever higher than 38.3°C (100.9°F) on several occasions, persisting without diagnosis for at least 3 weeks in spite of at least 1 week's investigation in hospital."[3] Later investigators have modified and extended this classic definition to reflect evolutionary changes in clinical practice.[6,7] These changes include the conduct of most diagnostic tests in the outpatient setting rather than in the hospital, the increasing number of immunocompromised patients (especially those with neutropenia), the proliferation of increasingly complex surgical and intensive care treatment protocols, and the advent of human immunodeficiency virus (HIV) infection leading to the acquired immunodeficiency syndrome (AIDS). In response to this evolving environment, Durack and Street,[7] in 1991, proposed a revised definition in which cases of FUO require 3 days of investigation and must be codified into four distinct subclasses of the disorder: classic FUO, nosocomial (health care–associated) FUO, neutropenic (immune-deficient) FUO, and HIV-related FUO. Computed tomography (CT), magnetic resonance imaging (MRI), ultrasound imaging, nucleic acid–based diagnostic testing, and rapid tests for pathogens have enlarged the diagnostic options for FUO. One could argue that the definitions of types of FUO have much overlap and are not as clinically useful as they were in the past. In a prospective study of 80 patients based on these two main definitions, Ergonul and colleagues[8] found that although the 1991 definition included more cases within the infectious diseases group, the overall distribution of diseases among the two definitions was not significantly different.

CLASSIC FEVER OF UNKNOWN ORIGIN

Classic FUO refers to the type of FUO defined by Petersdorf and Beeson in 1961.[3] The only alteration to their definition required to conform to modern medical practice is to incorporate investigation in the outpatient setting, which today has become the preferred venue for evaluation and treatment. Most patients with classic FUO have subacute or chronic symptoms and therefore can be safely investigated as outpatients. In published series of such patients, for example, the median duration of fever before diagnosis was between 40 and 44 days.[1,9]

Of the many publications concerning the etiology of FUO,[3,4,9,10,11,12,13,14,15] most have dealt with classic FUO rather than with the three other more recently defined subclasses listed earlier.[7] Over the years a recurrent theme has become clear: of the myriad disorders causing classic FUO almost all fall within one of five categories: infections, neoplasms, connective tissue diseases, miscellaneous other disorders, and undiagnosed illnesses. The relative frequencies of individual diagnoses within these five categories vary depending on the decade (Fig. 56.1), geographic region, ages of the patients, type of medical practice, and other factors.

In more recent published series, infections have comprised the largest category, accounting for 16% to 55% of cases (Table 56.1).[4] However, in patients older than 65 years, infections become less common, falling into second or third place as a cause of classic FUO.[4,8,10] In the series

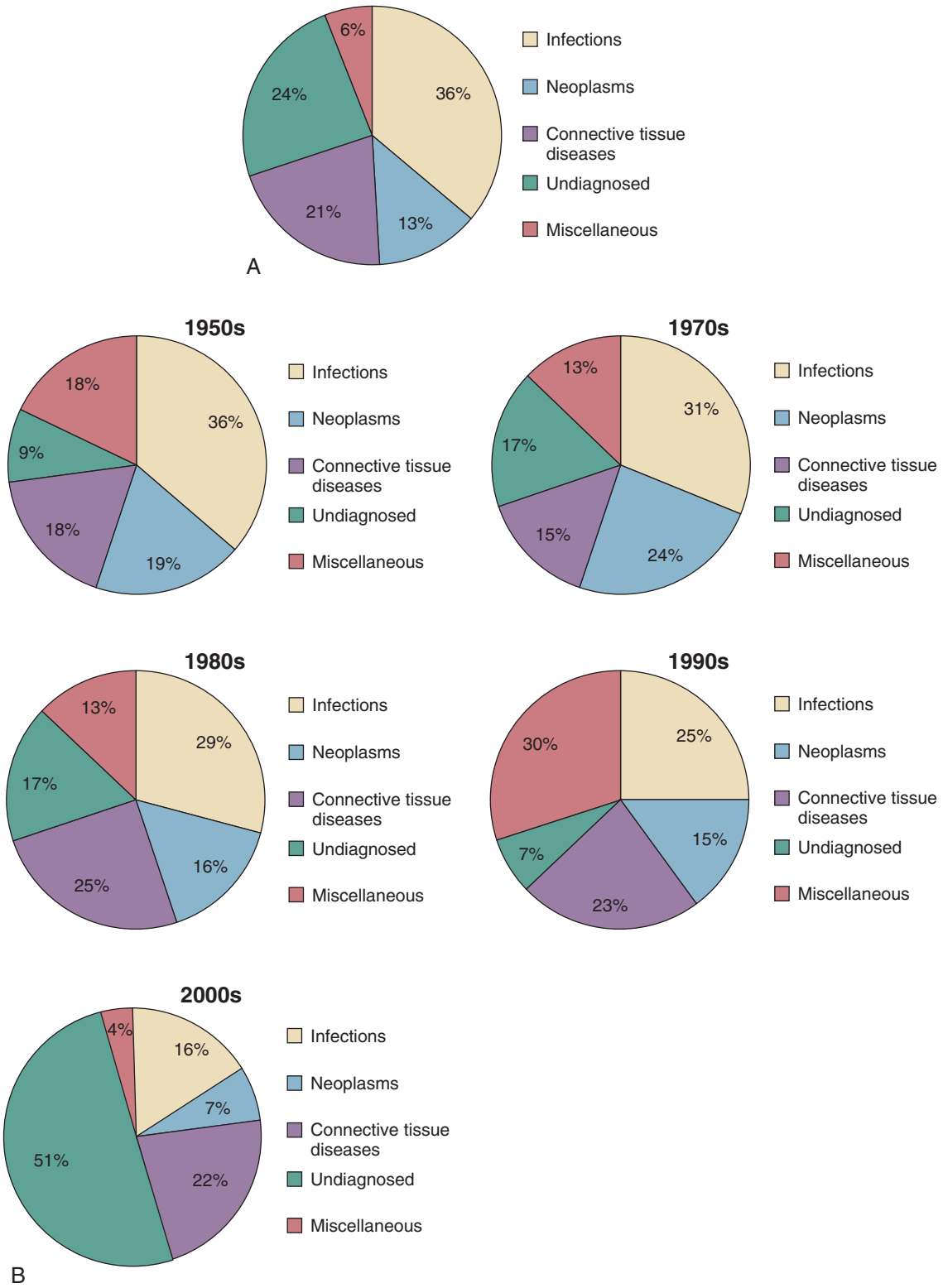

FIG. 56.1 (A) Frequency of the five main etiologic categories of fever of unknown origin. (B) Frequency of the five main etiologic categories of fever of unknown origin by decade. *(A from Hayakawa K, Ramasamy B, Chandrasekar PH. Fever of unknown origin: an evidence-based review.* Am J Med Sci. *2012;344:307–316; B from Mourad O, Palda V, Detsky AS. A comprehensive evidence-based approach to fever of unknown origin.* Arch Intern Med. *2003;163:545–551.)*

of Knockaert and associates,[10] infection was the cause of FUO in only 25% of patients 65 years of age or older; temporal arteritis and various connective tissue diseases accounted for 31% of cases, and tumors accounted for 12%. Only 8% of cases went undiagnosed, which was a percentage similar to that reported by Colpan and colleagues[9] but one substantially lower than that reported in surveys involving younger adults, in which as many as 30% of cases remained undiagnosed.[16] The longer the duration of fever before medical consultation, the less likely that a definitive diagnosis will be made.[17]

Among the infections responsible for classic FUO, abscesses, endocarditis, tuberculosis, and complicated urinary tract infections have consistently been among the most important. These tend to vary

TABLE 56.1 Frequencies of Diagnoses Within the Five Categories of Fever of Unknown Origin (FUO)

PUBLICATION	TOTAL NO. OF PATIENTS	CATEGORY OF FUO (%)				
		Infection	Neoplastic	Rheumatologic	Miscellaneous	Undiagnosed
Petersdorf and Beeson (1961)[3]	100	36.0	19.0	19.0	19.0	7.0
Petersdorf and Larson (1983)[93]	105	30.0	31.0	17.0	10.0	12.0
Larson et al. (1982)[94]	105	30.0	31.0	16.0	11.0	12.0
Knockaert et al. (1992)[72]	199	22.6	7.0	21.5	14.5	25.6
De Kleijn et al. (1997)[16]	167	26.0	12.0	25.0	8.0	30.0
Bleeker-Rovers et al. (2007)[67]	73	16.0	7.0	22.0	4.0	51.0
Colpan et al. (2007)[9]	71	45.1	14.1	26.8	5.6	8.5
Mansueto et al. (2008)[84]	91	31.8	14.2	12.0	9.8	31.8
Bandyopadhyay et al. (2011)[15]	164	55.0	22.0	11.0	3.5	8.5

in incidence according to locale. Visceral leishmaniasis, for example, although absent from most series of classic FUO, accounted for 8% of cases in a study reported in 1997 from Spain.[18] Other examples of causes of classic FUO in distinct populations include familial Mediterranean fever in Ashkenazi Jews; Kikuchi-Fujimoto disease, an unusual form of necrotizing lymphadenitis seen primarily in Japan[19]; and tumor necrosis factor receptor–associated periodic syndrome (TRAPS) fever, formerly called familial Hibernian fever, an inherited periodic fever syndrome described originally in Ireland.[20] The miscellaneous category contains both varied and individually rare causes of classic FUO (Table 56.2).

Of the connective tissue diseases responsible for classic FUO, Still disease (juvenile rheumatoid arthritis), other variants of rheumatoid arthritis, and systemic lupus erythematosus predominate in younger patients, whereas temporal arteritis and polymyalgia rheumatica syndromes are more common in elderly patients.

Malignant neoplasms, another important cause of FUO, can induce fever directly through the production and release of pyrogenic cytokines, as in the case of certain lymphomas. They may also generate fevers indirectly by undergoing induced or spontaneous necrosis and/or by creating conditions conducive to secondary infections.[1] Among the malignant neoplasms responsible for FUO, hematologic cancers, hypernephromas, and gastrointestinal (mainly colorectal) and central nervous system cancers have been documented as common causes.[3,4] In a recent series of 80 patients with FUO, Ergonul and colleagues[8] established a malignant neoplasm etiology in 14 cases (18%).

The relative frequency with which the major diagnostic categories are represented in series of classic FUO varies according to both the era in which the series was published[6,14] and its country of origin.[4,8,15,21,22,23,24] Since the mid-1990s, the frequency with which infections and malignant neoplasms have been identified as causes of classic FUO has fallen steadily, whereas the proportion of miscellaneous causes and undiagnosed conditions has risen.[24] However, in developing countries, the frequency with which infections are diagnosed has changed little.[15] Consequently, in these countries, malignant neoplasms and connective tissue disorders are comparatively less important as causes of classic FUO than in developed countries.[9,15]

Infants and Children

The diseases responsible for classic FUO in infants differ from those in older children and adults. Respiratory infections cause classic FUO in infants more often than in children older than 12 months or in adults.[11] The relative frequency of infections as the cause of FUO in infants is high because connective tissue diseases and cancers are rare in this age group. Kawasaki disease occurs predominantly in children younger than 5 years. Whereas connective tissue diseases are rarely seen in children younger than 12 months, Still disease is a leading cause of FUO in older children and young adults. Joint involvement in children with FUO usually signifies a serious underlying disorder, such as a connective tissue disease, endocarditis, or leukemia.[11]

In a series of 146 pediatric cases of FUO, Jacobs and Schutze[25] established a specific diagnosis in only 84 (57.5%). Of these, 64 (43.8%) had infections, 11 (7.5%) had autoimmune disorders, 4 (2.7%) had malignant neoplasms, and 5 (3.4%) had a variety of other disorders,

TABLE 56.2 Examples of Uncommon or Rare Causes of Prolonged Fever

Addison disease	Infected urachal cyst
Adult-onset Still disease	Inflammatory bowel disease
Alcoholic hepatitis	Kikuchi-Fujimoto disease
Allergic alveolitis	Löfgren syndrome
Aortic dissection	Lymphomatoid granulomatosis
Aortitis	Metal fume fever
Atrial myxoma	Myeloproliferative syndromes
Autoimmune cholangitis	Pancreatitis
Bartonellosis	Parathyroid apoplexy
Behçet syndrome	Paroxysmal hemoglobinurias
Carcinomatous meningitis	Pericarditis
Castleman disease	Periodic fever
Chronic meningitis	Pheochromocytoma
Cirrhotic fever	Polyarteritis nodosa
Cyclic neutropenia	Postpericardiotomy syndrome
Drug fever and other hypersensitivities	Pulmonary emboli
Erythema multiforme	Resorbing hematoma
Fabry disease	Retroperitoneal fibrosis
Factitious fever	Rosai-Dorfman disease
Familial Hibernian fever	Sarcoidosis
Familial Mediterranean fever	Schnitzler syndrome
Giant coronary aneurysm	Serum sickness
Granulomatous hepatitis	Sinusitis
Granulomatous peritonitis	Sjögren syndrome
Hantavirus infection	Subacute necrotizing lymphadenitis
Hemoglobinopathies	Thrombotic thrombocytopenic purpura
Hemolytic anemias	Thyroiditis and thyrotoxicosis
Hemophagocytic syndrome	Venoocclusive disease
Histiocytosis X	Vitamin B_{12} deficiency
Human picornavirus infection	Wegener granulomatosis
Hypereosinophilic syndrome	Whipple disease
Immunoblastic lymphadenopathy	

Modified from Durack DT. Fever of unknown origin. In: Mackowiak PA, ed. Fever: Basic Mechanisms and Management. *2nd ed. Philadelphia: Lippincott-Raven; 1997:237–249.*

such as drug-induced fever, sarcoidosis, and mercury poisoning. The most common infectious diseases diagnosed in their series were Epstein-Barr virus (EBV) infection (15%), osteomyelitis (10%), bartonellosis (5%), and urinary tract infections (4%).

Chow and Robinson[26] analyzed 18 papers concerned with pediatric FUO published between 1968 and 2008. Of 1638 children ages birth to 18 years, 832 (51%) had infections, 93 (6%) had malignant neoplasms, 150 (9%) had noninfectious inflammatory diseases, 179 (11%) had miscellaneous causes such as inflammatory bowel disease and Kawasaki disease, and 384 (23%) had no diagnosis. Although the distribution of diagnostic categories was similar among developed versus developing countries, urinary tract infections, brucellosis, tuberculosis, and typhoid fever were more common in developing countries. The most common infections diagnosed in cases of FUO in developed countries included urinary tract infections, osteomyelitis, tuberculosis, and bartonellosis (e.g., *Bartonella henselae*).

Although a daily rectal temperature greater than 38.3°C (100.9°F) lasting more than 2 weeks despite diagnostic evaluation has been defined as FUO in children, 9 of 18 papers analyzed by Chow and Robinson used the classic definition of FUO.[26]

In a more recent publication, Zhou and colleagues[27] investigated the presence of seven different human herpesvirus (HHV) types in whole blood from pediatric patients with classic FUO. Of 151 children ages 6 months to 15 years, 63 (33.9%) had detectable herpesvirus DNA. Cytomegalovirus (15.1%), HHV-6 (14%), and EBV (18%) were the viruses detected most commonly when compared to a nonfebrile cohort. Whereas fever alone occurred in the majority of these FUO patients, fever of at least 8 days' duration and hepatitis were more strongly associated with EBV and HHV-7.

