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473 Health Effects of Climate Change

Disorders Associated with Environmental Exposures PART 15 Eugene Richardson, Maxine A. Burkett

Health Effects of

Climate Change Climate change refers to the effects of accumulated greenhouse gases (GHGs) in the atmosphere on long-term weather patterns. Anthropo genic emissions—in particular from the burning of fossil fuels and land conversion—have increased mean global temperatures by approxi mately 1.1° Celsius above preindustrial levels. Extreme weather events, including heatwaves and ‘natural disasters’ (e.g., wildfires, droughts, and floods) are becoming more frequent and lead to resource scarcity (including access to safe drinking water and food), increased envi ronmental pollution and degradation, violent conflict, and precarious migration. The climate crisis thus has direct consequences for human health (Fig. 473-1), the practice of medicine, and the stability of health care systems and as such represents a health emergency. See Chap. 474 for an overview of climate science. EFFECTS OF CLIMATE CHANGE

ON HEALTH The World Health Organization predicts that between 2030 and 2050, there will be an additional 250,000 deaths from undernutrition, malaria, diarrhea, and heat stress alone (Chap. 474). As with much of the global burden of disease, this increase in mortality will be dis proportionately borne by low- and middle-income countries (LMICs) whose health infrastructures have been weakened by neocolonialism and structural adjustment. Within wealthier countries such as the United States, climate change will amplify existing health disparities between white people and black, Indigenous, and Latinx populations. Impact of Climate Change on Human Health Injuries, fatalities, mental health impacts Asthma, cardiovascular disease Heat-related illness and death, cardiovascular failure Extreme Heat s g n si Environmental Degradation Forced migration, civil conflict, mental health impacts a Water Quality Impacts Water and Food Supply Impacts Malnutrition, diarrheal disease FIGURE 473-1 Climate change impacts a wide range of health outcomes. This figure illustrates the most significant climate change impacts (rising temperatures, more extreme weather, rising sea levels, and increasing carbon dioxide levels), their effect on exposures, and the subsequent health outcomes that can result from these changes in exposures. (Source: https://www.cdc.gov/climateandhealth/effects/default.htm.)

■ ■AIR POLLUTION AND SYNERGISTIC EFFECTS Asthma and Other Respiratory Ailments Climate change exacerbates the negative health effects of harmful air pollutants (e.g., particulate matter, ozone, sulfur dioxide, and nitrogen dioxide). While increases in fine particulate matter (<2.5 microns—PM2.5) are a func tion of wildfires and the burning of fossil fuels, the latter is the pre dominate driver of anthropogenic climate change. Exposure to ambient air pollution and/or indoor air pollution is estimated to cause 7 million premature deaths worldwide per year, making it the largest global envi ronmental risk factor for reversible death and disability (see Chap. 300 for an overview). Notably, air pollution from coal-burning power plants is associated with double the mortality risk when compared with other sources of PM2.5. By increasing ground-level ozone and/or particulate matter con centrations in some regions, the higher temperatures associated with climate change will directly increase the global burden and severity of asthma (Chap. 298), the respiratory effects of allergies (Chap. 363), rhi nosinusitis, chronic obstructive pulmonary disease (COPD), respira tory tract infections, interstitial lung disease, and lung cancer, resulting in increased hospital admissions and premature death. Figure 473-2 illustrates potential pathophysiologic mechanisms by which this may occur. Cardiovascular Disease Cardiovascular (CV) complications of climate change share similar mechanisms with climate-sensitive respiratory disease. Concentrations of PM2.5 are the most important environmental risk factor for myocardial infarction, cerebrovascular disease, heart failure, hypertension, diabetes mellitus, arrhythmias, and venous thromboembolism. Studies have shown that the relative risk of acute CV events is increased 1–3% in the setting of short-term elevations of PM2.5. Longer-term exposures convey an amplified risk (~10%), which is partially attributable to the exacerbation of chronic conditions (e.g., hypertension and diabetes). This holds true for areas with low mean Malaria, dengue, encephalitis, hantavirus, Rift Valley fever, Lyme disease, chikungunya, West Nile virus Severe Weather Air Pollution

M g s e in r Changes in Vector Ecology o u t is r a e r W R e

p E e m xt a e t r h T e e m r e l e v e S L e Increasing Allergens

a e O

R L r C c e is v n e in I l s Respiratory allergies, asthma g

Cholera, cryptosporidiosis, campylobacter, leptospirosis, harmful algal blooms

Ultrafine particles ROS Ca2+ TNF-α Activated T-cell MAPK NFKB AP-1 Cell barrier damage Innate immunity Adaptive immunity Oxidative stress Lung diseases Asthma, COPD, Lung cancer, Interstitial lung diseases, Lung fibrosis, Acute lung injury FIGURE 473-2 Mechanisms of ultrafine particle–induced respiratory health effects. (Reproduced from GD Leikauf et al: Mechanisms of ultrafine particleinduced respiratory health effects. Exp Mol Med 52:329, 2020.) concentrations of PM2.5 (i.e., where risk is determined by recurring short-term elevations). The biologic pathways whereby PM2.5 promotes these complications are complex and multifactorial (Fig. 473-3). PART 15 Disorders Associated with Environmental Exposures For clinicians, there are subtle management strategies to bear in mind for climate-sensitive CV disease. For example, in new heart fail ure patients, prescribers should be judicious about starting diuretics (especially diuretic-angiotensin–converting enzyme [ACE] inhibitor combinations) before the summer months or in

areas with increased heatwaves in order to avoid exacerbating dehydration or heat-related illness. These patients may also benefit from increasing potassium uptake. Figure 473-4 presents personal- and local-level interventions to reduce climate-sensitive disease associated with air pollution. Pregnancy Women exposed to high temperatures and air pollution may be more likely to experience serious adverse pregnancy outcomes. A systematic review of studies across diverse U.S. populations found a statistically significant association of PM2.5, ozone, and heat exposure with preterm birth, low birth weight at term, and stillbirth. As these environmental exposures become more common with climate change, an increased incidence of these complications is likely. Potential pathophysiologic mechanisms for these outcomes are mul tifactorial: preterm birth may result from hematogenous transport of inhaled PM2.5 and varied noxious chemicals and subsequent systemic inflammation or perturbation of the autonomic nervous system; low birth weight could be caused by the cumulative effect of alterations in maternal cardiac, pulmonary, and renal function, placental inflamma tion, and direct exposure to oxidative stress; and stillbirth may involve derangements in oxygen transport, DNA damage, and direct placental injury. Extreme heat events may lead to adverse pregnancy outcomes through dehydration and subsequent alterations in thermoregulation, blood viscosity, uterine blood flow, placental-fetal exchange, amniotic fluid volume, and hormone release (e.g., prostaglandin or oxytocin). These risks are disproportionately borne by black mothers. Thus, failure to reduce air pollution to the World Health Organization guide line level of 10 μg/m3 compounds structural racism. ■ ■HEAT-RELATED ILLNESSES Renal Disease Various populations of agricultural workers who labor in hot climates around the world have been noted to suffer from chronic kidney disease (CKD), even those without common risk fac tors such as diabetes mellitus, hypertension, glomerular disease, or HIV. Although the cause has not been identified, potential mechanisms

include genetic polymorphisms, nephrotoxicity secondary to agro chemicals or heavy metals, and heat-associated injury (Fig. 473-5). Heat Exhaustion and Heatstroke Please see Chap. 478 for an overview of heat-related illnesses. These include heat cramps, heat exhaustion, and heatstroke and can be expected to increase in incidence as temperatures rise. Certain communities suffer from sig nificant peaks in average temperature resulting from the urban heat island effect, which in the United States is related to policies such as redlining, racial covenants, and strategic underinvestment in neighbor hoods segregated through such policies. Possible preventive measures include developing clear heatwave strategies and establishing early warning systems, mapping vulnerable populations, enhancing green space, and providing cool-down zones. It is important that clinicians provide guidance about heat-related illnesses prior to the start of sum mer because waiting for heat warnings will not obviate risk. Medication storage is an issue, especially for those that are carried by patients (e.g., epinephrine injections, naloxone, insulin). There are some data to sug gest that exposure to extreme heat (e.g., leaving an albuterol inhaler in a vehicle on a hot day) can impair delivery mechanisms, degrade active ingredients of the medication, or cause inhalers to explode. ■ ■NATURAL DISASTERS, COASTAL FLOODING,

AND DISPLACEMENT Injury and Trauma While models predict fewer cyclones and hur ricanes in a warmer late-twenty-first-century climate, they do forecast events of higher average intensity, precipitation, and the number and occurrence days of very intense category 4 and 5 storms (Fig. 473-6). Such natural disasters would be expected to result in injuries and trauma seen in contemporary storms of high intensity (albeit with higher frequency), but there are other ways climate change will affect the inci dence of physical trauma. Studies have shown associations

between anomalously warm tem peratures and increased deaths from drownings (from people swim ming longer and more frequently), transportation accidents (driving performance worsens at higher temperatures and traffic increases), and assaults (potentially from increased alcohol consumption and illicit drug use). These deaths were partly offset by decreased falls, especially among the elderly, in warmer years. In addition, as more than half the world's population lives within 60 km of the ocean, rising sea levels will destroy homes, medical infra structure, and other essential services, including sewage treatment systems and drinking water supplies. In concert with climate impacts such as extreme heat and lack of freshwater, subsequent displacement and migration will lead to increased mental illness, food insecurity, and communicable disease. Finally, extreme sudden-onset events can affect the availability of medications through medical supply chain disruptions. Loss of electric ity during intense storms can also compromise vaccination programs and the availability of needed medications. For example, in 2024, Hur ricane Helene interrupted the production of essential parenteral drug products and intravenous (IV) fluids manufactured in North Carolina, resulting in nationwide shortages in the United States. Providers should ensure that patients with electricity-dependent medical devices have a reasonable contingency plan in case of power outages while noting that climate-related displacements can interrupt patients' access to medica tions for chronic diseases and limit access to clinical care in general. Mental Illness As of 2022, an estimated 108.4 million people (i.e., 1.4% of humanity) were forcibly displaced from their homes, mainly on account of violent conflict. It is expected that millions more will be displaced in response to the effects of climate change. This has ramifications for mental health (as do natural disasters) where resul tant psychosocial stress can lead to an increased incidence of anxiety, depression, and posttraumatic stress disorder (PTSD). Increased tem peratures have also been found to be associated with higher rates of suicide and domestic violence. Lastly, regarding clinical practice, many psychoactive prescription drugs can interfere with thermoregulation; their use therefore confers added risk during extreme heat events.

CNS Inflammation Neural Reflex Arc Direct Translocation Biologic Intermediates Autonomic Imbalance Endothelial Dysfunction Adhesion Molecules ↑ eNOS Uncoupling Impaired EPC Function ↑ NADPH Oxidase ↑ Proliferation ↑ Vasoconstriction ↓ Vasodilation ↑ Superoxide + ↑ Nitric Oxide ↑ Inflammation ↑ Peroxynitrite ↑ ROS and RNS Low-grade Inflammation Cardiometabolic Disease FIGURE 473-3 Biologic pathways whereby PM2.5 promotes cardiovascular events. (Reproduced with permission from S Rajagopalan: Air pollution and cardiovascular disease: JACC state-of-the-art review. J Am Coll Cardiol 72:2054, 2018.) ■ ■FOOD SECURITY AND OCEAN RESOURCES Malnutrition Climate change threatens food and nutritional secu rity through decreased crop yields in the setting of changes in precipi tation, desertification, severe weather events, temperature extremes, GHG emissions, ocean warming and acidification, coastal inundation affecting dryland agriculture and aquaculture, and increasing competi tion from weeds and pests (Fig. 473-7). Livestock and fish production are also projected to decline. For many, food will be less available, less nutritious, and more expensive. As chronic noncommunicable diseases, both undernutrition (Chap. 345) and obesity (Chap. 413)—which affect nearly 3 billion

Air Pollution Oxidative Stress Systemic Inflammation Thrombotic Pathways HPA Axis Activation CHAPTER 473 Platelet Activation ↑ TLR Macrophage Health Effects of Climate Change Thrombosis Activated Endothelium ↑ Fibrinogen MMP-2 MMP-9 ↑ Inflammatory cytokine ↑ NF-κB Smooth Muscle Proliferation ↑ people worldwide—share common drivers with climate change. Cur rent dietary practices (through land conversion and overconsumption of ruminant meats) contribute to

excess GHGs, decreases in biodiver sity, and depletion of water supplies. Variable rainfall and increased flooding, which can contaminate freshwater supplies, will make water security a defining challenge of this century. Plant-based diets have the potential to decrease GHG emissions; improve food security in LMICs; reduce mortality from stroke, type 2 diabetes mellitus, coronary heart disease, and cancer by 6–10%; and reduce diet-related GHGs by 29–70% by 2050 compared with a refer ence diet (Fig. 473-8).

• Switch coal-fired power plants to low-polluting renewable energy sources such as wind, tidal, geothermal, and solar. Shifting to clean fuels • Promote use of low-emission and zero-emission vehicles. Reduce sulfur content of motor fuels. Restrict trucks from city centers, encourage active transport (walking and cycling). SOCIETAL AND GOVERNMENTAL INTERVENTIONS PERSONAL INTERVENTIONS Transportation reform Reduce traffic emission(s) • Diesel particle traps, catalytic converters, alternative fuels (natural gas, electric cars) • Land-use assessment, minimum distances between sources and people, relocation of traffic sources (including major trafficked roads), avoidance of mixed-use areas (industrial-residential) Urban landscape reform • Revenues raised through taxes can be directed to pollution control. Emissions trading programs compensate companies who adhere to controls through credits that can be traded akin to carbon credits Emission trading programs Redirection of science and funding • Modifying priorities of climate change mitigation investments to a focus on near-term health co-benefits. Focus on the imminent near-term danger of health effects of air pollution. • Publicity and awareness campaigns through local data on air pollution within cities, counties Empowering civil society • Hard-hitting media campaigns akin to smoking on media to mitigate lobbying by industries involved in power and automobiles Governmental and NGOled publicity Face masks and air purifiers • Wearing face masks and installing air purifiers in homes PART 15 Disorders Associated with Environmental Exposures • Avoid commutes during rush hour Reduce in-traffic exposures Reduce in-home penetration of outdoor air pollution • Indoor air purifiers and closing windows; air conditioners Lifestyle changes and preventive medicine • Exercise and healthy diet • Preventive medications and screening programs FIGURE 473-4 Social ecological interventions to reduce exposures or susceptibility to air pollution. (Reproduced with permission from S Rajagopalan: Air pollution and cardiovascular disease: JACC state-of-the-art review. J Am Coll Cardiol 72:2054, 2018.) Dehydration and extracellular volume loss Hyperosmolarity (increased vasopressin and aldose reductase) Crystalluria (urate) Rhabdomyolysis Toxins and toxicants Pesticides Heavy metals Silica Other FIGURE 473-5 Possible mechanisms for the development of chronic kidney disease of unknown cause in agricultural communities. (Adapted from RJ Johnson et al: Chronic kidney disease of unknown cause in agricultural communities. N Engl J Med 380:1843, 2019. Copyright © 2019 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.)

Heat exposure lncreased core temperature Proximal tubular uptake of toxin from low renal blood flow Primary organ dysfunction Kidney inflammation and tubular injury Mesoamerican nephropathy

Present-day simulation

–15 –30 –45

A RCP4.5 late 21st century projection

–15 –30 –45

B Late 21st century minus present-day

–15 –30 –45

C FIGURE 473-6 Simulated occurrence of all tropical storms (tropical cyclones with winds exceeding 17.5 m s−1) for (A) present-day or (B) late-twenty-first-century (RCP4.5; CMIP5 multimodel ensemble) conditions; unit: storms per decade. Simulated tropical cyclone tracks were obtained using the Geophysical Fluid Dynamics Laboratory (GFDL) hurricane model to resimulate (at higher resolution) the tropical cyclone cases originally obtained from the HiRAM C180 global mode. Occurrence refers to the number of days, over a 20-year period, in which a storm exceeding 17.5 m s−1 intensity was centered within the 10° × 10° grid region. (C) Difference in occurrence rate between latetwenty-first century and present day [(B) minus (A)]. White regions are regions where no tropical storms occurred in the simulations [in (A) and (B)] or where the difference between the experiments is zero [in (C)]. (From TR Knutson et al: Global projections of intense tropical cyclone activity for the late twenty-first century from dynamical downscaling of CMIP5/RCP4.5 scenarios. J Clim 28:7203, 2015 © American Meteorological Society. Used with permission.) Average temperature & weather variability Air humidity Precipitation level Greenhouse gas emissions (GHG) Evapotranspiration rate Infectious diseases Climate/ weather Evaporation rate Precipitation index Soil moisture fertilizer Food crop yields Soil quality Food prices Labor capacity Food affordability Household income FIGURE 473-7 Complex pathways from climate/weather variability to undernutrition in subsistence farming households. The factors involved in and the probable impacts of weather variables on crop yields (blue arrows) and of food crop yields on undernutrition (red arrows). (Reproduced with permission from RK Phalkey et al: Climate change impacts on childhood undernutrition. Proc Natl Acad Sci USA 112:E4522, 2015.)

–20 –40 –60 –80 –100 –120 CHAPTER 473 Health Effects of Climate Change Health care Utilization rate Child undernutrion Rate of child malnutrition Household access to food Rate of malnutritionrelated child mortality Children’s quality of life Per capita food availability consumption & utilization Mothers’ quality of life Malnourished mothers Rate of maternal malnutrition Rate of malnutritionrelated maternal mortality

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474 Climate Change and Infectious Disease

Government actions/public policy shifts Effects Impact on human health Establish sustainable dietary guidelines Eliminate subsidies for commodity crops Add cost of environmental degradation to foods with high environmental footprint Reduce demand for beef Reduced meat consumption Shift to more plant-based diets Make improvements in urban design Eliminate subsidies for fossil fuels Increased use of public transportation Impact on climate change Reduced greenhouse gases FIGURE 473-8 Strategies to mitigate the impact of climate change on human nutrition. (Reproduced with permission of Journal of Clinical Investigation from Climate change and malnutrition: we need to act now. WH Dietz 130:556, 2020.) ■ ■INFECTIONS AND DIARRHEAL DISEASE (See Chap. 474.) POTENTIAL SOLUTIONS Reductions in GHG emissions will require health professionals to voice their evidence-based understandings of climate-sensitive pathologies to lobby for political action. Other important systemic interventions in health care include achieving universal health coverage (including financial risk protection); equitable access to quality essential health care services as well as safe, effective, and affordable medicines and vaccines; making health care and health systems net-zero carbon; add ing a climate-change lens to existing lines of research; improving data quality and enhancing, standardizing, and integrating data collection in LMICs; and anticipating and correcting disaster-related health care system failures, such as impacts to supply chains or loss of electric power resulting from extreme weather events. PART 15 Disorders Associated with Environmental Exposures Interventions related to environmental policy include advocat ing for a tighter particulate-matter air-quality standard, supporting institutional divestment from fossil fuels, and advocating for the rapid drawdown of emissions and negative emissions strategies. Ecosocial interventions, supported by national or global institutions, include the distribution of clean cookstoves globally, switching to plant-based diets, decreased air travel, reducing air conditioner use, and increased access to more public transportation. Finally, advocating for wealth-redistribution schemes (e.g., reparations, progressive taxation, debt cancellation, improved safety nets, underemployment insurance) to empower dis advantaged populations to cope with climate hazards will have positive ancillary effects on the social determinants of health, the administration of health services, and the outcomes of clinical interventions. CONCLUSIONS Without sweeping reductions in GHG emissions, over the next 50 to 100 years, models predict increases in average global temperature of 2–5°C (with localized highs), rising sea levels, and more frequent and severe extreme-weather events, with resultant

complications for population health globally. The hostile consequences of climate change will dis proportionately affect vulnerable and marginalized groups, particularly those whose ability to cope with climate hazards is curtailed by systemic racism, colonial legacies, illicit financial flows, and human rights failings. Health care professionals find themselves on the front line of the climate crisis and remain, in many settings, sources of information and counsel. In order to mitigate the impact of climate-sensitive diseases and resulting health disparities, they must continue to extend their clinical purview to socioecological determinants and structural interventions.

Reduced risk of cardiovascular disease, T2D, stroke, cancer, obesity Increased biking/walking Impact on nutrition Improved food security Preservation of protein and micronutrient content of crops Acknowledgment Paul Farmer contributed to this chapter in the 21st edition and some material from that chapter has been retained here. ■ ■FURTHER READING Bekkar B et al: Association of air pollution and heat exposure with preterm birth, low birth weight, and stillbirth in the US: A systematic review. JAMA Netw Open 3:e208243, 2020. Brief of Amici Curiae Public Health Experts, Public Health Organiza tion, and Doctors In Support of Plaintiffs-Appellees' Petition for Hearing En Banc, Juliana v. United States of America, No. 18-36082 (9th Cir. Mar. 13, 2020). Centers for Disease Control and Prevention: Climate Effects on Health. Available from https://www.cdc.gov/climateandhealth/effects/ default.htm. Accessed January 19, 2024. Hoffman JS et al: The effects of historical housing policies on resident exposure to intra-urban heat: A study of 108 US urban areas. Climate 8:12, 2020. The Lancet: Countdown on health and climate. Available at https:// www.thelancet.com/countdown-health-climate- Accessed January 19, 2024. The New England Journal of Medicine: Climate Change. Available from https://www.nejm.org/climate-crisis Accessed January 19, 2024. Rajagopalan S et al: Air pollution and cardiovascular disease: JACC state-of-the-art review. J Am Coll Cardiol 72:2054, 2018. Aaron S. Bernstein, Jonathan A. Patz

Climate Change and

Infectious Disease Since the late nineteenth century, humans have released greenhouse gases—mainly carbon dioxide and methane—into the atmosphere, creating a new climate unseen in human times. This new climate has already altered the epidemiology of infectious diseases, and the accu mulation of more greenhouse gases in the atmosphere will further alter the incidence and severity of infections. In certain instances, climate

change may establish conditions promoting the emergence of infec tious diseases, while in other instances, it may render areas that are presently suitable for certain diseases unsuitable. This chapter presents the current state of knowledge regarding the known and prospective infectious-disease consequences of climate change. OVERVIEW The term climate change refers to multidecadal alterations in temperature, precipitation, wind, humidity, and other components of weather outside of the natural climate variability seen in comparable time periods. Over the past 2.5 million years, the earth has warmed and cooled, cycling between glacial and interglacial periods during which average global tem peratures moved up and down by 4–7°C. During the last glacial period, which ended roughly 12,000 years ago, global temperatures were, on aver age, 5°C cooler than in the mid-twentieth century (Fig. 474-1). The present climate period, known as the Holocene, is remarkable for its stability: temperatures have largely remained within a range of 2–3°C. This stability has enabled the successful population and culti vation of much of the earth's

landmass by humanity. Current climate change differs from that in the past not only because its primary cause is human activities but also because its pace is faster. The current rate Observed warming Contributions to warming based on two complementary approaches (a) Observed warming 2010–2019 relative to 1850–1900 (b) Aggregated contributions to (c) Contributions to 2010–2019

2010–2019 warming relative

warming relative to 1850–1990,

to 1850–1990, assessed from

assessed from radiative

attribution studies

forcing studies °C 2.0 1.5 1.0 0.5 0.0 –0.5 –1.0 Internal variability Solar and volcanic drivers Other human drivers Well-mixed greenhouse gases Total human influence FIGURE 474-1 Assessed contributions to observed warming in 2010–2019 relative to 1850–1900. Assessed contributions to observed warming in 2010–2019 relative to 1850– 1900. A. Observed global warming (increase in global surface temperature). Whiskers show the very likely range. B. Evidence from attribution studies, which synthesize information from climate models and observations. Temperature change attributed to total human influence; changes in well-mixed greenhouse gas (GHG) concentrations; other human drivers due to aerosols, ozone, and land-use change (land-use reflectance); solar and volcanic drivers; and internal climate variability. Whiskers show likely ranges. C. Evidence from the assessment of radiative forcing and climate sensitivity. Temperature changes from individual components of human influence: emissions of GHGs, aerosols, and their precursors; land-use changes (land-use reflectance and irrigation); and aviation contrails. Whiskers show very likely ranges. Estimates account for both direct emissions into the atmosphere and their effect, if any, on other climate drivers. For aerosols, both direct effects (through radiation) and indirect effects (through interactions with clouds) are considered. (Used with permission from IPCC, 2021: Summary for Policymakers. In: Climate Change 2021: The Physical Science Basis. Contribution of Working Group I to the Sixth Assessment Report of the Intergovernmental Panel on Climate Change [V Masson-Delmotte et al (eds.)]. Cambridge University Press, Cambridge, United Kingdom and New York, NY, USA, pp. 3−32, doi:10.1017/9781009157896.001. Reproduced with permission of the Licensor through PLSclear.)

of warming on Earth is unprecedented in the last 50 million years. The 5°C of warming that occurred at the end of the last ice age about 12,000 years ago took roughly 5000 years, whereas such a temperature increment may occur within the next 150 years unless the release of greenhouse gases is substantially reduced in coming decades.

