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CLINICAL REVIEW

Travellers' diarrhoea

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Diarrhoea is a common problem affecting between 20% and 60% of travellers,[1] particularly those visiting low and middle income countries. Travellers' diarrhoea is defined as an increase in frequency of bowel movements to three or more loose stools per day during a trip abroad, usually to a less economically developed region. This is usually an acute, self limiting condition and is rarely life threatening. In mild cases it can affect the enjoyment of a holiday, and in severe cases it can cause dehydration and sepsis. We review the current epidemiology of travellers' diarrhoea, evidence for different management strategies, and the investigation and treatment of persistent diarrhoea after travel.

Who is at risk?

Variation in incidence[1 2] may reflect the degree of risk for different travel destinations and dietary habits while abroad. Destinations can be divided into low, medium, and high risk (see box 1). Rates of diarrhoea are likely to correlate closely with the quality of local sanitation.

Backpackers have roughly double the incidence of diarrhoea compared with business travellers.[4] Travel in cruise ships is associated with large outbreaks of viral and bacterial gastroenteritis.[5] General advice is to avoid eating salads, shellfish, and uncooked meats. There is no strong evidence that specific dietary measures reduce incidence of diarrhoea, but studies examining this are likely to be biased by imperfect recall of what was eaten.[6] Risk factors for travellers' diarrhoea are listed in box 2.

What are the most important causes of travellers' diarrhoea?

Most studies report a failure to identify the causative pathogen in between 40% and 70% of cases.[10] This includes multicentre studies based in high prevalence settings (that is, during travel).[3-12] This low diagnostic yield is partly due to delay in obtaining samples and partly due to the insensitivity of laboratory investigations. Older studies did not consistently attempt to identify enteroaggregative *Escherichia coli* (EAEC), and surveillance studies vary in reporting of other *E coli* species.[3] Where a pathogen is identified, bacteria are the commonest cause of acute travellers' diarrhoea, with the remainder being caused by norovirus, rotavirus, or similar viruses (see table 1⇓). Protozoa such as *Giardia lamblia* can also cause acute diarrhoea, but they are more often associated with persistent diarrhoea, lasting more than two weeks. *Cyclospora catayensis*, another protozoan cause of diarrhoea, was identified in an increased number of symptomatic travellers returning from Mexico to the UK and Canada in 2015.[13]

Table 1⇓ illustrates overall prevalence of causative agents in returning travellers with diarrhoea. However relative importance varies with country of exposure. Rates of enterotoxigenic *E coli* (ETEC) are lower in travellers returning from South East Asia than in those returning from South Asia, sub-Saharan Africa, and Latin America, whereas rates of *Campylobacter jejuni* are higher. Norovirus is a more common cause in travellers to Latin America and sub-Saharan Africa, and *Giardia lamblia* and *Entamoeba histolytica* are more common in travellers to South and South East Asia.[10]

The importance of enterotoxigenic *E coli* as a cause for diarrhoea in travellers returning from Latin America has been decreasing over the past four decades.[10] A large scale analysis of EuroTravNet surveillance data shows increasing incidence of *Campylobacter jejuni* infection in travellers returning from India, Thailand, and Pakistan.[2]

How does travellers' diarrhoea present?

Most episodes of travellers' diarrhoea start during the first week of travel, with the peak incidence on the second or third day after arrival.[8 14]

Typically diarrhoea caused by enterotoxigenic *E coli* ("turista") is watery and profuse, and preceded by abdominal cramps, nausea, and malaise. Symptoms are not a reliable guide to aetiology, but upper gastrointestinal manifestations such as bloating and belching tend to predominate with *Giardia lamblia*, while colitic symptoms such as urgency, bloody diarrhoea, and cramps are seen more often with *Campylobacter jejuni* and *Shigella* spp.

Most episodes will last between one and seven days, with approximately 10% lasting for longer than one week, 5% lasting more than two weeks, and 1% lasting more than 30 days.[8] During the illness, few patients will be severely incapacitated (in one large prospective cohort about 10% of 2800 participants were confined to bed or consulted a physician), but planned activities are often cancelled or postponed.[8]

What you need to know

- Enterotoxic *Escherichia coli* (ETEC) is the most common cause of acute travellers' diarrhoea globally
- Chronic (>14 days) diarrhoea is less likely to be caused by bacterial pathogens
- Prophylactic antibiotic use is only recommended for patients vulnerable to severe sequelae after a short period of diarrhoea, such as those with ileostomies or immune suppression
- A short course (1-3 days) of antibiotics taken at the onset of travellers' diarrhoea reduces the duration of the illness from 3 days to 1.5 days
- Refer patients with chronic diarrhoea and associated symptoms such as weight loss for assessment by either an infectious diseases specialist or gastroenterologist

Methods

We searched PubMed and Cochrane Library databases for "travellers' diarrhoea," and "travel-associated diarrhoea," to identify relevant articles, which were added to personal reference collections and clinical experience. Where available, systematic reviews and randomised controlled trials were preferentially selected.

Box 1: Risk of travellers' diarrhoea according to destination[1 3]

High risk destinations

- South and South East Asia*
- Central America*
- West and North Africa*
- South America
- East Africa

Medium risk

- Russia
- China
- Caribbean
- South Africa

Low risk

- North America
- Western Europe
- Australia and New Zealand

*Regions with particularly high risk of travellers' diarrhoea

Box 2: Factors increasing risk of travellers' diarrhoea[4-9]

By increased dietary exposure

- Backpacking
- Visiting friends and family
- All-inclusive holidays (such as in cruise ships)

By increased susceptibility to an infectious load

- Age <6 years
- Use of H_2 receptor antagonists and proton pump inhibitors
- Altered upper gastrointestinal anatomy
- Genetic factors (blood group O predisposes to shigellosis and severe cholera infection)

How can travellers' diarrhoea be prevented?

Several controlled trials have failed to demonstrate an impact of food and drink hygiene advice on rates of diarrhoea.[15] However, the clear food-related source of most diarrhoeal pathogens means that general consensus among travel physicians is to continue to recommend boiling water, cooking food thoroughly, and peeling fruit and vegetables.[6] Other basic advice includes avoiding ice, shellfish, and condiments on restaurant tables, using a straw to drink from bottles, and avoiding salads and buffets where food may have been unrefrigerated for several hours. Travellers should be advised to drink bottled water where available, including in alcoholic drinks, as alcohol does not sterilise non-bottled water. If bottled water is not available, water can be purified by boiling, filtering, or use of chlorine based tablets.[16] There is some weak evidence that use of alcohol hand gel may reduce diarrhoea rates in travellers,[17] but, based on studies in non-travellers, it is reasonable to strongly encourage travellers to adhere to good hand hygiene measures. Two recent systematic reviews estimated hand washing with soap reduces the risk of diarrhoeal illness by 30-40%.[18 19]

When is antibiotic prophylaxis recommended?

For most travellers antibiotic chemoprophylaxis (that is, daily antibiotics for the duration of the trip) is not recommended. While diarrhoea is annoying and distressing, severe or long term consequences from a short period of diarrhoea are rare, and routine use of chemoprophylaxis would create a large tablet burden and expose users to possible adverse effects of antibiotic therapy such as candidiasis and diarrhoea associated with *Clostridium difficile*.

Chemoprophylaxis should be offered to those with severe immune suppression (such as from chemotherapy for malignancy or after a tissue transplant, or advanced HIV infection), underlying intestinal pathology (inflammatory bowel disease, ileostomies, short bowel syndrome), and other conditions such as sickle cell disease or diabetes where reduced oral intake may be particularly dangerous (table 2⇓).[22] These patient groups may be unable to tolerate the clinical effects and dehydration associated with even mild diarrhoea, or the consequences of more invasive complications such as bacteraemia. For such patients, it is important to discuss the benefits of treatment aimed at preventing diarrhoea and its complications against the risks of antibiotic associated diarrhoea and other side effects. If antibiotics are prescribed then consideration should be given to any possible interactions with other medications that the patient is taking.

A small comparative study in US soldiers showed that malaria prophylaxis with daily doxycycline has the added benefit of reducing rates of travellers' diarrhoea caused by enterotoxigenic *E coli* and *Campylobacter jejuni*.[23]

Do vaccines have a role in prevention of travellers' diarrhoea?

Vaccines have been developed and licensed against *Salmonella typhi*, *Vibrio cholerae*, and rotavirus—all with reasonable efficacy. However, unlike enterotoxigenic *E coli*, none of these is a major cause of travellers' diarrhoea, and only vaccines against *S typhi* are recommended for most travellers to endemic settings. Phase 3 trials of enterotoxigenic *E coli* toxin vaccines have been undertaken but have failed to demonstrate efficacy.[24] Studies suggest vaccines against enterotoxigenic *E coli* would have a major public health impact in high burden countries, and further candidate vaccines are in development.[25]

What are the options for self administered treatment?

Table 3⇓ summarises the options for self treatment.

Anti-motility agents and oral rehydration therapy

For most cases of travellers' diarrhoea, oral rehydration is the mainstay of treatment. This can be achieved with clear fluids such as diluted fruit juice or soups. Young children, elderly people, and those at greater risk from dehydration (that is, those with medical comorbidities) are recommended to use oral rehydration salts (or a mixture of six level teaspoons of sugar and half a teaspoon of salt in a litre of clean water if rehydration salts are unavailable) (see http://rehydrate.org/rehydration/index.html).

Anti-motility agents such as loperamide may be appropriate for mild symptoms, or where rapid cessation of diarrhoea is essential. Case reports of adverse outcomes such as intestinal perforation suggest anti-motility agents should be avoided in the presence of severe abdominal pain or bloody diarrhoea, which can signify invasive colitis.[26] Systematic review of several randomised controlled trials have demonstrated a small benefit from taking bismuth subsalicylate, but this has less efficacy in reducing diarrhoea frequency and severity than loperamide.[27]

Antibiotics

Symptomatic treatment is usually adequate and reduces antibiotic use. However, some travellers will benefit from rapid cessation of diarrhoea, particularly if they are in a remote area with limited access to sanitation facilities or healthcare. Several systematic reviews of studies comparing antibiotics (including quinolones, azithromycin, and rifaximin) against placebo have shown consistent shortening of the duration of diarrhoea to about one and a half days from around three days.[28-30] Short courses (one to three days) of antibiotics are usually sufficient to effect a cure.[30]

For some people travelling to high and moderate risk areas (see box 1) it will be appropriate to provide a short course of a suitable antibiotic, with advice to start treatment as soon as they develop diarrhoea and to keep well hydrated. Choice of antibiotic will depend on allergy history, comorbidities, concomitant medications, and destination. Avoid quinolones for both prophylaxis and treatment of travellers to South East and South Asia as levels of quinolone resistance are high.[31] Azithromycin remains effective in these areas, but resistance rates are likely to increase.

A meta-analysis of nine randomised trials showed that the addition of loperamide to antibiotic treatment (including azithromycin, ciprofloxacin, and rifamixin) resulted in statistically significantly higher rates of cure at 24 and 48 hours compared with antibiotic alone.[32] Travellers can be advised to add loperamide to their antibiotic treatment to reduce the time to symptomatic improvement as long as there are no features of invasive colitis such as severe pain, high fever, or blood visible in the diarrhoea.[30] If any of these symptoms develop, travellers are advised to seek medical advice immediately.

Returned travellers with persistent diarrhoea

Most bacterial causes mentioned do not cause persistent diarrhoea in immune competent adults. Travellers with diarrhoea persisting beyond 14 days may present in primary or secondary care on their return and require assessment for other underlying causes of persistent diarrhoea.

Table 4⇓ lists the important clinical history and symptoms that can point to the underlying cause.

What investigations should be sent?