Elderly Persons

One of the most striking features of classic FUO in patients older than 65 years is the relatively high frequency with which connective tissue diseases are identified as the cause of the illness (Table 56.3).[4,10,28,29,30] In developed countries, connective tissue diseases surpass even infections as the leading cause of classic FUO in the elderly.[4,10,29] This is primarily because the temporal arteritis and polymyalgia rheumatica syndromes are common in this setting.[4,29,30,31] Unfortunately, these diagnoses are frequently missed or delayed because their symptoms are subacute and nonspecific. In elderly patients in whom infections are identified as the cause of FUO, intraabdominal abscesses, complicated urinary tract infections, tuberculosis, and endocarditis have predominated.[10] For unclear reasons, factitious fever is a rare cause of FUO in older adults. Relatively few cases of FUO go undiagnosed in elderly patients (see Table 56.3). The occurrence of classic FUO in an elderly patient has a distinctly poorer prognosis than for the younger patient because of the relatively high incidence of malignancies in the elderly.[32]

Returned Travelers

Fever in returned travelers (see Chapter 319) is most often due to common infections, such as malaria and respiratory or urinary tract infections.[33] However, exotic causes of fever that typically falls short of the duration for FUO, such as amebic liver abscess or dengue, are occasionally diagnosed, especially among international travelers returning from the tropics. Of the many febrile conditions encountered among returning travelers (Table 56.4), malaria, typhoid fever, and acute HIV infection are the ones most likely to manifest as FUO.

TABLE 56.3 Final Diagnosis in Elderly Compared With Younger Patients With Fever of Unknown Origin From Patient Series Pre-1990

DIAGNOSIS	<65 YEARS (*N* = 152)	>65 YEARS (*N* = 201)
Infections	33 (21%)	72 (35%)
Abscess	6	25
Endocarditis	2	14
Tuberculosis	4	20
Viral infections	8	1
Tumors	8 (5%)	37 (19%)
Hematologic	3	19
Solid	5	18
Multisystem diseases[a]	27 (17%)	57 (28%)
Miscellaneous[b]	39 (26%)	17 (8%)
Other	13	12
No diagnosis	45 (29%)	18 (9%)

[a]Rheumatic diseases, connective tissue disorders, vasculitis (including temporal arteritis), polymyalgia rheumatica, and sarcoidosis.
[b]Includes factitious fever (seven cases), habitual hyperthermia (five cases), and drug-induced fever (three cases).
Modified from Iikuni Y, Okada J, Kondo H, et al. Current fever of unknown origin 1982–1992. Intern Med. *1994;33:67–73; and Knockaert DC, Vanneste LJ, Bobbaers HJ. Fever of unknown origin in elderly patients.* J Am Geriatr Soc. *1993;41:1187–1192.*

TABLE 56.4 Causes of Fever in the Returned Traveler

DIAGNOSIS	PERCENT		
	Wilson et al.[95] (*n* = 6957)	O'Brien et al.[96] (*n* = 232)	Antinori et al.[97] (*n* = 147)
Malaria	35.0	27.0	47.6
Hepatitis	1.0	3.0	8.8
Respiratory tract infection[a]	14.0	24.0	2.7
Urinary tract infections	4.0	1.0	1.4
Gastroenteritis	2.0	14.0	4.8
Dengue fever	6.0	8.0	3.4
Enteric (typhoid) fever	2.0	3.0	4.1
Tuberculosis	0.0	0.4	0.7
Rickettsiosis	2.0	2.0	0.7
Acute HIV infection	0.01	0.4	4.5
Amebic liver abscess	0.3	1.0	0.0
Other miscellaneous infections	4.0	4.8	4.3
Miscellaneous noninfectious conditions	10.0	2.4	4.8
Undiagnosed	22.0	9.0	12.2

[a]Includes upper respiratory tract infection, pneumonia, and bronchitis.
HIV, Human immunodeficiency virus.
Modified from Suh KN, Kozarsky PE, Keystone JS. Evaluation of fever in the returned traveler. Travel Med. *1999; 83: 997–1017.*

NOSOCOMIAL (HEALTH CARE–ASSOCIATED) FEVER OF UNKNOWN ORIGIN

Nosocomial (health care–associated) FUO, as the name implies, is a condition in which patients first manifest fever during active medical treatment for some other illness. Such FUO cases, as might be expected, are frequently attributable to risk factors encountered in the health care environment, including surgical procedures, urinary and respiratory tract instrumentation, intravascular devices, drug therapy, and immobilization. Leading examples of causes attributable to health care–associated FUO include drug fever, postoperative complications (i.e., occult abscesses), septic thrombophlebitis, recurrent pulmonary emboli, myocardial infarction, cancers, blood transfusion, and *Clostridioides difficile* (formerly *Clostridium difficile*) colitis.[4,7,34]

Postoperative Patients

Several reports have highlighted the fact that it is often difficult to identify the precise cause of postoperative fevers. In a series of 537 consecutive patients undergoing major gynecologic surgery, 211 (39%)

developed postoperative fever.[35] Of 77 blood cultures performed on these patients, none was positive. Although 11 of 106 (10%) urine cultures were positive and 5 of 54 (9%) chest radiographs were abnormal, a specific pathologic process was detected in only 8% of febrile patients. Of patients with evidence of urinary tract infections and pneumonia, the median length of postoperative fever was 2 days (range: 1–7 days) and 3 days (range: 2–4 days), respectively. In a prospective study by Kendrick and colleagues[36] of postoperative fever among 292 patients admitted to a gynecologic oncology service after abdominal or vaginal operation, 58 (20%) patients developed postoperative fever. Among 37 (16%) low-risk surgical patients developing postoperative fever, only 6 (3%) had an infection diagnosis. The majority of infections occurred within 4 days of the operative procedure and included pneumonia, vaginal cuff cellulitis, and urinary tract infection. The authors proposed that postoperative fever is common and frequently represents the response to surgically induced tissue injury with the release of pyrogenic cytokines and interleukins rather than the result of infection. Although fever is a well-recognized manifestation of some surgical procedures, most episodes are short lived and do not meet the classic definition of FUO. Postoperative fevers generally do not require extensive diagnostic investigation for unusual causes of fever.

In another series concerned with the etiology of persistent postoperative fever in patients undergoing total joint arthroplasty, few definitive diagnoses were established, causing the authors to conclude that postoperative fever (postoperative days 1 through 5) is a normal component of the inflammatory response to this type of major surgery.[37]

Intensive Care Unit Patients

Fever is common in intensive care units (ICUs), most often developing relatively early after admission to the ICU, in which case it tends to be of noninfectious origin and carries a favorable prognosis.[38] Prolonged fever, however, is associated with a worse prognosis. One of the most significant findings is the simultaneous occurrence of multiple infections in the majority of these patients. Health care–associated sinusitis, often a complication of mechanical ventilation arising from supine positioning and the use of endotracheal, gastric, and feeding tubes, is common[39] and should always be considered when evaluating FUO in ICU patients. More often than not, the causes of fever in the ICU are essentially no different from general causes of health care–associated fevers (i.e., abscesses, drug fever, postoperative complications, septic thrombophlebitis, recurrent pulmonary emboli, myocardial infarction, cancers, blood transfusion, and *C. difficile* colitis). Ventilator-associated pneumonia is frequently underdiagnosed among patients with respiratory failure, fever, and nonspecific radiographic pulmonary densities. Patients with acute respiratory distress syndrome (ARDS) tend to develop pneumonia earlier than non-ARDS patients. Pulmonary abscesses are usually readily recognized on radiologic imaging and therefore would be an unlikely cause of FUO.

Stroke Patients

In patients with a recent stroke, fever is usually the result of an infection, most commonly a urinary tract infection related to urinary catheterization or a respiratory tract infection. However, in some cases a focus of infection cannot be identified, and when the fever does not respond to empirical antibiotic treatment, it is presumed to be due to the stroke itself. In a study of 330 patients hospitalized for acute stroke, Georgilis and associates[40] observed that noninfectious fevers were most often associated with intracranial mass effects and tended to occur earlier after the onset of stroke than fevers due to infection.

NEUTROPENIC (IMMUNE-DEFICIENT) FEVER OF UNKNOWN ORIGIN

Obviously, various forms of immunosuppression predispose more or less strongly to a wide variety of infectious complications. Thus it is not surprising that immunosuppressed patients have perhaps the highest incidence of FUO of any group of patients. In a recent series of 116 hematology-oncology patients, for example, Engelhart and associates[41] observed 33 FUOs in 28 patients, for an overall rate of 8.2 episodes per 1000 patient-days. Because of impaired immune responses, signs of inflammation other than fever are notoriously absent or diminished in such patients, leading to atypical clinical features and absence of radiologic abnormalities in what otherwise would be readily diagnosed infections.[42]

In patients with impaired cell-mediated immunity, FUO is often due to conditions other than pyogenic bacterial infections, as illustrated in a prospective evaluation of patients with leukemia and lymphoma by Toussaint and coworkers.[43] In that series, infections were the cause of 319 (67%) of the 477 episodes of fever. The majority of infections included respiratory tract infections (28.8%), secondary bacteremia due to gram-negative bacilli (15.7%), genitourinary tract infections (12.9%), skin and soft tissue infections (11.3%), and primary bacteremia (11.0%). One hundred nine (23%) cases were due to noninfectious conditions: malignant neoplasm, metastatic disease, and drug-induced fever. While noninfectious neoplastic-related fever was more common (41%) among nonneutropenic patients, noninfectious drug-induced fever was more common among neutropenic patients (13%). In 47 (10%) cases, the cause of the fever could not be determined.

Neutropenia and lymphopenia occur frequently among cancer patients undergoing myelosuppressive chemotherapy.[44] Neutropenia is a dangerous condition that can be considered a special subclass of immunodeficiency. The number of patients with episodes of neutropenia resulting from cytotoxic therapy or from various malignancies affecting the bone marrow is rising, even as the median duration of neutropenia in such patients is falling, owing to the increasing application of treatment with colony-stimulating factors. Not only are the duration and nadir of neutropenia correlated with the incidence of fever and infections, but so are outcomes related to morbidity and mortality. The highest percentages of deaths occur among patients with persistent severe neutropenia (<100 cells/mm^3 for more than 7 days) or further declining initial neutropenia (<1000 cells/mm^3). Furthermore, severe infections increase with the increasing proportion of time neutropenia and lymphopenia levels are less than 500 cells/mm^3. However, the incidence of fever and infectious episodes decreases when levels are 1500 cells/mm^3, above which level there is no associated decreased incidence, or the expected duration of neutropenia is less than 7 days.

Episodes of fever are common in patients with neutropenia. Many such episodes are short lived because they either respond quickly to treatment or are manifestations of rapidly fatal infections. Because bacteremia and sepsis are frequent causes, empirical broad-spectrum antibiotics should be administered promptly, without waiting for the results of cultures, when fever develops in neutropenic patients. However, only about 35% of prolonged episodes of febrile neutropenia (usually defined as persistent fevers for >7 days after initiation of empirical antimicrobial therapy in association with a negative workup, and neutropenia expected to last >7 days) respond to broad-spectrum antibiotic therapy. Practitioners often assume that if fever does not respond promptly to antibacterial therapy, fungal infection must be responsible, but other potential causes are at least as likely to be identified.[42,44]

HIV-RELATED FEVER OF UNKNOWN ORIGIN

Episodes of fever are commonplace in patients infected with HIV—a special subgroup of immunodeficient patients now so numerous that a separate category of FUO is justified.[45,46,47,48] The primary phase of HIV infection is characterized by a mononucleosis-like illness in which fever is a prominent feature. All too often, primary HIV infection eludes diagnosis because the illness is nonspecific and precedes seroconversion. For this reason it represents an important cause of HIV-associated FUO. Once symptoms of the primary phase of the HIV infection resolve, HIV-infected patients enter a long period of subclinical infection during which they are usually afebrile.[48] However, in the later phases of untreated HIV infection, episodes of fever become common, often signifying a superimposed illness. Many of these are potentially devastating opportunistic infections, which tend to manifest in atypical fashion owing to the tendency of the disordered immune response or prior therapy, or both,[49] to distort their clinical features.

Once highly active antiretroviral therapy (HAART) has been started and HIV viral load effectively suppressed, the frequency of FUO in

HIV-infected patients falls markedly. In a report of 274 HIV-infected patients, for example, Abellan-Martinez and colleagues[45] observed an incidence range of 2.57 to 3.66 FUO episodes per 100 HIV-infected patients per year prior to the initiation of HAART and an incidence range of 0.84 to 1.24 episodes after the introduction of therapy. Because of the lack of well-established diagnostic criteria during the study period, the immune reconstitution inflammatory syndrome was not reported as a cause of fever. In another study, the frequency of FUO was 3% in untreated patients compared with 0.6% in those receiving therapy.[50] Mycobacterial infections have been the most common cause of FUO in such patients; collagen vascular diseases have been distinctly uncommon.[45,51] In a series reported by Armstrong and colleagues,[52] the etiology of the FUO was identified in 56 of 70 (80%) patients. A single cause was identified in 43 cases; three distinct causes of FUO were identified in 3 cases and two causes in 10 others. The causes of FUO in 70 patients in whom the etiology was determined are listed in Table 56.5. Most cases of FUO in HIV-infected patients are the result of opportunistic infections, the specific frequencies of which are dictated, at least in part, by geographic variation in the prevalence of these infections.[53]

DIAGNOSIS

A point deserving emphasis is that most patients diagnosed with "classic FUO" were not suffering from unusual or rare conditions; rather, they exhibited atypical manifestations of common illnesses in an era when advanced diagnostic laboratory or imaging studies were not available. Changes to the original FUO definition by Durack and Street[7] emphasize that treatment is clearly more time critical for certain classes than others. Despite revised definitions and introduction of improved serologic, laboratory, and imaging technologies, FUOs continue to elude diagnosis, suggesting that fevers may have many origins. The most important lesson learned from the "classic FUO" concept is that, in many instances, available information from the history and physical examination should be utilized more often. The evaluation of a patient with FUO typically includes a comprehensive history, verification that the patient actually has fever, consideration of the fever pattern, repeated physical examinations, and a host of laboratory investigations, key imaging studies, and invasive diagnostic procedures (Table 56.6).

History

It is axiomatic that a comprehensive history is a cornerstone of the evaluation of any complex illness such as FUO. The history can be especially important in determining the choice of the initial laboratory investigations. Particular attention should be given to recent travel, exposure to pets and other animals, the work environment, and recent contact with people exhibiting similar symptoms. The family history should be carefully scrutinized for possible hereditary causes of fever—for example, familial Mediterranean fever. Likewise, the past medical history must be scrutinized for prior episodes of FUO and for any previously diagnosed conditions, such as lymphoma, rheumatic fever, or intraabdominal disorders, complications or reactivation of which might account for the source of fever. In cases of recurrent FUO, rare disorders are more common than in nonrecurrent cases and are also more likely to remain undiagnosed.[54] Finally, a complete list of the patient's medications must be obtained so that each may be evaluated as a potential source of drug-induced fever.