■ ■GREENHOUSE GASES Greenhouse gases (Table 474-1) are a group of gases in Earth’s atmo sphere that absorb infrared radiation and thus warm the planet. Essen tially, greenhouse gases act as a blanket on the earth to keep more of the sun’s solar radiation in the atmosphere. Carbon dioxide, released into the atmosphere primarily from fossil fuel combustion and defor estation, has had the greatest effect on climate since the Industrial Revolution. Other greenhouse gases, such as

methane, nitrous oxides, and fluorinated gases, are more potent than carbon dioxide, but make up a smaller proportion of greenhouse gases. Both carbon dioxide and methane have increased considerably from the nineteenth century until 2023, with methane concentrations more than doubling. Water vapor is the most abundant and a highly potent greenhouse gas but, given its short atmospheric life span and sensitivity to temperature, is not a major factor in recently observed warming. °C 2.0 °C 2.0 CHAPTER 474 1.5 1.5 1.0 1.0 Climate Change and Infectious Disease 0.5 0.5 0.0 0.0 –0.5 –0.5 –1.0 –1.0 Aviation contrails Land-use reflectance and irrigation Black carbon Ammonia Organic carbon Sulphur dioxide Volatile organic compounds and carbon monoxide Nitrogen oxides Halogenated gases Nitrous oxide Methane Carbon dioxide Mainly contribute to changes in anthropogenic aerosols Mainly contribute to changes in non-CO2 greenhouse gases

TABLE 474-1 Greenhouse Gases: Sources, Sinks, and Forcings GAS HUMAN SOURCES SINKa RADIATIVE FORCINGb (95% CONFIDENCE INTERVAL) Carbon dioxide (CO2) Fossil fuel combustion, deforestation Uptake by oceans (~30%), plants 1.68 (1.33–2.03) Methane (CH4) Fossil fuel production, ruminant animals, decomposition in landfills Hydroxyl radicals in the troposphere 0.97 (0.74–1.20) Nitrous oxide (N2O) Fertilizer, fossil fuel combustion, biomass burning,

livestock manure Halocarbons Refrigerants, electrical insulation, aluminum production Hydroxyl radicals in the troposphere, sunlight in the stratosphere aIn this table, a sink refers to the place where greenhouse gases are naturally stored or the mechanism through which they are destroyed. bRadiative forcing, measured in watts per meter squared, refers to how much an entity can alter the balance of incoming and outgoing radiation to and from Earth’s atmosphere. It is measured relative to a preindustrial (i.e., 1750) baseline. Greenhouse gases have a positive “forcing”; that is, on balance, they increase the amount of radiation (and specifically infrared radiation) that is retained in Earth’s atmosphere. Source: Intergovernmental Panel on Climate Change Fifth Assessment Report, Working Group 1, Chapter 8; American Chemical Society “Greenhouse gas sources and sinks,” available at www.acs.org/content/acs/en/climatescience/greenhousegases/sourcesandsinks.html. The atmosphere, some of the aerosols suspended in it, and clouds reflect a portion of incoming solar radiation back toward space. The remainder reaches Earth’s surface, where it is absorbed and some is emitted back into the atmosphere. The earth emits energy absorbed from the sun at longer wavelengths, primarily infrared, that green house gases can absorb. The change in wavelength that occurs as solar radiation is absorbed and re-emitted from the earth’s surface is funda mental to the greenhouse effect (Fig. 474-2). ■ ■TEMPERATURE Climate change has clearly caused global warming with the average surface temperature of Earth increasing 1.09°C from 1880 to 2020. Moreover, the rate of global warming is faster now than at any time in the last 1000 years. Yet, this mean warming fails to show that warming is occurring much faster in certain regions. The Arctic has warmed twice as fast overall, and winters are warming faster than summers. Nighttime minimum temperatures are also rising faster than daytime high temperatures. Each of these nuances bears upon the incidence of infectious diseases in general and vector-borne disease specifically. PART 15 Disorders Associated with Environmental Exposures Due to climate change, extreme heat waves are expected to be more common, longer, and more severe in the future. The hottest 5-year Incoming solar radiation 342 W m–2 Reflected solar radiation 107 W m–2

Reflected by clouds, aerosol and atmosphere

Reflected by the surface

Absorbed by the surface Thermals

FIGURE 474-2 Earth’s energy balance. (Kiehl’s Earth’s Annual Global Mean Energy Budget, Bulletin of the American Meteorological Society, Vol. 78, No. 2, 1997 (Figure 7, page 206). © American Meteorological Society. Used with permission.)

Photolysis in the stratosphere 0.17 (0.14–0.23) 0.18 (0.01–0.35) period ever recorded since records started in the mid-nineteenth cen tury was 2016–2020. Besides contributing directly to morbidity and mortality in human populations, heat waves wilt crops and are pre dicted to contribute substantially to agricultural losses. For example, the 2010 heat wave in Russia, which was unprecedented in its severity, contributed to hundreds of forest fires that generated enough air pol lution to kill an estimated 56,000 people and that burned 300,000 acres of crops, including roughly 25% of the nation’s wheat fields. Nutritional deficiencies underlie a substantial portion of the global burden of many infectious diseases. ■ ■PRECIPITATION In addition to changing temperature, the emission of greenhouse gases and the consequent increase in energy in Earth’s atmosphere have influenced the planet’s water cycle. Since 1950, substantial increases in the heavi est precipitation events (i.e., those above the 95th percentile) have been observed in Europe and North America. Moreover, in 2022, floods harmed an estimated 58 million people globally. Other areas have seen greater drought, notably southern Australia and the southwestern United States. A warmer atmosphere holds more water vapor. Specifically, air holds 6–7.5% more water vapor per degree (Celsius) of warming in the lower Outgoing longwave radiation 235 W m–2

Emitted by the atmosphere Atmospheric window

Absorbed by the atmosphere

Greenhouse gases Latent heat

Back radiation

Surface radiation Evapotranspiration

Absorbed by the surface

atmosphere. For areas that have traditionally had more precipitation on average, warming tends to promote heavier precipitation events. In contrast, in regions prone to drought, warming tends to result in greater periods between rainfalls and in the risk of drought. Floods and droughts have been associated with outbreaks of waterborne infectious diseases. ■ ■HURRICANES The world’s oceans have absorbed 90% of the excess heat that green house gases have kept in Earth’s atmosphere since the 1960s. Ocean heat provides energy for hurricanes, and warmer years tend to have greater hurricane activity. Stronger hurricanes (category 4 and 5) are expected with climate change, though climate change influence on hurricane frequency is uncertain. Modeling of future tropical cyclones suggests that their intensity may increase 2–11% by 2100 and that the average storm will bring 20% more rainfall. ■ ■SEA LEVEL RISE Between 1901 and 2010, the global sea level rose ~200 mm, or ~1.7 mm per year on average. From 1993 to 2010, the rate of rise nearly

dou bled—i.e., to 3.2 mm annually. Most of this sea level rise has resulted from the thermal expansion of water. Glacial ice melt is the second greatest factor, and its contribution is accelerating. By 2100, global sea level may rise by 0.8–2 m, with an annual rate of rise of 8–16 mm at the century's end. Sea level rise is not uniform. The rate of rise on the eastern seaboard of North America has been roughly double the global rate. Compounding sea level rise is the subsidence of coastal areas due to human settlement. In the absence of levee upgrades, an estimated 300 million people living near coasts worldwide will be at risk of flooding in 2050 because of the combined effects of subsidence, ero sion, and sea level rise. Along with extreme storms and overuse of coastal aquifers, rising seas also contribute to salinization of coastal groundwater. About 1 billion people rely on coastal aquifers for potable water. ■ ■EL NIÑO SOUTHERN OSCILLATION The El Niño Southern Oscillation (ENSO) refers to periodic changes in water tem perature in the eastern Pacific Ocean that occur roughly every 4–5 years. ENSO cycles have dramatic effects on weather around the globe. Warmer-than-aver age water temperatures in the eastern Pacific define El Niño events (see below), whereas cooler-than-average water tem peratures define La Niña periods. Evi dence is accruing that climate change may be increasing the frequency and severity of El Niño events. El Niño events drive alterations in weather worldwide (Fig. 474-3) and are associated with extreme events and con sequently higher rates of morbidity and mortality. Hurricane Mitch, one of the most powerful hurricanes ever observed, with winds reaching 290 km/h, dropped 1–1.8 m (3–6 feet) of rain over 72 h on parts of Honduras and Nicaragua. As a result of this storm, 11,000 people died and 2.7 million were displaced. FIGURE 474-3 Characteristic weather anomalies, by season, during El Niño events. (Source: Climate Prediction Center, https://www.cpc.ncep.noaa.gov/products/analysis_monitoring/impacts/warm_impacts.shtml.)

Outbreaks of cholera, leptospirosis, and dengue occurred in the storm's aftermath.

■ ■POPULATION MIGRATION AND CONFLICT The final common outcome of all climate-change effects is human dis placement. Sea level rise, extreme heat and precipitation, droughts, and salinization of water supplies all conspire to make regions, including some inhabited by humans for millennia, uninhabitable. The 8 million inhabitants of low-lying South Pacific islands are vulnerable to sea level rise and could be a major source of climate migrants. Climate change may also be contributing to humanitarian crises and conflicts. A severe 2011 drought in East Africa may have incited the Somali famine that resulted in 1 million refugees; mortality rates reached 7.4/10,000 in some refugee camps. EFFECTS OF CLIMATE CHANGE ON INFECTIOUS DISEASE The incidence of most, if not all, infectious diseases depends on cli mate. For any given infection, however, climate change is but one of many factors determining disease epidemiology. In instances in which climate change creates conditions favorable to the spread of infections, CHAPTER 474 Climate Change and Infectious Disease

diseases may be kept in check through interventions such as vector control or antibiotic treatment.

Detecting the influence of climate change amid the many compet ing forces that bear on infectious disease emergence and spread can be challenging. Research on animal pathogens, which in most instances are less intervened upon than that with their human counterparts, has suggested how climate change may independently influence disease spread. Avian malaria in Hawaii, for example, has clearly moved to higher elevations where warmer temperatures have enabled disease transmission. Many putative pathways have been identified that con nect greenhouse gas

emissions to infectious disease risk in people. Cli mate change influences extend beyond contagious diseases and include diseases from microbial toxins, such as those that result from harmful algal blooms. Warmer ocean temperatures cause Pseudonitzschia spp., blue–green cyanobacteria, and dinoflagellates to grow faster, resulting in concurrent disease outbreaks. ■ ■VECTOR-BORNE DISEASE Because insects are cold-blooded, ambient temperature dictates their geographic distribution. With increases in temperatures (in particular, nighttime minimum temperatures), insects are freed to move pole ward and up mountainsides. At the same time, as new areas become climatically suitable, current mosquito habitats may become unsuitable because of heat extremes. In addition, insects tend to be sensitive to water availability. Mos quitoes that transmit malaria, dengue, and other infections may breed in pools of water created by heavy downpours. As has been observed in the Amazon, breeding pools can also appear during periods of drought when rivers recede and leave behind stagnant pools of water for Anopheles mosquitoes. These circumstances have raised interest in the potentially favorable impact of water-cycle intensification on the spread of mosquito-borne disease. PART 15 Disorders Associated with Environmental Exposures Malaria • TEMPERATURE Higher temperatures promote higher mosquito-biting rates, shorter parasite reproductive cycles, and the potential for the survival of mosquito vectors of Plasmodium infection in locations previously too cold to sustain them. Modeling experiments have identified highland areas of East Africa and South America as perhaps most vulnerable to increased malarial incidence as a result of rising temperatures. In addition, an analysis of interannual malaria in Ecuador and Colombia has documented a greater incidence of malaria at higher altitudes in warmer years. Highland populations may be more vulnerable to malaria epidemics because they lack immunity. Although rising temperature has the potential to expand the viable range of disease, malaria incidence is not linearly associated with temperature. While mosquitoes and parasites may adapt to a warm ing climate, the present optimal temperature for malaria transmission is ~25°C, with a range of transmission temperatures between 16°C and 34°C. Rising temperatures can also have differential effects on parasite development during external incubation and on the mosqui toes' gonotrophic cycle. Asynchrony between these two temperaturesensitive processes has been shown to decrease the vectorial capacity of mosquitoes.1 PRECIPITATION The abundance of Anopheles mosquitoes is strongly correlated with the availability of surface-water pools for mosquito breeding, and biting rates have been linked to soil moisture (a surrogate for breeding pools). Research in the East African highlands has docu mented that increased variance in rainfall over time has strengthened the association between precipitation and disease incidence. These disease-promoting effects of precipitation may be countered by the potential for extreme rainfall to flush mosquito larvae from breeding sites. 1rVc is the vectorial capacity relative to the vector-to-human population ratio and is defined by the equation rVc = a2bhbme–µmn/µm where a is the vector bit ing rate; bh is the probability of vector-to-human transmission per bite; bm is the probability of human-to-vector infection per bite; n is the duration of the extrinsic incubation period; and µm is the vector mortality rate.

PROJECTIONS Climate models have begun to deliver output on regional scales, permitting projections of climate-suitable regions to assist national and local health authorities. Climate models speak to the temperature and precipitation ranges necessary for malaria transmis sion but do not account for the capacity of malaria control programs to halt the spread of disease. The global reduction in malaria distribution over the past century makes it clear that, even with climate change, malaria occurs in far fewer places today because of public health inter ventions. Recent vaccine trials also show promise in further reducing malaria risk. Despite intensive efforts, malaria

remains the single greatest vectorborne disease cause of morbidity and death in the world. Particularly in regions that are most affected by malaria and where the public health infrastructure is inadequate to contain it, climate modeling may pro vide a useful tool in determining where the disease may spread. Mod eling studies in sub-Saharan Africa have suggested that, although East African nations may encompass regions that will become more climati cally suitable for malaria over this century, West African nations may not. By 2100, temperatures in West Africa may largely exceed those optimal for malaria transmission, and the climate may become drier; in contrast, higher temperatures and changes in precipitation may allow malaria to move up the mountainsides of East African countries. Cli mate change may create conditions favorable to malaria in subtropical and temperate regions of the Americas, Europe, and Asia as well. Dengue Like malaria epidemics, dengue fever epidemics depend on temperature (Fig. 474-4). Higher temperatures increase the rate of larval development and accelerate the emergence of adult Aedes mos quitoes. The daily temperature range may also influence dengue virus transmission, with a smaller range corresponding to a higher trans mission potential. Temperatures <15°C or >36°C substantially reduce mosquito feeding. In a Rhesus model of dengue, viral replication can occur in as little as 7 days with temperatures of >32–35°C; at 30°C, rep lication takes ≥12 days; and replication does not reliably occur at 26°C. Research on dengue in New Caledonia has shown peak transmission at ~32°C, reflecting combined effects of a shorter extrinsic incubation period, a higher feeding frequency, and more rapid development of mosquitoes. Along with temperature, peak relative humidity is a strong predictor of dengue outbreaks. The association between dengue epidemics and precipitation is less consistent in the peer-reviewed literature, possibly because of the mos quito vector’s greater reliance on domestic breeding sites than on natu ral pools of water. For instance, in some studies, increased access to a piped water supply has been linked to dengue epidemics, presumably because of associated increased domestic water storage. Nonetheless, several studies have established rainfall as a predictor of the seasonal timing of dengue epidemics. The current global distribution of dengue largely overlaps the geographic spread of Aedes mosquitoes (Fig. 474-5). The presence of Aedes without dengue endemicity in large regions of North and South America and Africa illustrates the relevance of variables other than climate to disease incidence. Nevertheless, coupled climatic–epidemiologic modeling suggests dramatic shifts in the relative vectorial capacity for dengue by the end of this century should little or no mitigation of greenhouse gas emissions occur (Fig. 474-6). Other Arbovirus Infections Climate change may favor increased geographic spread of other arboviral diseases, including Zika virus disease, chikungunya virus disease, West Nile virus disease, and east ern equine encephalitis. Zika virus moved to the Western Hemisphere from French Polynesia around 2013 and rapidly spread in Brazil in 2016. Although air travel was essential for the delivery of the virus to the Americas, the available evidence suggests that the 2015 El Niño event provided an optimal climate for the infection to take root and spread (see “ENSO-Related Outbreaks,” below). Aedes aegypti is the primary vector for Zika virus. Chikungunya virus disease emerged in Italy in 2007, having previously been mostly a disease of African nations. Climate models predict that, should competent vectors be present, conditions will be suitable for the chikungunya virus to gain a foothold in Western Europe, especially France, in the first half of

Days (EIP length and development to adult)

Temperature (°C)

FIGURE 474-4 Effects of temperature on variables associated with dengue transmission. Shown are the number of days required for development of immature Aedes aegypti mosquitoes to adults, the length of the dengue virus type 2 extrinsic incubation period (EIP), the percentage of Ae. aegypti mosquitoes that complete a blood meal within 30 min after a blood source is made available, and the percentage of hatched Ae. aegypti larvae surviving to adulthood. (Reproduced from CW Morin et al: Climate and dengue transmission: Evidence and implications. Environ Health Perspect 121:1264, 2013.) the twenty-first century. In North America, areas favorable to West Nile virus outbreaks are expected to shift northward in this century. Current hotspots in North America are the California Central Valley, southwestern Arizona, southern Texas, and Louisiana, which have both compatible climates and avian reservoirs for the disease. By midcentury, the upper Midwest and New England will be more climatically suited to West Nile virus; by the end of the century, the area of risk may shift even further north to southern Canada. Whether the disease will ultimately move northward will depend on reservoir availability and mosquito control programs, among other factors. Lyme Disease In the past few decades, Ixodes scapularis, the primary tick vector for Lyme disease as well as for anaplasmosis and FIGURE 474-5 Distribution of Aedes aegypti mosquitoes (turquoise) and dengue fever epidemics (red). (Map produced by the Agricultural Research Service of the U.S. Department of Agriculture.)

babesiosis in New England, has become estab lished in Canada because of warming tempera tures. With climate change, the range of the tick is expected to expand further (Fig. 474-7).

Development to adult

EIP length Percent (survival to adult and blood fed) Blood fed

Survival to adult Lyme disease, caused by the spirochete Bor relia burgdorferi, is the most commonly reported vector-borne disease in North America, with ~60,000 cases annually. In Europe, Lyme disease has also increased and expanded geographically. Furthermore, the timing and peaks of cases have been affected, with the annual peak case numbers in 2019 arriving 6 weeks earlier than 25 years prior.

■ ■WATERBORNE DISEASE Many microorganisms, from bacteria to toxinproducing algae, cause waterborne disease (Table 474-2). The outbreaks of waterborne disease are associated with heavy rainfall events. A review of 548 waterborne disease outbreaks in the United States found that 51% were preceded by pre cipitation levels above the 90th percentile. Since 1900, most regions of the United States except the Southwest and Hawaii have experienced an increase in heavy downpours with the greatest intensification of the water cycle in New England and Alaska. Most disease outbreaks after heavy precipitation occur through contamination of drinking-water supplies. While outbreaks related to surface-water contamination generally occur within a month of the precipitation event, disease outbreaks from groundwater contamina tion tend to occur ≥2 months later. According to a review of published reports of waterborne disease outbreaks, Vibrio and Leptospira spe cies are the pathogens most commonly involved in the wake of heavy precipitation.

CHAPTER 474 Climate Change and Infectious Disease Combined Sewer Systems Roughly 40 million people in the United States and millions more around the world rely on combined sewer systems in which storm water and sanitary wastewater are conveyed in the same pipe to treatment facilities.

These systems were

A PART 15 Disorders Associated with Environmental Exposures B FIGURE 474-6 Trend of annually averaged global dengue epidemic potential (rVc). Differences in rVc are based on 30-year averages of temperature and daily temperature range. A. Differences between 1980–2009 and 1901–1930. B. Differences between 2070–2099 and 1980–2009. The mean value of rVc was averaged from five global climate models under RCP8.5, a scenario of high greenhouse-gas emission. The color bar describes the values of the rVc. (From J Liu-Helmersson et al: Vectorial capacity of Aedes aegypti: Effects of temperature and implications for global dengue epidemic potential. PLoS One 9:e89783, 2014.) designed based on the nineteenth-century climate, in which heavy downpours were less frequent than they are today. The frequency of combined sewer overflows usually into freshwater bodies and resulting in untreated sewage and runoff potentially containing heavy metals and pesticides, has been increasing in cities worldwide. For instance, the channel leading into Lake Michigan from Milwaukee had its high est levels of Escherichia coli, up to 100 times the Environmental Protec tion Agency guidance for recreational waters, after combined sewer overflows (Fig. 474-8). Rising Temperatures and Vibrio Species Warmer temperatures favor proliferation of Vibrio species and disease outbreaks, as has been demonstrated in countries surrounding the Baltic Sea, Chile, Israel, northwestern Spain, and the U.S. Pacific Northwest. Around the Baltic Sea, outbreaks of Vibrio infection may be particularly likely because of faster warming near the poles and the sea’s relatively low salt content. In the United States, levels of vibriosis roughly tripled from 1996–2010, with the highest number of cases occurring each summer. ENSO-Related Outbreaks Weather extremes tied to El Niño events afford a window into a climate-changed future. Recent evidence indicates that climate change itself may be strengthening El Niño events. These events tend to promote epidemic infections in certain regions (Fig. 474-9). Associations of El Niño with outbreaks of Rift Valley fever in east ern and southern Africa have been known since the 1950s. El Niño favors wet conditions suitable for the insect vectors of the disease

in these regions. Given the strong asso ciation between El Niño conditions and disease incidence, models have successfully predicted Rift Valley fever epidemics in humans and animals. In the 2006–2007 El Niño season, for example, outbreaks of Rift Valley fever were accurately predicted 2–6 weeks prior to epidemics in Somalia, Kenya, and Tanzania. 0.21 0.12 0.06 0.03 –0.03 El Niño has had inconsistent associations with malaria incidence in African countries. Some of the strongest associations between El Niño and malaria have been identified in South Africa and Swaziland, where available data on incidence are relatively robust; how ever, even in these instances, the observed increased risk did not reach statistical sig nificance. A stronger link to El Niño has been found in several studies done in South America. Research on malaria incidence in Colombia between 1960 and 2006 found that a 1°C temperature rise contributed to a 20% increase in incidence. –0.06 0.52 0.41 0.26 0.12 In the desert Southwest of the United States, hantavirus erupted following the strong El Niño of 1997. Unseasonal rain fall caused the desert to bloom, providing food resources and resulting in a boon to the mouse population. The following year saw the climate revert back to normal (arid) conditions, and as a result, increased human/mouse contact occurred as mice were forced to seek out food and nest in human dwellings. 0.06 0.03 –0.03 –0.06 –0.12 –0.26 –0.41 –0.52 In Bangladesh, a strong association has been observed between the El Niño Southern Oscillation Index and cholera epi demics. During El Niño, a combination of warmer sea-surface temperatures (SSTs) and rich nutrient runoff lead to phytoplank ton blooms detectable by satellite. These blooms, in turn, feed zooplankton, which can

harbor V. cholerae and, therefore, amplify their presence in the environment, causing cholera epidemics in the region (Fig. 474-10). El Niño years are often associated with an increased incidence of dengue. Research on dengue outbreaks in Thailand from 1996 to 2005 revealed that 15–22% of the variance in monthly dengue disease inci dence was attributable to El Niño. In South America, data on dengue outbreaks between 1995 and 2010 showed an increased incidence dur ing the El Niño events of 1997–1998 and 2006–2007. El Niño may have contributed to the emergence of Zika virus in the wake of a very strong ENSO event during the winter of 2015–2016. Temperatures throughout South and Central America were exception ally high and, just prior to the Zika epidemic, the vectorial capacity of Ae. aegypti was at its highest level compared with the previous 60 years. Not surprisingly (because carried by the same mosquito vector), large epidemics of dengue also occurred in Brazil and Colombia at that time. But laboratory studies show that the temperature optimum for Zika virus is 5°C warmer than for dengue. Thus, it is possible the extreme temperature played a role in the extent of the Zika epidemic. CLIMATE CHANGE, POPULATION DISPLACEMENT, AND INFECTIOUS DISEASE EPIDEMICS For many reasons, including freshwater shortages, flooding, food shortages, and climate change–driven conflicts, climate change has and will continue to put pressure on human populations to move. Human migrations have long been associated with epidemic disease in the

2000–2019 2000–2019 N A 2020–2049 2020–2049 N B F 2050–2079 2050–2079 N C G 2080+ 2080+ N D H = High risk = Moderate risk = Low risk = Risk of bird-borne ‘adventitious’ ticks only FIGURE 474-7 Risk maps for the occurrence of the Lyme disease vector Ixodes scapularis. Expansion of I. scapularis–affected census subdivisions (CSDs) in Canada from the present (using 1971–2000 temperature normals) to the 2080s (using temperature conditions predicted by the CGCM2 climate model under emissions scenario A2). In A–D (“slow” scenario), the model assumes that by the end of each time period, only risk CSDs with an algorithm value in the top 10% will contain an I. scapularis population. In E–H (“fast” scenario), the model assumes that by the end of each time period, all CSDs within the “moderate”-risk zone for I. scapularis establishment (risk CSDs) contain an I. scapularis population. For both scenarios, the time steps are 2000–2019, 2020–2049, 2050–2079, and 2080– 2109. “High”-risk regions for I. scapularis population establishment are indicated in red. “Moderate”-risk regions are in orange. “Low”-risk regions are in yellow. Regions with no risk of established populations but some risk from bird-borne “adventitious” ticks are in green. Regions with no predicted risk of either are colorless. (Used from NH Ogden: Risk maps for range expansion of the Lyme disease vector, Ixodes scapularis, in Canada now and with climate change. Int J Health Geogr 7:1, 2008.)