For diarrhoeal symptoms that persist beyond 14 days following travel (or sooner if there are other concerning features such as fever or dysentery), offer patients blood tests for full blood count, liver and renal function, and inflammatory markers; stool samples for microscopy and culture; and examination for ova, cysts, and parasites. Historically, advice has been to send three stool samples for bacterial culture, but this is unlikely to increase the diagnostic yield. Instead, stool microscopy can be used to distinguish inflammatory from non-inflammatory causes: a small observational study found presence of faecal leucocytes was predictive of a positive bacterial stool culture.[33] Yield from stool culture may be increased by dilution of the faecal sample, and the introduction of molecular tests such as polymerase chain

reaction (PCR) for common gastrointestinal pathogens such as *Campylobacter* spp may decrease turnaround times and increase yield.[34]

Additional tests should be offered according to symptoms and risk (table 4⇓). If the patient has eosinophilia and an appropriate travel history, the possibility of schistosomiasis, strongyloides, and other helminthic infections should be considered. While schistosomiasis can rarely cause diarrhoea in the context of acute infection, serology may be negative in the first few months of the illness.

Imaging is required only if the patient has signs of severe colitis or local tenderness, in which instances toxic megacolon, inflammatory phlegmon, and hepatic collections should be excluded. Patients with severe colitis or proctitis may need joint assessment with gastroenterology and consideration of endoscopy, or laparotomy if perforation has occurred.

Where infectious and non-infectious causes have been appropriately excluded, the most likely diagnosis is post-infectious irritable bowel syndrome, although diarrhoea can also herald underlying bowel pathology and anyone with red flags for malignancy should be referred by the appropriate pathway for assessment. Post-infectious irritable bowel syndrome has an incidence of around 30% after an acute episode of travel associated gastroenteritis.[35 36] It is more commonly a sequela of prolonged episodes of diarrhoea or diarrhoea associated with fever and bloody stools.[36] There is weak evidence from small randomised trials suggesting that exclusion of foods high in fermentable carbohydrates (FODMAP) may be helpful.[37] Exclusion of dietary lactose and use of loperamide, bile acid sequestrants, and probiotics can also be tried, but there is limited evidence for long term benefit.[35-38]

How should giardiasis be managed?

The most common pathogen identified in returning travellers with chronic diarrhoea is *Giardia lamblia,* particularly among people returning from South Asia.[39] Use of *G lamblia* PCR testing has increased detection,[40] which potentially will identify infection in some patients previously labelled as having post-infectious irritable bowel syndrome and in those whose diarrhoea may have been attributed to non-pathogenic protozoa. Most patients respond to 5-nitroimidazoles (a systematic review of a large number of trials has shown similar cure rates with tinidazole 2 g once only or metronidazole 400 mg three times daily for five days[41]), but refractory cases are increasingly common and require investigation, identification of underlying risk factors, and repeated treatment (various antimicrobials have been shown to be effective but may have challenging risk profiles).

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Questions for future research

- What is the justification for using antibiotics to treat a usually self limiting illness, in the wider context of rising levels of global antimicrobial resistance rates? What is the clinical impact of resistant enterobacteriaciae found in stool samples from returning travellers?[42 43]
- To what extent do host genetic factors increase susceptibility to gastrointestinal pathogens, and can this help to identify at risk populations and tailor treatments to individual patients?
- What is the long term efficacy of new pharmacological treatments such as selective serotonin reuptake inhibitors and rifaximin in post-infectious irritable bowel syndrome?

Tips for non-specialists

- Include consideration of chemoprophylaxis for high risk individuals in pre-travel assessment
- Advise all travellers on hygiene measures (such as hand washing and food consumption) and symptom management of diarrhoea
- Avoid quinolones for prophylaxis or treatment in travellers to South East and South Asia
- Where diarrhoea persists beyond 14 days, consider investigations to rule out parasitic and non-infectious causes. The presence of white blood cells on stool microscopy indicates an inflammatory cause

Additional educational resources

Resources for patients

- National Travel Health Network and Centre (NaTHNaC): http://travelhealthpro.org.uk/travellers-diarrhoea/
  Provides pre-travel advice, as well as links to country-specific advice
- Fit for Travel: www.fitfortravel.nhs.uk/advice/disease-prevention-advice/travellers-diarrhoea.aspx
  Provides similar pre-travel advice on hygiene and disease prevention
- Patient.co.uk: http://patient.info/doctor/travellers-diarrhoea-pro
  Has patient leaflets and more detailed information about investigation and management of travellers' diarrhoea

Resources for healthcare professionals

- Centers for Disease Control and Prevention yellow book: http://wwwnc.cdc.gov/travel/yellowbook/2016/the-pre-travel-consultation/travelers-diarrhea
  Provides a guide to pre-travel couselling
- Rehydration Project website: http://rehydrate.org/rehydration/index.html
  Has additional information about non-pharmacological management of diarrhoea

How patients were involved in the creation of the article

No patients were involved in the creation of this review.

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Tables

Table 1| Frequency of pathogens causing travellers' diarrhoea23101112

Pathogen	Prevalence*	Clinical features
Bacterial		
Enterotoxigenic *Escherichia coli* (ETEC)	12-34%	Acute watery diarrhoea, abdominal cramping. Fever less common
Enteroaggregative *E coli* (EAEC)	1-24%	Acute watery diarrhoea
Campylobacter jejuni	8-32%	Acute diarrhoea, abdominal cramps, bloody stools, fever
Salmonella spp	4-9%	Acute diarrhoea, fever, vomiting, abdominal cramps
Shigella spp	2-14%	Acute diarrhoea, abdominal cramps, bloody stools, fever, tenesmus. Features may persist
Aeromonas spp	<5%	Acute watery diarrhoea, fever, abdominal cramps
Plesiomonas spp	<5%	Acute lower abdominal pain, bloody stools, tenesmus, fever
Vibrio cholerae	<1%	Acute profuse watery diarrhoea
Viral		
Norovirus	7-9%	Acute watery diarrhoea, vomiting
Rotavirus	13-17%	Acute watery diarrhoea, abdominal cramps, vomiting, low grade fever
Parasitic		
Giardia lamblia	1-6%	Chronic diarrhoea, may be steatorrhoea, flatus, distension
Cryptosporidium spp	1-3%	Watery diarrhoea, sometimes abdominal cramps, may be prolonged
Entamoeba histolytica	1-4%	Acute lower abdominal pain, bloody stools, tenesmus, fever

*Percentage of all cases of diarrhoea with identified cause in these studies

Table 2| **Antibiotic chemoprophylaxis options for immunosuppressed or other high risk travellers**

Antibiotic	Dose	Percentage protection[6-21]
Ciprofloxacin	500 mg once daily	80-100%
Norfloxacin	400 mg once daily	75-95%
Rifaximin	200 mg once or twice daily	72-77%
Bismuth subsalicylate	2 tablets four times daily	62-65%

Table 3| **Summary of self treatment choices**

Severity of symptoms	Treatment
All cases	Liberal intake of clear fluids. Oral rehydration salts for young children, elderly people, and travellers with medical comorbidities
Mild symptoms (1-2 unformed stools per 24 hours)	Loperamide: 4 mg taken immediately, then 2 mg for each loose stool to a maximum of 16 mg per day
Moderate symptoms:	
South and Central America, Africa	Ciprofloxacin: 500 mg twice daily for three days
South and South East Asia	Azithromycin: 1 g single dose, or 500 mg daily for three days Rifaximin: 200 mg three times daily for three days
High fever, severe abdominal pain, bloody diarrhoea	Seek local medical assistance Avoid loperamide

Table 4| **Assessment of chronic diarrhoea**

Symptoms	Cause
Bloating, nausea, belching	*Giardia lamblia,* microsporidiosis
Fever	*Salmonella typhi* or *S paratyphi,* malaria
Bloody diarrhoea	*Entamoeba histolytica,* inflammatory bowel disease
Arthropathy, uveitis	Inflammatory bowel disease, reactive arthritis after colitis
Greasy, malodorous stools	Malabsorption, *Giardia lamblia,* lactose intolerance
History	
Unprotected sexual intercourse	HIV, *Shigella* spp, *Lymphogranuloma venereum, Giardia lamblia*
Antibiotic use	*Clostridium difficile*
Symptoms before travel	Coeliac disease, inflammatory bowel disease, irritable bowel disease
Autoimmune disease	Hyperthyroidism, coeliac disease

Review Article

Wilderness medicine

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BACKGROUND: Human activity in wilderness areas has increased globally in recent decades, leading to increased risk of injury and illness. Wilderness medicine has developed in response to both need and interest.

METHODS: The field of wilderness medicine encompasses many areas of interest. Some focus on special circumstances (such as avalanches) while others have a broader scope (such as trauma care). Several core areas of key interest within wilderness medicine are discussed in this study.

RESULTS: Wilderness medicine is characterized by remote and improvised care of patients with routine or exotic illnesses or trauma, limited resources and manpower, and delayed evacuation to definitive care. Wilderness medicine is developing rapidly and draws from the breadth of medical and surgical subspecialties as well as the technical fields of mountaineering, climbing, and diving. Research, epidemiology, and evidence-based guidelines are evolving. A hallmark of this field is injury prevention and risk mitigation. The range of topics encompasses high-altitude cerebral edema, decompression sickness, snake envenomation, lightning injury, extremity trauma, and gastroenteritis. Several professional societies, academic fellowships, and training organizations offer education and resources for laypeople and health care professionals.

CONCLUSIONS: The future of wilderness medicine is unfolding on multiple fronts: education, research, training, technology, communications, and environment. Although wilderness medicine research is technically difficult to perform, it is essential to deepening our understanding of the contribution of specific techniques in achieving improvements in clinical outcomes.

KEY WORDS: Wilderness medicine; High-altitude sickness; Dive medicine; Envenomation; Trauma; Hyperthermia; Hypothermia; Frostbite; Avalanche; Combat injuries; Search and rescue; Travel medicine; Disaster medicine

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INTRODUCTION

Wilderness medicine is a multifaceted field of medical practice with a long history.[1] Its definition must consider concepts of distance and time from typical hospital care, the activity in which an injured or ill person was engaged, the possibility of prolonged environmental exposure, a scarcity of resources, and the risks faced by rescuers and health care providers. A flexible approach to planning, patient assessment, and evacuation is mandatory.[2,3] Howard D. Backer, MD, a past-president of the Wilderness Medical Society, eloquently described wilderness medicine by its remoteness, physiology, need for improvisation, and dependence on clinical examination and judgment.[4] In stark contrast, "street" medicine benefits from an abundance of rescue personnel, technologic capability, and rapid ground and air transportation to facilities that can provide definitive care.

Ongoing basic research and epidemiology continue

to define and refine wilderness medicine, reporting morbidity and mortality rates from diverse populations and regions. Data from U.S. National Parks indicate that the most common injuries treated by wilderness medicine specialists are soft-tissue lesions, sprains, strains, and lower-extremity fractures.[5–7]

Early development

In 1983, the Wilderness Medical Society (WMS) was founded by three physicians: Drs. Greer, Auerbach, and Kizer, from northern California. This non-profit organization is based in Salt Lake City, Utah, USA. Its objectives are to advance wilderness medicine health care, education, and research.[8] The society launched the *Journal of Wilderness Medicine* in 1987 as a peer-reviewed and indexed publication. As the journal matured, its name was changed to *Wilderness and Environmental Medicine*. It is published quarterly and contains articles on bench and clinical research as well as editorials. Other journals that address topics in wilderness medicine include *High Altitude Medicine and Biology*; *Military Medicine*; *Journal of Special Operations Medicine*; *Aviation Space and Environmental Medicine*; *Undersea and Hyperbaric Medicine*; *Diving and Hyperbaric Medicine*; *Journal of Applied Physiology*; *Medicine & Science in Sports & Exercise*; and the *Journal of Venom Research*. An additional resource is the quarterly newsletter *Wilderness Medicine Magazine* (www.wildernessmedicinemagazine.com), which started as a pamphlet and has developed into an online, interactive, hyperlinked publication.

Basic care recommendations were first published in *WMS Practice Guidelines for Wilderness Emergency Care*, edited by William Forgey, MD; the fifth edition of this book was published in 2006.[9] These practice guidelines are updated by subject matter experts, ranked by class of evidence, and published individually as the *Wilderness Medical Society Practice Guidelines*. They are indexed and published in the journal *Wilderness and Environmental Medicine*.

Paul Auerbach, MD, edits the primary textbook on the topic, *Wilderness Medicine*.[10] The sixth edition, published in 2012, contains 114 chapters.