Verification of Fever and Fever Pattern

The next step in the evaluation of the patient with FUO is to verify the presence of fever. The importance of this step should be self-evident, yet it is often overlooked. In fact, in a series of 347 patients admitted to the National Institutes of Health for investigation of prolonged fever, 35% were ultimately determined either not to have significant fever at all or to have fever of factitious origin.[55]

Clinicians have endeavored to diagnose particular diseases by analyzing the associated fever patterns since the earliest days of clinical thermometry.[56] These efforts have given rise to an extensive and frequently arcane terminology, including descriptors such as *remittent, intermittent, hectic, quotidian, picket fence, sustained, quartan,* and *saddleback fevers.* Such terms have been used to codify fever patterns into general categories

TABLE 56.5 Diseases Established as the Etiology of Fever in 70 Cases of HIV-Associated Fever of Unknown Origin

ETIOLOGY	NO. (%) OF TIMES DIAGNOSIS WAS ESTABLISHED
Infection	
DMAC	22 (31)
Pneumocystis jirovecii pneumonia	10 (13)
CMV	8 (11)
Histoplasmosis	5 (7)
Viral (not CMV) [a]	5 (7)
Bacterial	4 (5)
Mycobacterium tuberculosis	4 (5)
Fungal (not histoplasmosis)[b]	2 (3)
Parasitic[c]	2 (3)
Mycobacterium genavense	1 (1)
TOTAL	63 (88)
Neoplasia	
Lymphoma	5 (7)
Kaposi sarcoma	1 (1)
TOTAL	6 (8)
Miscellaneous	
Drug fever	2 (3)
Castleman disease	1 (1)
TOTAL	3 (4)

[a]Includes hepatitis C, hepatitis B, adenovirus pneumonia, herpes simplex esophagitis, and varicella-zoster encephalitis (one case each).
[b]Includes disseminated cryptococcosis and pulmonary aspergillosis (one case each).
[c]Includes cerebral toxoplasmosis and disseminated cryptosporidiosis (one case each).
CMV, Cytomegalovirus; DMAC, disseminated *Mycobacterium avium* complex; HIV, human immunodeficiency virus.
Modified from Armstrong WS, Katz JT, Kazanjian PH. Human immunodeficiency virus–associated fever of unknown origin: a study of 70 patients in the United States and review. Clin Infect Dis. *1999;28:341–345.*

TABLE 56.6 General Diagnostic Evaluation of Patients With Fever of Unknown Origin

Comprehensive history
Repeated physical examinations
Complete blood cell count
Routine blood chemistry determinations, including LDH, LFTs, and ferritin
Urinalysis, including microscopic examination
Chest radiograph
Erythrocyte sedimentation rate
Antinuclear antibodies
Rheumatoid factor
Blood cultures: three or more separate specimens obtained in absence of antimicrobial therapy
Cytomegalovirus IgM antibodies or viral detection in blood
Heterophil antibody test in children and young adults
Tuberculin skin test or whole blood interferon-γ release assay
Computed tomography of abdomen, pelvis, or other sites
Magnetic resonance imaging
Radionuclide scans
Human immunodeficiency virus antibodies or viral detection assay
Further evaluation of any abnormality detected by above tests
Venous duplex imaging of lower limbs

IgM, Immunoglobulin M; *LDH,* lactate dehydrogenase; *LFTs,* liver function tests (for liver enzymes).
Modified from Arnow PM, Flaherty JP. Fever of unknown origin. Lancet. *1997;350:575–580, with permission from Elsevier.*

in an attempt to enhance their diagnostic utility.[57] A few, such as the Pel-Ebstein pattern seen in some cases of Hodgkin disease, the typhus inversus (i.e., reversal of the normal diurnal pattern) in some cases of disseminated tuberculosis, and the pulse-temperature disassociation sometimes seen in typhoid fever, have been posited as having diagnostic value (Fig. 56.2). Unfortunately, with the possible exception of the well-known periodicity of tertian and quartan malaria, these fever patterns are neither sufficiently sensitive nor specific for diagnosis of any disease.

Thus, although fever patterns per se are rarely diagnostic, they occasionally offer useful information[57] and should be considered in the context of other signs, symptoms, and laboratory data. The resolution of fever after the institution of a disease-specific therapy (e.g., empirical therapy for suspected tuberculosis) sometimes provides strong evidence to support a presumptive diagnosis.

In pediatric populations, the height of a fever correlates roughly with the likelihood of bacteremia. McCarthy and coworkers[58,59] reported that in young children with febrile illnesses, the likelihood of bacteremia is 7% in those with temperatures of 40°C (104°F) or less, 13% with temperatures of 40.5°C to 41°C (104.9°F to 105.8°F), and 26% with temperatures of 41.1°C (106°F) or greater. It is commonly believed that there may be a similar relationship between high fever and the likelihood

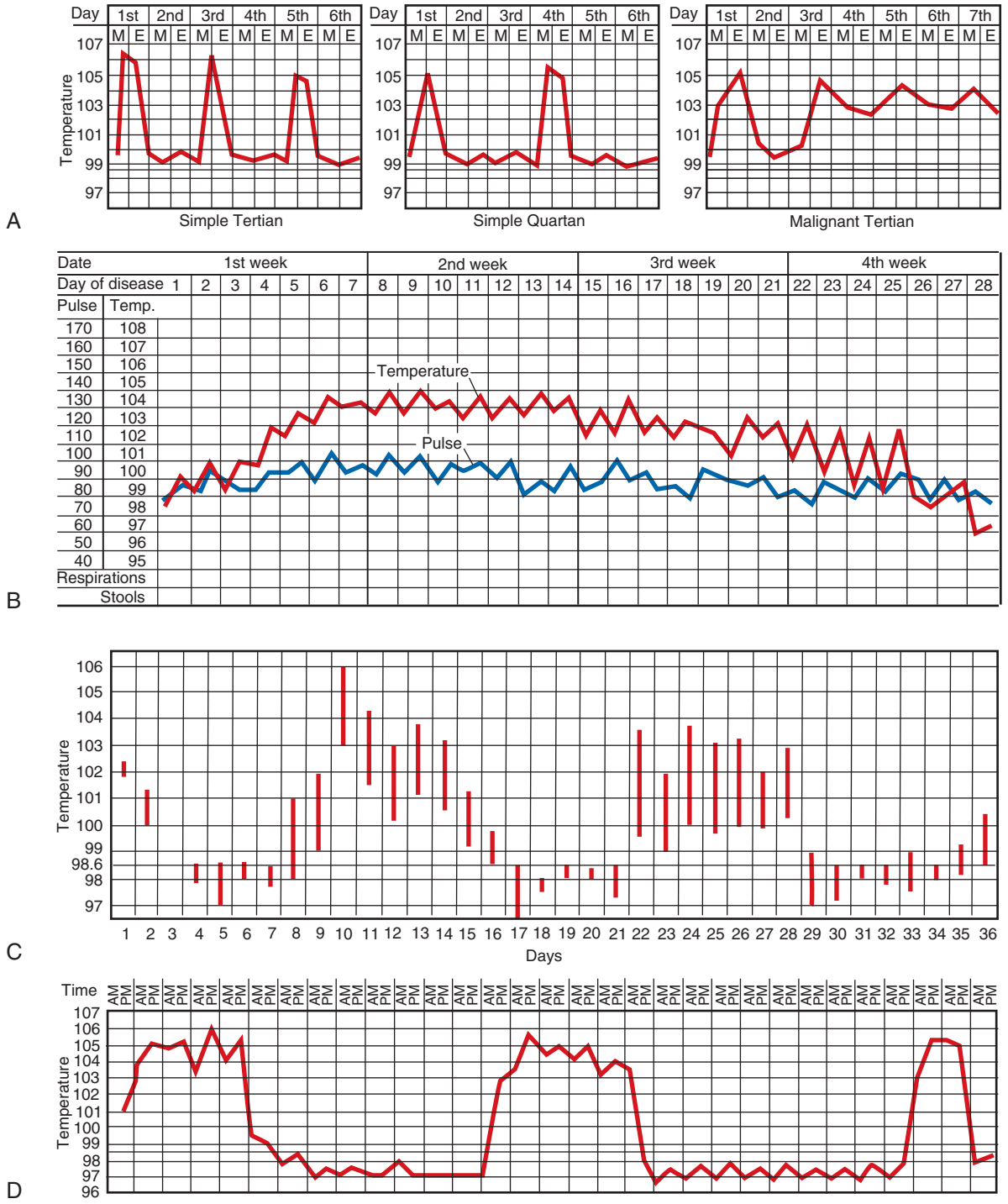

FIG. 56.2 Distinctive fever patterns. (A) Malaria. (B) Typhoid fever (demonstrating relative bradycardia). (C) Hodgkin disease (Pel-Ebstein pattern). (D) Borreliosis (relapsing fever pattern). *(From Woodward TE. The fever pattern as a clinical diagnostic aid. In: Mackowiak PA, ed.* Fever: Basic Mechanisms and Management. *2nd ed. Philadelphia: Lippincott-Raven; 1997:215–236.)*

of bacteremia in adults; this belief has not been substantiated. In any case, the relationship is at best loose, even in children, with numerous examples of bacteremia in which there is little or no fever and nonbacteremic conditions, such as drug-induced fever, thrombophlebitis, and recurrent pulmonary emboli, in which extremely high fevers sometimes are encountered.

Physical Examination

In the investigation of FUO, several aspects of the physical examination should be accorded closer scrutiny than generally given during the evaluation of other illnesses (Table 56.7). Frequently, key physical abnormalities in patients with FUO are so subtle as to require repeated examinations to be appreciated. Examples include the nodular or weakly pulsatile temporal artery of temporal arteritis, the telltale oral ulcers of disseminated histoplasmosis or Behçet syndrome, the choroid granuloma or epididymal nodule of extrapulmonary tuberculosis, the testicular nodule of polyarteritis nodosa, and the vague rectal fluctuance of a perirectal abscess. The diagnostic yield of the physical examination alone in the evaluation of FUO has not been studied directly. Nevertheless, in two pediatric series, abnormal physical findings were reported to have contributed to the diagnosis in 60% of cases of FUO.[60,61] In half of these, the abnormalities were detected only after repeated examinations. A vigorous search for lymphadenopathy is recommended. When enlarged lymph nodes are detected in a patient with FUO, lymph node biopsy is often undertaken. However, with the exception of the lymphomas, the diagnostic yield of lymph node biopsy in FUO is disappointingly low.[60,62]

Laboratory Investigations

The literature is replete with algorithms indicating which laboratory tests should be performed to evaluate FUO.[4,21,29,63,64,65,66,67] Although useful as general guides, blind application of such algorithms may result in performance of an excessive number of tests. They should be selectively applied using clues gleaned from the history and physical examination, also referred to as potentially diagnostic clues, to direct the choice and sequence of tests (Table 56.8). When formulating a diagnostic plan for FUO patients, the clinician should remember the old saying that the cause is more often a common disease presenting in atypical fashion than a rare disease presenting in typical fashion. Inappropriate diagnostic tests in the evaluation of FUO may not only delay identification of the correct diagnosis but also result in false-positive tests leading to misguided treatment plans.[4,21,66] A well-conducted history and physical examination is perhaps more important than any other diagnostic procedure in focusing the FUO evaluation, accelerating initiation of appropriate therapy while minimizing the cost and potential toxicity of unnecessary interventions.

In most series, noninvasive laboratory tests have yielded the diagnosis in approximately a fourth of the cases.[10,24] The most useful of these have been serologic tests for microbial pathogens and for various rheumatologic disorders. Examination of blood smears is occasionally diagnostic, especially in patients with tick-borne or louse-borne relapsing fever, anaplasmosis, and ehrlichiosis. Paradoxically, the advent of enhanced microbial culture systems has had less of an impact on the proportion of successful diagnoses than might have been anticipated. This is because modern culture systems have become so proficient at recovering fastidious bacteria, mycobacteria, and fungi from blood that they provide the diagnosis promptly, before the time required to meet the definitions of FUO has elapsed. Bone marrow examination should be considered for diagnosis of suspected granulomatous diseases (e.g., tuberculosis, histoplasmosis, and sarcoidosis), carcinomatosis, and hemophagocytic syndrome, especially in patients with abnormal complete blood cell counts.[68,69,70] In two series, bone marrow examination contributed to the diagnosis of FUO in approximately a fourth of cases.[68,69] Whereas the majority of HIV-infected patients were diagnosed with an infectious etiology, nonimmunocompromised patients were more likely to have a neoplastic or noninfectious inflammatory condition. In transplant patients, procalcitonin levels may be of use in differentiating infection from acute organ rejection, in that elevated levels are seen in the former but not the latter condition.[71]

TABLE 56.7 Examples of Subtle Physical Findings Having Special Significance in Patients With Fever of Unknown Origin

BODY SITE	PHYSICAL FINDING	DIAGNOSIS
Head	Sinus tenderness	Sinusitis
Temporal artery	Nodules, reduced pulsations	Temporal arteritis
Oropharynx	Ulceration; tender tooth	Disseminated histoplasmosis, periapical abscess
Fundi or conjunctivae	Choroid tubercle, petechiae, Roth spot	Disseminated granulomatosis,[a] endocarditis
Thyroid	Enlargement, tenderness	Thyroiditis
Heart	Murmur	Infective or marantic endocarditis
Abdomen	Enlarged iliac crest lymph nodes, splenomegaly	Lymphoma,[b] endocarditis, disseminated granulomatosis[a]
Rectum	Perirectal fluctuance, tenderness	Abscess
	Prostatic tenderness, fluctuance	Abscess
Genitalia	Testicular nodule	Periarteritis nodosa
	Epididymal nodule	Disseminated granulomatosis
Lower extremities	Deep venous tenderness	Thrombosis or thrombophlebitis
Skin and nails	Petechiae, splinter hemorrhages, subcutaneous nodules, clubbing	Vasculitis, endocarditis

[a]Includes tuberculosis, histoplasmosis, coccidioidomycosis, sarcoidosis, and syphilis.
[b]See text for note on the nonspecificity of lymphadenopathy identified on physical examination.

Imaging Studies

The constant advancement of imaging and biomarker analysis techniques, such as ^{18}F-fluorodeoxyglucose–positron emission tomography (FDG-PET) and diffusion-weighted MRI, provides an opportunity to readily and more quickly identify focal inflammatory or infectious processes prior to patients fulfilling the criteria of FUO. In the past, imaging studies were used primarily to localize abnormalities as a preamble to more definitive invasive tests. Computed tomography of the abdomen and, to a lesser extent, ultrasound imaging of the gallbladder and hepatobiliary system have been used extensively to evaluate cases of FUO. In one series, more than three CT or ultrasound examinations, or both, were performed for each FUO patient evaluated.[72] Nevertheless, the diagnostic yield per test performed was low—about 10%. Of the major diagnostic imaging modalities, another more recent series reported sensitivities of 60% for plain-film chest radiography, 82% for chest CT, 86% for abdominal ultrasound, and 92% for abdominal CT.[67] False-negative CT studies have occasionally been encountered, even in cases of abscesses in solid organs, as a result of distortions of normal anatomy, small abscess size, or failure to use both oral and intravenous contrast agents.[67,73] Computed tomography pulmonary angiograms can be very helpful in diagnosis of pulmonary emboli. Diffusion-weighted MRI is especially useful for evaluation of the central nervous system and, in the abdomen, the spleen and lymph nodes. In a series of 67 patients undergoing evaluation for FUO, Wagner and colleagues[74] reported that application of MRI of the aortic arch and proximal cervical arteries in selected patients improved the diagnosis of large vessel vasculitis by 20%. Although one case did not demonstrate vasculitic changes by cervical imaging, four cases would have remained undiagnosed without the application of MRI. The most common diseases diagnosed by this testing modality were giant cell arteritis (55%), Takayasu arteritis (27%), Wegener granulomatosis (9%), and microscopic polyangiitis (9%). In another series involving prolonged fevers among neutropenic patients,

TABLE 56.8 Examples of Potential Diagnostic Clues to Infections Presenting as Fever of Unknown Origin