TABLE 474-2 Climate Sensitive Agents of Water-Related Illness PATHOGEN OR TOXIN PRODUCER EXPOSURE PATHWAY SELECTED HEALTH OUTCOMES AND SYMPTOMS Algae: Toxigenic marine species of Alexandrium, Pseudo-nitzschia, Dinophysis, Gambierdiscus; Karenia brevis Shellfish, fish Recreational waters (aerosolized toxins) Gastrointestinal and neurologic illness caused by shellfish poisoning (paralytic, amnesic, diarrhetic, neurotoxic) or fish poisoning (ciguatera). Asthma exacerbations, eye irritations caused by contact with aerosolized toxins (K. brevis). Cyanobacteria (multiple freshwater species producing toxins including microcystin) Drinking water Recreational waters Liver and kidney damage, gastroenteritis (diarrhea and vomiting), neurologic disorders, and respiratory arrest. Enteric bacteria and protozoan parasites: Salmonella enterica; Campylobacter

species; toxigenic Escherichia coli; Cryptosporidium; Giardia Drinking water Recreational waters Shellfish Enteric pathogens generally cause gastroenteritis. Some cases may be severe and may be associated with long-term and recurring effects. Enteric viruses: enteroviruses; rotaviruses; noroviruses; hepatitis A and E Drinking water Recreational waters Shellfish Most cases result in gastrointestinal illness. Severe outcomes may include paralysis and infection of the heart or other organs. Leptospira and Leptonema bacteria Recreational waters Mild to severe flu-like illness (with or without fever) to severe cases of meningitis, kidney, and liver failure. Vibrio bacteria species Recreational waters Shellfish Varies by species but include gastroenteritis (V. parahaemolyticus, V. cholerae), septicemia (bloodstream infection) through ingestion or wounds (V. vulnificus), skin, eye, and ear infections

(V. alginolyticus). Source: Climate impacts on water-related illness, in The Impacts of Climate Change on Human Health in the United States: A Scientific Assessment. U.S. Global Change Research Program, Washington, DC, 2016. https://health2016.globalchange.gov/water-related-illness. migrating populations themselves and in the communities in which they settle. The specific pathogens and patterns of disease that may appear after population migration relate to endemic diseases present in the migrant populations. PART 15 Disorders Associated with Environmental Exposures Large-scale migrations are common after extreme precipitation events. In August 2022, Pakistan experienced over three times the average rainfall, resulting in extensive flooding. Roughly 33 million people were affected, over 1400 people died, and 1.7 million homes were destroyed, all resulting in large-scale displacement. Additionally, standing water provided ideal breeding sites for vectors, and contami nated flood waters in two southern provinces led to outbreaks of diar rhea, cholera, and malaria. Accelerated computing power now allows 1e+5 1e+4 CFU/100 ml 1e+3 1e+2 1e+1 1e+0 CSO Rain with no CSO Base flow FIGURE 474-8 Levels of Escherichia coli in the Milwaukee estuary, which discharges to Lake Michigan, 2001–2007. Levels of E. coli in the Milwaukee estuary, which discharges to Lake Michigan, 2001–2007, during base flow (n = 46); following rain events with no CSO (n = 70); and following CSO events (n = 54). Boxes indicate 75% of values, with median values drawn in each. Whiskers are 95% of values, and outliers are shown as closed circles. There were significant differences in E. coli levels following rainfall and CSOs compared to base flow ($p \leq 0.05$). CFU, colony forming units; CSO, combined sewer overflow. (Reproduced with permission from JA Patz et al: Climate change and waterborne disease risk in the Great Lakes region of the U.S. Am J Prev Med 35:451, 2008.)

MAJOR CLIMATE CORRELATION

OR DRIVER (STRONGEST DRIVERS LISTED FIRST) Temperature (increased water temperature), ocean surface currents, ocean acidification, hurricanes (Gambierdiscus spp. and K. brevis) Temperature, precipitation patterns Temperature (air and water; both increase and decrease), heavy precipitation, and flooding Heavy precipitation, flooding, and temperature (air and water; both increase and decrease) Flooding, temperature (increased water temperature), heavy precipitation Temperature (increased water temperature), sea level rise, precipitation patterns (as it affects coastal salinity) for improved attribution of single weather events to climate change. For Pakistan, climate attribution analysis suggests that intense rainfall over short periods (5 days) has become more extreme with warming temperatures. In low- and middle-income countries, infectious disease outbreaks associated with population displacement may be harder to detect and respond to. People forced to leave their homes en masse are at risk for contracting infections with any

pathogen that may be present within the displaced population, including sexually transmitted diseases such as HIV, or airborne or droplet transmitted diseases such as tuberculosis and measles. Reducing disease risk requires overlaying of climaterelated migration risk with foci of disease epidemics. A BROADER VIEW OF CLIMATE

CHANGE AND HEALTH While climate change has far-reaching implications for the distribu tion and severity of infectious diseases worldwide, the greatest disease burdens related to climate change may not be due to infections, at least primarily. Climate change erodes the foundations of health, such as safe drinking water and food security, due to climatic extremes such as flooding or droughts. In addition, resource scarcity and climate instability are increasingly associated with conflicts. For example, severe droughts made more likely by climate change may have been a factor in the revolutions of the Arab Spring and the Syrian civil war. Of course, without adequate nutrition, water, or shelter, infectious disease risks rise. The public health response to climate change entails both mitiga tion and adaptation measures. Mitigation represents primary preven tion and involves the reduction of greenhouse gas emissions into the atmosphere. Although no clear safety threshold of greenhouse gas emissions has been agreed upon, in 2015 at the 21st Conference of the Parties (COP21) of the United Nations Framework Convention on Climate Change (UNFCCC) held in Paris, national governments from the major industrialized countries agreed to set a warming target of <2°C above preindustrial levels by 2050; the attainment of this goal will require reducing greenhouse gas emissions by 40–70% below 2010 levels. At COP21, a framework was established for a global carbon mar ket and nationally determined contributions (NDCs) for countries to commit to greenhouse gas reductions to meet the Paris Climate Agree ment. At the 2023 Conference of the Parties (COP28) held in Dubai,

HPS, PL MAL CHOL RVF DENG RI MAL FIGURE 474-9 Characteristic patterns of disease outbreaks associated with El Niño events, determined on the basis of 2006–2007 conditions. (From A Anyamba et al: Developing global climate anomalies suggest potential disease risks for 2006–2007. Int J Health Geogr 5:60, 2006.) for the first time the “need to transition from fossil fuels” was explicitly included in the final text of the agreement. Mitigation also confers health co-benefits, including better air qual ity and lower incidence and severity of respiratory infections, associ ated with less bio- or fossil fuel combustion. One study estimated that by eliminating air quality pollutants (PM 2.5, sulfur dioxide, nitrous oxides) from energy generation across the United States, >53,000 premature deaths would be avoided. Of note, evidence has shown that long-term air pollution exposure may contribute to mortality risk from COVID-19 and influenza. Dietary and agricultural changes can also afford climate change mitigation and improve human health.

Relevant Units Jan 98 Jan 99 Jan 2000 Jan 2001 Jan 2002

Relevant Units Jan 98 Jan 99 Jan 2000 Jan 2001 Jan 2002 FIGURE 474-10 Predicting cholera rates. Sea surface temperature, sea surface height, and chlorophyll-a predicting cholera in Bangladesh. Top graph illustrates environmental data detected by satellite measurements from the Bay of Bengal from January 1998–January 2002 and includes sea surface temperature (green line), sea surface height (blue line), and chlorophyll-a levels (yellow line), an indicator for the abundance of phytoplankton. Bottom graph illustrates the incidence rate of cholera (red) in Bangladesh over that time period. The black line combines the three environmental parameters and, superimposed over cholera incidence rate, shows a strong correlation. (Reproduced with permission from D Grimes et

al: Viewing marine bacteria, their activity and response to environmental drivers from orbit: Satellite remote sensing of bacteria. Microb Ecol 67:489, 2014.)

DENG–Dengue Fever RI–Respiratory Illness CHOL–Cholera MAL–Malaria RVF–Rift Valley Fever HPS–Hantavirus Pulmonary Syndrome PL–Plague CHOL DENG RI Resource-intensive foods, like red meat and dairy, can lead to higher cases of diabetes and cardiovascular disease, so switching to plantbased diets can improve human health and reduce greenhouse gas emissions. CHAPTER 474 Climate adaptation is secondary prevention and seeks to reduce harms associated with sea level rise, heat waves, floods, droughts, wildfires, and other greenhouse gas–driven events. The efficacy of adaptation is constrained by the challenges inherent in predicting the precise location, duration, and severity of extreme weather events and flooding related to sea level rise, among other considerations (Fig. 474-11). Climate Change and Infectious Disease Sea Surface Temperatures Sea Surface Heights Chlorophyll-a Levels Cholera Incident Rate Predicted Cholera Rate

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475 Altitude Illness

Strengthening Public and Political Support Implementing Policies for Mitigation (Primary Prevention) Improving the Public's Understanding of Climate Change Policymaking Process Energy Policy Building Movements for Addressing Climate Change Transportation Policy Agriculture Policy Promoting Climate Justice Increased Greenhouse Gas Levels Fossil Fuel Combustion Carbon Dioxide Other Greenhouse Gas Sources Methane Loss of Carbon Sinks Nitrous oxide Other GHGs FIGURE 474-11 Conceptual framework of climate change and its health impacts. (Reproduced with permission from JA Patz, BS Levy.) PART 15 Disorders Associated with Environmental Exposures ■ ■FURTHER READING Caminade C et al: Global risk model for vector-borne transmission of Zika virus reveals the role of El Niño 2015. Proc Natl Acad Sci USA 114:119, 2017. Colón-González FJ et al: The effects of weather and climate change on dengue. PLoS Negl Trop Dis 7:e2503, 2013. Glass GE et al: Satellite imagery characteristics local animal reservoir populations of Sin Nombre virus in the southwestern United States. Proc Natl Acad Sci USA 99:16817, 2002. Goren A et al: The emergence and shift in seasonality of Lyme bor reliosis in Northern Europe. Proc Biol Sci 290:20222420, 2023. Levy BS, Patz JA (eds): Climate Change and Public Health, 2nd ed. Oxford University Press, 2024. Mora C et al: Over half of known human pathogenic diseases can be aggravated by climate change. Nat Climate Change 12:869, 2022. Ogden NH: Risk maps for range expansion of the Lyme disease vec tor, Ixodes scapularis, in Canada now and with climate change. Int J Health Geogr 7:1, 2008. Paaijmans KP et al: Temperature-dependent pre-bloodmeal period and temperature-driven asynchrony between parasite development and mosquito biting rate reduce malaria transmission intensity. PLoS One 8:e55777, 2013. Patz JA et al: Impact of regional climate change on human health. Nature 438:310, 2005. Patz JA et al: Climate change and waterborne disease risk in the Great Lakes region of the U.S. Am J Prev Med 35:451, 2008. Ryan SJ et al: Warming temperatures could expose more than 1.3 billion new people to Zika virus risk by 2050. Glob Change Biol 27:84, 2021. Trtanj J et al: Climate impacts on water-related illness, in The Impacts of Climate Change on Human Health in the United States: A Scientific Assessment. U.S. Global Change Research Program, Washington, DC, 2016, pp 157–188.

Implementing Actions for Adaptation (Secondary Prevention) Implementing Health Adaptation *Also supports GHG mitigation Planning Healthy and Sustainable Built Environments* Promoting Nature-Based Climate Solutions* Health Impacts Climate Change Heat-related Disorders Temperature Rise Respiratory Disorders Sea-level Rise Vectorborne Diseases Hydrologic Extremes: Waterborne Diseases • Droughts Food Insecurity & Malnutrition • Floods Mental Health Impacts • Wildfires Violence Buddha Basnyat, Geoffrey Tabin, Steven Roy

Altitude Illness ■ ■EPIDEMIOLOGY Mountains cover one-fifth of the earth's surface; 140 million people live permanently at altitudes ≥2500 m, and 100 million people travel to high-altitude

locations each year. Skiers in the Alps or Aspen; tourists to La Paz, Ladakh, or Lahsa; religious pilgrims to Kailash-Manasarovar or Gosainkunda; trekkers and climbers to Kilimanjaro, Aconcagua, or Everest; miners working in high-altitude sites in South America; and military personnel deployed to high-altitude locations are all at risk of developing acute mountain sickness (AMS), high-altitude cerebral edema (HACE), high-altitude pulmonary edema (HAPE), and other altitude-related problems. AMS is the benign form of altitude illness, whereas HACE and HAPE are life-threatening. Altitude illness is likely to occur above 2500 m but has been documented even at 1500–2500 m. In the Mount Everest region of Nepal, ~50% of trekkers who walk to altitudes >4000 m over ≥5 days develop AMS, as do 84% of people who fly directly to 3860 m. The incidences of HACE and HAPE are much lower than that of AMS, with estimates in the range of 0.1–4%. Finally, reentry HAPE, which in the past was generally limited to highlanders (long-term residents of altitudes >2500 m) in the Americas, is now being seen in Himalayan and Tibetan highlanders—and often mis diagnosed as a viral illness—as a result of recent rapid air, train, and motorable-road access to high-altitude settlements. ■ ■PHYSIOLOGY Ascent to a high altitude subjects the body to a decrease in barometric pressure that results in a decreased partial pressure of oxygen in the inspired gas in the lungs. This change leads in turn to less pressure, driving oxygen diffusion from the alveoli and throughout the oxygen cascade. A normal initial “struggle response” to such an ascent includes increased ventilation—the cornerstone of acclimatization—mediated

by the carotid bodies. Hyperventilation may cause respiratory alkalosis and dehydration. Respiratory alkalosis may be extreme, with an arterial blood pH of >7.7 (e.g., at the summit of Everest). Alkalosis may depress the ventilatory drive during sleep, with consequent periodic breathing and hypoxemia. During early acclimatization, renal suppression of car bonic anhydrase and excretion of dilute alkaline urine combat alkalosis and tend to bring the pH of the blood to normal. Other physiologic changes during normal acclimatization include increased sympathetic tone; increased erythropoietin levels, leading to increased hemoglobin levels and red blood cell mass; increased tissue capillary density and mitochondrial numbers; and higher levels of 2,3-bisphosphoglycerate, enhancing oxygen utilization. Even with normal acclimatization, how ever, ascent to a high altitude decreases maximal exercise capacity (by ~1% for every 100 m gained above 1500 m) and increases susceptibility to cold injury due to peripheral vasoconstriction. If the ascent is made faster than the body can adapt to the stress of hypobaric hypoxemia, altitude-related disease states can result. ■ ■GENETICS Hypoxia-inducible factor, which acts as a master switch in highaltitude adaptation, controls transcriptional responses to hypoxia throughout the body and is involved in the release of vascular endothelial growth factor (VEGF) in the brain, erythropoiesis, and other pulmonary and cardiac functions at high altitudes. In particular, the gene EPAS1, which codes for transcriptional regulator hypoxiainducible factor 2α, appears to play an important role in the adaptation of Tibetans living at high altitude, resulting in lower hemoglobin con centrations than are found in Han Chinese or South American high landers. Other genes implicated include EGLN1 and PPARA, which are also associated with hemoglobin concentration. Some evidence indi cates that these genetic changes occurred within the past 3000 years, which is very fast in evolutionary terms. An intriguing question is whether the Sherpas’ well-known mountain-climbing ability is par tially attributable to their Tibetan ancestry, with overrepresentation of variants of EPAS. A striking recent finding is that some of these genetic characteristics may stem from those of Denisovan hominids who were contemporaries of the Neanderthals. For acute altitude illness, a single gene variant is unlikely to be found, but differences in the susceptibility of individuals and popula tions, familial clustering of cases, and a

positive association of some genetic variants all clearly support a role for genetics. ■ ■ACUTE MOUNTAIN SICKNESS AND HIGHALTITUDE CEREBRAL EDEMA AMS is a neurologic syndrome characterized by nonspecific symptoms (headache, nausea, fatigue, and dizziness), with a paucity of physical findings, developing 6–12 h after ascent to a high altitude. AMS is a clinical diagnosis. For uniformity in research studies, the Lake Louise Scoring System, created at the 1991 International Hypoxia Symposium, is generally used without the sleep disturbance score. AMS must be distinguished from exhaustion, dehydration, hypothermia, alcoholic hangover, and hyponatremia. AMS and HACE are thought to represent opposite ends of a continuum of altitude-related neurologic disorders. HACE (but not AMS) is an encephalopathy whose hallmarks are ataxia and altered consciousness with diffuse cerebral involvement but generally without focal neurologic deficits. Progression to these signal manifestations can be rapid. Papilledema and, more commonly, retinal hemorrhages may develop. In fact, retinal hemorrhages occur frequently at ≥5000 m, even in individuals without clinical symptoms of AMS or HACE. Risk Factors The most important risk factors for the development of altitude illness are the rate of ascent and a prior history of highaltitude illness. Exertion is a risk factor, but lack of physical fitness is not. An attractive but still speculative hypothesis proposes that AMS develops in people who have inadequate cerebrospinal capacity to buffer the brain swelling that occurs at high altitude. Children and adults seem to be equally affected, but people >50 years of age may be less likely to develop AMS than younger people. In general, there is no gender difference in AMS incidence. Sleep desaturation—a common

phenomenon at high altitude—is associated with AMS. Debilitating fatigue consistent with severe AMS on descent from a summit is an important risk factor for death in mountaineers. A prospective study involving trekkers and climbers who ascended to altitudes between 4000 and 8848 m showed that high oxygen desaturation and low venti latory response to hypoxia during exercise are independent predictors of severe altitude illness. However, because there may be a large overlap between groups of susceptible and nonsusceptible individuals, accu rate cutoff values are hard to define. Prediction is made more difficult because the pretest probabilities of HAPE and HACE are low. Neck irradiation or surgery damaging the carotid bodies, respiratory tract infections, and dehydration appear to be other potential risk factors for altitude illness. Unless guided by clinical signs and symptoms, pulse oximeter readings alone on a trek should not be used to predict AMS.

Pathophysiology Hypobaric hypoxia is the main trigger for alti tude illness. In established AMS, raised intracranial pressure, increased sympathetic activity, relative hypoventilation, fluid retention and redistribution, and impaired gas exchange have all been well noted; these factors may play an important role in the pathophysiology of AMS. Severe hypoxemia can lead to a greater than normal increase in cerebral blood flow. However, the exact mechanisms underlying AMS and HACE are unknown. Evidence points to a central nervous system process. Magnetic resonance imaging (MRI) studies have sug gested that vasogenic (interstitial) cerebral edema is a component of the pathophysiology of HACE. In the setting of high-altitude illness, the MRI findings shown in Fig. 475-1 are confirmatory of HACE, with increased signal in the white matter and particularly in the sple nium of the corpus callosum. In addition, hemosiderin deposits in the corpus callosum have been characterized as long-lasting footprints of HACE. Quantitative analysis in an MRI study revealed that hypoxia is associated with mild vasogenic cerebral edema irrespective of AMS. This finding is in keeping with case reports of suddenly symptomatic brain tumors and of cranial nerve palsies without AMS at high alti tudes. Vasogenic edema may become cytotoxic (intracellular) in severe HACE. CHAPTER 475 Altitude Illness Impaired cerebral autoregulation in the presence of hypoxic

cerebral vasodilation and altered permeability of the blood-brain barrier due to hypoxia-induced chemical mediators like histamine, arachidonic acid, and VEGF may all contribute to brain edema. In 1995, VEGF was first proposed as a potent promoter of capillary leakage in the brain at FIGURE 475-1 T2 magnetic resonance image of the brain of a patient with highaltitude cerebral edema (HACE) shows marked swelling and a hyperintense posterior body and splenium of the corpus callosum (area with dense opacity). The patient, a climber, went on to climb Mount Everest about 9 months after this episode of HACE. (From B Basnyat et al: Clinical images. A mystery. Wilderness Environ Med 15: 53, 2004. Reused with permission from the Wilderness Medical Society. ©2004 Wilderness Medical Society.)

high altitude, and studies in mice have borne out this role. Although studies of VEGF in climbers have yielded inconsistent results regard ing its association with altitude illness, indirect evidence of a role for this growth factor in AMS and HACE comes from the observation that dexamethasone, when used in the prevention and treatment of these conditions, blocks hypoxic upregulation of VEGF. Other factors in the development of cerebral edema may be the release of calciummediated nitric oxide and neuronally mediated adenosine, which may promote cerebral vasodilation. Venous outflow obstruction resulting in increased brain capillary pressure is also thought to play an impor tant role in the development of HACE. Lesions in the globus pallidum (which is sensitive to hypoxia) leading to Parkinson’s disease have been reported to be complications of HACE.

The pathophysiology of the most common and prominent symptom of AMS—headache—remains unclear because the brain itself is an insensate organ; only the meninges contain trigeminal sensory nerve fibers. The cause of high-altitude headache is multifactorial. Various chemicals and mechanical factors activate a final common pathway, the trigeminovascular system. In the genesis of high-altitude headache, the response to nonsteroidal anti-inflammatory drugs and glucocorticoids provides indirect evidence for involvement of the arachidonic acid pathway and inflammation. Prevention and Treatment (Table 475-1) Gradual ascent, with adequate time for acclimatization, is the best method for the preven tion of altitude illness. Even though there may be individual variation in the rate of acclimatization, a conservative approach would be a graded ascent of ≤300 m from the previous day’s sleeping altitude above 3000 m, and taking every third day of gain in sleeping altitude as an extra day for acclimatization is helpful. Spending one night at an inter mediate altitude before proceeding to a higher altitude may enhance acclimatization and attenuate the risk of AMS. Another protective fac tor in AMS is recent high-altitude exposure; for example, the incidence PART 15 Disorders Associated with Environmental Exposures TABLE 475-1 Management of Altitude Illness CONDITION MANAGEMENT Acute mountain sickness (AMS), milda Discontinuation of ascent Treatment with acetazolamide (250 mg q12h) Descentb AMS, moderatea Immediate descent for worsening symptoms Use of low-flow oxygen if available Treatment with acetazolamide (250 mg q12h) and/or dexamethasone (4 mg q6h)c Hyperbaric therapyd High-altitude cerebral edema (HACE) Immediate descent or evacuation Administration of oxygen (2–4 L/min) Treatment with dexamethasone (8 mg PO/IM/IV; then 4 mg q6h) Hyperbaric therapy if descent is not possible High-altitude pulmonary edema (HAPE) Immediate descent or evacuation Minimization of exertion while patient is kept warm Administration of oxygen (4–6 L/min) to bring O2 saturation to >90% Adjunctive therapy with nifedipinee (30 mg, extended-release, q12h) Hyperbaric therapy if descent is not possible aCategorization of cases as mild or moderate is a subjective judgment based on the severity of headache and the presence and severity of other manifestations (nausea, fatigue, dizziness). bNo fixed altitude is specified; the patient should

descend to a point below that at which symptoms developed. cAcetazolamide treats and dexamethasone masks symptoms. For prevention (as opposed to treatment) of AMS, 125 mg of acetazolamide q12h or (when acetazolamide is contraindicated— e.g., in people with a history of sulfa anaphylaxis) 4 mg of dexamethasone q12h may be used. dIn hyperbaric therapy (Fig. 475-2), the patient is placed in a portable altitude chamber or bag to simulate descent. eNifedipine at this dose is also effective for the prevention of HAPE, as are tadalafil (10 mg twice daily), sildenafil (50 mg three times per day), and dexamethasone (8 mg twice daily). Preventative therapy should be continued for about 3 days after arriving at the target altitude. If prompt descent follows arrival at target altitude, continuation of preventative therapy is unnecessary.

and severity of AMS at 4300 m are reduced by 50% with an ascent after 1 week at an altitude ≥2000 m rather than with an ascent from sea level. However, regarding the benefits of acclimatization, clear-cut randomized studies are lacking. Repeated exposure at low altitudes to hypobaric or normobaric hypoxia is termed preacclimatization. Preac climatization is gaining popularity with commercially available normo baric hypoxia “tents” used for weeks to months in preparation for the climb. However, current evidence has not shown significant effects of such technology. Clearly, a flexible itinerary that permits additional rest days will be helpful. Sojourners to high-altitude locations must be aware of the symptoms of altitude illness and should be encouraged not to ascend further if these symptoms develop. Any hint of HAPE (see below) or HACE mandates descent. Proper hydration (but not overhydration) in high-altitude trekking and climbing, aimed at countering fluid loss due to hyperventilation and sweating, may play a role in avoiding AMS. Pharmacologic prophylaxis at the time of travel to high altitudes is warranted for people with a history of AMS or when a graded ascent and acclimatization are not possible—e.g., when rapid ascent is neces sary for rescue purposes or when flight to a high-altitude location is required. Acetazolamide is the drug of choice for AMS prevention. It inhibits renal carbonic anhydrase, causing prompt bicarbonate diuresis that leads to metabolic acidosis and hyperventilation. Acetazolamide (125 mg twice daily), administered for 1 day before ascent and con tinued for about 3 days at the same altitude, is effective. Treatment can be restarted if symptoms return after discontinuation of the drug. Higher doses are not required. A meta-analysis limited to randomized controlled trials revealed that 125 mg of acetazolamide twice daily was effective in the prevention of AMS, with a relative-risk reduc tion of ~48% from values obtained with placebo. Paresthesia and a tingling sensation are common side effects of acetazolamide. Some other uncommon side effects are myopia and drowsiness. This drug is a nonantibiotic sulfonamide that has low-level cross-reactivity with sulfa antibiotics; as a result, severe reactions are rare. Dexamethasone (8 mg/d in divided doses) is also effective. A large-scale, randomized, double-blind, placebo-controlled trial in partially acclimatized trekkers clearly showed that Ginkgo biloba is ineffective in the prevention of AMS. In randomized studies, ibuprofen (600 mg three times daily) has been shown to be beneficial in the prevention of AMS. Recently, acet aminophen (1 g three times daily) was as effective as ibuprofen at the above dosage in a randomized, double-blind study, which did not have a placebo arm. However, more definitive studies are needed to clarify whether these medications mask the symptoms of altitude illness or whether they prevent the pathophysiology of AMS and assess the risk profile of side effects before these drugs can be routinely recommended for AMS prevention. Many drugs, including spironolactone, medroxy progesterone, magnesium, calcium channel blockers, and antacids, confer no benefit in the prevention of AMS. Starkly conflicting results from a number of trials of inhaled budesonide for the prevention of AMS have recently been published, but, in all likelihood, the drug is ineffective.