Areas of interest

The field of wilderness medicine encompasses many areas of interest. Some focus on special circumstances (such as avalanches) while others have a broader scope (such as trauma care). Several core areas of key interest within wilderness medicine are discussed in this section.

High altitude

High-altitude travel is common and increasing. From ski resorts to mountaineering, the incidence of acute mountain sickness (AMS) is high, estimated to affect 25% of people who ascend to even moderate altitudes.[11] High-altitude pulmonary edema (HAPE) and high-altitude cerebral edema (HACE) are more serious life-threatening conditions and, thankfully, are less common.[12–15] The primary treatment for these conditions involves descent and administration of oxygen. Pharmacologic management usually begins with acetazolamide and glucocorticoid steroids.[16,17]

Dive medicine

Diving for recreation and technical purposes is increasingly popular worldwide. Dive-specific injuries include decompression illness and barotrauma. The incidence of decompression illness appears to be stable across recreational, professional, and scientific venues (0.003%–0.01%). Scientific diving has the lowest rate of injury.[18,19] Decompression illness is triggered by decompression stress and subsequent nitrogen bubble formation, possibly pro-inflammatory microparticle formation.[20] Interestingly, inner-ear decompression illness has been diagnosed more frequently in recent years.[21,22] Treatment includes recompression in a hyperbaric chamber; portable chambers for use in remote areas are being developed.[23] A number of descriptions of in-water recompression have been published.[24–27]

Envenomation

The toxicology and pathology of snake bites, arthropod stings, and marine envenomations vary widely, with significant differences in management based on location. This variation is related to local fauna as well as the availability (or lack) of anti-venoms.[28] Victims' reactions to envenomation are often self-limiting, but systemic reactions leading to coagulopathy or respiratory arrest induced by neurotoxins are certainly possible. Some envenomations, such as from Cubozoa jellyfish, can lead to massive adrenergic surge and cardiovascular collapse.[29–36]

Trauma

Trauma is a common cause of wilderness morbidity. A leading cause of trauma mortality is head injury after a fall from height during hiking, rock climbing, mountain biking, and snow-related activities. Although most traumatic injuries are "minor" and involve the lower extremities, they often end outdoor activities and extended trips. In rare events, trauma involves multiple systems and becomes life-threatening.

This category of wilderness medicine includes injuries sustained in motor vehicle crashes that occur during travel to and within remote areas.[6] Retrospective surveys have shed light on the nature and frequency of traumatic injuries sustained while climbing.[37–46]

Advances in cervical spine management and immobilization, opiate-based pain control, and invasive procedures are being discussed.[47–51] Advanced techniques such as shoulder reduction are being taught to lay providers.[52] Even such specialized injuries as prolonged harness suspension are being considered.[53]

Hyperthermia

Heat exposure and heat stress can cause a spectrum of illness, ranging from benign heat cramps to life-threatening heatstroke.[54] Heatstroke is a severe, sometimes fatal, disease that is defined as elevated core temperature accompanied by neurologic dysfunction. Heatstroke is a complex process that involves cellular dysfunction, cardiac conduction dysfunction, release of pro-inflammatory cytokines, concomitant intravascular depletion, and subsequent circulatory collapse.[55] The degree of dehydration varies. In contrast to classic heatstroke, exertional heatstroke can occur even in moderate temperatures, especially among endurance wilderness athletes.[56]

Removal from the heat stress and rapid whole body cooling are essential to mitigate encephalopathy, coagulopathy, and multi-organ failure.[57–59] The optimal cooling technique is total body immersion in ice or cold water, but this intervention is usually not practical in wilderness settings. Under these circumstances, skin wetting and aggressive fanning can be used in an attempt to lower the patient's temperature. This technique might induce shivering, but there is no evidence suggesting that the concomitant heat production conflicts with the attempt to lower the core temperature.[60,61]

Hypothermia

Accidental hypothermia is a common concern in wilderness medicine both as a primary condition and as a complication of illness or trauma. The mortality rate increases when the core temperature falls below 95 ˚F (35 ˚C) in association with trauma, resulting in acidosis, coagulopathy, and multiple organ dysfunction.[62,63] Hypothermia occurs when cold stress is not matched by heat production. Interestingly, hypothermia can even occur in temperate climates.[64]

Multiple physiologic and behavioral mechanisms work together to maintain euthermia; however, they can fail when certain temperature thresholds are reached. "Paradoxic undressing" is thought to be caused by cutaneous vasodilation and alterations in cognition; "terminal burrowing" might be a primitive reflex.[65–67]

The basics of hypothermia resuscitation include prevention of further heat loss, rewarming, and support of physiologic processes.[68,69] Field research with healthy subjects and invasive monitoring has clarified the physiology of cooling and afterdrop. Improvised and commercial methods for preventing further body heat loss are being developed.[70–75] Arteriovenous anastomoses rewarming with or without negative-pressure devices could offer a technique to rapidly rewarm severely hypothermic patients in the field.[76,77]

Resuscitation protocols for hypothermia and cardiac arrest have long engendered controversy, because of the resources that are required and the dismal recovery statistics. In some cases, prolonged resuscitation will be successful in achieving a positive neurologic outcome. But, in remote settings, the required resources are usually not available.[9,78] Nonetheless, the state of Alaska has had progressive emergency medical services (EMS) protocols in place for a long time to guide the pre-hospital response to victims hypothermia combined with cardiac arrest in remote settings.[79,80]

Frostbite

Frostbite is a complex process in which tissue cooling causes vasoconstriction, ischemia, and intracellular and extracellular ice crystal formation, leading to cell lysis and cell death. Reperfusion-ischemia injury is possible, and repeated thawing and refreezing is particularly damaging. Recent practice guidelines from the Wilderness Medical Society discuss the dichotomy between intentional field rewarming of a frozen body part, with maintenance of thawed tissue, and keeping the tissue frozen when the risk of re-freezing is significant.[81]

Basic field care includes administration of anti-prostaglandins, pain control, and placement of protective dressings in addition to treating concomitant hypothermia and injuries. Debridement of nonhemorrhagic blisters might be beneficial, but evidence is lacking. In medical facilities, advanced care with tissue plasminogen activator or prostaglandins/PG analogues has been documented. In the past, a "wait-and-see" approach was used to determine demarcation of the frozen area; now, tissue viability can be determined rapidly with advanced imaging such as magnetic resonance angiography or

bone scintigraphy.[81]

Avalanche

Avalanches most commonly occur in mountainous terrain with 35% slope when a buried layer fails and releases an overlying slab of snow. Victims caught in an avalanche are subjected to tremendous traumatic forces and are at risk of suffocation and, eventually, hypothermia. The severity of avalanche injury is generally based on several factors: depth of burial, length of burial, airway obstruction, and concurrent trauma.[82–84] Avalanche rescue and resuscitation have been advanced by an improved understanding of snow burial physiology, including cooling, afterdrop, and the role of exhaled carbon dioxide.[85,86] Technologic advances designed to mitigate the risk of avalanche-associated injury and death include exhaled air diversion devices, flotation devices, and transceivers.[87] The science of avalanche forecasting has improved; detailed reports are available online.[88] Despite these advances, North American avalanche fatalities continue their upward trend.[89] Morbidity and mortality rates associated with non-avalanche snow burial (tree well and deep snow immersion asphyxia) are also being documented.[90]

Military medicine

Tactical/battlefield medicine has advanced dramatically in the past decade, including the development of tactical combat casualty care guidelines and training. Significant advances have been achieved in hemorrhage control with tourniquets and hemostatic agents, surgical cricothyroidotomy, intraosseous access, needle decompression, pain management, prophylactic antibiotics, and low-volume field resuscitation. These advances are now crossing over to civilian EMS systems, tactical units, and wilderness medicine.[91–98]

Epidemiology

Wilderness medicine epidemiology is a rapidly growing field that describes the incidence of morbidity and mortality in the wilderness. Detailed information is still being collected, but general trends can be described. The most common injuries are soft-tissue lesions (e.g., blisters), sprains, strains, and fractures. The most common causes of death are head trauma, cardiac arrest (males >55 years old), drowning, hypothermia, hyperthermia, and suicide.[5,6,10,99–106] These data are important for general educational programs, risk mitigation, trip planning, and medical kit stocking.[7]

Search and rescue

Search and rescue operations are conducted under many organizational structures, typically citizen volunteer groups, law enforcement agencies, or, in many localities, a blend of the two.[107] Participants' medical training ranges from basic first aid to wilderness first aid, wilderness first responder, wilderness emergency medicine technician, paramedic, mid-level provider, as well as physician. Search and rescue missions are often used for missing children, recreationalists, and individuals with developmental delay, autism, Alzheimer's disease, or dementia.[99–101,108–112] Search management has evolved to the point of using statistical models of subjects' behavior along with computer analysis and mapping.[113,114] Helicopters facilitate rapid identification and extrication when they are deployed under appropriate circumstances.[115–119]

Travel medicine

Travel medicine involves the epidemiology of travelers' diseases, education, and vaccination.[120] This specialty has become especially important in this era of easy long-distance travel.[121] A particularly important disease in travel medicine is malaria, which carries significant morbidity and mortality rates, especially among children.[122–124] Geosentinel monitoring is used to detect disease propagation and assist with management.[125,126]

Disaster medicine

Disaster medicine and wilderness medicine have significant overlap. Both are practiced under sudden, unexpected, difficult, and austere conditions and have an inherent delay in emergency response and evacuation. Disaster conditions can be created in urban, suburban, and rural locations and are all associated with delays in emergency response, extraction, and evacuation to medical resources. Diseases that are typical in wilderness or remote settings can emerge in the aftermath of disasters. Although dramatic scenarios such as crush injuries and amputations grab news media attention, the basics of hygiene and water sanitation are just as critical in disaster management as is the deployment of trained response personnel into devastated areas.[127–129]

Ultrasound

Small, portable ultrasound machines are being used as an extension of the physical examination of patients with a number of clinical conditions: trauma (Focused Assessment with Sonography in Trauma [FAST] and pneumothorax examination), HAPE (pulmonary

examination), HACE (determination of the diameter of the optic nerve sheath), and obstetric emergencies (determination of the age of the fetus).[130,131] Increasing use of this technology is being reported by the US military, particularly by remote special forces medics in Afghanistan and at small remote receiving centers.[132,133] Disaster medicine has used ultrasound in the field and in hospitals when other resources are overwhelmed or unavailable.[134–138] These situations often employ ultrasound for the focused scans delineated in ACEP's Emergency Ultrasound Guidelines.[139] The use of ultrasound in conjunction with telemedicine is intriguing. Real-time ultrasound images have even been transmitted from the International Space Station.[140,141]

WMS practice guidelines

Formal recommendations for clinical care and decision-making were lacking until 1979, when Forgey published *Wilderness Medicine*.[142] Six editions have been published, the latest in 2006.[143]

Over the past several years, the evidence-based Wilderness Medical Society Practice Guidelines have been developed and published in several areas of wilderness medicine. The topics addressed in these guidelines include: high-altitude illness,[16] frostbite,[81] lightning,[144] eye injuries,[145] epinephrine,[146] use of extrication devices in crevasse rescue,[147] exercise-associated hyponatremia,[148] spine trauma management,[51] heat-related illness,[149] anesthesia and pain management (in press), wound management (pending), hypothermia (pending), drowning and immersion injuries (pending). They are based on case series and expert consensus, because, for many topics, research studies using randomized controls have not yet been conducted. The guidelines were developed in accordance with the templates suggested by the American College of Chest Physicians.[149]

Professional organizations

The Wilderness Medical Society (WMS) is the primary professional organization representing wilderness medicine physicians and other health care providers. It sponsors a variety of meetings in North America: an annual summer meeting, an annual winter meeting, and a fall specialty meeting (organized around themes such as travel medicine, desert medicine, or environmental health). The WMS has developed a series of online video recordings from past conferences for continuing medical education (CME). The World Congress in Wilderness Medicine has met every 10 years since 1991, providing a forum for the exchange of current ideas and concepts related to wilderness medicine. The International Society for Mountain Medicine sponsors the International Hypoxia Symposium and the Congress on High Altitude Medicine and Physiology. The Undersea and Hyperbaric Medical Society, the Divers Alert Network, and the South Pacific Undersea Medicine Society focus on dive medicine.