ETIOLOGY	HISTORICAL CLUES	PHYSICAL CLUES
Anaplasmosis	Transmitted by the bite of an *Ixodes* tick in association with outdoor activity in north central and eastern United States	Fever, headache, arthralgia, myalgia, pneumonitis, thrombocytopenia, lymphopenia, and elevated liver enzymes
Babesiosis	Transmitted by the bite of an *Ixodes* tick in association with outdoor activity in the northeastern United States	Arthralgias, myalgias, relative bradycardia, hepatosplenomegaly, anemia, thrombocytopenia, and elevated liver enzymes
Bartonellosis	Recent travel to the Andes mountains with fever and bacteremia (Oroya fever; *Bartonella bacilliformis*), association with homelessness in urban settings *(Bartonella quintana)* or contact with either fleas or the scratch of an infected kitten or feral cat *(Bartonella henselae)*	Conjunctivitis, retro-orbital pain, anterior tibial bone pain, macular rash, nodular plaque lesions, and/or regional lymphadenopathy
Blastomycosis	Contact with soil adjacent to the Mississippi and Ohio River valleys, Saint Lawrence River in New York and Canada, and North American Great Lakes, or exposure to infected dogs	Arthritis, atypical pneumonia, pulmonary nodules, and/or fulminant adult respiratory distress syndrome; verrucous, nodular, or ulcerative skin lesions; and prostatitis
Brucellosis	Associated with contact with or consumption of products from infected goats, pigs, camels, yaks, buffalo, or cows and with abattoir work	Arthralgias, hepatosplenomegaly, suppurative musculoskeletal lesions, sacroiliitis, spondylitis, uveitis, hepatitis, and pancytopenia
Coccidioidomycosis	Exposure to soil or dust in the southwestern United States	Arthralgias, pneumonia, pulmonary cavities, pulmonary nodules, erythema multiforme, and erythema nodosum
Ehrlichiosis	Transmitted by the bite of an *Amblyomma, Dermacentor,* or *Ixodes* tick in association with outdoor activity in midwestern and southeastern United States	Pneumonitis, hepatitis, thrombocytopenia, and lymphopenia
Enteric fever (*Salmonella enterica* serovar Typhi)	Recent travel to a Third World country with consumption of potentially contaminated food or water	Headache, arthritis, abdominal pain, relative bradycardia, hepatosplenomegaly, and leukopenia
Histoplasmosis	Exposure to bat or black bird excreta in roosts, chicken houses, or caves in the region surrounding the Ohio and Mississippi River valleys of the United States or regions of Central and South America, Africa, Asia, and Australia	Headache, pneumonia, pulmonary cavities, mucosal ulcers, adenopathy, erythema nodosum, erythema multiforme, hepatitis, anemia, leukopenia, and thrombocytopenia
Leptospirosis	Occupational exposure among workers in sewers, rice and sugar cane fields, and abattoirs; recreational water sports and exposure to contaminated waters or infected dogs	Bitemporal and frontal headache, calf and lumbar muscle tenderness, conjunctival suffusion, hepatic and renal failure, and hemorrhagic pneumonitis
Leishmaniasis (visceral disease)	Associated with recent travel to areas endemic for sand flies	Hepatosplenomegaly, lymphadenopathy, and hyperpigmentation of the face, hand, foot, and/or abdominal skin (kala azar)
Malaria	Recent travel to endemic areas in Asia, Africa, and Central and South America	Fever, headaches, nausea, emesis, diarrhea, hepatomegaly, splenomegaly, and anemia
Psittacosis *(Chlamydia psittaci)*	Associated with contact with birds, especially psittacine birds	Fever, pharyngitis, hepatosplenomegaly, pneumonia, blanching maculopapular eruptions, erythema multiforme, erythema marginatum, and erythema nodosum
Q fever *(Coxiella burnetii)*	Associated with farm, veterinary, or abattoir work; consumption of unpasteurized milk; and contact with infected sheep, goats, or cattle	Atypical pneumonia, hepatitis, hepatomegaly, relative bradycardia, and/or splenomegaly
Rat-bite fever (*Streptobacillus moniliformis*)	Recent bite or scratch by a rat, mouse, or squirrel and/or ingestion of food or water contaminated by rat excrement	Headaches, myalgias, polyarthritis, and maculopapular, morbilliform, petechial, vesicular, or pustular rash over the palms, soles, and extremities
Relapsing fever *(Borrelia recurrentis)*	Associated with poverty, crowding, and poor sanitation (louse-borne); or with camping (tick-borne), particularly in the Grand Canyon	High fever with rigors, headache, delirium, arthralgias, myalgias, and hepatosplenomegaly
Rocky Mountain spotted fever	Associated with outdoor activity in the South Atlantic or southeastern United States and exposure to *Dermacentor* tick bites	Headache, petechial rash involving the extremities, hand palms, and feet soles
Tuberculosis	Recent contact with tuberculosis, recent immigration from an endemic country, and work or residence in homeless shelters, correctional facilities, or health care facilities	Night sweats, weight loss, atypical pneumonia, cavitary pulmonary lesions
Tularemia	Associated with bites by *Amblyomma* or *Dermacentor* ticks, deer flies, and mosquitoes or direct contact with the tissues of infected animals such as rabbits, squirrels, deer, raccoons, cattle, sheep, and swine	Ulcerated skin lesions at a bite site, pneumonia, relative bradycardia, lymphadenopathy, and conjunctivitis
Whipple disease *(Tropheryma whippelii)*	Potential association with exposure to sewage	Chronic diarrhea, arthralgia, weight loss, malabsorption, and malnutrition

diffusion-weighted MRI offered a reliable radiation-free option for diagnosing suspected pulmonary infections.[75]

Scanning with labeled autologous leukocytes has been used for evaluating cases in which infections and malignant neoplasms are the cause of FUO. Although this scan has generally fallen out of favor as contributing very little to diagnosis, there are reports that labeled leukocyte scans can provide a higher diagnostic yield than that obtained by either CT or ultrasound scanning.[76,77] Another technique for evaluating undiagnosed fever, especially FUO, is gallium-67 (^{67}Ga) scanning. Its ability to image inflammation was first described by Lavender and

colleagues in 1971.[78] Shortly thereafter, Hilson and Maisey[79] reported positive results by ^{67}Ga scanning in 50 of 67 patients with FUO, of whom 32 had abscesses. The ^{67}Ga scan was considered at one time to be particularly effective in visualizing chronic infections and lymphomas,[80] but this older test for FUO has been largely displaced by CT and MRI. Disadvantages of this image testing method include a 24- to 72-hour delay period between injection and imaging, relatively high radiation dose to patients, and suboptimal image quality.

Positron emission tomography using the positron-emitting glucose analogue FDG has generally not been helpful in the workup of patients with FUO, but there are reports to the contrary.[81,82,83] In a prospective comparison of the two diagnostic modalities, Meller and colleagues[81] reported a sensitivity of 81% and a specificity of 86% for FDG-PET in detecting the focus of the fever, as compared with 67% and 78%, respectively, for ^{67}Ga scintigraphy. In a meta-analysis reported by Dong and colleagues,[83] FDG-PET/CT exhibited an overall pooled sensitivity of 98.2% and specificity of 85.9% for establishing a diagnosis in patients with FUO. Of the major diagnostic categories, the reported sensitivities were 86.7% for malignant neoplasms, 81.5% for infectious diseases, and 76.3% for noninfectious inflammatory conditions. The authors concluded that FDG-PET/CT should be considered when conventional diagnostic methods have been unsuccessful in the diagnosis of an etiology for FUO.

FDG uptake is related to increased cellular glucose metabolism present in numerous hypermetabolic conditions, including tumors, focal areas of infection, and noninfectious inflammatory conditions. FDG-PET and PET/CT have assumed an increasingly important role in the diagnostic workup of patients with FUO. ^{18}F-fluorodeoxyglucose is especially useful for localizing lesions and areas of interest for further evaluation. In contrast to gallium and labeled leukocyte imaging, recent data indicate that FDG contributes more diagnostically useful information than anatomic imaging such as ultrasound and CT, which leads to earlier institution of appropriate therapy.[82,83] These findings suggest that FDG imaging should be performed earlier, rather than later, in the diagnostic evaluation of the patient with FUO. Diagnostic considerations for which this technology may be most helpful included localized abscesses, osteomyelitis, sinusitis, sarcoidosis, vasculitis, adult-onset Still disease, Crohn disease, and subacute thyroiditis.

Invasive Diagnostic Procedures

Histopathologic examination of tissues obtained by excisional biopsy, needle biopsy, or laparotomy can provide a definitive diagnosis in some cases; however, in most published series of FUO patients, biopsy gave the final answer in fewer than half of cases.[73] The majority of patients with FUO undergo at least one such procedure, even though the diagnostic yield is only fair, with an average of two or three, sometimes even more, separate biopsies required to establish a final diagnosis.[14,84] The diagnostic yield of operative and CT-guided biopsies is higher than that of old-style bedside biopsy procedures.[14] For this reason, bedside biopsies should rarely be performed today unless guided by localizing information gained from imaging studies. An important exception to the injunction against blind biopsies concerns the temporal artery, which may merit biopsy in an elderly FUO patient with an erythrocyte sedimentation rate greater than 50 to 100 mm/h, even in the absence of localizing signs.[10]

Patients in whom FUO remains undiagnosed after extensive noninvasive evaluation generally undergo more invasive procedures in an effort to establish an etiology. In a recent retrospective study of 100 patients continuously observed for classic FUO, Mete and associates[85] successfully identified specific etiologies in 61% of patients based on clinical features and noninvasive tests. While invasive procedures were performed in 79% of patients, a diagnostic benefit was obtained in only 49% of the cases. Biopsy procedures were the most common invasive procedure performed, yielding a diagnosis in 42% of cases. The contribution of laparoscopy and laparotomy to the diagnosis of FUO may be most helpful in patients with solid cancers, lymphomas, and disseminated tuberculosis.[85,86]

Molecular Genetic Testing

Familial Mediterranean fever (FMF) is a hereditary inflammatory disease transmitted in an autosomal-recessive pattern characterized by short, recurrent attacks of fever with abdominal, chest, or joint pain and erysipelas-like erythema.[54,63,64,87] Fever is the main clinical manifestation, lasting up to 96 hours, followed by a relatively long interval between attacks. The disease occurs predominantly among Sephardic Jews, Armenians, Turks, and Arabs. Diagnosis is relatively easy in patients with typical clinical manifestations, family history, and appropriate ethnic origin. In 1997, two consortia independently cloned a gene (*MEFV*) on chromosome 16 that is responsible for FMF.[54,63,64,87] This has led to important diagnostic tools to identify polymorphisms or mutations responsible for the disease, which may help in making a definitive diagnosis of FMF in questionable or atypical cases.[64,88,89]

THERAPY

Therapeutic Trials

In the past, empirical therapy with antiinflammatory agents, such as corticosteroids, aspirin, or antimicrobial agents, was often given with the intent of providing an indirect diagnostic test in patients with unexplained FUO.[1] In rare cases, even antineoplastic drugs were used for this purpose. Today such trials are seldom indicated. However, in carefully selected cases, therapeutic trials employing agents with limited spectrums of activity (e.g., antimycobacterial drugs) continue to be an acceptable means of strengthening a presumptive diagnosis when all other means have failed.

The limitations and risks of empirical therapeutic trials are obvious. Underlying diseases may remit spontaneously during the course of ineffective therapy, giving the false impression of success. Furthermore, empirical treatment is rarely specific. Rifampin, for example, is likely to be included in empirical therapeutic regimens for tuberculosis but is highly active against numerous bacterial species other than *Mycobacterium tuberculosis*. Conversely, fluoroquinolones given for other reasons may have a beneficial effect on tuberculosis or Q fever. Similarly, fevers caused by malignant neoplasms have been reported to respond better to nonsteroidal antiinflammatory agents such as naproxen than fevers of infectious origin,[90,91] but the action of naproxen is nonspecific; the ability of the so-called naproxen test to differentiate malignant from nonmalignant causes of FUO remains unvalidated. For these reasons, therapeutic trials, even when successful in reducing fever, may delay the correct diagnosis and thus the appropriate treatment of FUO. Therefore empirical therapeutic trials should be reserved for those very few patients in whom all other approaches have failed or those so seriously ill that therapy cannot be withheld for a further period of observation, or both. In practice, this occurs most often in the case of suspected tuberculosis.

Management

Traditional classic FUO cases are much less common than the complex and multifactorial FUO cases encountered among ICU patients. The differential diagnosis for prolonged febrile episodes has expanded well beyond infectious causes to what has recently been termed *fever of too many origins*.[92] Because there are few formal guidelines, decisions regarding FUO management have certainly become more complex as infectious disease physicians encounter increasingly vague or inconclusive diagnostic test results.

A fundamental principle in the management of classic FUO is that therapy should be withheld, whenever possible, until the cause of the fever has been determined, so that treatment can be tailored to a specific diagnosis.[1] This approach is based on the oft-repeated observation that nonspecific treatment rarely cures FUO and has the potential to delay reaching a specific diagnosis. This ideal is, however, frequently ignored in clinical practice because the road to diagnosis of FUO is, by definition, often long and frustrating. As a result, clinicians may feel compelled to treat symptoms empirically, even though the agents used may obscure the very signs and symptoms on which the diagnosis depends. An important exception is that empirical treatment with corticosteroids may be appropriate in patients with suspected temporal arteritis to prevent vascular complications such as blindness or stroke. Primary care physicians, who have learned from experience that the most cost-effective approach to many acute febrile illnesses is to try empirical antimicrobial therapy before undertaking expensive diagnostic exercises,

should appreciate that this approach is less likely to succeed in patients with FUO.

In febrile neutropenic patients, the principles of treatment are entirely different. Because of the relatively high prevalence of serious bacterial infections responsible for these fevers, febrile neutropenic patients should generally receive broad-spectrum antipseudomonal antimicrobial therapy immediately after samples for appropriate cultures have been obtained (see Chapter 305).[44]

PROGNOSIS

The prognosis of FUO is determined by the cause of the fever and by the nature of any underlying disease or diseases. The time required to establish the diagnosis is less important. Elderly patients and those with malignant neoplasms have the poorest prognosis.[1] Diagnostic delay affects the prognosis adversely in intraabdominal infections, miliary tuberculosis, disseminated fungal infections, and recurrent pulmonary emboli.[73]

Patients in whom FUO remains undiagnosed after extensive evaluation generally have a favorable outcome, characteristically with resolution of their fever in 4 or more weeks without sequelae.[3,84,87] In a study of 61 patients observed long term for undiagnosed FUO, Knockaert and associates[87] were largely unsuccessful in identifying specific etiologies. Most cases eventually resolved spontaneously, generally obviating the need for corticosteroid therapy. Some patients, however, required nonsteroidal antiinflammatory drugs for symptomatic relief. In this series, the 5-year mortality rate for undiagnosed FUO was only 3.2%. In a series of 91 patients undergoing evaluation for FUO, Mansueto and colleagues[84] reported 29 patients (31.8%) who were discharged without a diagnosis and followed over a period of 48 months. Although a definitive diagnosis was established in eight cases, four of such patients died as a result of noninfectious complications related to neoplastic conditions.

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57 The Acutely Ill Patient With Fever and Rash

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SHORT VIEW SUMMARY

Definition

- Skin lesions are frequently present in acutely ill patients with serious infectious diseases and may provide important clues that aid in early diagnosis and treatment.

Epidemiology

- Acutely ill patients with a potential infectious disease and skin lesions (or rash) should have a history obtained that elicits the following: recent drug ingestion; travel outside the local area; potential occupational exposures; recent immunizations; risk factors for sexually transmitted infections, including human immunodeficiency virus infection; factors affecting host resistance or immunocompromising conditions; prior allergies to antibiotics; recent exposures to febrile or ill persons; exposure to rural habitats, insects, arthropods, and wild animals; and exposure to pets or animals.
- Patients with skin lesions or rashes consistent with a communicable infectious disease (e.g., invasive meningococcal infection) should be immediately placed on appropriate isolation precautions (i.e., contact, droplet, airborne, or special precautions for highly communicable diseases, such as Lassa and Ebola virus infections).
- Infectious disease physicians should be familiar with the skin lesions (or rash) that might accompany a patient with disease that could be the result of the intentional use of a bioweapon (e.g., anthrax, smallpox, plague, viral hemorrhagic fevers).

Microbiology

- Serious bacterial infections with skin lesions include *Staphylococcus aureus* (toxic shock syndrome [TSS], scalded skin syndrome), *Streptococcus pyogenes* (TSS), *Salmonella enterica* serovar Typhi, *Neisseria meningitidis,* and *Rickettsia rickettsii.*
- Potentially serious viral infections with skin lesions include measles, rubella, Epstein-Barr virus infection, cytomegalovirus, human herpesvirus 6, and viral hemorrhagic fevers (e.g., dengue hemorrhagic fever, Ebola, Marburg, Lassa).
- Life-threatening drug reactions may result from antibiotic therapy for disorders such as Stevens-Johnson syndrome/toxic epidermolysis necrosis and from drug reaction with eosinophilia and systemic symptoms (DRESS).