Similarly, no efficacy studies are available for coca leaves (a weak form of cocaine), which are offered to high-altitude travelers in the Andes, or for soroche pills, which contain aspirin, caffeine, and acetaminophen and are sold over the counter in Bolivia and Peru. Finally, a word of caution applies in the pharmacologic prevention of altitude illness. A fast-growing population of climbers in pursuit of a summit are injudiciously using prophylactic drugs such as gluco corticoids in an attempt to improve their performance; the outcome can be tragic because of potentially severe side effects of these drugs, especially if taken for a long duration. For the treatment of mild AMS, rest alone with analgesic use may be adequate. Descent and the use of acetazolamide and (if available) oxy gen are sufficient to treat most cases of moderate AMS. Even a minor descent (400–500 m) may be adequate for symptom relief. For moder ate AMS or early HACE, dexamethasone (4 mg orally or parenterally) is highly effective. For HACE, immediate descent is mandatory. When descent is not possible because of poor weather conditions or darkness, a simulation of descent in a portable hyperbaric chamber (Fig. 475-2) can be very effective. Pressurization in the bag for 1–2 h often leads

FIGURE 475-2 A hyperbaric bag. The cylindrical, portable (<7 kg) nylon bag has a one-way valve to prevent carbon dioxide buildup. A patient with severe acute mountain sickness (AMS), high-altitude cerebral edema (HACE), or high-altitude pulmonary edema (HAPE) is zipped inside the bag, which is continuously inflated with a foot pedal. The increased barometric pressure (2 psi) inside the bag simulates descent; for example, at 4250 m, the equivalent “elevation” inside the bag is ~2100 m. No supplemental oxygen is required. to spectacular improvement and, like dexamethasone administration, “buys time.” Thus, in certain high-altitude locations (e.g., remote pil grimage sites), the decision to bring along the lightweight hyperbaric chamber may prove lifesaving. Like nifedipine, phosphodiesterase-5 inhibitors have no role in the treatment of AMS or HACE. Finally, short-term oxygen inhalation using small cannisters of oxygen or by visiting oxygen bars is unhelpful in the prevention of AMS. ■ ■HIGH-ALTITUDE PULMONARY EDEMA Risk Factors and Manifestations Unlike HACE (a neurologic disorder), HAPE is primarily a pulmonary problem and therefore is not necessarily preceded by AMS. HAPE develops within 2–4 days after arrival at high altitude; it rarely occurs after >4 or 5 days at the same altitude, probably because of remodeling and adaptation that render the pulmonary vasculature less susceptible to the effects of hypoxia. A rapid rate of ascent, a history of HAPE, respiratory tract infections, and cold environmental temperatures are risk factors. Men are more susceptible than women. People with abnormalities of the cardiopul monary circulation leading to pulmonary hypertension—e.g., mitral stenosis, primary pulmonary hypertension, and unilateral absence of the pulmonary artery—may be at increased risk of HAPE, even at moderate altitudes. Although patent foramen ovale, a common condi tion, is four times more common among HAPE-susceptible individu als than in the general population, there is no compelling evidence to suggest causal effect. Echocardiography is recommended when HAPE develops at relatively low altitudes (<3000 m) and whenever cardio pulmonary abnormalities predisposing to HAPE are suspected. The differential diagnosis of HAPE includes anxiety attack, pneumonia, pneumothorax, and pulmonary embolism. The initial manifestation of HAPE may be a reduction in exercise tolerance greater than that expected at the given altitude. Although a dry, persistent cough may presage HAPE and may be followed by the production of blood-tinged sputum, cough in the mountains is almost universal and the mechanism is poorly understood. Tachypnea and tachycardia, even at rest, are important markers as illness progresses. Crackles may be heard on auscultation but are not diagnostic. HAPE may be accompanied by signs of HACE. Patchy or localized opaci ties (Fig. 475-3) or streaky interstitial edema may be noted on chest

radiography. In the past, HAPE was mistaken for pneumonia due to the cold or for heart failure due to hypoxia and exertion. Kerley B lines or a bat-wing appearance are not seen on radiography. Electro cardiography may reveal right ventricular strain or even hypertro phy. Hypoxemia and respiratory alkalosis are consistently present in patients with HAPE. Alkalemia is often present, unless the patient is

FIGURE 475-3 Chest radiograph of a patient with high-altitude pulmonary edema shows opacity in the right middle and lower zones simulating pneumonic consolidation. The opacity cleared almost completely in 2 days with descent and supplemental oxygen. taking acetazolamide, in which case metabolic acidosis may super vene. Assessment of arterial blood gases is not necessary in the evalu ation of HAPE; an oxygen saturation reading with a pulse oximeter is generally adequate. The existence of a subclinical form of HAPE has been suggested by an increased alveolar-arterial oxygen gradient in Everest climbers near the summit, but hard evidence correlating this abnormality with the development of clinically relevant HAPE is lack ing. Comet-tail scoring—an ultrasound technique initially validated in cardiogenic pulmonary edema—has been used for evaluation of extravascular lung water at high altitude. However, B-lines are not just seen in patients with HAPE and are frequently detected in individuals who never go on to develop clinical HAPE. For this reason, comet-tail scoring is sensitive but not specific for HAPE, and clinical correlation is important. CHAPTER 475 Altitude Illness Pathophysiology HAPE is a noncardiogenic pulmonary edema with normal pulmonary artery wedge pressure. It is characterized by patchy pulmonary hypoxic vasoconstriction that leads to overperfu sion in some areas. This abnormality leads in turn to increased pul monary capillary pressure (>18 mmHg) and capillary “stress” failure. The exact mechanism for this hypoxic vasoconstriction is unknown. Endothelial dysfunction due to hypoxia may play a role by impairing the release of nitric oxide, an endothelium-derived vasodilator. At high altitude, HAPE-prone persons have reduced levels of exhaled nitric oxide. The effectiveness of phosphodiesterase-5 inhibitors in allevi ating altitude-induced pulmonary hypertension, decreased exercise tolerance, and hypoxemia supports the role of nitric oxide in the patho genesis of HAPE. One study demonstrated that prophylactic use of tadalafil, a phosphodiesterase-5 inhibitor, decreases the risk of HAPE by 65%. In contrast, the endothelium also synthesizes endothelin-1, a potent vasoconstrictor whose concentrations are higher than average in HAPE-prone mountaineers. Exercise and cold lead to increased pulmonary intravascular pres sure and may predispose to HAPE. In addition, hypoxia-triggered increases in sympathetic drive may lead to pulmonary venoconstric tion and extravasation into the alveoli from the pulmonary capillaries. Consistent with this concept, phentolamine, which elicits α-adrenergic blockade, improves hemodynamics and oxygenation in HAPE more than do other vasodilators. The study of tadalafil cited above also inves tigated dexamethasone in the prevention of HAPE. Surprisingly, dexa methasone reduced the incidence of HAPE by 78%—a greater decrease than with tadalafil. Besides possibly increasing the availability of endo thelial nitric oxide, dexamethasone may have altered the excessive sym pathetic activity associated with HAPE: the heart rate of participants in the dexamethasone arm of the study was significantly lowered. Finally, people susceptible to HAPE also display enhanced sympathetic activity during short-term hypoxic breathing at low altitudes. Because many patients with HAPE have fever, peripheral leukocy tosis, and an increased erythrocyte sedimentation rate, inflammation

has been considered an etiologic factor in HAPE. However, strong evidence suggests that inflammation in HAPE is an epiphenomenon rather than the primary cause. Nevertheless,

inflammatory processes (e.g., those elicited by viral respiratory tract infections) do predispose persons to HAPE—even those who are constitutionally resistant to its development.

Another proposed mechanism for HAPE is impaired transepithelial clearance of sodium and water from the alveoli. β-Adrenergic agonists upregulate the clearance of alveolar fluid in animal models. In a single double-blind, randomized, placebo-controlled study of HAPE-suscep tible mountaineers, prophylactic inhalation of the β-adrenergic agonist salmeterol reduced the incidence of HAPE by 50%. However, the dos age of salmeterol (125 μg twice daily) used was very high, which could result in excessive tachycardia and tremors. Other effects of β agonists may also contribute to the prevention of HAPE, and these findings are in keeping with the concept that alveolar fluid clearance may play a pathogenic role in this illness. Prevention and Treatment (Table 475-1) Allowing sufficient time for acclimatization by ascending gradually (as discussed above for AMS and HACE) is the best way to prevent HAPE. Sustained-release nifedipine (30 mg), given twice daily, prevents HAPE in people who must ascend rapidly or who have a history of HAPE. Other drugs for the prevention of HAPE are listed in Table 475-1 (footnote e). Although dexamethasone is listed for prevention, its adverse effect profile requires close monitoring. Acetazolamide has been shown to blunt hypoxic pulmonary vasoconstriction in animal models, and this observation warrants further study in HAPE prevention. However, one large study failed to show a decrease in pulmonary vasoconstric tion in partially acclimatized individuals given acetazolamide. Inhaled salmeterol is not recommended as clinical experience with this drug is limited at high altitude. Finally, potent diuretics like furosemide should be avoided in the treatment of HAPE. Early recognition is para mount in the treatment of HAPE, especially when it is not preceded by the AMS symptoms of headache and nausea. Fatigue and dyspnea at rest may be the only initial manifestations. Descent and the use of supplementary oxygen (aimed at bringing oxygen saturation to >90%) are the most effective therapeutic interventions. Exertion should be kept to a minimum, and the patient should be kept warm. Hyperbaric therapy (Fig. 475-2) in a portable altitude chamber may be lifesav ing, especially if descent is not possible and oxygen is not available. Oral sustained-release nifedipine (30 mg twice daily) can be used as adjunctive therapy. No studies have investigated phosphodiesterase-5 inhibitors in the treatment of HAPE, but reports have described their use in clinical practice. The mainstays of treatment remain descent and (if available) oxygen. PART 15 Disorders Associated with Environmental Exposures In AMS, if symptoms abate (with or without acetazolamide), the patient may reascend gradually to a higher altitude. Unlike that in acute respiratory distress syndrome (another noncardiogenic pulmonary edema), the architecture of the lung in HAPE is usually well preserved, with rapid reversibility of abnormalities (Fig. 475-3). This fact has allowed some people with HAPE to reascend slowly after a few days of descent and rest. In HACE, reascent after a few days may not be advis able during the same trip. ■ ■OTHER HIGH-ALTITUDE PROBLEMS Sleep Impairment The mechanisms underlying sleep problems, which are among the most common adverse reactions to high altitude, include increased periodic breathing; changes in sleep architecture, with increased time in lighter sleep stages; and changes in rapid eye movement sleep. Sojourners should be reassured that sleep qual ity improves with acclimatization. In cases where drugs do need to be used, acetazolamide (125 mg before bedtime) is especially use ful because this agent decreases hypoxemic episodes and alleviates sleeping disruptions caused by excessive periodic breathing. Whether combining acetazolamide with temazepam or zolpidem is more effec tive than administering acetazolamide alone is unknown. In com binations, the doses of temazepam and zolpidem should not be increased by >10 mg at high altitudes. Limited evidence suggests that

diazepam causes hypoventilation at high altitudes and therefore is con traindicated. For trekkers with obstructive sleep apnea who are using a continuous positive airway pressure (CPAP) machine, the addition of acetazolamide, which will decrease centrally mediated sleep apnea, may be helpful. There is evidence to show that obstructive sleep apnea at high altitude may decrease and “convert” to central sleep apnea. Gastrointestinal Issues High-altitude exposure may be associ ated with increased gastric and duodenal bleeding, but further studies are required to determine whether there is a causal effect. Because of decreased atmospheric pressure and consequent intestinal gas expan sion at high altitudes, many sojourners experience abdominal bloating and distension as well as excessive flatus expulsion. In the absence of diarrhea, these phenomena are normal, if sometimes uncomfortable. Accompanying diarrhea, however, may indicate the involvement of bacteria or Giardia parasites, which are common at many high-altitude locations in the developing world. Prompt treatment with fluids and empirical antibiotics may be required to combat dehydration in the mountains. Hemorrhoids are common on high-altitude treks; treat ment includes hot soaks, application of hydrocortisone ointment, and measures to avoid constipation. High-Altitude Cough High-altitude cough can be debilitating and is sometimes severe enough to cause rib fracture, especially at

> 5000 m. The etiology of this common problem is probably multifac torial. Although high-altitude cough has been attributed to inspiration of cold dry air, this explanation appears not to be sufficient by itself; in long-duration studies in hypobaric chambers, cough has occurred despite controlled temperature and humidity. The implication is that hypoxia also plays a role. Exercise can precipitate cough at high alti tudes, possibly because of water loss from the respiratory tract. In gen eral, infection does not seem to be a common etiology. Many trekkers find it useful to wear a balaclava to trap some moisture and heat. In most situations, cough resolves upon descent. High-Altitude Neurologic Events Unrelated to “Altitude Illness” Transient ischemic attacks (TIAs) and strokes have been well described in high-altitude sojourners outside the setting of altitude sickness. However, these descriptions are not based on cause (hypoxia) and effect. In general, symptoms of AMS present gradually, whereas many of these neurologic events happen suddenly. The population that suffers strokes and TIAs at sea level is generally an older age group with other risk factors, whereas those so afflicted at high altitudes are gener ally younger and probably have fewer risk factors for atherosclerotic vascular disease. Other mechanisms (e.g., migraine, vasospasm, focal edema, hypocapneic vasoconstriction, hypoxia in the watershed zones of minimal cerebral blood flow, or cardiac right-to-left shunt) may be operative in TIAs and strokes at high altitude. Subarachnoid hemorrhage, transient global amnesia, delirium, and cranial nerve palsies (e.g., lateral rectus palsy) occurring at high altitudes but outside the setting of altitude sickness have been well described. Syncope is common at moderately high altitudes, gener ally occurs shortly after ascent, usually resolves without descent, and appears to be a vasovagal event related to hypoxemia. Seizures occur rarely with HACE, but hypoxemia and hypocapnia, which are prevalent at high altitudes, are well-known triggers that may

> contribute to new or breakthrough seizures in predisposed individuals. Nevertheless, the consensus among experts is that sojourners with well-controlled seizure disorders can ascend to high altitudes. Finally, persons with hypercoagulable conditions (e.g., antiphos pholipid syndrome, protein C deficiency) who are asymptomatic at sea level may experience cerebral venous thrombosis (possibly due to enhanced blood viscosity triggered by polycythemia and dehydration) at high altitudes. Proper history taking, examination, and prompt investigations where possible will help define these conditions as enti ties separate from altitude sickness. Administration of oxygen (where available) and prompt descent are the cornerstones of treatment of most of these neurologic conditions. Ocular Problems Ocular issues are common in sojourners to high altitudes. Hypoxemia induced by altitude leads to increased retinal

blood flow, which can be visible as engorged retinal veins on ophthal moscopic examination. Both high flow and hypoxemic vascular dam age causing permeability have been implicated in a breakdown of the blood-retina barrier and the formation of retinal hemorrhages. Blot, dot, flame, and white-centered hemorrhages can be observed. These hemorrhages usually resolve spontaneously with descent, with only mild symptoms and no lasting visual damage in most healthy eyes. The exception is hemorrhage in the macular area. Macular hemor rhages can cause devastating initial visual loss, particularly if bilateral, and have been reported to cause permanently decreased vision in a few cases. Stroke syndromes such as retinal vein occlusion, retinal artery occlusion, ischemic optic neuropathy, and cortical visual loss have all been reported. With unilateral vision loss, it is always important to check for a relative afferent pupillary defect. Increased hematocrit combined with dehydration may contribute to these maladies. Glauco matous optic nerve damage may progress with hypoxemia of altitude. Acetazolamide is helpful both in combating the respiratory alkalosis that comes with increased ventilation at high altitude and in lower ing the interocular pressure; its use should be considered in patients with stable controlled glaucoma. Macular degeneration and diabetic eye disease are not directly exacerbated by ascent to high altitude. Dry eye and solar damage to the cornea, known as “snow blindness,” are common. Wearing of high-quality UV-blocking sunglasses, even on cloudy days, and attention to protecting and supplementing the tear film with artificial tear drops can greatly improve comfort and vision. Although modern refractive surgeries, such as photorefractive keratec tomy (PRK) and laser in situ keratomileusis (LASIK), are stable at high altitude, patients who have undergone radial keratotomy should be cautioned that hypoxemia to the cornea can lead to swelling that shifts the refraction during ascent. Psychological/Psychiatric Problems Delirium characterized by a sudden change in mental status, a short attention span, disorga nized thinking, and an agitated state during the period of confusion has been well described in mountain climbers and trekkers without a prior history. In addition, anxiety attacks, often triggered at night by excessive periodic breathing, are well documented. The contribution of hypoxia to these conditions is unknown. Expedition medical kits need to include antipsychotic injectable drugs to control psychosis in patients in remote high-altitude locations. ■ ■PREEXISTING MEDICAL ISSUES Because travel to high altitudes is increasingly popular, common con ditions such as hypertension, coronary artery disease, and diabetes are more frequently encountered among high-altitude sojourners. This situation is of particular concern for the millions of elderly pilgrims with medical problems who visit high-altitude

sacred areas (e.g., in the Himalayas) each year. In recent years, high-altitude travel has attracted intrepid trekkers who are taking immunosuppressive medications (e.g., kidney transplant recipients or patients undergoing chemotherapy). Recommended vaccinations and other precautions (e.g., hand wash ing) may be especially important for this group. Although most of these medical conditions do not appear to influence susceptibility to altitude illness, they may be exacerbated by ascent to altitude, exertion in cold conditions, and hypoxemia. Advice regarding the advisability of high-altitude travel and the impact of high-altitude hypoxia on these preexisting conditions is becoming increasingly relevant, but there are no evidence-based guidelines. In addition, recommendations made for relatively low altitudes (~3000 m) may not hold true for higher altitudes (>4000 m), where hypoxic stress is greater. Personal risks and benefits must be clearly thought through before ascent. Hypertension At high altitudes, enhanced sympathetic activity may lead to a transient rise in blood pressure. Occasionally, nonhyper tensive, healthy, asymptomatic trekkers have pathologically high blood pressure at high altitude that rapidly normalizes without medicines on descent. Sojourners should continue to take their antihypertensive medications at high altitudes. Importantly, hypertensive patients are not more likely than others to develop altitude illness. Because the

probable mechanism of high-altitude hypertension is α-adrenergic activity, anti-α-adrenergic drugs such as prazosin have been suggested for symptomatic patients and those with labile hypertension. It is best to start taking the drug several weeks before the trip and to carry a sphygmomanometer if a trekker has labile hypertension. Sustainedrelease nifedipine may also be useful. A recent observational cohort study of 672 hypertensive and nonhypertensive trekkers in the Hima layas showed that most travelers, including those with well-controlled hypertension, can be reassured that their blood pressure will remain relatively stable at high altitude. Although blood pressure may be extremely elevated at high altitude in normotensive and hypertensive people, it is unlikely to cause symptoms.

Coronary Artery Disease Myocardial oxygen demand and maxi mal heart rate are reduced at high altitudes because the VO2 max (maximal oxygen consumption) decreases with increasing altitude. This effect may explain why signs of cardiac ischemia or dysfunction usually are not seen in healthy persons at high altitudes. Asymptom atic, fit individuals with no risk factors need not undergo any tests for coronary artery disease before ascent. For persons with ischemic heart disease, previous myocardial infarction, angioplasty, and/or bypass surgery, an exercise treadmill test is indicated. A strongly positive treadmill test is a contraindication for high-altitude trips. Patients with poorly controlled arrhythmias should avoid high-altitude travel, but patients with arrhythmias that are well controlled with antiarrhyth mic medications do not seem to be at increased risk. Sudden cardiac deaths are not noted with a greater frequency in the Alps than at lower altitudes; although sudden cardiac deaths are encountered every trek king season in the higher Himalayan range, accurate documentation is lacking. CHAPTER 475 Cerebrovascular Disease Patients with TIAs should avoid travel to high altitude for at least 3 months. Patients with known cerebral aneurysm should also avoid high-altitude travel because of possible rupture of the aneurysm due to increased cerebral blood flow at high altitude. Altitude Illness Migraine Trekkers with a history of migraine may have an increased likelihood of suffering from AMS and may also be predisposed to headaches including altered character of their migraine presenting with focal neurologic deficits. Oxygen inhalation may reduce AMStriggered headache, whereas a migraine headache usually persists even after 10–15 min of oxygen inhalation. Asthma Although cold air and

exercise may provoke acute bron choconstriction, asthmatic patients usually have fewer problems at high than at low altitudes, possibly because of decreased allergen levels and increased circulating catecholamine levels. Nevertheless, asthmatic individuals should carry all their medications, including oral gluco corticoids, with proper instructions for use in case of an exacerbation. Severely asthmatic persons should be cautioned against ascending to high altitudes. Pregnancy In general, low-risk pregnant women ascending to 3000 m are not at special risk except for the relative unavailability of medical care in many high-altitude locations, especially in developing coun tries. Despite the lack of firm data on this point, venturing higher than 3000 m to altitudes at which oxygen saturation drops steeply seems unadvisable for pregnant women. Obesity Although living at a high altitude has been suggested as a means of controlling obesity, obesity has also been reported to be a risk factor for AMS, probably because nocturnal hypoxemia is more pro nounced in obese individuals. Hypoxemia may also lead to greater pul monary hypertension, thus possibly predisposing the trekker to HAPE. Sickle Cell Disease High altitude is one of the rare environmental exposures that occasionally provokes a crisis in persons with sickle cell anemia. Even when traversing mountain passes as low as 2500 m, peo ple with sickle cell anemia have been known to have a vaso-occlusive crisis. Patients with known sickle cell anemia who need to travel to high altitudes should use supplemental oxygen and travel with caution. Thalassemia has not been known to cause problems at high altitude.

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Diabetes Mellitus Well-controlled diabetes is not a contraindi cation for travel to high altitude. Most of the high-altitude diabetes advice is based on patients with type 1 diabetes and not type 2 diabetic patients with comorbidities. Altitude is known to both increase and decrease insulin sensitivity. An eye examination before travel may be useful. Insulin pumps are increasingly used, but bubble formation in the system may need to be closely monitored. For most diabetic patients, a continuous glucose monitor (CGM) is likely the best choice for glucose monitoring in the high-altitude environment, but a reliable glucometer should be carried by all diabetic patients. Regard less of the glucose monitoring modality selected, patients should be comfortable with the plan and transition appropriately. It is important for companions of diabetic trekkers to be fully aware of potential prob lems like hypoglycemia and have ready access to sweets.