Several other professional societies play important roles in wilderness medicine. The International Society of Travel Medicine (www.istm.org), founded in 1988, focuses on travel-related disease, including immunization recommendations. ISTM is involved in global monitoring of infectious diseases. Together with the Centers for Disease Control and Prevention (CDC), ISTM manages Geosentinel, a global surveillance network for infectious diseases that provides nearly real-time data for analysis of evolving disease patterns. The International Commission for Alpine Rescue (www.ikar-cisa.org), founded in 1948 and based in Switzerland, represents European mountain rescue groups. ICAR publishes recommendations on both medical and technical issues for a variety of issues facing mountain rescue teams. The International Society for Mountain Medicine (http://ismmed.org), founded in 1985 and also based in Switzerland, publishes the journal *High Altitude Medicine and Biology*.

Fellowships

The purpose of wilderness medicine fellowships is to develop academic leaders in the specialty. Multiple postgraduate fellowships are based in emergency medicine and family medicine graduate medical education programs. Generally, they have a research component, a teaching component, and a field component. A typical pattern is 1 year of training, with part-time clinical attending duties and part-time wilderness medicine training. The program at the University of California, Fresno, has an optional 1-year extension to obtain a master's degree in public health. The program at George Washington University also offers the opportunity to complete a master of science or a master of public health degree. The original and best known wilderness medicine fellowship is based at Stanford University in Palo Alto, California. The Society for Academic Emergency Medicine lists eight other wilderness medicine fellowships associated with emergency medicine residency programs. They are located at Baystate Medical Center; the University of California, San Francisco-Fresno; the Medical College of

Georgia; the University of Utah; Massachusetts General Hospital; the University of Colorado; the State University of New York; and Loma Linda University. Additionally, the Madigan Army Medical Center hosts an Austere and Wilderness Medicine fellowship for military physicians.

Several family medicine programs also host wilderness medicine fellowships: the Montana Family Medicine Program (www.riverstonehealth.org), the family medicine residency of Idaho (www.fmridaho.org), and Saint Vincent Wilderness Medicine Track (www.stvincenthealth.com).

Academy of wilderness medicine

Under the auspices of the Wilderness Medical Society, the Academy of Wilderness Medicine offers a fellowship that provides rigorous education through a 100-hour core curriculum as well as requirements for service, teaching, research, and experience. As of June 2013, the Academy recognizes more than 260 fellows as well as more than 700 fellowship candidates.

Master's degree

The Wilderness Medical Society opened its master's degree program (http://wms.org/fawm/acad_information.asp) in 2009. This program offers advanced, post-fellow certification in the participant's chosen sub-discipline within the scope of wilderness medicine. The master's program is developed by the student and a mentor and must meet requirements in education, scholarly activity, and experimental activity. For example, a master's program in the subspecialty of dive medicine could focus on the clinical management of decompression illness. Most participants fulfill the requirements of their program within 2 to 5 years.

Diploma in mountain medicine

In collaboration with the University of Utah and the University of Colorado, the Wilderness Medical Society also awards diplomas in mountain medicine, certifying academic and advanced skills in mountain rescue techniques (http://wms.org/education/dimm.asp). Started in 1997, the diploma program is co-sponsored by the Union Internationale Des Associations D'Alpinisme, the International Committee for Alpine Rescue, and the International Society for Mountain Medicine. The program is open to physicians, nurses, and paramedics who work in or aspire to work in austere environments. The 100 hours of coursework blend didactic and practical education in wilderness medicine, technical rescue, and self-sufficiency in the backcountry. This skill set crosses a number of disciplines, including expedition medicine, search and rescue operations, mountain guiding, ski patrol, and mountain recreation. The program consists of four week-long sessions that should be completed within 2 or 3 years. Participants must pass written and skills examinations to complete the program.

Student interest groups

The Wilderness Medical Society supports student interest groups that sponsor lecture series, workshops, and outdoor trips in conjunction with their sponsoring medical schools and faculty advisors. The events are organized by medical students, often in their second year of training. As of July 2013, approximately 43 of these interest groups, most of them in the United States and Europe, were active and operational. In addition, a number of emergency medicine and family medicine training programs in the United States offer 1- to 4-week electives in wilderness medicine for medical students and residents (see below).

Schools of wilderness medicine

Training in wilderness medicine is decentralized. Several organizations (based primarily in North America) teach wilderness medicine courses and skills throughout the world:

• Stonehearth Open Learning Opportunities (SOLO), Conway, New Hampshire, USA

• National Outdoor Leadership School, Wilderness Medicine Institute, Lander, Wyoming, USA

• Wilderness Medical Associates International, Portland, Maine, USA; Haliburton, Ontario, Canada; Tsukubamirai, Ibaraki, Japan (runs courses in China regularly)

• National Ski Patrol, Lakewood, Colorado, USA (outdoor emergency care)

• Advanced Wilderness Life Support, University of Utah, Salt Lake City, Utah, USA

• Aerie Backcountry Medicine, Missoula, Montana, USA

Their programs include basic introductory courses for the general public and pre-hospital care providers, such as wilderness first aid (WFA), a 2-day course; advanced wilderness first aid (AWFA), a 4-day course; wilderness first responder (WFR), a 9-day course; and wilderness emergency medical technician (WEMT), a 4-week course. Wilderness medicine courses for advanced care providers are available as well, e.g., Advanced Wilderness Life Saving.

Table 1. Grants offered by the Wilderness Medical Society in Support of Health Research in Wilderness Medicine (www.wms.org/research).

Grants
Charles S. Houston Award
Audience
Medical students
Article by recent recipients
• Fischer MD, Willmann G, Schatz A, Schommer K, Zhour A, Zrenner E, Bartz-Schmidt KU, Gekeler F. Structural and functional changes of the human macula during acute exposure to high altitude. PLoS One 2012; 7: e36155.
Research-in-Training Award
Audience
Residents and fellows of accredited graduate medical education programs or PhD candidates
Articles by recent recipients
• Graves JM, Whitehill JM, Stream JO, Vavilala, MS, Rivara FP. Emergency department-reported head injuries from skiing and snowboarding among children and adolescents, 1996–2010. Inj Prev, March 19, 2013 [Epub ahead of print].
• Muller MD, Mast JL, Patel H, Sinoway LI. Cardiac mechanics are impaired during fatiguing exercise and cold pressor test in healthy older adults. J Appl Physiol 2013; 114: 186–194.
• Muller MD, Gao Z, Mast JL, Blaha CA, Drew RC, Leuenberger UA, Sinoway LI. Aging attenuates the coronary blood flow response to cold air breathing and isometric handgrip in healthy humans. Am J Physiol Heart Circ Physiol 2012; 302: 1737–1746.
Herbert N. Hultgren Award
Audience
Members of the Wilderness Medical Society
Article by recent recipients
• Chang CY, Trehan I, Wang RJ, Thakwalakwa C, Maleta K, Deitchler M, Manary MJ. Children successfully treated for moderate acute malnutrition remain at risk for malnutrition and death in the subsequent year after recovery. J Nutr 2013; 143: 215–220.
Peter Hackett-Paul Auerbach Research Grant
Audience
Young investigators, physicians or non-physicians, with projects that will improve wilderness medicine practice
WMS Adventure Travel Research Grant
Audience
Investigators conducting field research associated with the WMS Adventure Travel Experiences

Medical direction

In the United States, street-based emergency medical services (EMS) systems are regulated by state agencies and the Department of Transportation at the federal level. Wilderness EMS does not have such a defined system of regulation. If present, medical oversight varies by jurisdiction. Only a few states have wilderness medicine integrated into their EMS protocols. In Pennsylvania and Maryland, two states with such integration, wilderness medicine practitioners are considered an extension of the pre-hospital system and have medical direction, follow wilderness specific protocols, and have quality assurance programs. In other states, wilderness medicine providers are not directly subservient to pre-hospital systems.

Many medical directors of EMS systems are unfamiliar with the practice of wilderness medicine, particularly its logistical limitations. To facilitate understanding and the integration of wilderness medicine into pre-hospital protocols, the Wilderness Medicine Society and the National Association of EMS Physicians (www.naemsp.org) have designed a Wilderness Medicine EMS Director Course, which is designed to support physicians who provide medical oversight to EMS systems with jurisdictions that cover wilderness environments.[150,151] Topics include search and rescue teams, technical rescue teams, ski patrols, and disaster response teams.

Wilderness research and grants

The Wilderness Medical Society offers a number of grants intended to support health-related research projects in outdoor and wilderness activities. Examples are listed in Table 1.

Future

The future of wilderness medicine is unfolding on multiple fronts: education, research, training, technology, communications, and environment. A wide range of individuals is showing an interest in learning wilderness medicine skills. Although wilderness medicine research is technically difficult to perform, it is essential to deepening our understanding of the contribution of specific techniques in improving clinical outcomes.

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REVIEW Open Access

Frostbite: a practical approach to hospital management

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Abstract

Frostbite presentation to hospital is relatively infrequent, and the optimal management of the more severely injured patient requires a multidisciplinary integration of specialist care. Clinicians with an interest in wilderness medicine/freezing cold injury have the awareness of specific potential interventions but may lack the skill or experience to implement the knowledge. The on-call specialist clinician (vascular, general surgery, orthopaedic, plastic surgeon or interventional radiologist), who is likely to receive these patients, may have the skill and knowledge to administer potentially limb-saving intervention but may be unaware of the available treatment options for frostbite. Over the last 10 years, frostbite management has improved with clear guidelines and management protocols available for both the medically trained and winter sports enthusiasts. Many specialist surgeons are unaware that patients with severe frostbite injuries presenting within 24 h of the injury may be good candidates for treatment with either TPA or iloprost. In this review, we aim to give a brief overview of field frostbite care and a practical guide to the hospital management of frostbite with a stepwise approach to thrombolysis and prostacyclin administration for clinicians.

Keywords: Frostbite, Hypothermia, Rewarming, Thrombolysis, Heparin, TPA, Iloprost

Review

Introduction

Frostbite is a freezing, cold thermal injury, which occurs when tissues are exposed to temperatures below their freezing point (typically −0.55°C, but can occur as high as 2°C) for a sustained period of time [1]. It is a condition that has far-reaching consequences in terms of functional morbidity to a population that are often young, fit and healthy prior to the thermal injury. Many frostbite patients in urban areas are homeless and/or suffer from mental health issues. Frostbite is well documented in the military and in countries with extreme temperatures for centuries. The earliest documented evidence of frostbite may be a 5,000-year-old pre-Columbian mummy discovered in the Andes [2]. The first report of mass cold injuries was by Baron Larrey, Surgeon-in-Chief to Napoleon's Army throughout the invasion of Russia during the winter of 1812–1813 [3]. Larrey introduced the concept that the physiologic response to cold injuries was similar to that of burn injuries and recognized that warming frozen tissue was advantageous for recovery.

Today, the presentation of frostbite is increasing within the civilian population, in particular those who partake in winter sports such as skiing, hiking, mountain and ice climbing [4]. The outdoors is more accessible, and individuals with limited experience/inadequate preparation and protection find themselves at risk of cold thermal injury [5]. Vagrancy, homelessness, industrial injury and malfunctioning or misuse of equipment using NO or CO_2 have also been described [6,7].

Severity of injury depends on factors such as absolute temperature, wind chill, duration of exposure, wet/dry cold, immersion, clothing quality and patient comorbidities such as smoking, peripheral vascular disease, neuropathies, Raynaud's disease, mental health issues, substance abuse and dementia [1,4,8,9]. Alcohol consumption is potentially particularly devastating as it causes heat loss through peripheral vasodilatation and also impairs judgement. This may affect the individual's ability to seek adequate shelter, compounding the injury. Amputation of injured parts has been shown to correlate more closely

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with the duration of cold exposure rather than temperature [9]. Anatomically, the hands and feet account for 90% of reported injuries [10,11]. Frostbite can also affect the face (nose, chin, earlobes, cheeks and lips), buttocks/perineum (from sitting on metal seats) and penis (joggers and Nordic skiers). Patients at the extremes of age (elderly and infants/young children) are at greater risk because of immobility and higher surface area-to-mass ratio (children); however, studies show that frostbite is uncommon in these age groups and instead is seen more commonly in adults between the ages of 30 and 49 years, most likely due to increased exposure to cold or risk-taking behaviour [10,11].