Diagnosis

- Key aspects of skin lesions that aid in a proper diagnosis include (1) primary type(s) of skin lesions, (2) distribution of the lesions, (3) pattern of progression of the rash, and (4) timing of onset of the rash relative to the onset of fever and other systemic signs.
- The appearance of skin lesions may be very useful in the diagnosis of specific infectious diseases. Maculopapular rashes are usually seen in viral illnesses, drug eruptions, and immune complex–mediated diseases. Nodular lesions are suggestive of mycobacterial or fungal infections. Diffuse erythema suggests scarlet fever, TSS, Kawasaki disease, or Stevens-Johnson syndrome/toxic epidermal necrolysis. Bullous lesions suggest streptococcal erysipelas with necrotizing fasciitis, ecthyma gangrenosum, and *Vibrio* infections. Petechial eruptions suggest gram-negative sepsis, invasive *N. meningitidis* infection, rickettsial infections, and viral hemorrhagic fever.
- Consideration should be given to biopsy of skin lesions, if present, in acutely ill immunocompromised patients for appropriate stains (e.g., Gram stain, fungal stain) and cultures and for pathologic study.

Therapy

- Empirical therapy should often be initiated in acutely ill patients with skin lesions based on the clinical diagnosis.
- Most acutely ill patients with skin lesions will require systemic therapy.

Prevention

- Standard vaccines should be provided to children and adults because many vaccine-preventable diseases produce rashes (e.g., measles, rubella, varicella).
- Underlying noninfectious diseases that lead to disruption of skin should be treated because the damaged skin serves as a risk factor for infection.

A recognizable rash can lead to immediate diagnosis and appropriate therapy. Material isolated from involved skin, when properly handled, can confirm a specific diagnosis. Unfortunately, rashes often present a bewildering array of diagnostic possibilities. Dermatologists, who are generally more comfortable with evaluation of the skin, are not always available for immediate consultation. Furthermore, dermatologists and infectious disease specialists frequently differ in their approach to the patient with a rash.

A framework is provided in this chapter for investigation of the cause of rash, with emphasis on the following: (1) a diagnostic approach to patients with fever and rash, (2) categories of skin lesions, and (3) brief descriptions of the most important febrile illnesses characterized by a rash.

APPROACH TO THE PATIENT

In the initial evaluation of a patient with fever and rash, four concerns must be addressed immediately. The first is if the patient is well enough to provide further history or whether cardiorespiratory support is required. The second is whether the nature and presentation of the rash demands immediate institution of isolation precautions. Isolation is required primarily for patients whose illnesses allow droplet or airborne spread of the pathogen, including both viral (e.g., possible viral hemorrhagic fever) and bacterial diseases (e.g., possible invasive meningococcal infection). Isolation precautions should be adhered to scrupulously. Health care personnel should exercise caution in all interactions with patients with undiagnosed infectious diseases, and they should use standard precautions, including the avoidance of direct contact with all excretions and secretions with the exception of sweat.[1–4] Although the vast majority of skin eruptions are noninfectious, gloves should always be worn during the examination of the skin whenever an infectious cause is being considered because some infections (e.g., syphilis, herpes simplex virus [HSV]) may be acquired via direct skin contact. In the event of potential exposure to a pathogen, health care personnel should be evaluated by their occupational health service for postexposure prophylaxis or the need for work restrictions or both.[4–7] The third concern is if skin lesions suggest a life-threatening infection, such as bacterial sepsis, staphylococcal or streptococcal toxic shock, Kawasaki disease, necrotizing fasciitis, toxic epidermal necrolysis, or Rocky Mountain

spotted fever (RMSF).[8–11] Early diagnosis is important because prompt initiation of appropriate therapy may improve survival.[12,13] If skin lesions are consistent with meningococcal disease (see later discussion), the immediate institution of antibacterial therapy is crucial.[14,15–17] Finally, consideration must be given to the possibility that the patient has an exotic disease acquired as a result of travel or the intentional release of an agent of bioterrorism.[18] Bioterrorist agents that may be acquired via person-to-person transmission and characteristically cause a generalized rash include smallpox[1,19] and the viral hemorrhagic fevers (i.e., Ebola, Lassa, Marburg, Crimean-Congo, Bolivian, and Argentinean).[1,20] Patients with plague[1,21] and anthrax[1,22] may present with localized skin lesions.

The history obtained from the patient should elicit the following information:

1. Drug ingestion within the past 60 days
2. Travel outside the local area
3. Occupational exposure
4. Sun exposure
5. Immunizations
6. Sexually transmitted disease exposure, including risk factors for infection with human immunodeficiency virus (HIV)
7. Factors affecting immunologic status, including chemotherapy, corticosteroid use, use of immune modulators, hematologic malignancy, solid-organ or stem cell transplantation, and functional or anatomic asplenia
8. Valvular heart disease, including heart valve replacement
9. Prior illnesses, including a history of drug or antibiotic allergies
10. Exposure to febrile or ill persons within the recent past
11. Exposure to wild or rural habitats, insects, arthropods, and wild animals
12. Exposure to outdoor water sources such as lakes, streams, or oceans
13. Pets, animal exposures, and habits

The clinician should pay particular attention to the season of the year, which dramatically affects the epidemiology of febrile rashes of infectious origin.

Physical examination should focus on the following:

1. Vital signs
2. General appearance
3. Signs of toxicity
4. Presence and location of adenopathy
5. Presence and morphology of genital, mucosal, or conjunctival lesions
6. Detection of hepatosplenomegaly
7. Presence of arthritis
8. Signs of nuchal rigidity, meningismus, or neurologic dysfunction

Key ingredients in arriving at a correct diagnosis, or at least a useful, limited, "working" list of likely diagnoses, include determination of (1) the primary type(s) of skin lesions present, (2) the location and distribution of the eruption, (3) the number and size of the lesions, (4) the pattern of progression of the rash, and (5) the timing of the onset of the rash relative to the onset of fever and other signs of systemic illness.[23–31] It is important for physicians who observe a rash to carefully document the characteristics or take images of the skin lesions in the medical record to aid other providers in the later care of the patient. Although histologic findings from lesional skin biopsies may help to confirm some diagnoses,[29] the patterns observed are frequently not specific for a single organism, the presence of infectious agents may not always be detectable, and laboratory studies often require at least 24 hours to complete. Thus the clinician must attempt to use other diagnostic skills during the early evaluation of a patient with fever and rash. As discussed elsewhere, specific types of primary skin lesions frequently suggest different infectious disorders in patients with fever and rash. For example, palpable purpura, the hallmark feature of leukocytoclastic vasculitis, is the prototypic early finding in meningococcemia and RMSF, whereas rapidly enlarging but asymptomatic red dermal nodules instead suggest candidemia in the appropriate host. Skin nodules noted on very deep palpation are probably located within the subcutaneous fat, suggesting one of several types of panniculitis, including erythema nodosum, a disorder caused by many different types of inflammatory or infectious processes, and erythema induratum, which is a classic tuberculoid reaction.

Examples of differences in the types of primary skin lesions present in the setting of underlying systemic infectious diseases are summarized in Table 57.1, although it should be clear that such a classification, by itself, rarely ever suggests only a single diagnosis. On the other hand, the presence of other more specific lesions, most notably "target" or "iris" lesions (as in erythema multiforme [EM]), may suggest a

TABLE 57.1 Systemic Infections With Prominent Cutaneous Manifestations

ORGANISM/DISEASE	MACULES, PAPULES	VESICLES, BULLAE	PETECHIAE, PURPURA
Viruses			
Human immunodeficiency virus type 1	X		
Echoviruses	X	X	X
Coxsackieviruses	X	X	X
Rubeola (measles)	X		
Atypical measles	X		X
Adenovirus	X		X
Lymphocytic choriomeningitis	X		
Dengue	X		X
Zika virus	X		
West Nile virus	X		
Viral hemorrhagic fevers			X
Rubella (German measles)	X		X
Colorado tick fever	X		
Yellow fever			X
Varicella-zoster (disseminated)		X	
Herpes simplex (disseminated)		X	
Varicella (chickenpox)		X	
Vaccinia		X	

TABLE 57.1 Systemic Infections With Prominent Cutaneous Manifestations—cont'd

ORGANISM/DISEASE	MACULES, PAPULES	VESICLES, BULLAE	PETECHIAE, PURPURA
Variola		X	X
Cytomegalovirus	X		
Congenital cytomegalovirus			X
Epstein-Barr virus	X		X
Hepatitis B virus	X		X (as palpable purpura)
Monkeypox	X		
Parvovirus B19 (erythema infectiosum)	X		
Human herpesvirus 6	X		
Human herpesvirus 7	X		
Bacteria			
Chlamydia psittaci	X	X	
Mycoplasma pneumoniae	X		
Ehrlichia spp.	X		
Rickettsia rickettsii (RMSF)	X		X
Rickettsia akari (rickettsialpox)	X	X	
Rickettsia prowazekii (epidemic/louse-borne typhus)	X		X
Rickettsia typhi (endemic/murine typhus)	X		
Rickettsia tsutsugamushi (scrub typhus)	X		
Bartonella henselae	X		
Bartonella quintana	X		
Salmonella enterica serovar Typhi	X		
Francisella tularensis	X		
Streptobacillus moniliformis (rat-bite fever)	X		X
Treponema pallidum (secondary syphilis)	X		
Mycobacterium haemophilum	X		
Neisseria gonorrhoeae	X		X
Neisseria meningitidis			X
Leptospira spp.	X		
Listeria monocytogenes		X (rare)	
Bartonella bacilliformis	X		
Borrelia spp. (relapsing fever)	X		X
Borrelia burgdorferi (Lyme disease)	X (annular)		
Pseudomonas aeruginosa	X		
Spirillum minus (rat-bite fever)	X		X
Staphylococcus aureus	X		X
Streptococci—group A (scarlet fever)	X		
Capnocytophaga canimorsus			X
Vibrio vulnificus		X	
Fungi (Disseminated Infection)			
Candida spp.	X		
Cryptococcus neoformans	X		
Histoplasma capsulatum	X		
Blastomyces dermatitidis	X		
Coccidioides immitis	X		
Fusarium spp. (agents of mucormycosis)	X		
Protozoa			
Plasmodium falciparum (malaria)			X

single diagnosis, implicating a limited group of underlying infectious diseases as possible causes. Similarly, the presence of some lesions in the setting of fever may immediately exclude an infectious disorder as the cause of rash. For example, high fever accompanying a paucity of tender, red to violaceous, peripherally mammillated plaques suggests Sweet syndrome (acute febrile neutrophilic dermatosis), a rare hypersensitivity reaction frequently associated with selected underlying malignancies,[32] or neutrophilic eccrine hidradenitis, a rare neutrophilic dermatosis most commonly found in patients treated with chemotherapy for malignancies.[33]

Distribution or direction of spread of an eruption may be highly informative. The rash of RMSF and acute meningococcal infection, for example, most often begins on the lower extremities and then spreads centrally (i.e., centripetally), whereas most drug- and viral-infection–associated eruptions (with the exception of those caused by echoviruses and coxsackieviruses) begin on the face or trunk and spread outward (centrifugally). "Streaky" facial involvement, usually without other skin findings, is characteristic of infection due to parvovirus B19 (fifth disease, erythema infectiosum).

The number of lesions can also provide useful insight. For example, "rose spots" (see later discussion), the hallmark cutaneous feature of *Salmonella* infection, are characteristically present in much greater numbers in patients who have paratyphoid fever than in those who have typhoid fever. In contrast, brucellosis may be associated with only one or a few clinically subtle skin lesions, as seen in a fixed-drug eruption.

Finally, timing of the rash may be particularly helpful in allowing the clinician to exclude reactions due to certain drugs as the underlying cause. With the exception of urticarial eruptions, which usually occur within a few minutes to a few hours of the administration of a systemic agent, the more typical generalized maculopapular or morbilliform drug eruption typically occurs within the first 7 to 14 days of the first dose of the offending agent, suggesting the need for a very careful drug history (including start and stop dates for all medications taken within 30 days of the onset of eruption).

It must be emphasized that noninfectious processes often include rash and fever and should be among the diagnostic considerations in the initial evaluation.[34] As noted previously, the presence of some highly specific morphologic types or patterns of skin lesions may quickly suggest a noninfectious cause to the astute clinician, thereby obviating the need to pursue a more extensive clinical and laboratory evaluation.

Between 5% and 15% of all patients to whom a drug is administered experience an adverse reaction.[35–37] Adverse cutaneous reactions to drugs are frequent, affecting 2% to 3% of all hospitalized patients,[38–44] 20% of emergency department visits,[44] and 0% to 8% of all patients placed on medications.[41] Fortunately, only about 2% of adverse cutaneous reactions are severe and very few fatal.[36] The rate of cutaneous reactions to drugs is highest for antibiotics (1%–8% depending on the class of antibiotic), mainly penicillins and cephalosporins.[42,44] Exanthems (75%–95%) and urticaria (5%–6%) account for most drug reactions. Because of their frequency, a drug reaction must be considered in any patient with a generalized maculopapular rash, especially if associated with palmoplantar involvement. Severe cutaneous reactions often induced by drugs include Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN),[11,38,45] hypersensitivity syndromes (urticaria, angioedema, anaphylaxis),[38,46] small vessel vasculitis,[38,39] serum sickness,[11,38] and drug reaction with eosinophilia and systemic symptoms (DRESS).[11,39,47,48] As with other rashes, a morphologic approach to drug eruptions should be used in evaluating the patient.[35,40,43]

Rashes and skin infections associated with occupational exposures,[49–53] athletics,[54–61] animal exposures,[62] international travel,[63,64–69] and working in a clinical or research laboratory[70] have been reviewed in other chapters in this textbook.

PATHOGENESIS OF RASH

Rash with fever can result from a local infectious process due to virtually any class of microbe that has been allowed to penetrate the stratum corneum and multiply locally. A typical example is streptococcal cellulitis. In rare cases such localized inoculations result in more generalized eruptions, and the diagnosis is then relatively straightforward. However, eruptions that begin as generalized exanthems are the "rashes" that constitute the focus of the discussion in this chapter.

An *exanthem* is a cutaneous eruption due to the systemic effects of a microorganism infecting the skin. An *enanthem* is an eruption caused in similar fashion but involving the mucous membranes. Microorganisms may produce eruptions through (1) multiplication in the skin (e.g., HSV); (2) release of toxins that act on skin structures (e.g., in scarlet fever, infections due to *Pseudomonas aeruginosa,* toxic shock syndrome [TSS], staphylococcal scalded skin syndrome [SSSS]); (3) inflammatory response involving phagocytes and lymphocytes, in which the microbicidal/tumoricidal metabolism of host defense cells is directed at the skin; and (4) effects on vasculature, including vasoocclusion and necrosis or vasodilation with edema and hyperemia. Obviously, for many eruptions, several concurrent mechanisms can play a role.

DIFFERENTIAL DIAGNOSIS IN RASH

There are two ways to approach the investigation of infectious rash: either by the type of lesion visualized or by knowledge of individual pathogens and the rashes they produce (Table 57.2). Unfortunately, neither system alone serves both to generate a complete list of diagnostic possibilities to rule out disorders as appropriate. In accordance, both approaches should be incorporated into evaluation of the patient with rash and fever.

Characteristics of the Lesion

Morphologic types of primary skin lesions include macules, papules, nodules, vesicles, bullae, pustules, and plaques. *Macules* are flat, nonpalpable lesions in the plane of the skin. *Papules* are small, solid, palpable lesions elevated above the plane of the skin. Masses that are located deeper within or below the skin are referred to as *nodules. Vesicles* and *bullae* are small and large blisters, respectively, and *pustules* are usually small, palpable lesions filled with pus. *Plaques* are large, flat lesions, usually greater than 1 cm in diameter, that are palpable. In addition to morphology, lesions are characterized by their color and, particularly in the setting of a systemically ill–appearing patient, by the presence or absence of hemorrhage, with hemorrhagic lesions being termed *purpura* or *petechiae.* Lesions may be skin colored, hyperpigmented, or hypopigmented or any of several other colors, of which red is the most common; the presence of such reddening is termed *erythema.* Blanching erythematous lesions are those in which erythema is due to vasodilation, whereas nonblanching erythema may be due to extravasation of blood. For purposes of the following discussion, it is useful to divide eruptions into those that are maculopapular (characterized by both flat and elevated lesions), nodular, vesiculobullous, erythematous, and purpuric. Enanthums and neutrophilic dermatoses are also important in the differential diagnosis of fever and rash.