Chronic Lung Disease Depending on disease severity and access to medical care, preexisting lung disease may not always preclude high-altitude travel. A proper pretravel evaluation must be conducted. Supplemental oxygen may be required if the predicted PaO2 for the alti tude is <50–55 mmHg. Preexisting pulmonary hypertension may also need to be assessed in these patients. If the result is positive, patients should be discouraged from ascending to high altitudes; if such travel is necessary, treatment with sustained-release nifedipine (30 mg twice a day) should be considered. Small-scale studies have revealed that when patients with bullous disease reach ~5000 m, bullous expansion and pneumothorax are not noted. Compared with information on chronic obstructive pulmonary disease, fewer data exist about the safety of travel to high altitude for people with pulmonary fibrosis, but acute exacerbation of pulmonary fibrosis has been seen at high altitude. A handheld pulse oximeter can be useful to check for oxygen saturation. PART 15 Disorders Associated with Environmental Exposures Chronic Kidney Disease Patients with chronic kidney disease can tolerate short-term stays at high altitudes, but theoretical concern persists about progression to end-stage renal disease. Acetazolamide, the drug most commonly used for altitude sickness, should be avoided by anyone with preexisting metabolic acidosis, which can be exacer bated by this drug. In addition, the acetazolamide dosage should be adjusted when the glomerular filtration rate falls to <50 mL/min, and the drug should not be used at all if this value falls to <10 mL/min. Cirrhosis Of patients with cirrhosis, 16% may have portopul monary arterial hypertension, and 32% may have hepatopulmonary syndrome; these conditions may be detrimental at high

altitude as they may cause exaggerated hypoxemia. Thus, screening for these problems is important in cirrhotic patients planning a high-altitude trip. In addi tion, acetazolamide may be inadvisable in these patients as the drug may increase the risk of hepatic encephalopathy. COVID-19 Evaluation is warranted before planned high-altitude travel in individuals who required care in an intensive care unit or suffered from myocarditis or arterial or venous thromboembolism. Preparticipation evaluation is also warranted in patients with persistent symptoms at least 2 weeks after a positive COVID-19 test or hospital discharge. Depending on the results of this evaluation, planned highaltitude travel may need to be modified or even deferred pending resolution of the identified abnormalities. Dental Problems Air resulting from decay in the root system could expand on ascent and lead to increasing pain. A good dental checkup before a trekking or climbing trip may be prudent. Malignancy Patients with current or previous malignancy may be affected in a variety of ways by altitude. Both radiation of the neck or paraganglioma/chemodectomas (which are seen at higher rates in residents of high-altitude areas) may result in carotid body dysfunction and reduced acclimatization. Pulmonary toxicities from chemothera pies (e.g., bleomycin) and radiation of the chest increase pulmonary artery pressures and impair lung function, theoretically increasing the risk of HAPE and decreasing exercise tolerance. Some chemotherapies such as bleomycin have traditionally been thought to increase suscep tibility of lung tissue to oxygen toxicity and may complicate the use

of supplemental oxygen, if needed. Cardiotoxic therapies for cancer decrease exercise tolerance and increase cardiovascular disease. Such patients will be at increased cardiovascular risk with strenuous activ ity or hypoxic stress that is expected at altitude. Patients with known metastasis to bone or those at high risk should be evaluated prior to expedition travel. ■ ■CHRONIC MOUNTAIN SICKNESS AND HIGHALTITUDE PULMONARY HYPERTENSION IN HIGHLANDERS The largest populations of highlanders live in the South American Andes, the Tibetan Plateau, and parts of Ethiopia. Chronic mountain sickness (Monge’s disease) is a disease in highlanders that is character ized by excessive erythrocytosis with moderate to severe pulmonary hypertension leading to cor pulmonale. This condition was origi nally described in South America and has also been documented in Colorado and in the Han Chinese population in Tibet; it is much less common in Tibetans or in Ethiopian highlanders. Migration to a low altitude results in the resolution of chronic mountain illness. Venesec tion and acetazolamide are helpful. High-altitude pulmonary hypertension is also a subacute disease of long-term high-altitude residents. Unlike Monge’s disease, this syndrome is characterized primarily by pulmonary hypertension (not erythrocytosis) leading to heart failure. Indian soldiers living at extreme altitudes for prolonged periods and Han Chinese infants born in Tibet have presented with the adult and infantile forms, respectively. High-altitude pulmonary hypertension bears a striking pathophysi ologic resemblance to brisket disease in cattle. Descent to a lower alti tude is curative. ■ ■FURTHER READING Basnyat B: High altitude pilgrimage medicine. High Alt Med Biol 15:434, 2014. Basnyat B, Murdoch D: High altitude illness. Lancet 361:1967, 2003. Hillebrandt D et al: UIAA medical commission recommendations for mountaineers, hillwalkers, trekkers, and rock and ice climbers with diabetes. High Alt Med Biol 24:110, 2023. Keyes LE et al: Blood pressure and altitude: An observational cohort study of hypertensive and nonhypertensive Himalayan trekkers in Nepal. High Alt Med Biol 18:267, 2017. Luks AM et al: Return to high altitude after recovery from coronavirus disease 2019. High Alt Med Biol 22:119, 2021. Luks AM et al: Wilderness Medical Society clinical practice guidelines for the prevention, diagnosis, and treatment of acute altitude illness: 2024 update. Wilderness Environ Med 35:2S, 2024. Patterson RD, Roy S: High altitude illnesses, in Mountain Emergency Medicine, H

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Hyperbaric and Diving

Medicine Hyperbaric medicine is the treatment of certain health disorders using whole-body exposure to pressures >101.3 kPa (1 atmosphere or 760 mmHg). In practice, this invariably includes breathing oxygen during the exposure, thus the administration of hyperbaric oxygen therapy (HBO2T). The Undersea and Hyperbaric Medical Society (UHMS) defines HBO2T as “a medical procedure requiring a physi cian’s prescription and oversight” in which “patients must have their entire body placed within a hard sided hyperbaric chamber that meets

FIGURE 476-1 A monoplace chamber. The chamber is compressed with 100% oxygen. Although direct patient access is not possible, intravenous administration of fluids and drugs, ventilation, and invasive monitoring can be performed. (Prince of Wales Hospital, Sydney.) the American Society of Mechanical Engineers and Pressure Vessels for Human Occupancy (ASME-PVHO-1) code, and the National Fire Protection Agency (NFPA 99) code and standards for hyperbaric chambers, at a pressure of not less than 2.0 atmospheres absolute (ATA) (202.65 kPa) while breathing physician prescribed medical grade oxy gen for an amount of time that is typically between 90-120 minutes per treatment.” Historically, compression chambers were first used for the treatment of divers and compressed air workers suffering decompression sickness (DCS; “the bends”). Now they are used for treating a variety of prob lems, and relevant chambers are variously called a hyperbaric chamber, recompression chamber, or decompression chamber, depending on the clinical and historical context. They may be capable of compress ing a single patient (a monoplace chamber) or multiple patients and attendants as required (a multiplace chamber) (Figs. 476-1 and 476-2). In multiplace chambers, the chamber atmosphere is pressurized with air and the patient breathes oxygen through a special delivery system. The same may be true of monoplace chambers, although in some, the chamber environment is pressurized with oxygen and the patient sim ply breathes from that environment. ■ ■MECHANISMS OF HYPERBARIC

OXYGEN THERAPY In the late 1800s, the earliest systematic use of pressure as a thera peutic modality was in treating decompression sickness, a disorder caused by bubbles in blood or tissues. The use of pressure (recom pression) to instantly reduce bubble size made mechanistic sense FIGURE 476-2 A multiplace chamber. Multiplace chambers are compressed with air; 100% oxygen is administered via head tent, mask, or endotracheal tube. These chambers can treat several patients simultaneously and can easily accommodate critically ill and intubated patients. (Karolinska University Hospital.)

and met with obvious clinical success when instituted. In the 1960s, oxygen breathing during hyperbaric exposure was incorporated into recompression protocols to increase the diffusion gradient for inert gas from bubble to tissue to blood and alveoli. This too appeared to improve outcomes. Recompression of divers is further discussed under “Diving Medicine.”

Use of HBO2T in nondiving disease focused initially on indica tions such as carbon monoxide poisoning, nonhealing wounds, and radiation tissue injury, where it was believed that hypoxia was a fundamental contributory problem and that hyperbaric oxygen could ameliorate this. Indeed, breathing oxygen at hyperbaric pressures not only ensures complete saturation of hemoglobin in

blood but also results in markedly elevated quantities of dissolved oxygen in arte rial plasma at a very high Po2. Most HBO2T regimens involve oxygen breathing at between 203 and 284 kPa (2 and 2.8 ATA). Breathing oxygen at 284 kPa (2.8 ATA) can theoretically increase the arterial Po2 to more than ~270 kPa (~2025 mmHg) and the volume of oxygen dissolved in plasma to ~60 mL/L, with the latter being sufficient to sustain life without hemoglobin as proven in animal studies. The very high arte rial Po2 markedly improves oxygen diffusion distances through tissues. As with pressure and oxygen breathing for bubble disorders in diving, the use of markedly elevated plasma oxygen levels in treating hypoxic wounds and irradiated tissue also met with apparent success, initially reinforcing the belief that intermittent support of oxygen-dependent healing processes such as fibroblast replication, collagen deposition and cross-linking, and angiogenesis was the principal mechanism by which HBO2T could be helpful. As important as this mechanism may be, more recent research has revealed that intermittent hyperbaric hyperoxia has physical and biochemical/cell signaling effects that extend well beyond simple sup port of oxygen-dependent healing processes and the duration of the hyperbaric exposure. Indeed, there are pharmacologic effects that are profound and relatively long-lasting. Some of these are summarized in Fig. 476-3. CHAPTER 476 Hyperbaric and Diving Medicine Thus, although removal from the hyperbaric chamber results in a rapid return of poorly vascularized tissues to their hypoxic state, even a single dose of HBO2T produces changes in fibroblast, leukocyte and angiogenic functions, and antioxidant defenses that persist many hours after oxygen tensions are returned to pretreatment levels. Explanations for this effect focus on production of reactive oxygen species (ROS) such as superoxide (O_2 –), hydrogen peroxide (H_2O_2), and reactive nitrogen species (RNS) such as nitric oxide (NO) during exposure to hyperbaric hyperoxia. It appears that these species, often considered harmful in biological tissues, participate in diverse cell signaling path ways involved in production of a range of cytokines, angiogenic growth factors, and other modulators of inflammation and tissue repair whose net effect is to accelerate healing. Such mechanisms are complex and at times apparently paradoxical. For example, it is well established by in vitro and in vivo studies that notionally proinflammatory pulses of oxidative stress induced by hyperbaric hyperoxia actually result in subsequent anti-inflammatory effects such as reduced leukocyte β2 integrin adhesion molecule expression, an effect that may be protective when flaps and grafts are threatened or if endothelium is damaged by circulating bubbles. Most of the important indications for HBO2T are now recognized as benefiting in some way from activity in these cell signaling pathways. For example, when used to treat chronic hypoxic wounds, HBO2T has been shown to enhance bacterial killing and phagocytosis by providing the oxygen substrate for macrophage activity; stimulate the synthesis of multiple angiogenic growth factors; inhibit leukocyte activation and adherence to damaged endothelium; and mobilize pluripotent vasculo genic progenitor cells from the bone marrow. The interactions between these mechanisms remain a very active field of investigation. Figure 476-3 also depicts several other mechanisms of action that may be relevant in certain situations. Hyperoxia tends to induce vaso constriction and that, along with the exaggerated standing osmotic gra dient between an ultra-high Po2 in arteriolar blood and the much lower Po2 in tissues, may reduce tissue edema. Hyperoxia is also directly toxic or bacteriostatic to anaerobic bacteria.

Hyperbaric oxygen Enhanced inert gas diffusion gradients between bubble, tissue, and lungs High arterial PO_2 Hydrostatic compression Bubble volume reduction Enhanced O_2 diffusion Generation of ROS and RNS Osmotic effect Restoration of tissue normoxia Enhanced phagocytosis, angiogenesis, and fibroblast activity DCS CAGE Wound healing, radiation tissue injury PART 15

Disorders Associated with Environmental Exposures FIGURE 476-3 Mechanisms of action of hyperbaric oxygen. There are many consequences of compression and oxygen breathing. The cell-signaling effects are potentially most important. Examples of indications are shown in the shaded boxes. CAGE, cerebral arterial gas embolism; DCS, decompression sickness; RNS, reactive nitrogen species; ROS, reactive oxygen species. ■ ■INDICATIONS FOR HYPERBARIC

OXYGEN THERAPY The “accepted” indications for HBO2T are evolving and sometimes controversial. In 1977, the UHMS systematically examined claims for the use of HBO2T in >100 disorders and found sufficient evidence to support routine use in only 12. The Hyperbaric Oxygen Therapy Committee of that organization has continued to update this list periodically (to the current list of 15) (Table 476-1) with an increas ingly formalized system of appraisal for new indications and emerging evidence. Around the world, other relevant medical organizations have generally taken a similar approach. However, accepted indications vary considerably—particularly those recommended by hyperbaric medical societies in Russia and China where HBO2T has gained much wider support than in the United States, Europe, and Australasia. Nevertheless, there are now >30 Cochrane reviews summarizing the randomized trial evidence for 27 putative indications, and numerous other systematic reviews, including attempts to examine the costeffectiveness of HBO2T. Following are short reviews of three important indications currently accepted by the UHMS, and a brief summary of several exploratory indications. Late Radiation Tissue Injury Radiotherapy is a well-established treatment for suitable malignancies. In the United States alone, ~300,000 individuals annually will become long-term survivors of can cer treated by irradiation. Developments in radiotherapy techniques such as intensity-modulated radiation therapy and hypofractionated stereotactic radiation therapy have improved the precision of radiation delivery. This has allowed the use of higher doses of radiation with better cure rates, but the incidence of radiation-related complica tions has not changed much. Serious radiation-related complications developing months or years after treatment (late radiation tissue injury [LRTI]) will significantly affect between 5 and 10% of long-term sur vivors, although incidence varies widely with dose, age, and site. LRTI may involve bone or soft tissue and is most common in the head and neck, chest wall, breast, and pelvis (where it may involve the bowel or bladder).

Hyperoxic vasoconstriction Edema reduction Anti-inflammatory effects e.g. ↓β2 integrins ↑Wound growth factors Stem cell mobilization Threatened grafts/flaps DCS CAGE Crush injury PATHOLOGY AND CLINICAL COURSE One explanation for long-term injury to irradiated tissue is that initial radiation exposure produces fibrosis and an obliterative endarteritis from which the tissue may be incapable of recovering because of its hypovascular hypoxic nature. Indeed, its microvascularity may continue to deteriorate slowly over months to years with breakdown occasionally occurring spontane ously or when accelerated by an event like trauma or surgery. An alternative model of pathogenesis suggests that rather than a primary hypoxic state, the principal trigger is an overexpression of inflamma tory cytokines that promote fibrosis, probably through oxidative stress and mitochondrial dysfunction, with tissue hypoxia as a secondary provocation. Ultimately, and once again often triggered by a further physical insult such as surgery or infection, there may be insufficient TABLE 476-1 Current List of Indications for Hyperbaric Oxygen Therapy

1. Air or gas embolism (includes diving-related, iatrogenic, and accidental causes)
2. Carbon monoxide poisoning (including poisoning complicated by cyanide poisoning)
3. Clostridial myositis and myonecrosis (gas gangrene)

4. Crush injury, compartment syndrome, and acute traumatic ischemias
5. Decompression sickness
6. Arterial insufficiency including central retinal arterial occlusion and problem wounds
7. Severe anemia
8. Intracranial abscess
9. Necrotizing soft tissue infections (e.g., Fournier's gangrene)
10. Osteomyelitis (refractory to other therapy)
11. Delayed radiation injury (soft tissue injury and bony necrosis)
12. Skin grafts and flaps (compromised)
13. Acute thermal burn injury
14. Sudden sensorineural hearing loss
15. Avascular necrosis (aseptic osteonecrosis) Source: The Undersea and Hyperbaric Medical Society (2024).

oxygen to sustain normal function, and the tissue becomes necrotic (radiation necrosis). LRTI may be life-threatening and significantly reduce quality of life. Historically, the management of these injuries has been unsatisfactory. Conservative treatment is usually restricted to symptom management, whereas definitive treatment traditionally entails surgery to remove the affected part and extensive repair. Surgical intervention in an irradiated field is often disfiguring and associated with an increased incidence of delayed healing, breakdown of a surgical wound, or infection. HBO2T may act by several mechanisms, including edema reduction, vasculogenesis, and enhancement of macrophage activity (Fig. 476-3). However, the ability of HBO2T to promote angiogenesis in irradiated tissue represents the most important effect. The intermittent applica tion of HBO2T is the only intervention shown in multiple studies to increase the microvascular density in irradiated tissue in both animals and humans. CLINICAL EVIDENCE The typical course of HBO2T consists of 30–60 once-daily compressions to 202.6–243.1 kPa (2–2.4 ATA) for 1.5–2 h each session, often bracketed around surgical intervention if required. Although HBO2T has been used for LRTI since at least 1975, most clinical studies have been limited to small case series or individual case reports. A 2023 Cochrane systematic review included 18 randomized controlled trials (RCTs) published since 1985 and was able to draw the following conclusions based on meta-analysis. Pooled analysis of studies across all LRTI types suggested HBO2T improves tissue healing (risk ratio [RR] of healing with HBO2T, 1.39; 95% confidence interval [CI], 1.02–1.89). In patients with osteoradionecrosis of the jaw or at risk of osteoradionecrosis of the jaw following planned surgery, HBO2T reduced the risk of wound dehiscence (RR, 0.24; 95% CI, 0.06–0.94). The report also detailed individual randomized studies with notable positive results, particularly in regard to radiation proctitis and radia tion cystitis. There were also negative randomized studies in both these indications. Current UHMS guidelines (see Huang in "Further Reading") sup port use of HBO2T for most forms of LRTI, a problem that is notori ously difficult to treat by other means. The American Society of Colon and Rectal Surgeons designated HBO2T as a class 1B intervention (strongly indicated based on moderate-quality evidence) for radiation proctitis. A previous strongly positive RCT in treating bleeding radia tion cystitis (RR for complete or significant improvement after HBO2T, 3.63; 95% CI, 1.69–7.79) was recently corroborated by the Dartmouth Multicenter International Registry Initiative. In 370 bleeding patients One schema for using transcutaneous oximetry to assist in patient selection for HBO2T. If the wound area is hypoxic and responds to the administration of oxygen at 1 ATA or 2.4 ATA, treatment may be justified. Problem wound referred for assessment Transcutaneous wound mapping on air PtcO2 <40 mmHg* PtcO2 >100 mmHg

Transcutaneous mapping on 100% oxygen 1 ATA PtcO2 35–100 mmHg Transcutaneous mapping on 100% oxygen 2.4 ATA HBO2T indicated PtcO2 >200 mmHg FIGURE 476-4 Determining suitability for hyperbaric oxygen therapy guided by transcutaneous oximetry around the wound bed. *In diabetic patients, <50 mmHg may be more appropriate. PtcO2, transcutaneous oxygen pressure.

treated with HBO2T, the Radiation Therapy Oncology Group hema turia score fell from a median of 2 (interquartile range [IQR], 2) to 0 (IQR, 2) (see Moses et al. in “Further Reading”). Despite occasional positive case reports, results for radiation-induced neurologic injuries (brain and spinal cord) are less encouraging.

Selected Problem Wounds A problem wound is any cutaneous ulceration that requires a prolonged time to heal, does not heal, or recurs. In general, wounds referred to hyperbaric facilities are those for which sustained attempts to heal by other means have failed. Problem wounds are common and constitute a significant health problem. It has been estimated that 1% of the population of industrialized countries will experience a leg ulcer at some time. The global cost of chronic wound care may be as high as U.S. $25 billion per year. PATHOLOGY AND CLINICAL COURSE By definition, chronic wounds are indolent or deteriorating and resistant to the wide array of treat ments applied. Although there are many contributing factors, these wounds most commonly arise in association with one or more comor bidities such as diabetes, peripheral venous or arterial disease, or pro longed pressure (decubitus ulcers). A common denominator among these various contributors is hypoxia. First-line treatments are aimed at correction of the underlying pathologies (e.g., vascular reconstruction, compression bandaging, normalization of nutritional deficiencies or normalization of blood glucose level). HBO2T should be regarded as an adjunctive therapy to be applied simultaneously with amelioration of all modifiable risk factors for nonhealing wounds and good general wound care practice to maximize the chance of healing. Not all problem wounds will respond to HBO2T. A selection process based on responses to an oxygen challenge is often recommended. Wounds in hypoxic tissues often display poor or absent healing and have potential to benefit from HBO2T depending on the cause, mag nitude, and reversibility of hypoxia. Some causes of tissue hypoxia will be reversible with HBO2T (e.g., microvascular disease and tissue edema), whereas some will respond better to surgical revascularization (e.g., critical arterial stenosis). When tissue hypoxia can be overcome by a high driving pressure of oxygen in the arterial blood, this can be demonstrated by measuring transcutaneous Po2 using a modified transcutaneous Clarke electrode. It follows that many guidelines for patient selection for HBO2T include the interpretation of transcutane ous oxygen tensions around the wound while breathing air and oxygen at pressure (Fig. 476-4). Other methods include simple ankle-brachial index and skin perfusion pressure. CHAPTER 476 Hyperbaric and Diving Medicine Contraindication, critical major vessel disease, or surgical option available No Suitable for compression? Yes Not hypoxic (PtcO2 >40 mmHg) PtcO2 <35 mmHg unresponsive HBO2T unlikely to be effective PtcO2 <100 mmHg HBO2T indicated on a case-by-case basis. Consider alternatives. PtcO2 >100 but <200 mmHg

CLINICAL EVIDENCE The typical course of HBO2T consists of 20–40 once-daily compressions to 2–2.4 ATA for 1.5–2 h each session but is highly dependent on the clinical response. Both retrospective and pro spective cohort studies suggest that 6 months after a course of therapy, ~70% of indolent ulcers will be substantially improved or healed. Often these ulcers have been

present for many months or years, suggesting the application of HBO2T significantly improves the healing trajec tory, either primarily or in conjunction with other strategies. A 2015 Cochrane review included 12 RCTs and concluded that the chance of a diabetic ulcer healing improved with HBO2T (10 trials; RR, 2.35; 95% CI, 1.19–4.62). Although there was a trend toward reduced risk of major amputations with HBO2T, it did not reach statistical significance (RR, 0.36; 95% CI, 0.11–1.18). A 2024 meta-analysis of 29 RCTs (see Chen et al. in “Further Reading”) reported that in patients with diabetic foot ulcers treated with HBO2T there was increased complete healing (odds ratio [OR], 2.8; 95% CI, 2.3–3.5) and reduced amputations (OR, 0.41; 95% CI, 0.18–0.95). Using data from a recent randomized trial, the cost per limb saved in treating severe (Wagner stage III/IV) dia betic foot ulcers with HBO2T in the Netherlands was €19,005 (95% CI, –€18,487 to €264,334) (see Brouwer et al. in “Further Reading”).

Carbon Monoxide Poisoning Carbon monoxide (CO) is a color less, odorless gas formed during incomplete hydrocarbon combustion. Although CO is an essential endogenous neurotransmitter linked to NO metabolism and activity, it is also a leading cause of poisoning deaths and, in the United States alone, results in >50,000 emergency department visits per year and ~2000 deaths. Although there are large variations from country to country, about half of nonlethal exposures are due to self-harm. Accidental poisoning is commonly associated with defective or improperly installed heaters, house fires, and indus trial exposures. The motor vehicle is by far the most common source of intentional poisoning. PART 15 Disorders Associated with Environmental Exposures PATHOLOGY AND CLINICAL COURSE The pathophysiology of CO exposure is incompletely understood. CO binds to hemoglobin with an affinity >200 times that of oxygen, directly reducing the oxygencarrying capacity of blood and further promoting tissue hypoxia by shifting the oxyhemoglobin dissociation curve to the left. CO is also an anesthetic agent that inhibits evoked responses and narcotizes experi mental animals in a dose-dependent manner. The associated loss of airway patency together with reduced oxygen carriage in blood may cause death from acute arterial hypoxia. CO also causes harm by other mechanisms including direct disruption of cellular oxidative processes, binding to heme proteins including cytochrome a/a3, and peroxidation of brain lipids. The brain and heart are the most sensitive target organs, in part due to their high blood flow, poor tolerance of hypoxia, and high oxygen requirements. Minor exposures may be asymptomatic or present with vague constitutional symptoms such as headache, lethargy, and nau sea, whereas higher doses may present with poor concentration and cognition, short-term memory loss, confusion, seizures, and loss of consciousness. Carboxyhemoglobin (COHb) levels on admission may confirm exposure but do not reliably reflect the severity or the prog nosis of CO poisoning. Over the longer term, surviving patients com monly have neuropsychological sequelae that, for uncertain reasons, are sometimes delayed after an interval of days, weeks, or even months of apparent recovery. Motor disturbances, peripheral neuropathy, hearing loss, vestibular abnormalities, dementia, and psychosis have all been reported. Risk factors for poor outcome are age >35 years, exposure for >24 h, acidosis, and loss of consciousness. CO poisoning is one of the longest-standing indications for HBO2T, based traditionally on the obvious connection between exposure and tissue hypoxia and the ability of HBO2T to rapidly overcome this hypoxia. Moreover, CO is eliminated rapidly via the lungs on applica tion of HBO2T, with a half-life of ~21 min breathing oxygen at 2.0 ATA versus 5.5 h or 71 min breathing air or oxygen (respectively) at sea level. In practice, it seems unlikely that HBO2T could be delivered in time to prevent either acute hypoxic death or irreversible global cere bral hypoxic injury in severe cases. Thus, if HBO2T is beneficial in CO

poisoning, it must be by reducing the likelihood of persisting and/or delayed neurocognitive deficits through a mechanism(s) other than the simple reversal of arterial hypoxia due to high levels of COHb. There is evidence that relevant mechanisms include reversal of CO binding to cytochromes, upregulation of oxidative stress defenses, reduction in leukocyte adherence, impairment of lipid peroxidation, and others. CLINICAL EVIDENCE The typical course of HBO2T consists of two to three compressions to 2–2.8 ATA for 1.5–2 h each session. It is com mon for the first two compressions to be delivered within 24 h of the exposure. To date, there have been six RCTs of HBO2T for CO poison ing, although only four have been reported in full. While a Cochrane review suggested there is insufficient evidence to confirm a beneficial effect of HBO2T on the chance of persisting neurocognitive deficit fol lowing poisoning (34% of patients treated with oxygen at 1 atmosphere vs 29% of those treated with HBO2T; OR, 0.78; 95% CI, 0.54–1.1), this may have more to do with poor reporting and inadequate follow-up than with evidence that HBO2T is not effective. In the most method ologically rigorous of the analyzed studies (see Weaver et al. in “Further Reading”), at 6 weeks after poisoning, 46% of patients treated with normobaric oxygen alone had cognitive sequelae compared to 25% of those who received HBO2T ($p = .007$; number needed to treat [NNT] = 5; 95% CI, 3–16). At 12 months, the difference remained significant (32 vs 18%; $p = .04$; NNT = 7; 95% CI, 4–124) despite considerable loss to follow-up. On this basis, HBO2T remains widely advocated for the routine treatment of patients with moderate to severe CO poisoning, in partic ular in those older than 35 years, presenting with a metabolic acidosis on arterial blood-gas analysis, exposed for lengthy periods, or with a history of unconsciousness. ■ ■EXPLORATORY INDICATIONS Inflammatory Bowel Disease There is mounting evidence that HBO2T enhances healing in flairs of fistulizing Crohn’s disease or severe ulcerative colitis. Indeed, there are already two small positive RCTs along with numerous observational studies and case reports of apparent benefit. A multicenter RCT is underway. Benefit in these disorders may arise from enhancement of healing processes described earlier and/or anti-inflammatory activity. Mild Traumatic Brain Injury After anecdotal reports of success, HBO2T became a focus of interest for the treatment of veterans return ing from Afghanistan with postconcussive syndromes. This led to the execution of three sham-controlled RCTs by the different branches of the U.S. military, which demonstrated improvements in patients receiv ing both HBO2T and the sham. These improvements were considered due to placebo effects. However, a fourth study appeared to show benefit for HBO2T independent of any placebo effect, and collective re-evaluation of all studies suggests that placebo effects account for some but not all of the measured improvements. It follows that there is ongoing interest in HBO2T for mild traumatic brain injury, but a large definitive study is needed. SARS-CoV-2 (COVID-19) Infection Although currently of dwindling relevance, it is notable that during the COVID-19 pandemic there were two RCTs of relatively small size and low quality that evalu ated the benefit from HBO2T in hypoxic patients at risk of requiring intubation and ventilation. The studies were underpowered for out comes such as death or need for mechanical ventilation but did show a faster trajectory of recovery in patients treated with HBO2T. Those studies along with several observational studies and case reports were recently summarized (see Boet et al. in “Further Reading”). To date, cases of pulmonary barotrauma precipitated by gas trapping in COVID pneumonia have not emerged, but little can be concluded about safety based on reporting of relatively low numbers of cases. ■ ■ADVERSE EFFECTS HBO2T is generally well tolerated and safe in clinical practice. Patients often experience an adverse event at some time during their treatment course, but most are mild and self-limiting. Adverse effects are associ ated with both alterations in pressure (barotrauma) and the adminis tration of oxygen. Barotrauma Barotrauma may occur when