Frostbite can result in a wide spectrum of injury, ranging from complete resolution without significant sequelae to major limb amputation and its functional consequences. Once in the hospital setting, the best outcomes will be achieved for the patient when a multidisciplinary approach is utilized [11]. In this practical guide, we review key current frostbite literature, classification strategies and recommendations for management of frostbite in the hospital setting.

Literature search

A systematic literature search of the related articles published between January 1969 and July 2013 was performed using PubMed (restricted to the English language) with keywords 'frostbite', 'frostbite management' and 'freezing cold injury'. The search included both human and animal studies, original research, case series/reports, review articles and guidelines. Priority was given to human studies and more recent publications since 2005. The studies were identified by title and abstract and screened by the authors; relevant cross-references were added.

Recommendation grade

Using the criteria defined by the American College of Chest Physicians (ACCP), each form of intervention was attributed a recommendation grade where appropriate. For further details on the criteria, please refer to Table 1 [12].

Pre-hospital care and prevention

Prevention is always preferable, and education of those working or recreating in cold environments should focus on modification of risk factors, selection and use of proper clothing, optimal nutrition and hydration [4]. Those working with equipment that uses coolant such as liquid nitrogen or carbon dioxide should also have adequate education in safe handling of such products.

Whilst pre-hospital care is not the focus of this article, key field management of frostbite concepts are summarized in the following texts [13,14]. In general, the patient should be moved out of the wind, provided with shelter and be given warm fluids (*recommendation grade 1C*).

Remove boots (but consider problems of replacement if swelling occurs), and replace wet gloves and socks with dry ones. Warm the cold extremity by placing it in a companion's armpit or groin for 10 min and then replace the boots/gloves. Rubbing the affected part is not recommended because of the potential for worsening direct tissue injury (*recommendation grade 1C*).

If sensation returns, the patient may mitigate risks (e.g. add a layer and change to warmer or dryer socks or boots) and continue to walk. If there is no return of sensation, the injured should go to the nearest warm shelter (hut or base camp) and seek medical treatment. If at high altitude (>4,000 m), supplementary oxygen should be considered [11] (*recommendation grade 2C*).

Aspirin 75 mg can be given for its rheologic effect. Ibuprofen 12 mg/kg/day divided into two daily doses (maximum of 2,400 mg/day) should be given for its prostaglandin effect (*recommendation grade 2C*).

Field rewarming should only be attempted if there is no further risk of refreezing [14,15]. Tissue that thaws then refreezes results in more extensive injury (*recommendation grade 1B*).

The decision to thaw the frostbitten tissue in the field commits to a course of action that may involve pain control, maintaining warm water baths at a constant temperature, protecting tissue from further injury during rewarming and eventual transport. In extreme circumstances, it may be better to let a casualty walk on a frozen limb to safety rather than risk refreezing [16] (*recommendation grade 1C*).

Hospital management

Immediate and general care for those admitted with frostbite

On arrival to a hospital setting, it is vitally important to fully reassess the patient. Underlying unstable comorbidities, trauma or hypothermia must be assessed and managed before frostbitten extremities are treated. Moderate or severe hypothermia should be corrected to bring core temperature above 35°C before initiating frostbite warming [14,17] (*recommendation grade 1C*).

A detailed history should include time the injury occurred, either early (<24 h) or late (>24 h) as this will dictate some treatment options. History of the conditions surrounding the injury (i.e. temperature, wind chill, wet/dry exposure, duration and use or not use of thermal protection) can also be helpful. Any pre-hospital treatment and time of rewarming, if applicable, should be noted [14].

Remove jewellery from affected digits early as significant swelling can be expected post thaw, and vascular compromise may occur with tight rings, etc. [14]. Examination of the frostbitten tissue after rewarming can predict depth of injury more accurately than examination before thawing. There may be different depths of injury even on digits

Table 1 ACCP classification criteria for grading evidence in clinical guideline [13]

Grade	Description	Benefits vs. risks and burdens	Methodological quality of supporting evidence
1A	Strong recommendation, high-quality evidence	Benefits clearly outweigh risks and burdens or vice versa	RCTs without important limitations or overwhelming evidence from observational studies
1B	Strong recommendation, moderate-quality evidence	Benefits clearly outweigh risks and burdens or vice versa	RCTs with important limitations or exceptionally strong evidence from observational studies
1C	Strong recommendation, low-quality or very low-quality evidence	Benefits clearly outweigh risks and burdens or vice versa	Observational studies or case series
2A	Weak recommendation, high-quality evidence	Benefits closely balanced with risks and burdens	RCTs without important limitations or overwhelming evidence from observational studies
2B	Weak recommendation, moderate-quality evidence	Benefits closely balanced with risks and burdens	RCTs with important limitations or exceptionally strong evidence from observational studies
2C	Weak recommendation, low-quality or very low-quality evidence	Uncertainty in the estimates of benefits, risks and burden; benefits, risk and burden may be closely balanced	Observational studies or case series

RCT, randomized controlled trial.

of the same extremity, so careful examination and documentation in either diagram form or with photographs are useful. Clinical photography obviates the need for repeated removal of dressings for each consultant examination, reducing pain and risk of infection. Loss of sensation after rewarming is a poor prognostic indicator, and the converse is also true. Figure 1 suggests how one should proceed with initial in hospital management.

Classification

There exist a number of frostbite classifications to assess the severity and predict likely outcome. Cauchy et al. have suggested a useful classification consisting of four grades and three key descriptors (Table 2) [18]. At 24 h post insult after rewarming, a grade can be attributed according to the level of any visible lesion. Then, at day two, a technetium^{99} triple-phase bone scan should be performed on the more severe injuries (see Imaging section) and a further assessment of any blisters undertaken. Injuries receiving grade 1 classification require no hospitalisation and full recovery is likely. Grades 2 through 4 injuries require hospitalisation and full investigation as they are associated with an increased risk of amputation and long-term sequelae [18].

Fluids

Rehydration can be oral or intravenous, and depending upon severity and ability of the patient to tolerate oral fluids. High altitude increases the risk of dehydration. If the patient is also hypothermic, dehydration may be compounded by cold diuresis due to suppression of antidiuretic hormone, requiring correction with warmed intravenous fluids (*recommendation grade 1C*).

Rewarming

Rewarming is beneficial if there remains a partially or fully frozen part and is ideally accomplished using a whirlpool bath set at 38°C with added antiseptic solution (povidone iodine or chlorhexidine). The Wilderness Medical Society and State of Alaska Cold Injury Guidelines recommend a temperature of 37°C–39°C, which decreases the pain experienced by the patient whilst only slightly slowing rewarming time [14,15]. The time period for optimal rewarming varies from 15–30 min up to 1 h [16]. Rewarming should continue until a red/purple colour appears and the extremity tissue becomes pliable [14]. Active motion during the rewarming process is beneficial, but care should be taken to prevent the extremity from touching the sides of the whirlpool. It is important to provide good analgesic cover and is likely to include narcotic medication (*recommendation grade 1B*).

Blisters and dressings

It is important to note the type of any blisters that form; they can be clear/cloudy or haemorrhagic in nature. There is current debate as to whether blisters should be deroofed as this may desiccate the underlying tissue, but there is little comparative data to settle this argument. The recommended practice is that of selective drainage of clear/cloudy blisters by needle aspiration (especially if bullae restrict movement) and to leave haemorrhagic blisters alone [14]. However, we would suggest that all blisters are debrided in the hospital (not in the field) because we believe it assists with wound care. Severe injuries require detailed assessment, and it may be that this appraisal and debriding of blisters may be best performed under a general anaesthetic (*recommendation grade 2C*).

Topical aloe vera cream or gel (a potent antiprostaglandin agent) should then be applied to thawed tissue before dressings are applied [14] (*recommendation grade 2C*). Splinting, elevating and wrapping the affected part in a loose, protective dressing with padding between affected patient's digits are ideal (*recommendation grade 1C*).

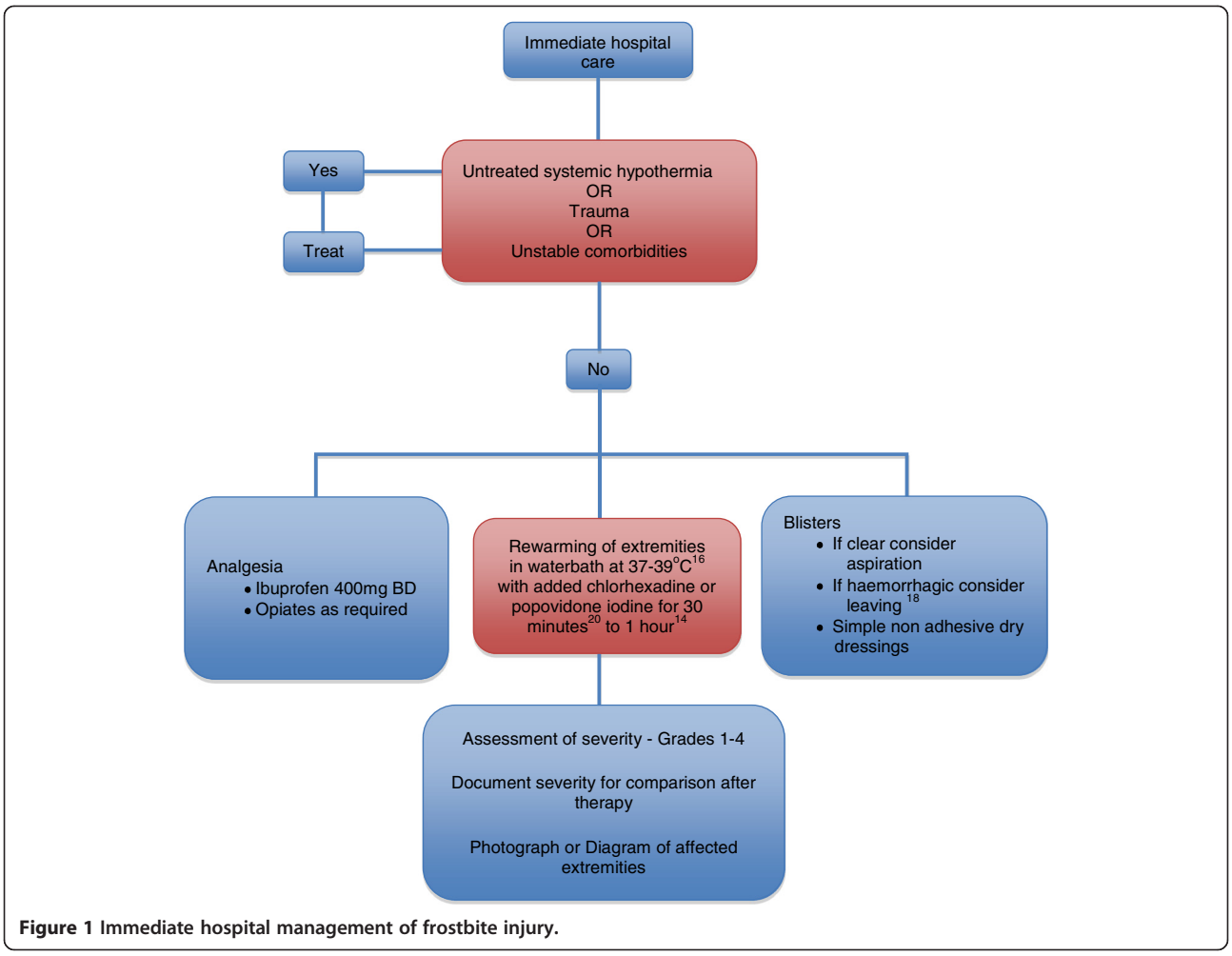

Figure 1 Immediate hospital management of frostbite injury.