Maculopapular Rash

Maculopapular rashes (see Table 57.1) (Fig. 57.1) are usually seen in a range of illnesses, including those due to viruses, bacteria, fungi, drug eruptions, and immune complex–mediated syndromes. Descriptions of some of the specific pathogens are included later in the chapter or are included in other chapters. Physicians, in particular, should be familiar with maculopapular rashes associated with EM and SJS/TEN.

EM and its variants may be considered a special category of maculopapular rash. EM is an uncommon acute, immune-mediated, self-limited, usually mild mucocutaneous syndrome that is often relapsing.[71,72,73] The disease is usually related to an acute infection, most commonly a recurrent HSV infection. It is uncommonly related to drug ingestion (i.e., <10%).

The following classification of EM is based on that provided by Bastuji-Garin and colleagues.[73,74] Subtypes of EM include (1) EM major: skin lesions with involvement of mucous membranes, (2) EM minor: skin lesions without involvement of mucous membranes, (3) herpes-associated EM, and (4) mucosal EM (Fuchs syndrome): mucous membrane lesions without cutaneous involvement. Until recently, EM was considered as a variant of the same pathophysiologic process as SJS and TEN. However, currently evidence suggests that EM with mucous membrane involvement and SJS are different diseases with distinct causes.[75] Further, the epidemiology of EM differs from SJS/TEN because

TABLE 57.2 Skin Lesions and Systemic Infections

LESION	COMMON PATHOGENS	HISTOLOGIC FINDINGS	SMEARS POSITIVE FOR PATHOGENS	TIME TO APPEARANCE (AFTER ONSET OF ILLNESS)
Symmetrical peripheral gangrene, purpura fulminans, acrocyanosis	Noninfectious or gram-negative bacteria, *Capnocytophaga canimorsus*	Bleeding in the skin, vascular thrombosis, perivascular infiltration	No	12–36 h
Multiple purpuric lesions in severely ill patients	*Neisseria meningitidis, Capnocytophaga canimorsus, Rickettsia* spp., other gram-negative bacteria	Vascular thrombosis, perivascular hemorrhage	Yes[a]	12–36 h[b]
Ecthyma gangrenosum, other bullous lesions	*Pseudomonas*, gram-negative bacteria, *Vibrio vulnificus*	Veins, mainly involved, intima spared, inflammatory reaction	Yes	Several days
Macronodular lesions	*Candida, Cryptococcus neoformans, Histoplasma capsulatum, Fusarium*	Hyphae, mononuclear perivascular reaction	No	Several days
Delayed-onset rash with nonsymmetrical, scattered maculopapular or vesicular lesions	*Neisseria gonorrhoeae, N. meningitidis* (chronic)	Perivascular mononuclear infiltrate, immune complex	Occasionally (few bacteria only)	3–10 days
Rose spots	*Salmonella* spp.	Perivascular mononuclear infiltrate, or leukocytoclastic vasculitis	No	5–10 days
"Toxic erythema"	*Staphylococcus aureus* (SSSS)	Dilation and perivascular edema	No	At presentation

[a]Except for Rocky Mountain spotted fever, in which therapy, biopsy, and immunofluorescent staining may aid early diagnosis.
[b]In Rocky Mountain spotted fever, 1–7 days.
SSSS, Staphylococcal scalded skin syndrome.
Modified from Kingston ME, Mackey D. Skin clues in the diagnosis of life-threatening infections. Rev Infect Dis. *1986;8:1–11.*

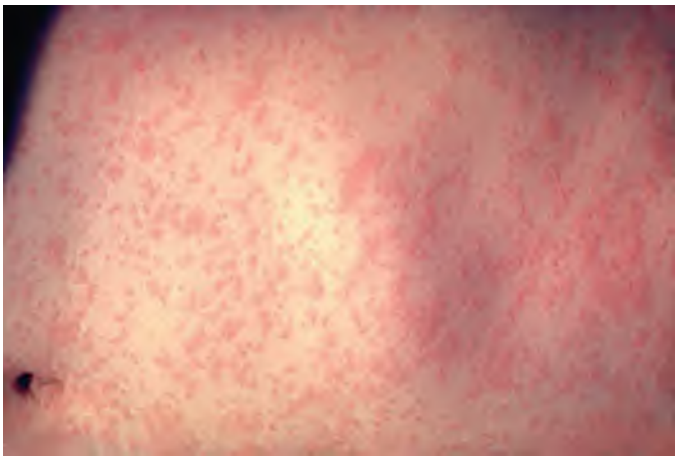

FIG. 57.1 Maculopapular rash. The maculopapular rash of measles showing coalescence of lesions *(From Ferri FF.* Ferri's Clinical Advisor. *1st ed. St. Louis: Elsevier; 2019.)*

patients with EM are younger, are more often male, have frequent recurrences, have less fever, have milder mucosal lesions, and lack association with collagen vascular diseases, HIV infection, or cancer.[76]

Target lesions are the hallmark of EM. The skin eruption generally arises abruptly; most commonly all lesions appear within 3 to 5 days and resolve in approximately 2 weeks. Initially, lesions may begin as round erythematous papules that evolve into classic target lesions. Typical target lesions consist of three components: a dusky central area or blister, a dark red inflammatory zone surrounded by a pale ring of edema, and an erythematous halo on the extreme edge of the lesion. Although there are often a limited number of lesions, in some cases hundreds may form. Most lesions occur in a symmetrical, acral distribution on the extensor surfaces of the extremities (hands and feet, elbows, and knees), face and neck, and, less commonly, thighs, buttocks, and trunk. They often appear acrally and then spread in a centripetal manner. Although the lesions are usually asymptomatic, patients occasionally report burning or itching. Mucous membrane (≈70% oral, ≈25% genital, ≈15% ocular) involvement usually accompanies the cutaneous lesions, although patients may present only with mucous membrane involvement.[77]

Although many factors (e.g., infections, medications, malignancy, autoimmune disease, immunizations, sarcoidosis, and radiation) have been linked to EM, infections account for approximately 90% of cases. HSV has been the infection most commonly linked to EM (≈80% of infectious cases),[78,79] but *Mycoplasma pneumoniae* is an important cause of EM (≈5%–10% of infectious cases), especially in children.[80] The differential diagnosis of target-appearing skin lesions has been reviewed and includes EM, SJS, TEN, ecthyma gangrenosum, syphilis, fixed-drug eruption, contact dermatitis, vasculitis, acute connective tissue diseases, and autoimmune blistering diseases.[81]

SJS and TEN are acute, life-threatening mucocutaneous reactions characterized by extensive necrosis and detachment of the epidermis.[82–87] Although TEN is rare, with an incidence of approximately two cases per million population per year, it is a devastating disease with a mortality rate of 30% to 50%. Owing to the similarity in clinical and histologic findings, risk factors, drug causality, and mechanisms, these two syndromes are considered severity variants of an identical process that differs only in the final extent of body surface involved.[87] TEN involves sloughing of greater than 30% of the body surface, whereas SJS involves less than 10% of the total body surface; total body surface area involvement between 10% and 30% is known as SJS-TEN overlap. SJS and TEN typically have a prodrome of fever and flulike symptoms beginning 1 to 3 days before the development of skin lesions. These may be accompanied by skin tenderness and photophobia. Both SJS and TEN are characterized by rapidly expanding, often irregular macules ("atypical target lesions") and involvement of more than one mucosal site (oral, conjunctival, and anogenital). If untreated, TEN rapidly progresses to widespread full-thickness necrosis of the epidermis, resulting in separation of large sheets of epidermis from the underlying dermis either spontaneously or after the application of minimal lateral traction or pressure to the skin. The Nikolsky sign (i.e., ability to extend the area of superficial sloughing by gentle lateral pressure on the surface of the skin at an apparently uninvolved site) may be positive. Constitutional symptoms and internal organ involvement occur often and may be severe.

A majority of cases in adults are drug induced; medications cause 30% to 50% of cases of SJS and up to 80% of cases of TEN. Although

infections may be an occasional trigger of SJS in adults, they uncommonly cause TEN. Rare precipitating causes include vaccinations, systemic diseases, chemical exposures, and foods. In contrast, in children, although medications are the leading cause of both SJS and TEN, infections such as *M. pneumoniae* and herpesviruses are more common causes of SJS and TEN. Although most of the highest-risk medications are not antiinfective agents, nevirapine is a confirmed high-risk drug.[82] Antiinfective agents most commonly associated with SJS and TEN include amoxicillin, sulfadiazine, and trimethoprim-sulfamethoxazole (TMP-SMX); less common antiinfective agents include cephalosporins, macrolides, tetracyclines, rifampin, thiabendazole, ethambutol, and fluoroquinolones (sulfonamides ≫ penicillins > cephalosporins). Patients infected with HIV have been reported to be at threefold increased risk for SJS/TEN, with a 40-fold increased risk for SJS/TEN due to TMP-SMX. Unfortunately, there is no laboratory test to support the diagnosis of SJS or TEN. The following diseases must always be excluded before making a diagnosis of SJS or TEN: varicella, EM major, SSSS, staphylococcal TSS, skin necrosis from disseminated intravascular coagulation or purpura fulminans, and chemical toxicity.[87] Treatment should always include appropriate fluid and wound care (for extensive disease the patient should be managed in a burn center), strict aseptic care to prevent infections, and consideration for topical antibiotic therapy (avoid silver sulfadiazine).[82,86,88] Adjunctive therapies that are based on extensive use but have not been studied in clinical trials include intravenous (IV) gamma globulin and glucocorticoids.[82,88–90] Plasmapheresis, cyclosporine, and tumor necrosis factor (TNF) antagonists (infliximab, etanercept) have been reported to be of benefit based on small case series.[82,86,88–90] Thalidomide increased mortality in a double-blind randomized placebo-controlled trial.[91]

Last, in several life-threatening infections, the presenting manifestations may include blanching erythematous maculopapular lesions that later evolve into petechiae, making initial diagnosis difficult on the basis of lesion morphology alone. These infections include acute meningococcemia, RMSF, and viral hemorrhagic fevers such as dengue. Although a diagnostic feature of rheumatic fever is an annular or a polycyclic, migrating (or expanding) erythema known as *erythema marginatum,* this disease may also be associated with the presence of a maculopapular eruption and subcutaneous nodules. Patients with enteric fever due to *Salmonella* may develop "rose spots," a transient scattering of rose-colored macules over the abdomen. Typically, the rose spots of typhoid fever are pale pink, oval or circular, completely blanchable, few in number, moderately sized (up to 0.5–1.0 cm in diameter), and usually present on the abdomen or trunk.[92] In contrast, rose spots of paratyphoid fever are typically smaller and more numerous.[93]

Nodular Lesions

A nodule is a palpable, solid, round or ellipsoidal lesion, usually resulting from disease in the dermis and/or subcutis (Fig. 57.2). Nodules may contain various inflammatory cells (as part of a hypersensitivity phenomenon), organisms (most notably fungi, as in septic emboli), or tumor cells (from metastatic cancer, lymphoma, or leukemia cutis). In the appropriate clinical setting, sudden development of dermal nodules may suggest candidal sepsis (see later discussion), but other fungal diseases, including blastomycosis, histoplasmosis, coccidioidomycosis, and sporotrichosis, may produce skin nodules. Bacteria such as *Nocardia* and nontuberculous mycobacteria[94–96] (especially *Mycobacterium marinum*)[97] may also cause nodular lesions that typically later ulcerate. Leishmaniasis can cause nodules. Lesions consistent with ecthyma gangrenosum, typified by the presence of deep, "punched-out" ulcerations with overlying black eschar and peripheral erythema, suggest *Pseudomonas* sepsis. A skin biopsy specimen with appropriate stains and cultures defines the diagnosis.

Subcutaneous nodules pose a real diagnostic challenge because they may reflect the presence of a variety of underlying disorders, including hypersensitivity reactions to systemic infection. The lesions of erythema nodosum are characterized by tender, erythematous nodules that range in diameter from less than a centimeter to several centimeters (Fig. 57.3).[98–100] They are usually multiple and located on the anterior portions of the legs but may be solitary and occur on other parts of the body.

FIG. 57.2 Nodular rash. Multiple erythematous skin nodules of *Mycobacterium abscessus (From Su S, Chen Y-H, Tsai T-Y, et al. Catheter-related* Mycobacterium abscessus *bacteremia manifested with skin nodules, pneumonia, and mediastinal lymphadenopathy.* Kaohsiung J Med Sci. *2013;29:50–54.)*

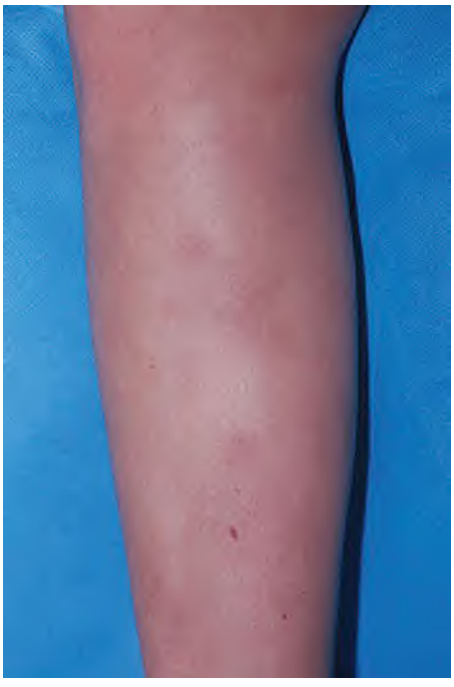

FIG. 57.3 Erythema nodosum. Erythematous nodules which are ill defined without epidermal changes on the lower leg. *(From Brinster NK, Liu V, Diwan H, McKee PH. Erythema nodosum. Brinster NK, Liu V, Diwan H, McKee PH, eds.* Dermatopathology: High-Yield Pathology. *Philadelphia: Saunders; 2011:170–171.)*

They typically do not suppurate. These lesions often develop in crops and usually heal in days to a few weeks without scarring. Infectious agents are a prominent cause of this lesion (Table 57.3). In contrast, erythema induratum, a known tuberculoid reaction, typically presents as painful, red, subcutaneous nodules over the posterior lower legs and

TABLE 57.3 Known Noninfectious and Infectious Causes of Erythema Nodosum

Noninfectious
Systemic lupus erythematosus
Sarcoidosis
Ulcerative colitis
Crohn disease
Malignancies (Hodgkin and non-Hodgkin lymphoma, leukemia, renal cell carcinoma)
Behçet syndrome
Drugs (especially oral contraceptives, sulfonamides)
Pregnancy
Infectious
Viral
Hepatitis B virus
Hepatitis C virus
Herpes simplex virus
Human immunodeficiency virus
Epstein-Barr virus
Measles
Parvovirus B19
Varicella
Bacterial
Bartonella henselae (cat-scratch disease)
Brucella spp. (brucellosis)
Campylobacter spp. (campylobacteriosis)
Chlamydia trachomatis (lymphogranuloma venereum)
Chlamydia psittaci (psittacosis)
Corynebacterium diphtheriae (diphtheria)
Coxiella burnetii (Q fever)
Francisella tularensis (tularemia)
Haemophilus ducreyi (chancroid)
Mycoplasma pneumoniae
Mycobacterium tuberculosis (tuberculosis)
Mycobacterium leprae (leprosy)
Mycobacterium marinum (atypical mycobacteriosis)
Neisseria gonorrhoeae (gonorrhea)
Neisseria meningitidis (meningitis)
Salmonella spp. (salmonellosis)
Shigella spp. (shigellosis)
Streptococcus pyogenes (respiratory tract infection)
Treponema pallidum (syphilis)
Yersinia spp. (gastroenteritis)
Fungal
Aspergillus spp. (aspergillosis)
Cryptococcus neoformans (cryptococcosis)
Blastomyces dermatitidis (blastomycosis)
Histoplasma capsulatum (histoplasmosis)
Coccidioides immitis (coccidioidomycosis)
Sporothrix schenckii (sporotrichosis)
Protozoal/Helminths
Ascaris lumbricoides (ascariasis)
Giardia lamblia (giardiasis)
Toxoplasma gondii (toxoplasmosis)
Wuchereria bancrofti (filariasis)

ankles. These lesions tend to suppurate, distinguishing them morphologically from erythema nodosum and most other types of panniculitis. Furthermore, erythema induratum can usually be easily differentiated from erythema nodosum on histologic examination of a wedge biopsy specimen. Inflammation can be seen within subcutaneous fat lobules in the former, rather than within septal connective tissue as classically seen in erythema nodosum. Acid-fast bacilli are rarely visible within the lesions of erythema induratum because this condition typically represents reactivation of long-standing infection with, or hypersensitivity to, the tuberculosis bacilli that are present at distant sites.