any noncompliant gasfilled space within the body does not equalize with environmental pressure during compression or decompression. Middle ear pain during compression (analogous to descent in an airplane) is the most common complication of HBO2T, reported in ~30% of patients. Most result in either no or only trivial injury as a result, and prevention by slower compression and training in insufflation of the middle ear via the Eustachian tube is usually successful. Patients unable to insufflate the middle ear and unconscious patients typically require myringoto mies or formal grommets across the tympanic membrane. Other less common sites for barotrauma of compression include the respira tory sinuses and dental caries. The lungs are potentially vulnerable to barotrauma of decompression (see “Diving Medicine” below), but the decompression following HBO2T is so slow that pulmonary baro trauma is extremely rare and has only been seen when a patient has slowly communicating gas trapping lesions such as bullae. Oxygen Toxicity The practical limit to the oxygen dose (whose components are inspired pressure and duration) in a single treatment session is cerebral oxygen toxicity. The most common acute mani festation is a tonic-clonic seizure, often preceded by facial twitching, anxiety, and agitation. The cause is thought to be an effect of ROSs on excitable neurons. Although clearly dose-dependent, onset is very variable both between individuals and within the same individual on different days. In large series reporting routine clinical hyperbaric practice (compressions to 2–2.4 ATA), the incidence of seizures is ~1–2/10,000 compressions. Chronic oxygen poisoning most commonly manifests as myopic shift. This is due to alterations in the refractive index of the lens follow ing oxidative damage that reduces the solubility of lenticular proteins, a process similar to that associated with senescent cataract formation. Up to 75% of patients show alteration in visual acuity after a course of 30 treatments at 202.6 kPa (2 ATA). Although most return to pretreatment values 6–12 weeks after cessation of treatment, a small proportion do not revert and may require a change in corrective lenses. A more rapid maturation of preexisting cataracts has occasionally been associated with HBO2T. Although a theoretical problem, the development of pulmonary oxygen toxicity over time does not seem to be problematic in practice—probably due to the short and intermittent nature of the exposures. ■ ■CONTRAINDICATIONS There are few absolute contraindications to HBO2T. Untreated pneu mothorax is considered a contraindication because intrapleural gas may expand on decompression and come under tension. Prior to any compression, patients with a pneumothorax should have a patent chest drain in place. The presence of other obvious risk factors for pulmo nary gas trapping such as bullae should trigger a careful analysis of the risks of treatment versus benefit. Recent systemic bleomycin or mitomycin C treatment deserves men tion because of its association with a partially dose-dependent pneumo nitis in ~20% of people. Patients treated with bleomycin, particularly those suffering pneumonitis, are often considered at risk of deteriora tion in ventilatory function following exposure to high oxygen tensions, even some years after treatment. Published experience suggests the relationship between distant bleomycin exposure and subsequent risk of pulmonary oxygen toxicity may have been overstated, and such patients have undergone uncomplicated HBO2T. Nevertheless, any patient with a history of receiving these drugs (particularly recently and particularly if there was a consequent pneumonitis) should be carefully evaluated and counseled prior to exposure to HBO2T. ■ ■CHALLENGES AND CONTROVERSIES IN HYPERBARIC MEDICINE Despite an increased understanding of mechanisms and an improv ing evidence base, hyperbaric medicine has struggled to achieve

widespread adoption in treating relevant disorders. There are several contributing factors, but high among them are a lack of relevant teach ing at medical schools and a paucity of large well-conducted RCTs that clearly demonstrate efficacy in the targeted indications.

In turn, it should be appreciated that there are multiple factors that combine as an impediment to large RCTs in hyperbaric medicine. First, funding for clinical research has been difficult in an environment where the pharmacologic agent under study is abundant, cheap, and unpatentable. Second, some of the indications (such as necrotizing fasciitis and central retinal artery occlusion) are rare, sporadic, and acute. Conducting RCTs of treatment in such problems is notoriously difficult, especially where the putative treatment is available in only a small minority of hospitals. Not surprisingly, many of the accepted treatments applied in such problems are not supported by large RCTs. Third, the natural history of an evolving indication in HBO2T is that treatment might first be tried sporadically in a small number of patients on the basis that its use makes biological sense. Unlike a new drug under development, there are no significant regulatory barriers to this. If apparently successful, then there is a risk that application of HBO2T may become “accepted” before an RCT is proposed or organized, and clinicians then become reluctant to have patients randomized into a study. Fourth, a course of HBO2T typically involves substantial com mitment in time and logistical effort. This is a disincentive to recruit ment of patients into a study with a high likelihood of being allocated to a placebo group. Finally, the potentially powerful placebo effect of HBO2T is well recognized and highlights the importance of blinded sham controls. Despite these impediments to RCTs, many have been successfully executed across the various indications for HBO2T. Some have emerged long after the indication was accepted onto the UHMS list on the basis of lower-level evidence. A good example is crush injury and trau matic ischemia, for which the best supporting RCT has only recently emerged (see Miller et al. in “Further Reading”). Recognizing these challenges, however, an international clinical registry has also been created and is now beginning to produce useful outcome data that, at the very least, can be compared to the known natural history during standard management of the various monitored indications (see “Late Radiation Tissue Injury,” above, and Moses et al. in “Further Reading”). CHAPTER 476 Hyperbaric and Diving Medicine Another challenge to the widespread acceptance of HBO2T for established uses is the continuing misguided advocacy for hyperbaric therapy (sometimes using air breathing) as a panacea for treating numerous diseases, improving general well-being, and slowing aging. The prescription and delivery of HBO2T requires no medical license in many jurisdictions. Some claims of efficacy refer to small supportive studies with a high risk of bias or placebo effect. Physicians should focus their practice on accepted or approved indications that are peri odically updated (see Huang in “Further Reading”). DIVING MEDICINE Underwater diving is both a popular recreational activity and a means of employment in a range of tasks from underwater construction to military operations. It is a complex activity with unique hazards and medical complications arising mainly as a consequence of the dramatic changes in pressure associated with both descent and ascent through the water column. For every 10.1-m increase in depth of seawater, the ambient pressure (Pamb) increases by 101.3 kPa (1 atmosphere) so that, for example, a diver at 20 m depth is exposed to a Pamb of 303.9 kPa (3 ATA), made up of 1 ATA due to atmospheric pressure and 2 ATA generated by the water column. ■ ■BREATHING EQUIPMENT Most diving is undertaken using a self-contained underwater breathing apparatus (scuba) consisting of one or more cylinders of compressed gas connected to a pressure-reducing regulator and a demand valve activated by inspiratory effort. Some divers use rebreathers, which comprise a closed or semi-closed breathing circuit with a carbon dioxide scrubber and an oxygen addition system designed to main tain a safe inspired Po2. Exhaled gas is recycled, and gas consumption is limited to little more than the oxygen metabolized by the diver.

Rebreathers are therefore popular for deep dives where expensive helium is included in the respired mix (see below). Occupational divers frequently use “surface supply” equipment where gas, along with other utilities such as communications and power, is supplied via an “umbili cal” cable from the surface.

All these systems must supply gas to the diver at the Pamb of the sur rounding water or inspiration would be impossible against the water pressure. For most recreational diving, the respired gas is air. Pure oxygen is rarely used because there is a dose-dependent risk (where “dose” is a function of exposure time and inspired Po2) that oxygen may provoke seizures above an inspired Po2 of 130 kPa (1.3 ATA). The maximum acceptable inspired Po2 in diving is often considered to be 161 kPa (1.6 ATA), which would be achieved when breathing pure oxygen at 6 m or air at 66 m. This is a conspicuously lower Po2 than routinely used for hyperbaric therapy (see earlier), reflecting a higher risk of oxygen toxic seizures during immersion and exercise. In order to maintain a safe Po2 and avoid dangerous oxygen exposures, very deep diving requires the use of inspired oxygen fractions lower than in air (Fo2 0.21), and divers tailor the oxygen content of their gases to remain within recommended exposure guidelines. Deep-diving gases include helium as a substitute for some or all of the nitrogen to reduce both the narcotic effect and high gas density that result from breathing nitrogen at high pressures. ■ ■SUITABILITY FOR DIVING The most common reason for physician consultation in relation to div ing is for the evaluation of suitability for diver training or continuation of diving after a health event. Occupational diver candidates are usu ally compelled to see doctors with specialist training in the field, both at entry to the industry and periodically thereafter, and their medical evaluations are usually conducted according to legally mandated stan dards. In contrast, in most jurisdictions, prospective recreational diver candidates simply complete a self-assessment medical questionnaire prior to diver training. If there are no positive responses, the candi date proceeds directly to training, but positive responses mandate the candidate see a clinician, often a primary care physician, for evaluation of the identified medical issue. In the modern era, such consultations have evolved from a simple proscriptive exercise of excluding those with potential contraindications to an approach in which each case is considered on its own merits and an individualized evaluation of risk is made. Such evaluations require integration of diving physiology, the impact of associated medical problems, and knowledge of the specific medical condition(s) of the candidate. A detailed discussion is beyond the scope of this chapter, but several important principles are outlined below. PART 15 Disorders Associated with Environmental Exposures There are three primary questions that should be answered in rela tion to any medical condition reported by a prospective diver: (1) Could the condition be exacerbated by diving? (2) Could the condition make a diving medical problem more likely? (3) Could the condition prevent the diver from meeting the functional requirements of div ing? As examples of positive answers to these questions (respectively): epilepsy is usually considered to imply high risk because there are epi leptogenic stimuli such as high inspired oxygen pressures encountered in diving that could make a seizure (and drowning) more likely; active asthma is considered to increase risk because it could predispose to air trapping and pulmonary barotrauma (see below); and ischemic heart disease increases risk because it could prevent a diver from exercising sufficiently to get out of a difficult situation such as being caught in a current. It can be a complex matter to recognize the relevant interac tions between diving and medical conditions and to determine their impact on suitability for diving. There may follow an equally complex discussion about whether such interactions impart a disqualifying risk, and this may be influenced by the individual candidate’s level of risk acceptance and the extent to which others involved (such as dive partners) might be

affected. Guidelines are occasionally published on assessment of diving candidates with risk factors for important comorbidities like cardiovascular disease or who have suffered topical problems such as COVID-19 infection (see Sadler in “Further Read ing”). Physicians interested in regularly conducting such evaluations

should obtain relevant training, for which short courses are offered by specialist groups in most countries. ■ ■BAROTRAUMA Barotrauma is essentially tissue injury arising as a result of ambient pressure changes. Middle-ear barotrauma (MEBT) in diving is similar to the problem that may occur during descent from altitude in an airplane, but difficulties with equalizing pressure in the middle ear are exaggerated underwater by both the rapidity and magnitude of pressure change as a diver descends or ascends. Failure to periodically insufflate the middle-ear spaces via the eustachian tubes during descent results in increasing pain. As the Pamb increases, the tympanic membrane may be bruised or even ruptured as it is pushed inward. Relative negative pressure in the middle ear results in engorgement of blood vessels in the surrounding mucous membranes and leads to effusion or bleeding, which can be associated with a conductive hearing loss (Chap. 36). MEBT is much less common during ascent because expanding gas in the middle-ear space tends to open the eustachian tube automatically. Barotrauma may also affect the respiratory sinuses, although the sinus ostia are usually widely patent and allow automatic pressure equaliza tion without the need for specific maneuvers. If equalization fails, pain usually results in termination of the dive. Difficulty with equalizing ears or sinuses may respond to oral or nasal decongestants. Much less commonly, divers may suffer inner ear barotrauma (IEBT). Several explanations have been proposed, of which the most favored holds that forceful attempts to insufflate the middle-ear space by Valsalva maneuvers during descent result in transmission of pres sure to the perilymph via the cochlear aqueduct and outward rupture of the round window, which is already under tension because of relative negative middle-ear pressure. The clinician should be alerted to possible IEBT after diving by a sensorineural hearing loss or true vertigo (which is often accompanied by nausea, vomiting, nystagmus, and ataxia). These manifestations can also occur in vestibulocochlear decompression sickness (DCS; see below) but should never be attrib uted to MEBT. Immediate review by an expert diving physician is rec ommended, and urgent referral to an otologist will often follow. The lungs are also vulnerable to barotrauma but are at most risk during ascent. If expanding gas becomes trapped in the lungs as Pamb falls, this may rupture alveoli and associated vascular tissue. Gas trapping may occur if divers intentionally or involuntarily hold their breath during ascent or if there are bullae. The extent to which asthma predisposes to pulmonary barotrauma is debated, but the presence of active bronchoconstriction must increase risk. For this reason, asth matics who regularly require bronchodilator medications or whose airways are sensitive to exercise or cold air are usually discouraged from diving. While possible consequences of pulmonary barotrauma include pneumothorax and mediastinal emphysema, the most feared is the introduction of gas into the pulmonary veins leading to cerebral arterial gas embolism (CAGE). Manifestations of CAGE include loss of consciousness, confusion, hemiplegia, visual disturbances, and speech difficulties appearing immediately or within minutes after surfacing. The management is the same as for DCS described below. The natural history of CAGE often includes substantial or complete resolution of symptoms early after the event. This is probably the clinical correlate of bubble involution and redistribution with consequent restoration of blood flow. Patients exhibiting such remissions should still be reviewed at specialist diving medical centers because secondary deterioration or re-embolization can occur. Unsurprisingly, these events can be misdi agnosed as typical strokes or transient ischemic attacks (TIAs) (Chap. 438) when patients are seen by clinicians

unfamiliar with diving medicine. All patients presenting with neurologic symptoms after diving should have their symptoms discussed with a specialist in diving medicine and be considered for recompression therapy. ■ ■DECOMPRESSION SICKNESS DCS is caused by the formation of bubbles from dissolved inert gas (usually nitrogen) during or after ascent (decompression) from a com pressed gas dive. Bubble formation is also possible following decom pression for extravehicular activity in space and with ascent to altitude

in unpressurized aircraft. DCS in the latter scenarios is probably rare in comparison with diving, where the incidence is ~1 in 5000–10,000 recreational dives. Breathing at elevated Pamb results in increased uptake of inert gas into blood and then into tissues. The rate at which tissue inert gas equili brates with the inspired inert gas pressure is proportional to tissue blood flow and the blood-tissue partition coefficient for the gas. Similar fac tors dictate the kinetics of inert gas washout during ascent. If the rate of gas washout from tissues does not match the rate of decline in Pamb, then the sum of dissolved gas pressures in the tissue will exceed Pamb, a condi tion referred to as supersaturation. This is the prerequisite for bubbles to form during decompression, although other less well-understood factors are also involved. Deeper and longer dives result in greater inert gas absorption and greater likelihood of tissue supersaturation during ascent. Divers control their ascent for a given depth and time exposure using algorithms that often include periods where ascent is halted for a prescribed period at different depths to allow time for gas washout (decompression stops). Although a breach of these protocols increases the risk of DCS, adherence does not guarantee that it will be prevented. DCS should be considered in any diver manifesting postdive symptoms not readily explained by an alternative mechanism. Bubbles may form within tissues themselves, where they cause symptoms by mechanical distraction of pain-sensitive or function ally important structures. They also appear in the venous circulation, almost certainly after forming in capillary beds as blood passes through supersaturated tissues. Some venous bubbles are tolerated without symptoms and are filtered from the circulation in the pulmonary capillaries. However, in sufficiently large numbers, these bubbles are capable of inciting inflammatory and coagulation cascades, damaging endothelium, activating formed elements of blood such as platelets, and causing symptomatic pulmonary vascular obstruction. Circulating bubbles can induce endothelial leak, intravascular hypovolemia, and high hematocrit. Moreover, if there is a right-to-left shunt through an atrial septal defect, patent foramen ovale (PFO), or an intrapulmonary shunt, then venous bubbles may enter the arterial circulation (25% of adults have a PFO). The risk of cerebral, spinal cord, inner ear, and skin manifestations appears higher in the presence of significant shunts, suggesting that these “arterialized” venous bubbles can cause harm, perhaps by disrupting flow in the microcirculation of target organs. Circulating microparticles, which are elevated in number and size after diving, are currently under investigation as indicators of decompres sion stress and as injurious agents in their own right. How they arise and their exact role in DCS remain unclear. Table 476-2 lists manifestations of DCS grouped according to organ system. The majority of cases present with mild symptoms, including musculoskeletal pain, fatigue, and minor neurologic mani festations such as patchy paresthesias. Serious presentations are much less common. Pulmonary and cardiovascular manifestations can be life-threatening, and spinal cord involvement frequently results in per manent disability. Latency is variable. Serious DCS usually manifests within 60 min of surfacing, but mild symptoms may not appear for several hours. Symptoms arising >24 h after diving are very unlikely to be DCS, unless the diver is exposed to reduced ambient pressure such as during commercial air travel or surface travel at higher altitude. The presentation may be confusing and nonspecific, and there are no useful diagnostic

investigations. Diagnosis is based on integration of findings from examination of the dive profile, the nature and temporal relationship of symptoms to diving, and the clinical examination. Some DCS presentations may be difficult to separate from CAGE following pulmonary barotrauma, but from a clinical perspective, the distinction is unimportant because the first aid and definitive management of both conditions are the same. TREATMENT Decompression Sickness First aid for either DCS or CAGE includes horizontal position ing, in the lateral decubitus position if consciousness is impaired;

TABLE 476-2 Manifestations of Decompression Sickness ORGAN SYSTEM MANIFESTATIONS Musculoskeletal Limb pain Neurologic Cerebral Confusion Visual disturbances Speech disturbances Spinal Muscular weakness Paralysis Upper motor neuron signs Bladder and sphincter dysfunction Dermatomal sensory disturbances Abdominal pain Girdle pain Vestibulocochlear Hearing loss Vertigo and ataxia Nausea and vomiting Peripheral Patchy nondermatomal sensory disturbance Pulmonary Cough Dyspnea Cardiovascular Hemoconcentration Coagulopathy Hypotension Cutaneous Rash, itch CHAPTER 476 Lymphatic Soft tissue edema, often relatively localized Constitutional Fatigue and malaise intravenous fluids (preferably glucose-free, isotonic intravenous, but if unavailable and the patient is sufficiently conscious, oral fluids); and sustained 100% oxygen administration. The latter accelerates inert gas washout from tissues and promotes resolution of bubbles. Definitive treatment of DCS or CAGE with recompres sion and hyperbaric oxygen is justified in most instances, although some mild or marginal DCS cases may be managed with first aid measures alone—an option that may be invoked by experienced diving physicians under various circumstances, but especially if evacuation for recompression is hazardous or extremely difficult. Long-distance evacuations are preferably undertaken using a heli copter flying at low altitude or a fixed-wing air ambulance pressur ized to 1 ATA, although for serious cases, evacuation should not be delayed only because normobaric evacuation is not possible. Breathing oxygen en route is recommended. If oxygen toxicity is a concern during prolonged evacuation, expert opinion can provide guidance as to a schedule (see below). Hyperbaric and Diving Medicine Recompression reduces bubble volume in accordance with Boyle’s law and increases the inert gas partial pressure difference between a bubble and surrounding tissue. At the same time, oxygen administration markedly increases the inert gas partial pressure dif ference between alveoli and tissue. The net effect is to significantly increase the rate of inert gas diffusion from bubble to tissue and tis sue to blood, thus accelerating bubble resolution. Hyperbaric oxy gen also helps oxygenate compromised tissues and may ameliorate some of the proinflammatory effects of bubbles. Various recom pression protocols have been advocated, but there are no data that define the optimum approach. Recompression typically begins with oxygen administered at 2.8 ATA, the maximum pressure at which the risk of oxygen toxicity remains acceptable in a hyperbaric cham ber. There follows a stepwise decompression over variable periods adjusted to symptom response. The most widely used algorithm is the U.S. Navy Table 6, whose shortest format lasts 4 h and 45 min. Typically, shorter follow-up recompressions are repeated daily while symptoms persist and appear responsive to treatment. Adjuncts to recompression include intravenous fluids and other supportive care

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as necessary. For cases of arterial gas embolism, evidence supports the use of intravenous lidocaine to achieve standard antiarrhythmic plasma levels. Occasionally, very sick divers require intubation, ventilation, and intensive care.

The presentation of sick divers to physicians or hospitals without diving medicine expertise creates a risk of misinterpretation of non specific manifestations and of consequent mistakes in diagnosis and management. Physicians finding themselves in this situation are strongly advised to expeditiously contact the 24-h worldwide diving emergency advisory service provided by the Divers Alert Network (DAN) at +1-919-684-9111. Acknowledgment The authors gratefully acknowledge the major contributions of Professor Michael Bennett (1956–2023) to previous editions of this chapter. ■ ■FURTHER READING Boet S et al: Efficacy and safety of hyperbaric oxygen treatment to treat COVID-19 pneumonia: A living systematic review update. Diving Hyperb Med 52:126, 2022. Brouwer R et al: Economic analysis of hyperbaric oxygen therapy for the treatment of ischaemic diabetic foot ulcers. Diving Hyperb Med 54:265, 2024. Chen H-R et al: Application of hyperbaric oxygen therapy in diabetic foot ulcers: A meta-analysis. Int Wound J 21:e14621, 2024. Huang E (ed): Undersea and Hyperbaric Medicine Society Hyperbaric Medicine Indications Manual, 15th ed. North Palm Beach, FL, Best Publishing, 2024. Krzyżak J, Korzeniewski K: Medical assessment of fitness to dive. PART 15 Disorders Associated with Environmental Exposures Parts I and II. Int Marit Health 72:36 and 115, 2021. Lin ZC et al: Hyperbaric oxygen for late radiation tissue injury. Cochrane Database Syst Rev 8:CD005005, 2023. Miller IL et al: Hyperbaric oxygen for lower limb trauma (HOLLT): An international multi-centre randomised clinical trial. Diving Hyperb Med 52:164, 2022. Mitchell SJ: Decompression illness: A comprehensive overview. Div ing Hyperb Med 54:1, 2024. Mitchell SJ et al: Decompression illness. N Eng J Med 386:1254, 2022. Moses RA et al: Patient reported outcome measures following hyper baric oxygen therapy for radiation cystitis: Early results from the mul ticenter registry for hyperbaric oxygen therapy. J Urol 211:765, 2024. Weaver LK et al: Hyperbaric oxygen for acute carbon monoxide poi soning. N Engl J Med 347:1057, 2002. Wendling J et al (eds). Medical Assessment for Work Under Pressure, 2nd ed. London, International Marine Contractors Association, 2024. Whelan HT (ed): Hyperbaric Medicine Practice, 5th ed. North Palm Beach, FL, Best Publishing, 2024. Daniel F. Danzl

Hypothermia and

Peripheral Cold Injuries ■ ■HYPOTHERMIA Accidental hypothermia occurs when there is an unintentional drop in the body’s core temperature below 35°C (95°F). At this temperature, many of the compensatory physiologic mechanisms that conserve heat begin to fail. Primary accidental hypothermia is a result of the direct exposure of a previously healthy individual to the cold. The mortality rate is much higher for patients who develop secondary hypothermia as a complication of a serious systemic disorder or injury.