Antibiotics

The role of prophylactic antibiotics is not proven but should be considered in more severe injuries (grades 3 and 4) and, in particular, when associated with significant oedema or malnutrition (homeless, chronic alcohol abuse or return from extreme altitude). Systemic antibiotics are required in the presence of proven infection, trauma or cellulitis (*recommendation grade 1C*).

Tetanus toxoid

The need for tetanus toxoid administration should be determined by following standard guidelines, as

Table 2 Classification scheme for the severity of frostbite injury [19]

Frostbite injuries of the extremity	Grade 1	Grade 2	Grade 3	Grade 4
Extent of initial lesion at day 0 after rewarming	Absence of initial lesion	Initial lesion on distal phalanx	Initial lesion on intermediary (and) proximal phalanx	Initial lesion on carpal/tarsal
Bone scanning at day 2	Useless	Hypofixation of radiotracer uptake area	Absence of radiotracer uptake on the digit	Absence of radiotracer uptake area on the carpal/tarsal region
Blisters at day 2	Absence of blisters	Clear blisters	Haemorrhagic blisters on the digit	Haemorrhagic blisters over carpal/tarsal region
Prognosis at day 2	No amputation	Tissue amputation	Bone amputation of digit	Bone amputation of the limb
	No sequelae	Fingernail sequelae	Functional sequelae	+/− systemic involvement
				+/− sepsis functional sequelae

frostbite injuries are not inherently tetanus-prone wounds (*recommendation grade 1C*).

Analgesia and NSAIDs

Rewarming the extremities can become extremely painful, so use of non-steroidal anti-inflammatory drugs or opiates should be administered. Oral ibuprofen 12 mg/kg divided over two daily doses provides systemic anti-prostaglandin activity that limits the cascade of inflammatory damage. This dose can be increased to a maximum of 2,400 mg/day if the patient is experiencing pain and can be continued until wounds are healed or amputation occurs. A dose of 400 mg BID is a practical regime on which to start most patients, and this can then be increased to 600 mg QDS as pain dictates. If aspirin has not been given in the field (providing no contraindications), 300 mg once a day can be given [4] (*recommendation grade 2C*).

Management specific to frostbite

For more superficial injuries, often, no more intervention or investigation is required after basic treatment has been initiated (Cauchy and Chetaille grade 1); however, in more severe cases, further intervention is required. Advanced imaging may be used to determine depth of tissue injury and guide therapy. It will also give an accurate prognosis at an early stage as to the subsequent likely clinical course. This is important for the patient, clinicians and occasionally for medico-legal reasons.

Imaging

For deep injuries, no surgical debridement should be planned until imaging is performed. Many modalities have been used, but angiography and technecium^{99} (^{99}Tc) triple-phase bone scanning give the best prognostic information and will direct therapy [1] (*recommendation grade 1C*).

A retrospective review of 92 patients with severe frostbite by Cauchy et al. [19] showed that ^{99}Tc scans obtained 2 days after the injury accurately predicted the level of amputation in 84% of cases. ^{99}Tc scanning has been performed on the day of presentation [20]. Case reports suggest magnetic resonance angiography (MRA) superiority to ^{99}Tc as it allows direct visualization of occluded vessels and surrounding tissue and may show a clearer demarcation of ischaemic tissues, but this has yet to be confirmed by larger studies [21]. However, MRA is easier to access in many units, and there appears to be a growing trend of using MRA as an alternative imaging technique.

Angiography and thrombolysis

A screening and treatment tool has been proposed for the use of thrombolytics in frostbite (see Table 3) [17].

An initial selective diagnostic digital subtraction angiography should be performed in patients being considered for thrombolysis. Intravenous vasodilators (nitroglycerin or papaverine) are useful (in conjunction with TPA) at this stage in the treatment of the vasospasm that often accompanies a frostbite injury [17,22,23]. It is possible that non-invasive MRA may offer a suitable alternative imaging modality (Figure 2).

In animal models, intravenous streptokinase limited the extent of tissue damage in a hind limb of a rabbit [24]. Streptokinase treatment and rapid rewarming resulted in reduced tissue damage and was most beneficial when given within 12 h of freezing and was still effective even when treatment was delayed up to 48 h [24].

Table 3 A proposed screening and treatment tool for the use of thrombolysis in cases of frostbite [17]

	Questions/indications to be considered
Treatment screen (four 'yes' answers required to proceed to angiography)	Are the patient's gas exchange and haemodynamics stable?
	Is flow absent after rewarming (no capillary refill or Doppler signals)?
	Was the cold exposure time less than 24 h?
	Is the warm ischaemia time less than 24 h?
Treatment protocol	Perform angiography with intra-arterial vasodilators
	If there is still no flow after angiography with vasodilators, infuse tissue plasminogen activator (rTPA) with systemic heparinization with priority to the hands; other sites receive a systemic dose
	Repeat angiography after 24 h
Indications for stopping the infusion of the rTPA	When restored flow has been confirmed by angiography or clinical examination
	If major bleeding complication occurs
	After 72-h treatment
Post lysis anticoagulation	One month of subcutaneous low-molecular weight heparin at prophylactic dose

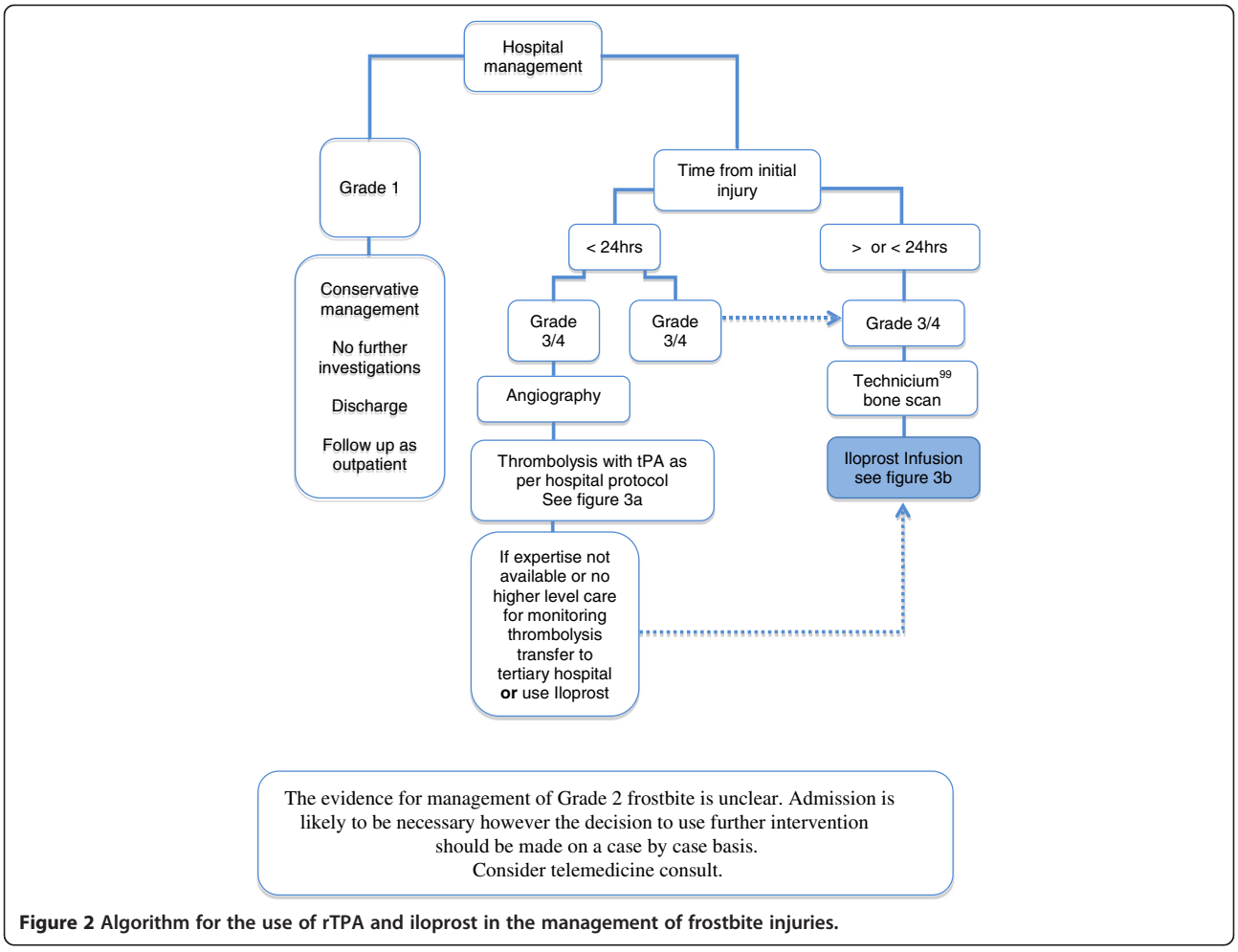

Figure 2 Algorithm for the use of rTPA and iloprost in the management of frostbite injuries.

Twomey et al. published results of an open-label study to evaluate the safety and efficacy of tissue plasminogen activator (rTPA) in the treatment of severe frostbite found that rTPA and heparin after rapid rewarming is safe and reduced predicted digit amputations. Similar efficacy was reported in both the intravenous and intra-arterial delivery arms [25]. Those patients with more than 24 h of cold exposure, warm ischaemia times greater than 6 h or evidence of multiple freeze-thaw cycles were least likely to benefit [25].

Bruen et al. demonstrated a reduction in digital amputation rates from 41% in those patients that did not receive rTPA to 10% in those receiving rTPA within 24 h of injury ($p < 0.05$) [26]. It was also noted that efficacy after 24 h decreased. Thrombolysis within 24 h (early group) appears to show the best outcomes in digit salvage [17]; however, thrombolysis after 24 h should be considered on an individual risk-benefit basis.

Delivery of rTPA can be either intravenous (IV) or via catheter-directed intra-arterial (IA) administration [17,25,26]. The latter is our preferred route, if rTPA is to be used rather than iloprost. Normal contraindications to TPA apply including existing trauma, recent surgery, neurological impairment or bleeding diathesis. It is not appropriate for superficial frostbite (grade 1), only deep tissue injuries that affect more proximal phalanges and the forefoot or foot should be considered, as treatment is not without risks of haemorrhage [17].

rTPA delivery should be provided at a centre accustomed to performing thrombolysis and that can provide adequate monitoring (usually in a critical care/high-dependency setting). If the patient presents less than 24 h after injury to a hospital without these facilities, consider urgent transfer in order not to delay commencement of therapy. rTPA is used in combination with heparin, which reduces the recurrence of microvascular thrombosis.