Diffuse Erythema

Diffuse erythema, especially if desquamation or peeling is present, should lead to consideration of scarlet fever, TSS, mucocutaneous lymph node syndrome (Kawasaki disease), SSSS, SJS, and TEN (Fig. 57.4). Desquamation may occur late in all of these syndromes, and its absence early in the clinical course should not be considered a reason for excluding any disease process. Most of these disorders can be easily diagnosed on the basis of the patient's history and appropriate tests.

FIG. 57.4 Diffuse erythema. Diffuse erythema associated with toxic shock syndrome. *(Courtesy Centers for Disease Control and Prevention Public Health Image Library.)*

FIG. 57.5 Vesicular rash. Vesicles associated with varicella infection. *(From Goering RV, Dockrell HM, Zuckerman M, et al. Infections of the skin, soft tissue, muscle and associated systems. In: Goering RV, Dockrell HM, Zuckerman M, et al, eds.* Mim's Medical Microbiology. *5th ed. St. Louis: Elsevier; 2013.)*

Vesiculobullous Eruptions

A vesicle is a circumscribed, elevated lesion containing free fluid (Fig. 57.5). A vesicular lesion larger than 0.5 cm is termed a *bulla*. Most vesiculobullous eruptions are immunologic in origin; few are associated with infectious systemic infections. Infectious diseases to be considered include varicella, disseminated herpes simplex, eczema herpeticum (HSV superinfection of atopic eczema), and infections due to echoviruses and coxsackieviruses (including coxsackievirus A16, a cause of hand-foot-and-mouth disease). In addition, other poxvirus infections, such as monkeypox, smallpox, and generalized vaccinia, need to be considered (see later). HSV infection, the most common of these infections causing vesiculobullous lesions, is characterized by a grouped clustering of vesicles on an erythematous base that progresses to mucocutaneous ulceration.[101–103] HSV can be detected by a viral culture of a scraping from a blister but more commonly is now accomplished by polymerase chain reaction assay. In addition, the demonstration of multinucleated giant cells in a scraping (Tzanck preparation) of the base of a vesicle indicates infection with HSV or varicella-zoster virus (VZV). Older

vesicles can be easily confused with pustules. A *pustule* is an elevation of the skin enclosing a purulent exudate. Vesicular lesions may at times become pustules, as can occur with HSV or VZV lesions. Diffuse pustular diseases usually represent a noninfectious dermatologic illness (e.g., pustular psoriasis) or a cutaneous infection (e.g., pustular *Pseudomonas* lesions developing after the use of contaminated hot tubs or staphylococcal folliculitis). Pustular skin lesions associated with arthralgias should lead to a consideration of gonococcemia, *Moraxella* bacteremia, chronic meningococcemia, subacute bacterial endocarditis, coxsackievirus infection, and Behçet syndrome.

Bullous skin lesions with sepsis are suggestive of the following infections: group A streptococcal erysipelas with necrotizing fasciitis (gangrenous erysipelas), ecthyma gangrenosum (due to *Pseudomonas aeruginosa* or *Aeromonas* spp.), *Vibrio* infections (especially those due to *Vibrio vulnificus*) (Fig. 57.6), staphylococcal cellulitis or impetigo, and streptococcal cellulitis. Rarely, in immunocompromised patients the initial manifestation of gram-negative sepsis may be the appearance of a solitary hemorrhagic blister. *V. vulnificus* infection should be strongly considered in patients with preexisting liver disease, or other immunocompromising states, who have recently ingested raw seafood, especially oysters.[104,105] *V. vulnificus* sepsis may also occur in persons with open wounds exposed to a marine environment.[106] *Aeromonas hydrophila* skin and tissue infections, which may be acquired from exposure to fresh or brackish water, may also present as cellulitis with bulla formation.[107] Vesicopustular eruptions in the neonate may be due to both noninfectious and infectious causes. Potential infectious causes include congenital and neonatal candidiasis, staphylococcal infections, streptococcal infections, *Listeria monocytogenes* infection, infection with HSV, neonatal varicella, and bacterial sepsis (due to various organisms).[108]

Petechial and Purpuric Eruptions

Petechiae are lesions less than 3 mm in diameter that contain extravasated red blood cells or hemoglobin (Fig. 57.7). Larger lesions are termed *ecchymoses* or *purpura.* Diffuse petechial lesions should always prompt urgent investigation. In critically ill patients these lesions are often associated with symmetrical peripheral gangrene (purpura fulminans), consumptive coagulopathy, and shock. The most common infectious agents include gram-negative organisms, especially *Neisseria meningitidis,* and rickettsiae. Less commonly, *L. monocytogenes* or staphylococci may be associated with a similar clinical picture. Physicians must also consider a hemorrhagic fever if the patient has a history of recent travel to an area experiencing an epidemic or there is a potential household contact with such a traveler. Asplenic patients are at an increased risk for overwhelming sepsis (lifetime risk of ≈5%), which may be accompanied by symmetrical peripheral gangrene.[109–112] The lifetime risk for sepsis in asplenic hosts has been reported to range from 3% to 5%. *Streptococcus pneumoniae* is responsible for 50% to 90% of infections in the asplenic patients and has a mortality rate of approximately 50%. Other important pathogens include *Haemophilus influenzae, N. meningitidis*, and *Capnocytophaga canimorsus.* Additional occasional pathogens include *Staphylococcus aureus,* group B streptococci, *Enterococcus, Escherichia coli* and other Enterobacteriaceae, *Salmonella, Campylobacter, Bacteroides, Bordetella holmesii, Pseudomonas,* and *Babesia* spp. The risks from many of these diseases can be significantly reduced by vaccination of asplenic patients using Centers for Disease Control and Prevention (CDC)/Advisory Committee on Immunization Practices (ACIP) guidelines.[113] Children should also receive *H. influenzae* type b vaccine. Immunizations with pneumococcal vaccines (i.e., PCV13 and PPSV23 as CDC/ACIP recommended) significantly reduces the risk for pneumococcal sepsis.[112]

Viral illnesses associated with petechial rashes include infections due to coxsackievirus A9, echovirus 9, Epstein-Barr virus (EBV), or cytomegalovirus (CMV); atypical measles; and the viral hemorrhagic fevers. Although children with coxsackievirus and echovirus infections are usually nontoxic in appearance, some may appear very ill. In these patients differential diagnosis from acute meningococcemia is difficult. However, in a series of children presenting with fever and petechiae, only 8% had meningococcal infections and 4% had bacterial sepsis secondary to other disorders.[114,115]

FIG. 57.6 *Vibrio vulnificus*. Bullae caused by infection with *Vibrio vulnificus*. (A) Prior to amputation. (B) and (C) Predébridement. (D) Post-débridement. *(From Ralph A, Currie BJ.* Vibrio vulnificus *and* V. parahaemolyticus *necrotising fasciitis in fishermen visiting an estuarine tropical northern Australian location.* J Infect. *2007;54: e111–e114.)*

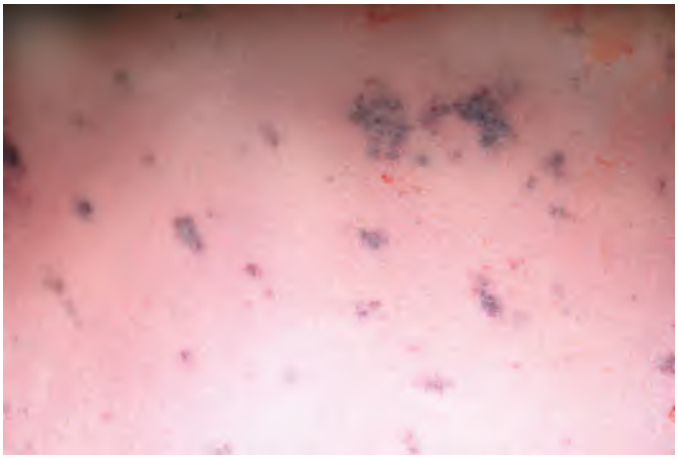

FIG. 57.7 Petichial rash. Diffuse petechial associated with meningococcemia. *(From Connolly AJ, Finkbeiner WE, Ursell PC, Davis RL. Atlas of gross autopsy pathology. In: Connolly AJ, Finkbeiner WE, Ursell PC, Davis RL, eds. 3rd ed.* Autopsy Pathology: A Manual and Atlas. *St. Louis: Elsevier; 2016:186–319.)*

A diffuse rash is often a prominent characteristic of the tick-borne diseases found in the United States (i.e., infections caused by *Rickettsia, Ehrlichia, Anaplasma, Borrelia,* and *Coxiella*), with the exception of tularemia.[116,117,118] The frequency of a diffuse rash has been reported as follows: RMSF, 99%; *Ehrlichia chaffeensis* (ehrlichiosis), 36%; *Anaplasma phagocytophila* (anaplasmosis), 2% to 11%; *Borrelia* spp. (relapsing fever), 28%; and *Coxiella burnetii* (Q fever), 5% to 21%.[116] Although Lyme arthritis is characterized by EM, a diffuse rash may occur at the time of disseminated infection. Lesions caused by rickettsiae are usually generalized and symmetrical. An eschar *(tache noire)* characteristically develops at the site of inoculation in the following rickettsial infections (infecting species): African tick bite fever *(R. africae),* Mediterranean spotted fever *(R. conorii),* North Asian tick typhus *(R. sibirica),* Queensland tick typhus *(R. australis),* rickettsialpox (due to *R. akari*), and scrub- or chigger-borne typhus *(R. tsutsugamushi).* New rickettsioses continue to be recognized worldwide that are characterized by generalized skin lesions, often with *tache noire* lesions, such as Japanese or Oriental spotted fever *(R. japonica),* Flinders Island spotted fever *(R. honei),* and Astrakhan fever (*R. conorii* Astrakhan).[116]

In patients with an appropriate travel history, infection with *Plasmodium falciparum* must be considered.[119] In addition, clinicians should be aware that malaria may occasionally be acquired in the United States.[120] Rash with petechiae secondary to thrombocytopenia is present in about 5% of affected patients heavily parasitized.

The most important causes of noninfectious petechiae are thrombocytopenia, large and small vessel necrotizing vasculitis (usually presenting as palpable purpura), and the pigmented purpuric eruptions (which usually represent capillaritis).

Enanthems

In attempting to classify the enanthem, it is essential that a thorough search of the mucous membranes (including the mouth, conjunctiva, and, on occasion, also the vagina, rectum, and glans penis) be made for the presence of enanthems. In many allergic reactions the mucous membranes are frequently involved. Koplik spots, diagnostic of rubeola, are tiny, white or blue-gray specks superimposed on an erythematous base, located on the buccal mucosa, most prominently on that adjacent to the molars. A "strawberry tongue" suggests the possibility of Kawasaki disease, TSS, or scarlet fever. Petechiae of the palate are common in scarlet fever and some vasculitides and with thrombocytopenia. In infectious mononucleosis, petechiae of both the hard palate and soft palate are common. Oral ulcers occur in a variety of noninfectious immunologic diseases and also with coxsackievirus A16 infection.

NEUTROPHILIC DERMATOSES, INCLUDING SWEET SYNDROME

The neutrophilic dermatoses are a heterogeneous group of diseases that can occur with localized, generalized, and systemic skin involvement and include Sweet syndrome, pyoderma gangrenosum, Behçet disease, and neutrophilic urticaria. Sweet syndrome, also known as acute febrile neutrophilic dermatosis, is characterized by a constellation of clinical symptoms, physical features, and pathologic findings that include fever, neutrophilia, tender erythematous skin lesions (papules, nodules, and plaques), and a diffuse infiltrate consisting predominantly of mature neutrophils that are typically located in the upper dermis.[121–124] Sweet syndrome occurs in a variety of clinical settings: idiopathic (or classic), malignancy associated, immunodeficiency associated, and drug induced. The classic syndrome is more frequent in women between the ages of 30 and 50 years, is often preceded by symptoms of an upper respiratory tract infection, and may be associated with inflammatory bowel disease and pregnancy. The skin demonstrates one or more tender, red, edematous, urticarial plaques or large papules. Often the border of each plaque is studded with papules (or, infrequently, with vesicles or pustules), giving an irregularly contoured, mammillated appearance reminiscent of that of the areolae of the breast. If solitary and large, such lesions may be confused with those caused by a variety of infectious processes, including primary HSV infection or streptococcal cellulitis. When solitary and present on the dorsum of the hand, a lesion of Sweet syndrome may mimic erysipeloid or a severe reaction to an arthropod bite. On occasion, these plaques become dusky in color and frankly hemorrhagic, suggesting instead EM or leukocytoclastic vasculitis. Some lesions may also become bullous, suggesting bullous EM or fixed drug eruption. Rare bullous lesions may erode or ulcerate, mimicking pyoderma gangrenosum. Mucosal surfaces may rarely be involved. Characteristically, patients with Sweet syndrome have associated fever; other findings may include leukocytosis, malaise, arthralgias, myalgias, conjunctivitis, and episcleritis.

The diagnosis of Sweet syndrome is one of exclusion and includes infectious and inflammatory disorders, neoplastic conditions, reactive erythemas, systemic diseases, and vasculitis. Sweet syndrome responds rapidly to high-dose systemic corticosteroids, but relapse is frequent if tapering is too rapid. Second-line systemic agents include colchicine, dapsone, potassium iodide, TNF-α antagonists, and cyclosporine.[124]

PATHOGENS OR INFECTIOUS CONDITIONS STRONGLY ASSOCIATED WITH RASH

As noted previously, the investigation of infectious rash requires consideration of not only the characteristics of the skin lesions but also the pathogens and infectious processes strongly associated with rash. The following discussion reviews the various skin manifestations of these pathologic processes.

Sepsis

Sepsis is a clinical syndrome that complicates severe infection and is characterized by inflammation, including vasodilation, increased microvascular permeability, and end-organ dysfunction. The inflammatory response has been divided into the systemic inflammatory response syndrome (SIRS), sepsis, severe sepsis, and septic shock,[125] and the pathophysiology has been reviewed.[126] Although SIRS may result from infection or from noninfectious causes (e.g., autoimmune disorder, pancreatitis, vasculitis, thromboembolism, burns, surgery, heat shock), sepsis results from a dysregulated inflammatory response to an infection.