TABLE 477-1 Risk Factors for Hypothermia Age extremes Elderly Neonates Environmental exposure Occupational Sports-related Inadequate clothing Immersion Toxicologic and pharmacologic Ethanol Anesthetics Antipsychotics Antidepressants Anxiolytics Benzodiazepines Neuromuscular blockers Insufficient fuel Malnutrition Marasmus Kwashiorkor Endocrine-related Diabetes mellitus Hypoglycemia Hypothyroidism Adrenal insufficiency Hypopituitarism Neurologic Cerebrovascular accident Hypothalamic disorders Parkinson’s disease Spinal cord injury Multisystemic Trauma Sepsis Shock Hepatic or renal failure Carcinomatosis Burns and exfoliative dermatologic disorders Immobility or debilitation ■ ■CAUSES Primary accidental hypothermia is geographically and seasonally per vasive. Although most cases occur in the winter months and in colder climates, this condition is surprisingly common in warmer regions as well. Multiple variables render individuals at the extremes of age—both the elderly and neonates—particularly vulnerable to hypothermia (Table 477-1). The elderly have diminished thermal perception and are more susceptible to immobility, malnutrition, and systemic illnesses that interfere with heat generation or conservation. Dementia, psychi atric illness, and socioeconomic factors often compound these prob lems. Neonates have high rates of heat loss because of their increased surface-to-mass ratio and their lack of effective shivering and adaptive behavioral responses. At all ages, malnutrition can contribute to heat loss because of diminished subcutaneous fat and as a result of depleted energy stores used for thermogenesis. Individuals whose occupations or hobbies entail extensive exposure to cold weather are at increased risk for hypothermia. Military history is replete with hypothermic tragedies. Hunters, sailors, skiers, and climbers also are at great risk of exposure, whether it involves injury, changes in weather, or lack of preparedness. Ethanol causes vasodilation (which increases heat loss), reduces thermogenesis and gluconeogenesis, and may impair judgment or lead to obtundation. Some antipsychotics, antidepressants, anxiolytics, benzodiazepines, and other medications reduce centrally mediated vasoconstriction. Many hypothermic patients are admitted to inten sive care because of drug overdose. Anesthetics can block shivering responses; these effects are compounded when patients are not insu lated adequately in the operating or recovery units. Several types of endocrine dysfunction cause hypothermia. Hypo thyroidism—particularly when extreme, as in myxedema coma— reduces the metabolic rate and impairs thermogenesis and behavioral responses. Adrenal insufficiency and hypopituitarism also increase susceptibility to hypothermia. Hypoglycemia, most commonly caused by insulin or oral hypoglycemic agents, is associated with hypothermia, in part because of neuroglycopenic effects on hypothalamic function. Increased osmolality and metabolic derangements associated with uremia, diabetic ketoacidosis, and lactic acidosis can lead to altered hypothalamic thermoregulation. Neurologic injury from trauma, cerebrovascular accident, subarach noid hemorrhage, and a hypothalamic lesion increases susceptibility to hypothermia. Agenesis of the corpus callosum (Shapiro’s syndrome) is one cause of episodic hypothermia. In this syndrome, profuse perspira tion is followed by a rapid fall in temperature. Acute spinal cord injury

disrupts the autonomic pathways that lead to shivering and will prevent cold-induced reflex vasoconstrictive responses. Hypothermia associated with sepsis is a poor prognostic sign. Hepatic failure causes decreased glycogen storage and gluconeogenesis as well as a diminished shivering response. In acute myocardial infarc tion associated with low cardiac output, hypothermia may be reversed after adequate resuscitation. With extensive burns, psoriasis, erythro dermas, and other skin diseases, increased peripheral-blood flow leads to excessive heat loss. ■ ■THERMOREGULATION Heat loss occurs through five mechanisms: radiation (55–65% of heat loss), conduction (10–15% of heat loss, increased in cold water), con vection (increased in the wind), respiration, and evaporation; both of the latter two mechanisms are affected by the ambient temperature and the relative humidity. The preoptic anterior hypothalamus normally orchestrates thermo regulation (Chap. 20). The immediate defense of thermoneutrality is via the autonomic nervous system, whereas delayed control is mediated by the endocrine system. Autonomic nervous system responses include the release of norepinephrine, increased muscle tone, and shivering, leading to thermogenesis and an increase in the basal metabolic rate. Cutaneous cold thermoreception causes direct reflex vasoconstriction to conserve heat. Prolonged exposure to cold also stimulates the thy roid axis, leading to an increased metabolic rate. ■ ■CLINICAL PRESENTATION In most cases of hypothermia, the history of exposure to environmental factors (e.g., prolonged exposure to the outdoors without adequate cloth ing) makes the diagnosis straightforward. In urban settings, however, the presentation is often more subtle, and other disease processes, toxin exposures, or psychiatric diagnoses should be considered. Predicting the core temperature based on the clinical presentation is very difficult. After initial stimulation by hypothermia, there is progressive depression of all organ systems. The timing of the appearance of these clinical manifestations varies widely (Table 477-2). Without knowing the core temperature, it can be difficult to interpret other vital signs. For example, tachycardia disproportionate to the core temperature sug gests secondary hypothermia resulting from hypoglycemia, hypovole mia, or a toxin overdose. Because carbon dioxide production declines progressively, the respiratory rate should be low; persistent hyperven tilation suggests a central nervous system (CNS) lesion or an organic TABLE 477-2 Physiologic Changes Associated with Accidental Hypothermia BODY TEMPERATURE CENTRAL NERVOUS SYSTEM CARDIOVASCULAR RESPIRATORY RENAL AND ENDOCRINE NEUROMUSCULAR SEVERITY Mild 35°C (95°F)–

32.2°C (90°F) Linear depression of cerebral metabolism; amnesia; apathy; dysarthria; impaired judgment; maladaptive behavior Tachycardia, then progressive bradycardia; cardiac cycle prolongation; vasoconstriction; increase in cardiac output and blood pressure Moderate <32.2°C (90°F)–

28°C (82.4°F) EEG abnormalities; progressive depression of level of consciousness; pupillary dilation; paradoxical undressing; hallucinations Progressive decrease in pulse and cardiac output; increased atrial and ventricular arrhythmias; suggestive (J-wave) ECG changes Severe <28°C (<82.4°F) Loss of cerebrovascular autoregulation; decline in cerebral blood flow; coma; loss of ocular reflexes; progressive decrease in EEG abnormalities Progressive decrease in blood pressure, heart rate, and cardiac output; reentrant dysrhythmias; maximal risk of ventricular fibrillation; asystole Abbreviations: ECG, electrocardiogram; EEG, electroencephalogram. Source: From DF Danzl, RS Pozos: Accidental hypothermia. N Engl J Med 331:1756, 1994.

acidosis. A markedly depressed level of consciousness in a patient with mild hypothermia suggests an overdose or CNS dysfunction due to infection or trauma.

Physical examination findings will also be altered by hypothermia. For instance, the assumption that areflexia is solely attributable to hypo thermia can obscure the diagnosis of a spinal cord lesion. Patients with hypothermia may be confused or combative; these symptoms abate more rapidly with rewarming than with chemical or physical restraint. A classic example of maladaptive behavior in patients with hypothermia is paradoxical undressing, which involves the inappropriate removal of clothing in response to a cold stress. The cold-induced ileus and abdominal rectus spasm can mimic or mask the presentation of an acute abdomen (Chap. 16). When a patient in hypothermic cardiac arrest is first discovered, cardiopulmonary resuscitation (CPR) is indicated unless (1) a do-notresuscitate status is verified, (2) obviously lethal injuries are identified, or (3) the depression of a frozen chest wall is not possible. Continuous CPR is normally recommended, and interruptions should be avoided if possible. In the field, when the core temperature is <28°C (82.4°F), intermittent CPR may also be effective. As the resuscitation proceeds, the prognosis is grave if there is evidence of widespread cell lysis, as reflected by potassium levels >12 mmol/L (12 meq/L). Other findings that may preclude continuing resuscitation include a core temperature <10–12°C (<50–54°F), a pH <6.5, and evidence of intravascular thrombosis with a fibrinogen value <0.5 g/L (<50 mg/dL). The decision to terminate resuscitation before rewarming the patient past 33°C (91°F) should be predicated on the type and severity of the precipitants of hypothermia. Survival has occurred with a cardiac arrest time over 7 h. A history of asphyxia, as in an avalanche, with secondary cooling is the most important negative predictor of survival. CHAPTER 477 ■ ■DIAGNOSIS AND STABILIZATION Hypothermia is confirmed by measurement of the core temperature. When feasible, placement of a temperature probe in the lower third of the esophagus is preferable, and continuous monitoring essential. Ancillary rectal or bladder monitoring often lags behind core tempera ture changes. Hypothermia and Peripheral Cold Injuries Pulses may be undetectable in perfusing patients, and the ampli tude of the QRS complex is decreased. Maximal amplification on the monitor is often helpful. Chest compressions, when not indicated, may convert a perfusing rhythm to a nonperfusing one. Bedside Tachypnea, then progressive decrease in respiratory minute volume; declining oxygen consumption; bronchorrhea; bronchospasm Diuresis; increase in catecholamines, adrenal steroids, triiodothyronine, and thyroxine; increase in metabolism with shivering Increased preshivering muscle tone, then fatiguing Hypoventilation: 50% decrease in carbon dioxide production per 8°C (17.6°F) drop in temperature; absence of protective airway reflexes 50% increase in renal blood flow; renal autoregulation intact; impaired insulin action Hyporeflexia; diminishing shivering-induced thermogenesis; rigidity Pulmonic congestion and edema; 75% decrease in oxygen consumption; apnea Decrease in renal blood flow that parallels decrease in cardiac output; extreme oliguria; poikilothermia; 80% decrease in basal metabolism No motion; decreased nerve-conduction velocity; peripheral areflexia; no corneal or oculocephalic reflexes

echocardiography and end-tidal carbon dioxide ($ETCO_2$) monitoring may confirm the perfusion status. If the core temperature is below 30°C (86°F) and there is no perfusion, consider up to three attempts at maximal power. If unsuccessful, rewarm to at least 30°C (86°F) before further attempts. Although cardiac pacing for hypothermic bradydysrhythmias is rarely indicated, the transthoracic technique is preferable. The J or Osborn wave at the junction of the QRS complex and ST segment suggests the diagnosis. Obvious J waves are routinely misdiagnosed by automated

readings as injury current.

Supplemental oxygenation is always warranted, since tissue oxygen ation is affected adversely by the leftward shift of the oxyhemoglobin dissociation curve. Pulse oximetry is often unreliable in patients with vasoconstriction. If protective airway reflexes are absent, gentle endo tracheal intubation should be performed. Adequate preoxygenation will prevent ventricular arrhythmias. Insertion of a gastric tube prevents dilation secondary to decreased bowel motility. Indwelling bladder catheters facilitate monitoring of cold-induced diuresis and can provide an ancillary approach for temperature monitoring. Dehydration is encountered commonly with chronic hypothermia, and most patients benefit from an intravenous or intraosseous crystalloid bolus. Normal saline is preferable to lactated Ringer's solution, as the liver in hypothermic patients inefficiently metabolizes lactate. The placement of a pulmonary artery catheter can cause perforation of the less compliant pulmonary artery. Insertion of a central venous catheter deeply into the cold right atrium should be avoided since this procedure, similar to transvenous pacing, can pre cipitate refractory arrhythmias. Arterial blood gases should not be corrected for temperature (Chap. 58). An uncorrected pH of 7.42 and a PCO_2 of 40 mmHg reflect appropriate alveolar ventilation and acid-base balance at any core temperature. Acid-base imbalances should be corrected gradually, since the bicarbonate buffering system is inefficient. A common error is overzealous hyperventilation in the setting of depressed CO_2 produc tion. When the PCO_2 decreases by 10 mmHg at 28°C (82°F), it doubles the pH increase of 0.08 that occurs at 37°C (99°F). Consider $ETCO_2$ monitoring to prevent hyperventilation. PART 15 Disorders Associated with Environmental Exposures The severity of anemia may be underestimated because the hema tocrit increases 2% for each 1°C drop in temperature. White blood cell sequestration and bone marrow suppression are common, potentially masking an infection. Although hypokalemia is more common in chronic hypothermia, hyperkalemia also occurs; the expected electro cardiographic changes are often obscured by hypothermia. Patients with renal insufficiency, metabolic acidosis, or rhabdomyolysis are at greatest risk for electrolyte disturbances. Coagulopathies are common because cold inhibits the enzymatic reactions required for activation of the intrinsic cascade. In addition, thromboxane B2 production by platelets is temperature dependent, and platelet function is impaired. The administration of platelets and fresh-frozen plasma is therefore not effective. Coagulation studies can be deceptively normal and contrast with the observed in vivo coagu lopathy. This contradiction occurs because all coagulation tests are rou tinely performed at 37°C (99°F), and the enzymes are thus rewarmed. ■ ■REWARMING STRATEGIES The key initial decision is whether to rewarm the patient passively or actively. Passive external rewarming simply involves covering and insu lating the patient in a warm environment. With the head also covered, the rate of rewarming is usually 0.5°–2°C (1.10°–4.4°F) per hour. This technique is ideal for previously healthy patients who develop acute, mild primary accidental hypothermia. The patient must have sufficient glycogen to support endogenous thermogenesis. The application of heat directly to the extremities of patients with chronic severe hypothermia should be avoided because it can induce peripheral vasodilation and precipitate core temperature "afterdrop," a response characterized by a continual decline in the core temperature after removal of the patient from the cold. Truncal heat application reduces the risk of afterdrop. Active rewarming is necessary under the following circumstances: core temperature <32°C (<90°F) (poikilothermia), cardiovascular

instability, age extremes, CNS dysfunction, hormone insufficiency, and suspicion of secondary hypothermia. Active external rewarming is best accomplished with forced-air heating blankets.

Other options include devices that circulate water through external heat exchange pads, radi ant heat sources, and hot packs. Monitoring a patient with hypother mia in a heated tub is extremely difficult. Electric blankets should be avoided because vasoconstricted skin is easily burned. There are numerous widely available options for active core rewarm ing. Airway rewarming with heated humidified oxygen (40°–45°C [104°–113°F]) via mask or endotracheal tube is a convenient option. Although airway rewarming provides less heat than do some other forms of active core rewarming, it eliminates respiratory heat loss and adds 1°–2°C (2.2°–4.4°F) to the overall rewarming rate. Crystalloids should be heated to 40°–42°C (104°–108°F), but the quantity of heat provided is significant only during massive volume resuscitation. The most efficient method for heating and delivering fluid or blood is with a countercurrent in-line heat exchanger. Heated irrigation of the gastrointestinal tract or bladder transfers minimal heat because of the limited available surface area. These methods should be reserved for patients in cardiac arrest and then used in combination with all avail able active rewarming techniques. If extracorporeal life support (ECLS) is unavailable, closed thoracic lavage is far more efficient in severely hypothermic patients with car diac arrest. The hemithoraxes are irrigated through two inserted largebore thoracostomy tubes. Thoracostomy tubes should not be placed in the left chest of a spontaneously perfusing patient for purposes of rewarming. Peritoneal lavage with the dialysate at 40°–45°C (104°– 113°F) efficiently transfers heat when delivered through two catheters with outflow suction. Another option involves the use of endovascular temperature control catheters. The HOPE (Hypothermia Outcome Prediction after Extracorporeal Life Support) score is a tool based on six covariates to help predict which patients may benefit from ECLS. ECLS options (Table 477-3) should be considered in severely hypothermic patients, especially those with primary accidental hypothermia. ECLS, including bypass, should be considered in nonperfusing patients without documented contraindications to resuscitation. Circulatory support may be the only effective option in patients with completely frozen extremities or those TABLE 477-3 Options for Extracorporeal Life Support EXTRACORPOREAL REWARMING TECHNIQUE CONSIDERATIONS Continuous venovenous (CVV) rewarming Circuit: CV catheter to CV, dual-lumen CV, or peripheral catheter No oxygenator/circulatory support Flow rates 150–400 mL/min ROR 2°–3°C (4.4°–6.6°F)/h Hemodialysis Circuit: single- or dual-vessel cannulation Stabilizes electrolyte or toxicologic abnormalities or rhabdomyolysis Exchange cycle volumes 200–500 mL/min ROR 2°–3°C (4.4°–6.6°F)/h Continuous arteriovenous rewarming (CAVR) Circuit: percutaneous 8.5-Fr femoral catheters Requires systolic blood pressure of 60 mmHg No perfusionist/pump/anticoagulation Flow rates 225–375 mL/min ROR 3°–4°C (6.6°–8.8°F)/h Cardiopulmonary bypass (CPB) Circuit: full circulatory support with pump and oxygenator Perfusate-temperature gradient 5°–10°C (11°–22° F) Flow rates 2–7 L/min (average 3–4 L/min) ROR up to 9.5°C (20.9°F)/h Venoarterial extracorporeal membrane oxygenation (VA-ECMO) Decreased risk of post-rewarming cardiorespiratory failure Improved neurologic outcome Abbreviations: CV, central venous; ROR, rate of rewarming.

with significant tissue destruction coupled with rhabdomyolysis. There is no evidence that extremely rapid rewarming improves survival in perfusing patients. TREATMENT Hypothermia When a patient is hypothermic, target organs and the cardiovas cular system respond minimally to most medications. Generally, medications are withheld below 30°C (86°F). In contrast to antiar rhythmics, low-dose vasopressor medications may improve the intra-arrest rates of return of spontaneous circulation. Because of increased binding of drugs to proteins as well as impaired metabo lism and excretion, either a lower dose or a longer interval between doses should be used to avoid toxicity. As an example, the adminis tration of repeated doses of digoxin or insulin would

be ineffective while the patient is hypothermic, but the residual drugs would be potentially toxic during rewarming. Achieving a mean arterial pressure of at least 60 mmHg should be an early objective. If the hypotension is disproportionate for temperature and does not respond to crystalloid/colloid infusion and rewarming, low-dose dopamine support (2–5 μg/kg per min) should be considered. Perfusion of the vasoconstricted cardiovas cular system also may improve with low-dose IV nitroglycerin. Atrial arrhythmias should be monitored initially without inter vention, as the ventricular response should be slow and, unless preexistent, most will convert spontaneously during rewarming. The role of prophylaxis and treatment of ventricular arrhythmias is complex. Preexisting ventricular ectopy may be suppressed by hypothermia and reappear during rewarming. There is limited evi dence to recommend any specific antiarrhythmic treatment. Initiating empirical therapy for adrenal insufficiency usually is not warranted unless the history suggests steroid dependence or hypoadrenalism or efforts to rewarm with standard therapy fail. The administration of parenteral levothyroxine to euthyroid patients with hypothermia, however, is potentially hazardous. Because labo ratory results can be delayed and confounded by the presence of the sick euthyroid syndrome (Chap. 394), historic clues or physical findings suggestive of hypothyroidism should be sought. When myxedema is the cause of hypothermia, the relaxation phase of the Achilles reflex is prolonged more than is the contraction phase. Hypothermia obscures most of the symptoms and signs of infec tion, notably fever and leukocytosis. Shaking rigors from infection may be mistaken for shivering. Except in mild cases, extensive cultures and repeated physical examinations are essential. Unless an infectious source is identified, empirical antibiotic prophylaxis is most warranted in the elderly, neonates, and immunocompromised patients. FROSTBITE Peripheral cold injuries include both freezing and nonfreezing cold injuries to tissue. Tissue freezes quickly when in contact with thermal conductors such as metal and volatile solutions. Other predisposing factors include constrictive clothing or boots, immobility, and vaso constrictive medications. Frostbite occurs when the tissue temperature drops below 0°C (32°F). Ice-crystal formation subsequently distorts and destroys the cellular architecture. Once the vascular endothelium is damaged, stasis progresses rapidly to microvascular thrombosis. After the tissue thaws, there is progressive dermal ischemia. The microvasculature begins to collapse, arteriovenous shunting increases tissue pressures, and edema forms. Finally, thrombosis, ischemia, and superficial necrosis appear. The development of mummification and demarcation may take weeks to months. CLINICAL PRESENTATION The initial presentation of frostbite can be deceptively benign. The symptoms always include a sensory deficiency affecting light touch, pain, or temperature perception. The acral areas and distal extremities

are the most common insensate areas. Some patients describe a clumsy or “chunk of wood” sensation in the extremity.

Deep frostbitten tissue can appear waxy, mottled, yellow, or vio laceous-white. Favorable presenting signs include some warmth or sensation with normal color. The injury is often superficial if the subcutaneous tissue is pliable or if the dermis can be rolled over bony prominences. Clinically, frostbite is superficial or deep. Superficial frostbite does not entail tissue loss but rather causes only anesthesia and erythema. The appearance of vesiculation surrounded by edema and erythema implies deeper involvement (Fig. 477-1). Hemorrhagic vesicles reflect a serious injury to the microvasculature and indicate severe frostbite. Damages in subcuticular, muscular, or osseous tissues may result in amputation. An alternative classification establishes grades based on the location of presenting cyanosis; that is grade 1, absence of cyanosis; grade 2, cyanosis on the

distal phalanx; grade 3, cyanosis up to the metacarpophalangeal (MP) joint; and grade 4 cyanosis proximal to the MP joint. The two most common nonfreezing peripheral cold injuries are chilblain (pernio) and immersion (trench) foot. Chilblain results from neuronal and endothelial damage induced by repetitive exposure to damp cold above the freezing point. Young females, particularly those with a history of Raynaud’s phenomenon, are at greatest risk. Persistent vasospasticity and vasculitis can cause erythema, mild edema, and pru ritus. Eventually plaques, blue nodules, and ulcerations develop. These lesions typically involve the dorsa of the hands and feet. In contrast, nonfreezing cold injury includes trench foot and immersion foot that results from repetitive exposure to wet cold above the freezing point. The feet initially appear cyanotic, cold, and edema tous. The subsequent development of bullae is often indistinguishable CHAPTER 477 Hypothermia and Peripheral Cold Injuries FIGURE 477-1 Frostbite with vesiculation, surrounded by edema and erythema.

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from frostbite. This vesiculation rapidly progresses to ulceration and liquefaction gangrene. Consider administering amitriptyline early for pain. Patients with milder cases report hyperhidrosis, cold sensitivity, and painful ambulation for many years.

TREATMENT Peripheral Cold Injuries When frostbite accompanies hypothermia, hydration may improve vascular stasis. Frozen tissue should be thawed rapidly and com pletely by immersion in circulating water at 37°–40°C (99°–104°F) for 30–60 min and not by using hot air. Rapid rewarming often produces an initial hyperemia. The early formation of large clear distal blebs is more favorable than that of smaller proximal dark hemorrhagic blebs. A common error is the premature termination of thawing, since the reestablishment of perfusion is intensely pain ful. Parenteral narcotics will be necessary with deep frostbite. If cyanosis persists after rewarming, the tissue compartment pressures should be monitored carefully. Many antithrombotic and vasodilatory treatment regimens have been evaluated. The prostacyclin analogue iloprost given within 48 h after rewarming is an option. There is no conclusive evidence that sympathectomy, steroids, calcium channel blockers, pentoxifylline, or hyperbaric oxygen salvages tissue. Patients who have deep frostbite injuries with the potential for significant morbidity should be considered for intravenous or intraarterial thrombolytic therapy. Angiography, fluorescence microangiography, or pyrophosphate scanning may help evaluate the injury and monitor the progress of tissue plasminogen activator therapy. Heparin is recommended as adjunctive therapy. Intraarte rial thrombolysis may reduce the need for digital and more proxi mal amputations when administered within 24 h of severe injuries. A treatment protocol for frostbite is summarized in Table 477-4. PART 15 Disorders Associated with Environmental Exposures Unless infection develops, any decision regarding debridement or amputation should generally be deferred. Angiography or tech netium-99 bone scan may assist in the determination of surgical margins. Magnetic resonance angiography may also demonstrate the line of demarcation earlier than does clinical demarcation. TABLE 477-4 Treatment for Frostbite BEFORE THAWING DURING THAWING AFTER THAWING Remove from environment. Consider parenteral analgesia and ketorolac. Gently dry and protect part; elevate; place pledgets between toes, if macerated. Prevent partial thawing and refreezing. Administer ibuprofen

(400 mg PO). If clear vesicles are intact, aspirate sterilely; if broken, debride and dress with antibiotic or sterile aloe vera ointment. Stabilize core temperature and treat hypothermia. Immerse part in 37°–39°C (99°–102.2°F) (thermometer-monitored) circulating water containing an antiseptic

soap until distal flush (10–45 min). Leave hemorrhagic vesicles intact to prevent desiccation and infection. Protect frozen part—no friction or massage. Encourage patient to gently move part. Continue ibuprofen

(400–600 mg PO [12 mg/kg

per day] q8 to 12h). Address medical or surgical conditions. If pain is refractory, reduce water temperature to 35°–37°C (95°–99°F) and administer parenteral narcotics. Consider tetanus prophylaxis; elevate part. Administer hydrotherapy at 37°C (99°F). Consider dextran or phenoxybenzamine or, in severe cases, thrombolysis rt-PA (IV or intraarterial). Abbreviation: rt-PA, recombinant tissue plasminogen activator.