Repeat angiograms should be performed every 12–24 h to evaluate response to therapy. rTPA treatment should be discontinued when perfusion is restored to distal vessels

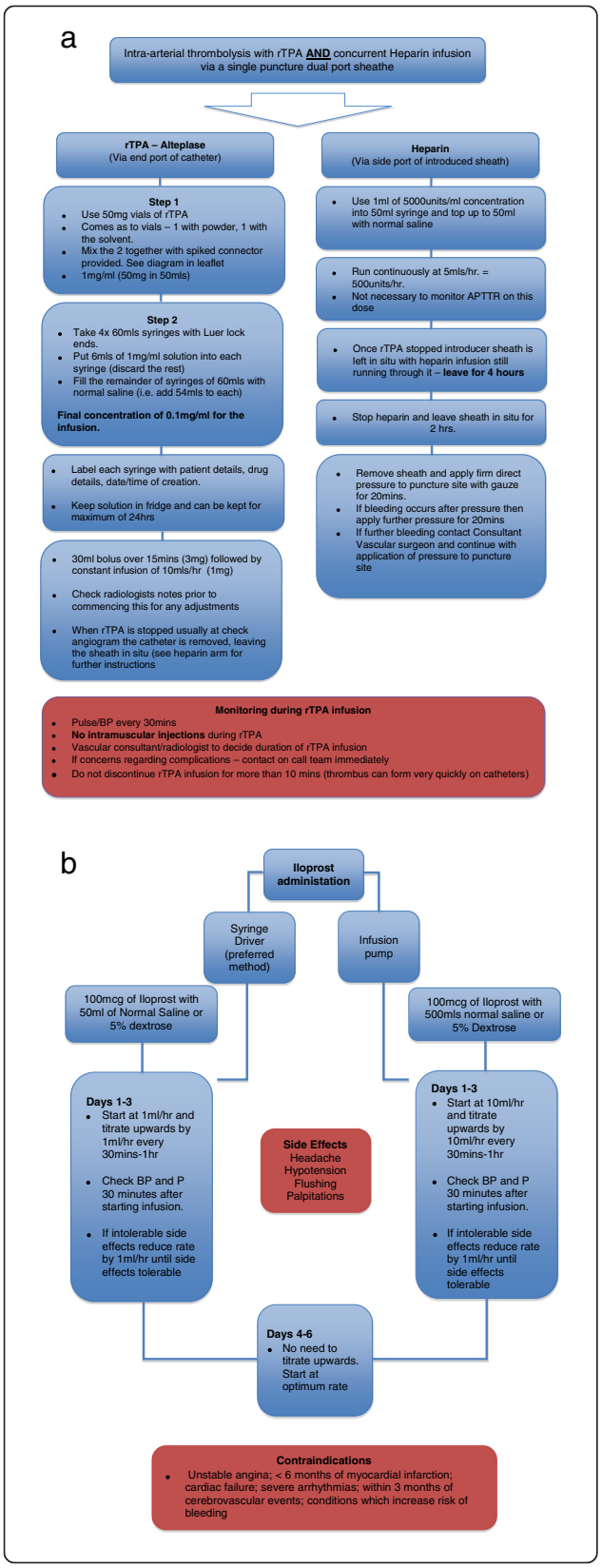

Figure 3 Intra-arterial administration of rTPA and heparin and administration of intravenous iloprost. (a) Algorithm for the intra-arterial administration of tTPA and heparin for in-hospital thrombolysis of severe frostbite injury. **(b)** Algorithm for the administration of intravenous iloprost for in-hospital thrombolysis of severe frostbite injury.

or at 48 h if no improvement is observed [26]. Figure 3a gives a stepwise approach to intra-arterial thrombolysis (*recommendation 1B-C*).

Iloprost

Iloprost is a prostacyclin analogue with vasodilatory properties that mimic the effects of a sympathectomy [27]. It may also affect platelet aggregation and therefore decrease microvascular occlusion. Unfortunately, intravenous iloprost is not currently available in the USA.

In 1994, Groechenig published his experience in treating four cases of severe frostbite with iloprost [28]. The results were promising, with no patients requiring amputation; however, since these initial findings were published, the focus has shifted towards rTPA, with no further data published on iloprost use until a recent paper by Cauchy et al [29]. In a randomized controlled trial designed to compare the efficacy of iloprost and rTPA, 47 patients were included with a total of 407 digits at risk. All patients underwent identical initial treatment and rewarming and then were randomized into three arms: buflomedil, iloprost or iloprost and IV rTPA. The risk of amputation on the buflomedil arm was the greatest with 39.9% of at-risk digits requiring amputation. In the iloprost and iloprost/rTPA arms, the amputation rates were 0% and 3.1%, respectively [29].

The administration of iloprost is via an IV infusion. The dose used is 0.5 up to a maximum of 2 ng/kg/min [29], incrementally increased every 30 min by 0.5 ng/kg/min until the patient develops unacceptable or intolerable side effects (headache and hypotension). The rate is then reduced by 0.5 ng/kg/min. The infusion is continued for 6 h/day for 5–8 days at the previously determined maximal rate a patient can tolerate.

The advantages of iloprost compared to rTPA are that it does not require radiological intervention during administration and can be managed on a general or vascular ward. Iloprost can be used when there is a history of trauma or when the exposure occurred over 24 h ago, unlike rTPA where trauma is a contraindication and efficacy is reduced beyond 24 h. Figure 3b gives a stepwise approach to iloprost administration (*recommendation grade 1B*).

Surgery

Immediate amputation should be avoided; there is rarely any need for early intervention unless there is wet gangrene, liquefaction, overwhelming infection or spreading sepsis [30,31]. Planning is vital with a goal of obtaining the

best functional outcome. Premature amputation increases morbidity and is likely to lead to poor subsequent function (*recommendation grade 1C*).

Fasciotomies are occasionally required post thaw if reperfusion is compromised by compartment syndrome [31] (*recommendation grade 1C*). The majority of amputations can be performed 6–12 weeks post injury once demarcation of ischaemic tissue has been well defined [4]. Negative pressure devices can aid in speeding up healing of amputation sites when left to heal by secondary intention [32].

Tissue protection

During the demarcation period, it is important to provide adequate protection especially footwear. Therefore, liaison with orthotic/podiatry department to provide bespoke footwear that protects and also attempts to maintain limb function is vital.

Following amputation, function is variable and injury specific. The biomechanics of the foot/hand can be radically altered and frostbite neuropathy can compound the problem; so, again, custom-made footwear may be required to optimize the long-term functional result and minimize secondary injuries [33].

Adjunctive therapies

The below therapies have insufficient trials performed to present any cognizant argument for their use but have been described in case reports or animal studies.

Hyperbaric oxygen therapy By increasing oxygen tension in the blood, more oxygen is delivered to the tissues; however, this requires patent microvasculature. Hyperbaric oxygen therapy (HBOT) increases the deformability of erythrocytes, diminishes oedema formation in burns and post ischaemic tissues and has some bacteriostatic properties [34].

HBOT in frostbite has had mixed results with no level 1 evidence available. Animal studies have demonstrated no benefit [35], yet two recent human case series have yielded excellent results [34,36]. Significant thrombosis of the microvasculature may be the cause of its variable effect. Thus, currently, there is insufficient data to recommend its routine use (*no recommendation grade due to insufficient evidence*).

Sympathectomy Surgical or chemical sympathectomy has yielded mixed results in improving blood flow. Early sympathectomy performed within the first few hours of injury is said to increase oedema formation and, consequently, tissue loss; however, if performed 24–48 h after thawing, resolution of oedema and decreased tissue loss are observed [37].

Sympathectomy may have a role in managing long-term sequelae of frostbite such as pain (often due to vasospasm), paraesthesias and hyperhidrosis [37]. However, since sympathectomy is irreversible, great caution should be exercised when considering its use, given the availability of alternative IV vasodilators [11] (*no recommendation grade due to insufficient evidence*).

Long-term management

The long-term sequelae of frostbite are less well studied. However, it is known that the tissue, which has recovered from frostbite, may be more susceptible to subsequent freezing injury. Consequently, patients should be educated about this risk especially if they plan to return to cold environments.

A long-term follow-up study of 30 patients with significant frostbite injuries showed that 53% exhibited cold hypersensitivity, 40% numbness of the digits and 33% had reduced sensitivity to touch [37]. The study postulates that these side effects may be secondary to a thermo-physiological response with an increased tendency to vasospasm. With this cold sensitization, the individual may be unable to tolerate cold temperature upon the previously frostbitten area, even when other body areas are comfortable at that temperature [38].

Chronic regional pain is perhaps the most common complaint post frostbite. The pain is often unresponsive to conventional analgesia and may be lifelong. Medications such as amitriptyline or gabapentin may have some benefit, but referral to a chronic pain specialist should be made in these cases.

Localized osteoporosis and sub-chondral bone loss can be seen post injury and reflect the severity of vascular damage. Changes can be seen within a month of injury but often progress over months such that by 16 months, radiographs can reveal multiple lucencies in the subchondral bone [39]. In children, the damage may be more significant with undergrowth of affected bone and development of early arthritis [39,40].

Skin areas that have been affected by frostbite are susceptible to chronic ulceration due to poor tissue quality after healing and can undergo a malignant transformation akin to the formation of Marjolin's ulcers observed in old burn scars [41].

Accessing expert advice (telemedicine)

Patients and clinicians with limited experience of frostbite can now use the internet and satellite phones to access expert advice in remote or difficult situations. A virtual opinion or more specialized advice can be sought from almost anywhere in the world using a combination of digital images and telephone advice [4,11,42,43].

Conclusions

Deep frostbite is a serious condition that is associated with significant morbidity, and it is becoming more

frequent in young active individuals who put themselves at risk. Timely pre-hospital and definitive hospital management are important to minimize final tissue loss and maximize functionality of the affected limb.

Surgeons should not to rush to early amputation; if managed correctly in the first few days, significant tissue can be salvaged, which is very important to the final functional outcome. We have outlined a series of management frameworks, which we hope will enable surgeons who rarely see this condition to have a greater understanding of frostbite and its management.

Either intravenous iloprost or thrombolysis with rTPA should be considered in all patients who present within 24 h of sustaining an appropriately severe injury and if the facility is capable of appropriate administration and monitoring. Both treatments should be started as soon as it is practical to gain maximal benefit. There is some evidence iloprost can be used beyond the 24 hour window and it is the treatment of choice where there are contraindications to thrombolysis. Bone scanning is helpful to ascertain deep tissue injury and response to therapy.

If iloprost is an available option (and it is not currently available in USA), then iloprost is the preferred option based upon its simplicity of administration, safety and efficacy. Prevention with education, behaviour modification and appropriate use of suitable equipment is important to reduce frostbite incidence.

Abbreviations

C: centigrade; *HBOT*: hyperbaric oxygen therapy; *IA*: intra-arterial; *IV*: intravenous; *kg*: kilogramme; *m*: metres; *mg*: milligramme; *MRA*: magnetic resonance angiography; *rTPA*: recombinant tissue plasminogen activator; ^{99}Tc: technetium-99.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

CH and CHEI have done the conception and design of the study and the writing and final approval of the manuscript. PB wrote the manuscript and approved the final manuscript. KR, SM, LF and AC were involved in manuscript writing and in its critical revision and final approval. CEAI wrote and approved the final manuscript. All authors read and approved the final manuscript.

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REVIEW ARTICLE

CURRENT CONCEPTS

Accidental Hypothermia

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Accidental hypothermia (i.e., an involuntary drop in core body temperature to <35°C [95°F]) is a condition associated with significant morbidity and mortality.[1-4] Each year, approximately 1500 patients in the United States have hypothermia noted on their death certificate; however, the incidence of primary and secondary hypothermia and the associated morbidity and mortality remain unknown.[5] In a single tertiary care center, 14 different rewarming methods were used to treat 84 cases of accidental hypothermia,[3] which reflects the uncertainties about treatment and the potential for complications.[3] Certain treatment approaches are available only in specialized centers, and clarification is needed regarding the choice between transporting a patient to a specialized center and providing treatment locally. Existing recommendations do not include recent developments in rewarming methods nor do they assist with decisions regarding transportation.[6-8]

PRESENTATION

With cold exposure, the initial response of the body is to maintain a normal core temperature (approximately 37°C [99°F]) by means of active movement and involuntary shivering. Primary hypothermia occurs when heat production in an otherwise healthy person is overcome by the stress of excessive cold, especially when the energy stores of the body are depleted. Secondary hypothermia can occur in ill persons with a wide variety of medical conditions (Table 1), even in a warm environment. Death in patients with secondary hypothermia is often caused by the underlying condition rather than by hypothermia. In all types of hypothermia, consciousness, breathing, and circulation are initially intact but are impaired as the body cools.[10] Some patients with a core temperature of less than 28°C (82°F) engage in paradoxical undressing.[11] Atrial fibrillation is common when the core temperature is less than 32°C (90°F) and is not worrisome in the absence of other signs of cardiac instability.[9] The risk of cardiac arrest increases as the core temperature drops below 32°C, and increases substantially if the temperature is less than 28°C.[12]

DIAGNOSIS

Patients should be considered to have hypothermia if they have a history of cold exposure or a disease that predisposes them to hypothermia and if they have a cold trunk or a core temperature of less than 35°C (95°F) (Fig. 1). Hypothermia can be staged clinically on the basis of vital signs with the use of the Swiss staging system of hypothermia (stages HT I to HT IV)[10] (Table 2); this system is favored over traditional staging (mild, moderate, severe, and profound hypothermia)[12] whenever the core temperature cannot be readily measured.