Kingston and Mackey[29] classified the skin lesions associated with sepsis into five pathogenic processes (major categories of infectious causes): (1) disseminated intravascular coagulation (DIC) and coagulopathy (due to *N. meningitidis,* streptococci, enteric gram-negative bacilli), (2) direct vascular invasion and occlusion by bacteria and fungi (*N. meningitidis, P. aeruginosa, Aspergillus* spp., agents of mucormycosis, *Rickettsia* spp.), (3) immune vasculitis and immune complex formation (associated with infection due to *N. meningitidis, Neisseria gonorrhoeae, Salmonella enterica* serovar Typhi), (4) formation of emboli in endocarditis (due

to *S. aureus,* streptococci), and (5) vascular effects of toxins (in SSSS, TSS, scarlet fever). Various systemic bacterial infections may spread to the skin, generally producing discrete lesions from which the organisms can be isolated or recognized on biopsy with special stains. The most characteristic finding in DIC is noninflammatory purpura with extensive microvascular occlusion referred to as purpura fulminans.[127–130] Other manifestations include diffuse bleeding, hemorrhagic necrosis of tissue, and skin necrosis. Although DIC may result from sepsis, it may also be caused by trauma, malignancy, obstetric calamities, severe hepatic failure, and severe toxic or immunologic reactions. Purpura fulminans, a severe skin disorder that is typically associated with DIC, occurs in three clinical settings: (1) as a consequence of severe sepsis, (2) after infection, and (3) in neonates (usually seen in association with homozygous protein C deficiency). *N. meningitidis* is the organism most commonly responsible for symmetrical peripheral gangrene (i.e., ischemic necrosis simultaneously involving the distal portion of two or more extremities without arterial obstruction), but this disorder may also be due to *S. pneumoniae* and other streptococcal species, *H. influenzae, S. aureus, E. coli, Klebsiella* spp., *Proteus* spp., *A. hydrophila,* other gram-negative organisms, and *Aspergillus.* Symmetrical peripheral gangrene is preceded by bleeding into the skin, ecchymosis, purpura, and acrocyanosis (a grayish cyanosis that does not blanch on pressure and occurs on the lips, legs, nose, ear lobes, and genitalia). Subsequently, the ecchymotic lesions become confluent, blister, undergo necrosis and ulceration, and develop overlying eschars. Histologic examination reveals a Schwartzman-like reaction in the skin characterized by diffuse and extensive hemorrhages, perivascular cuffing, and intravascular thrombosis. Bacteria are usually absent from smears of the lesions. Shock rather than DIC appears to be the major factor in the pathogenesis of symmetrical peripheral gangrene. As noted earlier, purpura fulminans may follow a benign infection, especially in children. Common preceding illnesses include scarlet fever, streptococcal pharyngitis, staphylococcal bacteremia, varicella, and measles.

Neisseria meningitidis Infection

With the widespread use of the *H. influenzae* vaccine, *N. meningitidis* is now the second-most common cause of bacterial meningitis after *S. pneumoniae* and has a similar incidence as gram-negative and staphylococcal meningitis.[131] Skin hemorrhages are the hallmark of invasive meningococcal disease.[132–134] *N. meningitidis* has been cultured from 0.5% to 27.5% of children presenting with fever and petechiae, but many of these studies were conducted before the availability of meningococcal vaccines. Hemorrhagic skin lesions have been present in 28% to 77% of patients with invasive meningococcal disease.[135] The lesions characteristically are petechial but may be noted to blanch with pressure early in the course of infection, thus resembling a viral exanthem. The petechiae are irregular and small and are often accompanied by palpable purpuric lesions, some of which may have pale centers. Coalescing lesions, often macular, may have a characteristic gun-metal gray color centrally, consistent with epidermal necrosis. Lesions most commonly occur on the extremities and trunk but may also be found on the head, palms and soles, and mucous membranes. Symmetrical peripheral gangrene may rapidly develop, often in association with DIC. Histologic examination reveals diffuse endothelial damage, fibrin thrombi, necrosis of the vessel walls, and perivascular hemorrhage in the involved skin. Gram staining of aspirates of the involved areas frequently reveals the presence of organisms.[136] In addition to the direct involvement of skin vessels by meningococci, excessive activation of the coagulation system and concomitant downregulation of the fibrinolytic system caused by high concentrations of endotoxin in the blood may lead to cutaneous hemorrhagic lesions.

Chronic meningococcemia is a rare disease. The classic clinical constellation of symptoms includes intermittent or sustained fevers; recurring maculopapular, nodular, pustular, or petechial eruptions; and migratory arthritis or arthralgias with little systemic toxicity.[137] In one large series comprising 148 patients, skin lesions were noted in 93%.[138] A variety of skin lesions may occur in chronic meningococcemia, the most frequently reported being pale to pink macules and papules, seen in greater than 40% of cases. Nodular lesions may occur, mostly on the lower extremities. Petechiae of variable size may be seen, with superimposed vesicles or pustules centrally. Small, irregularly round, subcutaneous hemorrhages with a bluish gray center containing pus cells are a distinctive lesion of this syndrome. Ecchymotic areas or hemorrhagic, tender nodules that are located deep in the dermis may also occur. Lesions associated with chronic meningococcemia tend to appear in showers in association with the onset of fever. In contrast to the lesions associated with fulminant meningococcemia, those of chronic meningococcemia rarely include organisms demonstrable on Gram-stained smear or biopsy specimen. In addition, purpura fulminans is not a typical finding in chronic meningococcemia. A number of diseases with periodic fever, skin lesions, and joint involvement may resemble chronic meningococcemia, including subacute bacterial endocarditis, acute rheumatic fever, Henoch-Schönlein purpura, rat-bite fever, EM, and chronic gonococcemia.

Pseudomonas Infection

Pseudomonas spp. are ubiquitous environmental organisms that are important pathogens in the hospital and in patients with certain underlying host defense abnormalities (e.g., cystic fibrosis). They may also cause infection in normal hosts, especially when the skin has been moistened. *P. aeruginosa* can cause folliculitis ("hot tub" folliculitis), which is characterized by follicular, macular, papular, vesicular, or pustular lesions on any part of the body that has been immersed in contaminated water and has followed bathing in contaminated whirlpools, hot tubs, and swimming pools.[139] Exposure to contaminated water may also result in nodular lesions on the palms and soles ("hot foot" syndrome).[140,141] Of importance, 96% of *P. aeruginosa* isolates from swimming and hot tubs have been reported to be multidrug resistant.[142]

Skin lesions have been reported to accompany *P. aeruginosa* sepsis in 13% to 39% of patients.[143–145] The dermatologic manifestations of *P. aeruginosa* sepsis consist of four types of lesions. First, vesicles and bullae may occur singly or in clusters and frequently are spread in random fashion over the skin. They may become hemorrhagic as they evolve. Second, gangrenous cellulitis may occur as a sharply demarcated, superficial, painless, necrotic lesion. It may also begin abruptly as an acute infection with local pain, swelling, and erythema and involve deep tissue and fascia. Third, macular or papular nodular lesions are located predominantly over the trunk; the lesions are small, oval, and painless. These lesions may resemble the rose spots of typhoid fever. Finally, ecthyma gangrenosum is a lesion characteristic but not pathognomonic of *P. aeruginosa* sepsis. Ecthyma gangrenosum has generally been reported to occur in 1.3% to 2.8% of septic patients,[143,146,147] but one report noted ecthyma gangrenosum in 28% of patients with *Pseudomonas* bacteremia.[145]

Ecthyma gangrenosum lesions begin as painless, round, erythematous macules, with or without adherent vesicles, that soon become indurated and progress to hemorrhagic bluish bullae. Later, the lesion sloughs to form a deep gangrenous ulcer with a gray-black eschar and a surrounding erythematous halo. The process evolves rapidly over 12 to 24 hours. Lesions may be discrete or multiple and are usually found in the groin, axillary, or perianal areas but may occur anywhere on the body. Although most commonly associated with *P. aeruginosa* sepsis, ecthyma gangrenosum–like lesions have also been reported in sepsis associated with other pseudomonal species, *S. pyogenes, S. aureus, A. hydrophila, K. pneumoniae, Serratia marcescens, Stenotrophomonas maltophilia, Morganella morganii, E. coli, Citrobacter freundii, N. gonorrhoeae, Yersinia pestis, Chromobacterium violaceum, Candida* spp., *Aspergillus* spp., *Mucor* spp., and HSV.[148] These lesions may also occur with vasculitis or malignant infiltration.[149] Rarely, ecthyma gangrenosum due to *P. aeruginosa* may be found in the absence of sepsis.[150–152]

Histologically, ecthyma gangrenosum is characterized by three features: bacterial invasion of the media and adventitia of vein walls deep in the dermis, sparing of the intima and lumen, and minimal inflammation.[149] Bacterial invasion results in marked fibrin exudation and frank hemorrhage, followed by bulla formation. Finally, necrosis of the dermis occurs. Bacteria are readily visible in biopsy samples and can be demonstrated in Gram-stained material scraped from the base of the lesion.

Subcutaneous nodules may also result from *P. aeruginosa* bacteremia. Characteristically, the nodules are erythematous and warm, may be

either fluctuant or nonfluctuant, and may be tender. Despite prolonged antibiotic therapy, these lesions may contain viable bacteria weeks after the blood has been cleared of infection. The absence of fluctuance may be due to either the lack of pus in neutropenic patients or the deep location of the abscess, or both. Although successful treatment may require incision and drainage,[153,154] prolonged antibiotic therapy without drainage may result in a cure.[155,156]

Bacterial Endocarditis

Skin lesions have been reported to accompany bacterial endocarditis in 4% to 50% of cases.[157–162] The cutaneous manifestations of bacterial endocarditis are important clues to the diagnosis, although they occur less frequently than in the preantibiotic era.[163] Cutaneous lesions are also less frequent in older patients (i.e., ≥65 years of age).[164] Skin lesions include Osler nodes, Janeway lesions, subungual splinter hemorrhages, cutaneous purpura and petechiae, and conjunctival petechiae (Roth spots). The prevalence of embolic and hypersensitivity lesions in skin and mucous membranes (50%) in heroin-associated infective endocarditis is similar to that described in patients with non–heroin-associated infective endocarditis.[165]

Petechiae are the most common skin and mucous membrane lesions observed in endocarditis, occurring in 20% to 40% of patients. The lesions are small, flat, and reddish brown and do not blanch on pressure. The petechiae may be observed on the skin, especially on the heels, shoulders, and legs. Mucous membrane (oral and conjunctiva) involvement is common. Petechiae frequently occur in small crops. Lesions usually are transient.

In the preantibiotic era, Osler nodes were present in 10% to 90% of patients with bacterial endocarditis.[166] In the 1980s they were seen in 10% to 20% of cases. Recent series suggests that they are now present in less than 10% of patients with endocarditis because endocarditis is now diagnosed more rapidly before the development of Osler nodes. These lesions are tender, indurated, erythematous nodules, with a pale center that is 1.0 to 1.5 mm in diameter.[166–168] Osler nodes most commonly occur on the pads of the fingers or toes but may also occur on the thenar and hypothenar eminences and over the arms. Pain may be elicited by palpating the tips of the digits. Osler nodes tend to occur in crops, are rarely numerous, and tend to be transient. The lesions usually resolve without necrosis or suppuration 1 to 3 days after antibiotic therapy is initiated. Histologically, Osler nodes show microabscesses with microemboli in adjacent arterioles. Osler nodes are most commonly associated with subacute bacterial endocarditis due to infection with streptococci but may occur in endocarditis due to infection with fungi or gram-negative bacilli or in systemic lupus erythematosus, typhoid fever, and gonococcemia. Osler nodes probably represent the sequelae of vascular occlusion by microemboli leading to localized vasculitis.[169]

Janeway lesions consist of small erythematous macules or, less commonly, small nodular hemorrhages in the palms and soles. Although they may be seen in subacute bacterial endocarditis, they are more common in acute endocarditis, especially that due to *S. aureus.* Unlike Osler nodes, Janeway lesions are painless. Histologically, they show microabscesses with neutrophil infiltration of capillaries.

Infections Due to *Staphylococcus aureus* and *Streptococcus pyogenes*

Most commonly, *S. aureus* and *Streptococcus pyogenes* cause local skin infections, including impetigo; folliculitis; furuncles and carbuncles; hidradenitis suppurativa (follicular infection of intertriginous regions); and erysipelas, mastitis, and cellulitis.[170] Both pathogens may produce serious local infection, including abscesses, myositis, and fasciitis. *S. aureus* is responsible for a variety of infectious syndromes that may produce local or diffuse skin lesions.[171–172] Skin lesions arise from (1) production of toxins,[173–175] (2) septic shock, and (3) vascular invasion, often in association with endocarditis. *S. aureus* strains may produce more than 30 different extracellular proteins.[144] Staphylococcal disease syndromes linked to toxins include toxic shock (TSS toxin 1 [TSST-1]), SSSS (mediated by exfoliative toxins, primarily exfoliative toxin A and exfoliative toxin B [ETA and ETB]), staphylococcal food poisoning (due to staphylococcal exotoxins, principally enterotoxin A and LukE-LukD), and community-associated *S. aureus* skin and soft tissue infections (α-toxins, phenol-soluble modulins, leukocidins).[176,177]

Community-associated methicillin-resistant *S. aureus* (CA-MRSA) strains are now the predominant cause of community staphylococcal skin infections.[178–185] In the United States most CA-MRSA strains carry the staphylococcal cassette chromosome (SCC) mec types IV or V, are typed as USA clones 300 or 400, and carry the gene for Panton-Valentine leukocidin. Groups at higher risk for CA-MRSA infections include athletes, HIV-infected persons, homeless persons, household members of infected people, injection drug users, military personnel, prisoners in correctional facilities, tattoo recipients, and urban dwellers who have lower socioeconomic status and live in crowded conditions. CA-MRSA strains are more likely to cause skin and soft tissue infections than methicillin-susceptible strains. Skin lesions may occur as tender red abscesses that are commonly misinterpreted as "spider bites" by the patient. CA-MRSA strains may manifest as furuncles, boils, erythematous patches and nodules, erythematous pustules (folliculitis), crusted plaques (impetigo), or any combination of these. Other soft tissue infections described include chronic external otitis, paronychia, cellulitis, necrotizing fasciitis, and necrotizing myositis. However, the clinical picture is not sufficiently distinct to allow a diagnosis of CA-MRSA based on clinical features.

Staphylococcal Scalded Skin Syndrome

SSSS (Ritter disease) describes a spectrum of superficial blistering skin disorders caused by the exfoliative toxins (also known as epidermolytic toxins, epidermolysins, and exfoliatins) of *S. aureus.*[186] Its severity varies from localized blisters to generalized exfoliation affecting the entire body surface. Although mortality in appropriately treated children is less than 4%, in adults it can reach almost 60%. Approximately 5% of all *S. aureus* strains produce exfoliative toxins; two serotypes have been identified as affecting humans, ETA and ETB.

Bullous impetigo, a disorder usually confined to children that results from toxin-producing strains of *S. aureus,* is characterized by discrete, flaccid bullae containing clear or cloudy yellow fluid. Lesions are frequently localized to the umbilicus, groin, or axillae. The surrounding skin may appear normal or mildly erythematous. The bullae rapidly rupture, leaving raw, denuded erosions that reepithelialize in 5 to 7 days. Affected infants are usually afebrile and lack constitutional signs.

SSSS usually occurs in neonates or young children (<5 years of age) but may affect older children or, rarely, adults. Most cases in adults occur in association with renal impairment, lymphoma, or immunosuppression. A well-characterized animal model exists for SSSS, demonstrating that decreased renal clearance of the causative toxin results in the clinical presentation. Unlike bullous impetigo, in which the staphylococcal infection produces skin lesions at the site of infection, in SSSS the infection produces a toxin (ETA or ETB) that disseminates, causing a diffuse, blanchable erythema in association with marked skin tenderness, fever, and irritability. Light stroking of involved skin causes rupture and separation of the upper portion of the epidermis (Nikolsky sign). Generalized desquamation usually occurs, especially in intertriginous areas. Unless secondary infection intervenes, the skin heals within 10 to 14 days. A skin biopsy specimen (or a frozen section of an induced peel for more rapid diagnosis) may be studied to distinguish between SSSS and TEN. In SSSS the cleavage plane of the early intraepidermal bulla is just beneath the granular cell layer, whereas in TEN the bulla is subepidermal and associated with full-thickness necrosis of the epidermis. In addition, mucous membranes are relatively spared in SSSS in contrast to TEN. Early distinction between these two diseases is important because the therapy for SSSS includes antistaphylococcal antibiotics, whereas in TEN the discontinuation of treatment with the offending drug and initiation of aggressive burn unit intervention may be lifesaving. SSSS due to MRSA has been reported.[186,187]

A mild form of SSSS is characterized by a generalized scarlatiniform eruption with exfoliation ("staphylococcal scarlet fever"). The skin has a sandpaper roughness, and Pastia lines are present, as in streptococcal scarlet fever, but the strawberry tongue and palatal enanthem of streptococcal scarlet fever are absent.