The most common symptomatic sequelae reflect neuronal injury and persistently abnormal sympathetic tone, including paresthe sia, thermal misperception, and hyperhidrosis. Delayed findings include nail deformities, cutaneous carcinomas, and epiphyseal damage in children. Management of the chilblain syndrome is usually supportive. With refractory perniosis, alternatives include nifedipine, steroids, and limaprost, a prostaglandin E1 analogue. ■ ■FURTHER READING Dow J et al: Wilderness medical society clinical practice guidelines for the out-of-hospital evaluation and treatment of accidental hypother mia: 2019 update. Wilderness Environ Med 30(4S):S47, 2019. Pasquier M et al: Hypothermia outcome prediction after extracorpo real life support for hypothermic cardiac arrest patients: An external validation of the HOPE score. Resuscitation 139:321, 2019. Pasquier M et al: On-site treatment of avalanche victims: Scoping review and 2023 recommendations of the international commission for mountain emergency medicine (ICAR MedCom). Resuscitation 184:109708, 2023. Snijders B et al: Incidences of underlying causes of hypothermia in older patients in the emergency department: A systemic review. Eur Geriatr Med 14:411, 2023. Takauji S et al: Outcome of extracorporeal membrane oxygenation use in severe accidental hypothermia with cardiac arrest and circulatory instability: A multicentre, prospective, observational study in Japan (ICE-CRASH study). Resuscitation 182:109663, 2023. Teien HK et al: Training videos to prevent cold weather injuries. Int J Circumpolar Health 82:2195137, 2023. Zafren K et al: Induced hypothermia to 4.2°C with neurologically intact survival: A forgotten case series. Wilderness Environ Med 31:367, 2020. Daniel F. Danzl

Heat-Related Illnesses Climate change is globally increasing heat-related morbidity and mor tality. Extreme heat events are more frequent and are occurring in more widespread locations. Heat-related illnesses include a spectrum of disorders ranging from heat syncope, muscle cramps, and heat exhaus tion to medical emergencies such as heatstroke. The core body tem perature is normally maintained within a very narrow range. Although significant levels of hypothermia are tolerated (Chap. 477), multiorgan dysfunction occurs rapidly at temperatures >40.5°C (104.9°C). In con trast to heatstroke, the far more common sign of fever reflects intact thermoregulation. ■ ■THERMOREGULATION Humans are capable of significant heat generation. Strenuous exercise can increase heat generation twentyfold. The heat load from metabolic heat production and environmental heat absorption is balanced by a variety of heat dissipation mechanisms. These central integrative dis sipation pathways are orchestrated by the central thermostat, which is located in the preoptic nucleus of the anterior hypothalamus. Efferent signals sent via the autonomic nervous system trigger cutaneous vaso dilation and diaphoresis to facilitate heat loss. Normally, the body dissipates heat into the environment via four mechanisms. The evaporation of

skin moisture is the single most efficient mechanism of heat loss but becomes progressively ineffective as the relative humidity rises to >70%. The radiation of infrared elec tromagnetic energy directly into the surrounding environment occurs

continuously. (Conversely, radiation is a major source of heat gain in hot climates.) Conduction—the direct transfer of heat to a cooler object—and convection—the loss of heat to air currents—become ineffective when the environmental temperature exceeds the skin temperature. Factors that interfere with the evaporation of diaphoresis signifi cantly increase the risk of heat illness. Examples include dripping of sweat off the skin, constrictive or occlusive clothing, dehydration, and excessive humidity. While air is an effective insulator, the thermal con ductivity of water is 25 times greater than that of air at the same tem perature. The wet-bulb globe temperature (WBGT) is a commonly used index to assess the environmental heat load. The WBGT is superior to the “heat index,” which is only based on air temperature and humidity. The WBGT also incorporates radiant heat and wind speed. The regulation of this heat load is complex and involves the cen tral nervous system (CNS), thermosensors, and thermoregulatory effectors. The central thermostat activates the effectors that produce peripheral vasodilation and sweating. The skin surface is in effect the radiator and the principal location of heat loss, since skin blood flow can increase 25–30 times over the basal rate. This dramatic increase in skin blood flow, coupled with the maintenance of peripheral vasodila tion, efficiently radiates heat. At the same time, there is a compensatory vasoconstriction of the splanchnic and renal beds. Acclimatization to heat reflects a constellation of physiologic adap tations that permit the body to lose heat more efficiently. This process often requires 1 to several weeks of exposure and work in a hot envi ronment. During acclimatization, the thermoregulatory set point is altered, and this alteration affects the onset, volume, and content of diaphoresis. The threshold for the initiation of sweating is lowered, and the amount of sweat increases, with a lowered salt concentration. Sweating rates can be 1–2 L/h in acclimated individuals during heat stress. Plasma volume expansion also occurs and improves cutane ous vascular flow. The heart rate lowers, with a higher stroke volume. After the individual leaves the hot environment, improved tolerance to heat stress dissipates rapidly, the plasma volume decreases, and deacclimatization occurs within weeks. ■ ■PREDISPOSING FACTORS AND

DIFFERENTIAL DIAGNOSIS When there is an excessive heat load, unacclimated individuals can develop a variety of heat-related illnesses. Heat waves exacerbate the mortality rate, particularly among the elderly and among persons lack ing adequate nutrition and access to air-conditioned environments. Secondary vascular events, including cerebrovascular accidents and myocardial infarctions, occur at least 10 times more often in conditions of extreme heat. Exertional heat illness continues to occur when laborers, military personnel, or athletes exercise strenuously in the heat. In addition to the very young and very old, preadolescents and teenagers are at risk since they may use poor judgment when vigorously exercising in high humidity and heat. Other risk factors include obesity, poor condition ing with lack of acclimatization, and mild dehydration. Cardiovascular inefficiency is a common feature of heat illness. Any physiologic or pharmacologic impediment to cutaneous perfusion impairs heat loss. Many patients are unaware of the heat risk associ ated with their medications. Anticholinergic agents impair sweating and blunt the normal cardiovascular response to heat. Phenothiazines and heterocyclic antidepressants also have anticholinergic properties that interfere with the function of the preoptic nucleus of the anterior hypothalamus due to central depletion of dopamine. Calcium channel blockers, beta blockers, and various stimulants also inhibit sweating by reducing peripheral blood flow. To maintain the mean

arterial blood pressure, increased cardiac output must be capable of compensating for progressive dehydration. A variety of stimulants and substances of abuse also increase muscle activity and heat production. Careful consideration of the differential diagnosis is important in the evaluation of a patient for a potential heat-related illness. The clinical setting may suggest other etiologies, such as malignant

hyperthermia after general anesthesia. Neuroleptic malignant syn drome can be triggered by certain antipsychotic medications, includ ing selective serotonin reuptake inhibitors. A variety of infectious and endocrine disorders as well as toxicologic or CNS etiologies may mimic heatstroke (Table 478-1).

■ ■MINOR HEAT-EMERGENCY SYNDROMES Heat edema is characterized by mild swelling of the hands, feet, and ankles during the first few days of significant heat exposure. The prin cipal mechanism involves cutaneous vasodilation and pooling of inter stitial fluid in response to heat stress. Heat also increases the secretion of antidiuretic hormone and aldosterone. Systemic causes of edema, including cirrhosis, nephrotic syndrome, and congestive heart failure, can usually be excluded by the history and physical examination. Heat TABLE 478-1 Heat-Related Illness: Predisposing Factors and Differential Diagnosis ILLNESS PREDISPOSING FACTORS Cardiovascular inefficiency Age extremes Beta/calcium channel blockade Congestive heart failure Dehydration Diuresis Obesity Poor physical fitness Central nervous system illness Cerebellar injury Cerebral hemorrhage Hypothalamic cerebrovascular accident Psychiatric disorders Status epilepticus CHAPTER 478 Impaired heat loss Antihistamines Heterocyclic antidepressants Occlusive clothing Skin abnormalities Heat-Related Illnesses Endocrine and immune-related illness Diabetic ketoacidosis Multiple-organ dysfunction syndrome Pheochromocytoma Systemic inflammatory response syndrome Thyroid storm Excessive heat load Environmental conditions Exertion Fever Hypermetabolic state Lack of acclimatization Infectious illness Cerebral abscess Encephalitis Malaria Meningitis Sepsis syndrome Tetanus Typhoid Toxicologic illness Amphetamines Anticholinergic toxidrome Cocaine Dietary supplements Hallucinogens Malignant hyperthermia Neuroleptic malignant syndrome Salicylates Serotonin syndrome Strychnine Sympathomimetics Withdrawal syndromes (ethanol, hypnotics)

edema generally resolves without treatment in several days. Simple leg elevation or compression stockings will usually suffice. Diuretics are not effective and, in fact, predispose to volume depletion and the development of more serious heat-related illnesses.

Prickly heat (miliaria rubra, lichen tropicus) is a maculopapular, pruritic, erythematous rash that commonly occurs in clothed areas. Blockage of the sweat pores by debris from macerated stratum cor neum causes inflammation in the sweat ducts. As the ducts dilate, they rupture and produce superficial vesicles. The predominant symptom is pruritus. In addition to antihistamines, chlorhexidine in a light cream or lotion provides some relief. In adults, localized areas may ben efit from 1% salicylic acid TID, with caution taken to avoid salicylate intoxication. Clothing with breathable fabric should be clean and loose fitting, and activities or environments that induce diaphoresis should be avoided. Heat syncope (exercise-associated collapse) can follow endurance exercise or occur in the elderly. Other common clinical scenarios include prolonged standing while stationary in the heat and sudden standing after prolonged exposure to heat. Heat stress routinely causes relative volume depletion, decreased vasomotor tone, and peripheral vasodilation. The

cumulative effect of this decrease in venous return is postural hypotension, especially in nonacclimated elderly individu als. Many of those affected also have comorbidities. Therefore, other cardiovascular, neurologic, and metabolic causes of syncope should be considered. After removal from the heat source, most patients will recover promptly with cooling and rehydration. Hyperventilation tetany occurs in some individuals when exposure to heat stimulates hyperventilation, producing respiratory alkalosis, paresthesia, and carpopedal spasm. Unlike heat cramps, heat tetany causes very little muscle-compartment pain. Treatment includes pro viding reassurance, moving the patient out of the heat, and addressing the hyperventilation. PART 15 Disorders Associated with Environmental Exposures ■ ■HEAT CRAMPS Heat cramps (exercise-associated muscle cramps) are intermittent, painful, and involuntary spasmodic contractions of skeletal muscles. They typically occur in an unacclimated individual who is at rest after vigorous exertion in a humid, hot environment. In contrast, cramps that occur in athletes during exercise last longer, are relieved by stretch ing and massage, and resolve spontaneously. Of note, not all muscle cramps are related to exercise, and the dif ferential diagnosis includes many other disorders. A variety of medica tions, myopathies, endocrine disorders, and sickle cell trait are other possible causes. The typical patient with heat cramps is usually profusely diaphoretic and has been replacing fluid losses with copious water or other hypo tonic fluids. Roofers, firefighters, military personnel, athletes, steel workers, and field workers are commonly affected. Other predisposing factors include insufficient sodium intake before intense activity in the heat and lack of heat acclimatization, resulting in sweat with a high salt concentration. The precise pathogenesis of heat cramps appears to involve a relative deficiency of sodium, potassium, and fluid at the intracellular level. Coupled with copious hypotonic fluid ingestion, large amounts of sodium in the diaphoresis cause hyponatremia and hypochloremia, resulting in muscle cramps due to calcium-dependent muscle relax ation. Total-body depletion of potassium may be observed during the period of heat acclimatization. Rhabdomyolysis is very rare with rou tine exercise-associated muscle cramps. Heat cramps that are not accompanied by significant dehydra tion can be treated with commercially available electrolyte solutions. Although the flavored electrolyte solutions are far more palatable, two 650-mg salt tablets dissolved in 1 quart of water produce a 0.1% saline solution. Individuals should avoid the ingestion of undissolved salt tablets, which are a gastric irritant and may induce vomiting. ■ ■HEAT EXHAUSTION The physiologic hallmarks of heat exhaustion—in contrast to heat stroke—are the maintenance of thermoregulatory control and CNS

function. The core temperature is usually elevated but is generally <40.5°C (<105°F). The two physiologic precipitants are water depletion and sodium depletion, which often occur in combination. Laborers, athletes, and elderly individuals exerting themselves in hot environ ments, without adequate fluid intake, tend to develop water-depletion heat exhaustion. Persons working in the heat frequently consume only two-thirds of their net water loss and are voluntarily dehydrated. In contrast, salt-depletion heat exhaustion occurs more slowly in unaccli mated persons who have been consuming large quantities of hypotonic solutions. Heat exhaustion is usually a diagnosis of exclusion because of the multitude of nonspecific symptoms. If any signs of heatstroke are present, rapid cooling and crystalloid resuscitation should be initi ated immediately during stabilization and evaluation. Mild neurologic and gastrointestinal influenza-like symptoms are common. These symptoms may include headache, vertigo, ataxia, impaired judgment, malaise, dizziness, nausea, and muscle cramps. Orthostatic hypoten sion and sinus tachycardia develop frequently. More significant CNS impairment suggests heatstroke or other infectious, neurologic, or toxicologic diagnoses. Hemoconcentration does not always develop, and rapid infusion of isotonic IV fluids

should be guided by frequent electrolyte determina tions and perfusion requirements. Most cases of heat exhaustion reflect mixed sodium and water depletion. Sodium-depletion heat exhaustion is characterized by hyponatremia and hypochloremia. Hepatic ami notransferases are mildly elevated in both types of heat exhaustion. Urinary sodium and chloride concentrations are usually low. Some patients with heat exhaustion develop heatstroke after removal from the heat-stress environment. Aggressive cooling of non responders is indicated until their core temperature is 39°C (102.2°F). Except in mild cases, free water deficits should be replaced slowly over 24–48 h to avoid a decrease of serum osmolality by >2 mOsm/h. The disposition of younger, previously healthy heat-exhaustion patients who have no major laboratory abnormalities may include hospital observation and discharge after IV rehydration. Older patients with comorbidities (including cardiovascular disease) or predisposing factors often require inpatient fluid and electrolyte replacement, moni toring, and reassessment. ■ ■HEATSTROKE The clinical manifestations of heatstroke reflect a total loss of thermo regulatory function. Typical vital-sign abnormalities include tachy pnea, various tachycardias, hypotension, and a widened pulse pressure. Although there is no single specific diagnostic test, the historical and physical triad of exposure to a heat stress, CNS dysfunction, and a core temperature >40.5°C (104.9°C) helps establish the preliminary diagno sis. Some patients with impending heatstroke will initially appear lucid. The definitive diagnosis should be reserved until the other potential causes of hyperthermia are excluded. Many of the usual laboratory abnormalities seen with heatstroke overlap with other conditions. If the patient’s mental status does not improve with cooling, toxicologic screening may be indicated, and cranial computed tomography (CT) and spinal fluid analysis can be considered. The premonitory clinical characteristics may be nonspecific and include weakness, dizziness, disorientation, ataxia, and gastrointestinal or psychiatric symptoms. These prodromal symptoms often resemble heat exhaustion. The sudden onset of heatstroke occurs when the main tenance of adequate perfusion requires peripheral vasoconstriction to stabilize the mean arterial blood pressure. As a result, the cutaneous radiation of heat ceases. At this juncture, the core temperature rises dramatically. Since many patients with heatstroke also meet the criteria for systemic inflammatory response syndrome (SIRS) and have a broad differential diagnosis, rapid cooling is essential during the extensive diagnostic evaluation. Heat-induced SIRS reflects the responses of both the innate and the adaptive immune systems (Table 478-1). There are two forms of heatstroke with significantly different mani festations (Table 478-2). Classic (epidemic) heatstroke (CHS) usually occurs during long periods of high ambient temperature and humid ity, as during summer heat waves. Patients with CHS commonly have

TABLE 478-2 Typical Manifestations of Heatstroke CLASSIC EXERTIONAL Older patient Younger patient Predisposing health factors/ medications Healthy condition Epidemiology (heat waves) Sporadic cases Sedentary Exercising Anhidrosis (possible) Diaphoresis (common) Central nervous system dysfunction Myocardial/hepatic injury Oliguria Acute renal failure Coagulopathy (mild) Disseminated intravascular coagulation Mild lactic acidosis Marked lactic acidosis Mild creatine kinase elevation Rhabdomyolysis Normoglycemia/calcemia Hypoglycemia/calcemia Normokalemia Hyperkalemia Normonatremia Hyponatremia chronic diseases that predispose to heat-related illness, and they may have limited access to oral fluids. Heat dissipation mechanisms are overwhelmed by both endogenous heat production and exogenous heat stress. Patients with CHS are often compliant with prescribed medications that can impair tolerance to a heat stress. In many of these dehydrated CHS patients, sweating has ceased and the skin is hot and dry. The duration of core temperature elevation directly impacts mor bidity and mortality. If cooling is delayed, severe

hepatic dysfunction, renal failure, disseminated intravascular coagulation, and fulminant multisystem organ failure may occur. Hepatocytes are very heat sensi tive. On presentation, the serum level of aspartate aminotransferase (AST) is routinely elevated. Eventually, levels of both AST and alanine aminotransferase (ALT) often increase to >100 times the normal val ues. Coagulation studies commonly demonstrate decreased platelets, fibrinogen, and prothrombin. Most patients with CHS require cau tious crystalloid resuscitation, electrolyte monitoring, and—in certain refractory cases—consideration of central venous pressure (CVP) measurements and point of care ultrasonography (Chap. 493). Hyper natremia is secondary to dehydration in CHS. Many patients exhibit significant stress leukocytosis, even in the absence of infection. Patients with exertional heatstroke (EHS), in contrast to those with CHS, are often young and previously healthy, and their diagnosis is usually more obvious from the history. Athletes, laborers, and mili tary recruits are common victims. Unlike those with CHS, many EHS patients present profusely diaphoretic despite significant dehydration. As a result of muscular exertion, rhabdomyolysis and acute renal fail ure are more common in EHS. Studies to detect rhabdomyolysis and its complications, including hypocalcemia and hyperphosphatemia, should be considered. Hyponatremia, hypoglycemia, and coagulopa thies are frequent findings. Elevated creatine kinase and lactate dehy drogenase levels also suggest EHS. Oliguria is a common finding. Renal failure can result from direct thermal injury, untreated rhabdomyolysis, or volume depletion. Common urinalysis findings include microscopic hematuria, myoglobinuria, and granular or red cell casts. With both CHS and EHS, heat-related increases in cardiac biomarker levels may be present and reversible. Heatstroke often causes thermal cardiomyopathy. As a result, the CVP may be elevated despite signifi cant dehydration. In addition, the patient often presents with potentially deceptive noncardiogenic pulmonary edema and basilar rales despite being significantly hypovolemic. The electrocardiogram commonly displays a variety of tachyarrhythmias, nonspecific ST-T wave changes, and heat-related ischemia or infarction. Rapid cooling—not the initial administration of antiarrhythmic medications—is essential. Above 42°C (107.6°F), heat can rapidly produce direct cellular injury. Thermosensitive enzymes become nonfunctional, and eventu ally, there is irreversible uncoupling of oxidative phosphorylation. The

production of heat-shock proteins increases, and cytokines mediate a systemic inflammatory response. The vascular endothelium is also damaged, and this injury activates the coagulation cascade. Significant shunting away from the splanchnic circulation produces gastrointesti nal ischemia. Endotoxins further impair normal thermoregulation. As a result, if cooling is delayed, severe hepatic dysfunction, permanent renal failure, disseminated intravascular coagulation, and fulminant multisystem organ failure may occur.

■ ■COOLING STRATEGIES Endotracheal intubation and continuous core-temperature monitor ing should be considered both at the scene and as cooling is initi ated. Peripheral methods to measure temperature are not reliable. Hypoglycemia is a frequent finding. Since peripheral vasoconstriction delays heat dissipation, repeated administration of discrete boluses of isotonic crystalloid for hypotension is preferable to the administration of α-adrenergic agonists. Patients who require inotropic support after cooling and fluid resuscitation may require norepinephrine, followed by epinephrine and dobutamine. Rapid cooling is essential in both CHS and EHS, and an immedi ate improvement in vital signs and mental status may prove valuable for diagnostic purposes. Cool water (15°C [60°F]) is sprayed on the exposed skin while fans direct continuous airflow over the moistened skin. Cold packs applied to the neck, axillae, and groin are useful cool ing adjuncts. If

cardiac electrodes will not adhere, they can be applied to the patient’s back. Immersion cooling in ice-cold water may be a preferable option with EHS if appropriate medical staff and materials for aggressive cooling are available on scene until emergency medical services arrival. The initial increase in temperature from peripheral vasoconstriction will rapidly be overcome by the large conductive thermal transfer into cold water. This technique presents significant monitoring and resuscitation challenges in many clinical settings. The safety of immersion cooling is best established for young, previously healthy patients with EHS (but not for those with CHS). To improve patient access and monitoring, an alternative is ice water therapy. Ice cold water is continuously poured over the supine patient lying on a porous stretcher. Muscular massage improves vasodilatation. Another option that allows patient access is ice cold immersion in a commercial “cooling body bag.” To avoid hypothermic afterdrop (continued cooling), active cooling should be terminated at ~38°–39°C (100.4°F–102.2°F). CHAPTER 478 Heat-Related Illnesses The rate of cooling with commercial cooling blankets is very slow. Other methods are less efficacious and rarely indicated, such as IV infusion of cold fluids and cold irrigation of the bladder or gastrointes tinal tract. Cold thoracic and peritoneal lavage are invasive and rarely necessary. Endovascular cooling also provides effective cooling. ■ ■RESUSCITATION Aspiration commonly occurs in heatstroke, and endotracheal intuba tion is usually necessary. Depolarizing agents should be avoided. The metabolic demands are high, and supplemental oxygenation is essential due to hypoxemia induced by thermal stress and pulmonary dysfunc tion. The oxyhemoglobin dissociation curve is shifted to the right. Pneumonitis, pulmonary infarction, hemorrhage, edema, and acute respiratory distress syndrome occur frequently in heatstroke patients. Seizures are common and can occur during therapeutic cooling. Coldinduced tonic-clonic muscular rigidity mimics seizure activity. Refrac tory seizures may require monitoring with an electroencephalogram. The circulatory fluid requirements, particularly in CHS, may be deceptively modest. Aggressive cooling and modest volume repletion usually elevate the CVP to 12–14 mmHg. The reading, however, may be deceptive. Many patients present with a thermally induced hyperdy namic circulation accompanied by a high cardiac index, low peripheral vascular resistance, and an elevated CVP caused by right-sided heart failure. In contrast, most patients with EHS require far more zealous isotonic crystalloid resuscitation. The hypotension that is initially common among patients with heat stroke results from both dehydration and high-output cardiac failure caused by peripheral vasodilation. Inotropes causing α-adrenergic

stimulation (e.g., norepinephrine) can impede cooling by causing significant vasoconstriction. Vasoactive catecholamines such as dopa mine or dobutamine may be necessary if the cardiac output remains depressed despite an elevated CVP, particularly in patients with a hyperdynamic circulation.

A wide variety of tachyarrhythmias are routinely observed on presentation and usually resolve spontaneously during cooling. The administration of atrial or ventricular antiarrhythmic medications is rarely indicated during cooling. Anticholinergic medications (includ ing atropine) inhibit sweating and should be avoided. With a car diac rhythm that sustains perfusion, electrical cardioversion of the hyperthermic myocardium should be deferred until the myocardium is cooled. Significant shivering, discomfort, or extreme agitation is preferably mitigated with short-acting benzodiazepines or propofol. On the other hand, chlorpromazine may lower the seizure threshold, has anticholinergic properties, and can exacerbate the hypotension or cause neuroleptic malignant syndrome. Coagulopathies more commonly occur after the first day of ill ness. After cooling, the

patient should be monitored for disseminated intravascular coagulation, and replacement therapy with fresh-frozen plasma and platelets should be considered. Consider a dose of empiric antibiotics after culturing during cooling if the etiology of the hyper thermia remains unclear. There is no therapeutic role for antipyretics in the control of envi ronmentally induced hyperthermia; these drugs block the actions of pyrogens at hypothalamic receptor sites. Salicylates can further uncouple oxidative phosphorylation in heatstroke and exacerbate coagulopathies. Acetaminophen may further stress hepatic func tion. Dantrolene is ineffective when the temperature elevation is not caused by malignant hyperthermia. Although aminocaproic acid impedes fibrinolysis, it may cause rhabdomyolysis and is not recom mended in heatstroke. PART 15 Disorders Associated with Environmental Exposures ■ ■DISPOSITION Most patients with minor heat-emergency syndromes (including heat edema, heat syncope, and heat cramps) require only stabilization and

treatment with outpatient follow-up. Although there are no decision rules to guide disposition choices in heat exhaustion, many of these patients have multiple predisposing factors and comorbidities that will require prolonged observation or hospital admission. Essentially all patients with actual heatstroke require admission to a monitored setting, and most require intensive care. There are reports of very high survival rates of patients following prehospital immersion cooling without intensive care. Most or all of these patients appear to have had heat exhaustion. Many actual heatstroke patients also require prolonged tracheal intubation, invasive hemodynamic monitoring, and support for various degrees of multiorgan dysfunction syndrome. The prognosis worsens if the initial core temperature exceeds 42°C (107.6°F) or if there was a prolonged period during which the core temperature exceeded this level. Other features of a negative prognosis include acute renal failure, massively elevated liver enzymes, and sig nificant hyperkalemia. As expected, the number of dysfunctional organ systems also correlates directly with mortality risk. ■ ■FURTHER READING Bouchama A et al: Classic and exertional heatstroke. Nat Rev Dis Primers 8:1, 2022. Epstein Y, Yanovich R: Heatstroke. N Engl J Med 380:2449, 2019. Filep E et al: Exertional heat stroke, modality cooling rate, and survival outcomes: a systematic review. Medicina 56:589, 2020. Kaewput W et al: Inpatient burden and mortality of heatstroke in the United States. Int J Clin Pract 75:e13837, 2020. Lipman GS et al: Wilderness Medical Society practice guidelines for the prevention and treatment of heat-related illness: 2019 Update. Wilderness Environ Med 30:S33, 2019. Platt M et al: Heat illness, in Rosen’s Emergency Medicine: Concepts and Clinical Practice, 10th ed. Walls RM et al (eds). Philadelphia, Elsevier, 2023, pp. 1771-1780. Rublee C et al: Evidence-based heatstroke management in the emer gency department. West J Emerg Med 22:186, 2021. Sorensen C, Hess J: Treatment and prevention of heat-related illness. N Engl J Med 387:1404, 2022.