Measurement of the core temperature will confirm staging and inform transport and management decisions. Properly calibrated, low-reading thermometers are required but are not always available in the prehospital setting. The recorded temperature can vary depending on the body site, perfusion, and environmental temperature. In an intubated patient, insertion of a thermistor probe in the lower third of the esophagus is the preferred method.[9] Measurements obtained with the use of a proximally placed esophageal probe may be falsely elevated owing to ventilation with warmed gases. A thermistor probe in contact with the tympanic membrane accurately reflects brain temperature, provided that the ear canal is free of snow and cerumen and is well insulated against the environment.[14] Measurements obtained with the use of infrared cutaneous, aural, and oral thermometers are often inaccurate in patients with hypothermia. The bladder temperature may be falsely elevated during peritoneal lavage. Rectal probes should be inserted to a depth of 15 cm, but readings may lag behind core temperature during rewarming.[9] When accurate measurement of the core temperature is not feasible, as in some field settings, decisions regarding management should be based on the clinical Swiss staging system.

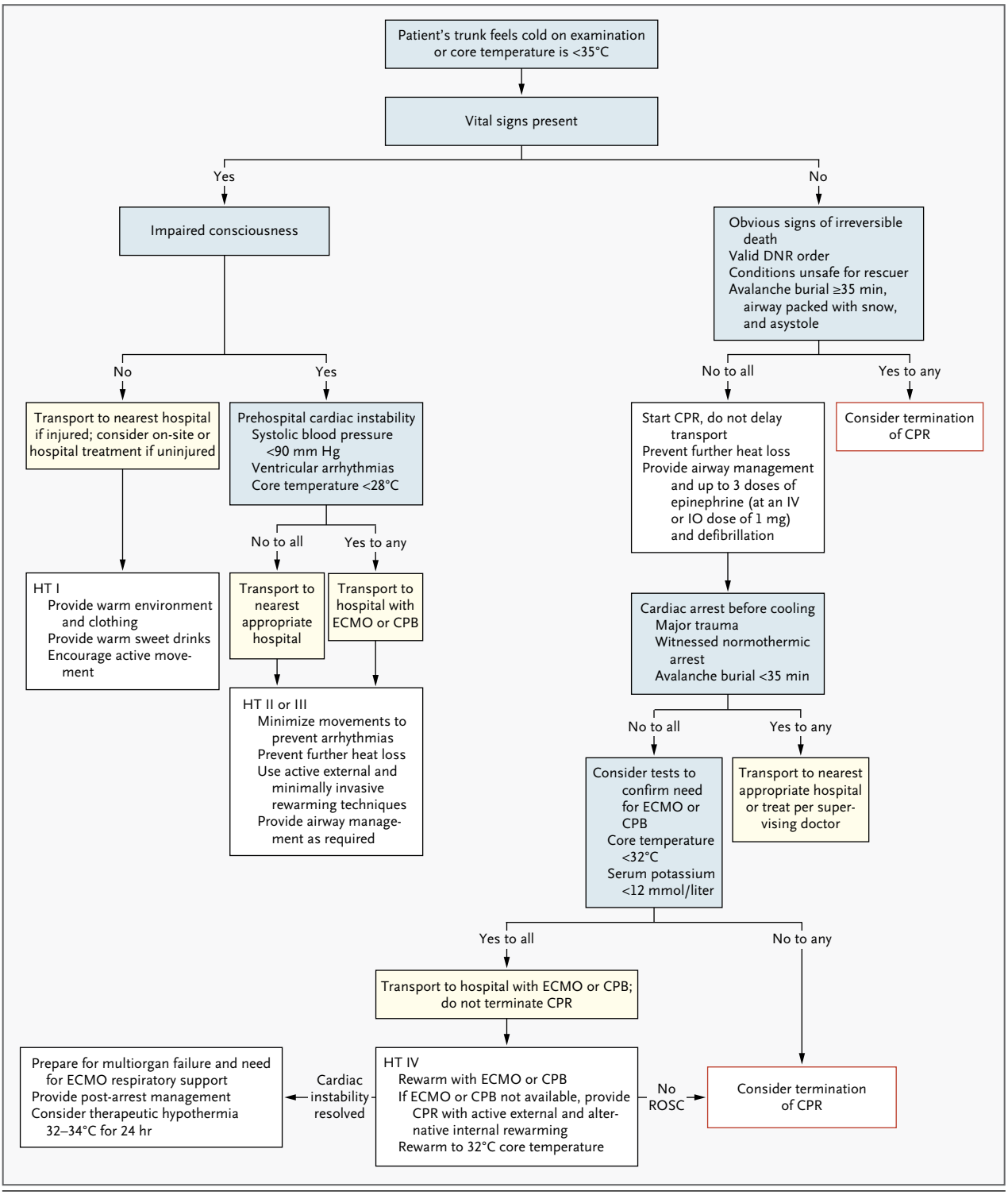
PREHOSPITAL TREATMENT

Priorities for prehospital treatment include careful handling of the patient, provision of basic or advanced life support, passive and active external rewarming, and transport to an appropriate facility. Detecting a pulse in a patient with hypothermia may be difficult, so signs of life and pulse should be checked carefully for 60 seconds. Persistent breathing or movement by the patient should prompt a strategy of watchful waiting, but if no signs of life are detected, then cardiopulmonary resuscitation (CPR) should be started.[7,8] Full-body insulation and rewarming should be provided for all patients as long as it does not impede CPR or delay transport.[7] For rewarming in the prehospital setting, only chemical, electrical, or forced-air heating packs or blankets provide a substantial amount of heat transfer (Table 3).[25,26] Advanced airway management[7] should be performed if indicated, since the risk of triggering a malignant arrhythmia is low.[13,27]

Table 1. Conditions Associated with Secondary Hypothermia.*

Impaired thermoregulation
Central failure
Anorexia nervosa
Cerebrovascular accident
Central nervous system trauma
Hypothalamic dysfunction
Metabolic failure
Neoplasm
Parkinson's disease
Pharmacologic effects
Subarachnoid hemorrhage
Toxins
Peripheral failure
Acute spinal cord transection
Decreased heat production
Neuropathy
Endocrinologic failure
Alcoholic or diabetic ketoacidosis
Hypoadrenalism
Hypopituitarism
Lactic acidosis
Insufficient energy
Extreme physical exertion
Hypoglycemia
Malnutrition
Neuromuscular compromise
Recent birth and advanced age with inactivity
Impaired shivering
Increased heat loss
Dermatologic disorder
Burns
Medications and toxins
Iatrogenic cause
Emergency childbirth
Cold infusions
Heat-stroke treatment
Other associated clinical states
Carcinomatosis
Cardiopulmonary disease
Major infection (bacterial, viral, parasitic)
Multisystem trauma
Shock

* Adapted from Danzl.[9]



RESUSCITATION FLUIDS

Intravenous fluids should be warmed (38 to 42°C [100 to 108°F])[7,8,16] to prevent further heat loss. In a cold prehospital environment, intravenous fluids cool rapidly, and cold fluids may aggravate hypothermia.[8,16,28] A considerable volume of fluid is often required because of the volume loss with cold diuresis (renal-fluid wasting due to hypothermia-induced vasoconstriction and di-

Figure 1 (facing page). Management and Transport in Accidental Hypothermia.

HT I, HT II, HT III, and HT IV refer to the four stages of hypothermia as defined by the Swiss staging system.[10] To convert values for temperature to degrees Fahrenheit, multiply by 9/5 and add 32. Obvious signs of irreversible death include decapitation, truncal transection, decomposition of the whole body, and a chest wall that is not compressible (i.e., the whole body is frozen solid). Rigor mortis as well as fixed and dilated pupils may be present in patients with reversible hypothermia. Active external and minimally invasive rewarming techniques include placement of the patient in a warm environment; use of chemical, electrical, or forced-air heating packs or blankets; and parenteral administration of warm fluids (38 to 42°C [100 to 108°F]). A systolic blood pressure of less than 90 mm Hg is a reasonable prehospital estimate of cardiac instability, but for in-hospital decisions, the minimum sufficient circulation for a patient with a core temperature of less than 28°C (82°F) has not been defined. Therefore, it is not known at what point a patient with refractory cardiac instability should be transitioned to extracorporeal membrane oxygenation (ECMO) or cardiopulmonary bypass (CPB). In remote areas, the transport adviser must balance the risk of increased transport time with the potential benefit of treatment in a center that can provide ECMO or CPB. For a patient with cardiac arrest in a remote area, the need for ECMO or CPB can be confirmed by measuring the serum potassium level at an intermediate hospital, ideally en route toward a center that can provide ECMO or CPB. When transfer to such a center is not feasible, active external and alternative internal rewarming techniques should be used. DNR denotes do not resuscitate, IO intraosseous, IV intravenous, and ROSC return of spontaneous circulation.

minished release of antidiuretic hormone) and vasodilatation during rewarming.[8] Warm crystalloid fluids should be administered on the basis of volume status and glucose, electrolyte, and pH measurements; resuscitation with a large volume of normal saline may aggravate acidosis, so alternative crystalloids should be considered. Vasopressors may be used to treat vasodilatory hypotension, but caution is required, owing to the potential for arrhythmia and the risk of peripheral-tissue perfusion, particularly in patients at risk for frostbite.[29]

TRANSPORT

Conscious, shivering patients (stage HT I) can be treated in the field if they are uninjured or transported to the closest hospital if rewarming is not possible in the field (Fig. 1 and Table 2). Patients with impaired consciousness (stage HT II, HT III, or HT IV) should be assessed for cardiac instability. Patients with stable circulation require active external and minimally invasive rewarming (placement in a warm environment; application of chemical, electrical, or forced-air heating packs or blankets; and administration of warm parenteral fluids) (Table 2) and should be taken to the closest hospital that can provide these measures. Patients with prehospital cardiac instability (e.g., systolic blood pressure of <90 mm Hg or ventricular arrhythmias),[9] those with a core temperature of less than 28°C (82°F), and those in cardiac arrest should be transported to a center capable of providing extracorporeal membrane oxygenation (ECMO) or cardiopulmonary bypass, unless coexisting conditions (e.g., trauma) mandate transport to a closer facility.

Owing to the decrease in cerebral oxygen requirements with cooling,[8] survival without neurologic impairment may be possible even when it is necessary to perform CPR for hours. The longest reported duration of CPR with full neurologic recovery after extracorporeal rewarming is 190 minutes.[30] Survival after 390 minutes of CPR has been documented when rewarming with forced-air blankets and peritoneal lavage was used.[31] If the decision is made to stop at a facility where the serum potassium level can be measured, a hospital en route to a center that can provide ECMO or cardiopulmonary bypass should be selected. If the serum potassium level is higher than 12 mmol per liter (see discussion below), termination of CPR should be considered (Fig. 1). When the patient transport time will be considerable, the use of a mechanical chest-compression device should be considered, since it preserves the energy of the rescue crew, increases safety, and may improve the outcome.[32] The destination hospital should be contacted in advance to ensure that ECMO or cardiopulmonary bypass is available. In remote areas, the transport adviser must balance the risk of a longer transport time against the potential benefit of treatment in a center that can provide ECMO or cardiopulmonary bypass.

RESCUE COLLAPSE AND AFTERDROP

Rescue collapse is defined as cardiac arrest that is related to the extrication and transport of a patient with deep hypothermia (stage HT III).[2,4,21,22,31,33,34] Rescue collapse has been attributed to circulatory collapse due to hypovolemia, cardiac arrhythmias triggered by interventions (e.g., movement of the

Table 2. Staging and Management of Accidental Hypothermia.*

Stage	Clinical Symptoms	Typical Core Temperature†	Treatment
HT I	Conscious, shivering	35 to 32°C	Warm environment and clothing, warm sweet drinks, and active movement (if possible)
HT II	Impaired consciousness, not shivering	<32 to 28°C	Cardiac monitoring, minimal and cautious movements to avoid arrhythmias, horizontal position and immobilization, full-body insulation, active external and minimally invasive rewarming techniques (warm environment; chemical, electrical, or forced-air heating packs or blankets; warm parenteral fluids)
HT III	Unconscious, not shivering, vital signs present	<28 to 24°C	HT II management plus airway management as required; ECMO or CPB in cases with cardiac instability that is refractory to medical management
HT IV	No vital signs	<24°C	HT II and III management plus CPR and up to three doses of epinephrine (at an intravenous or intraosseous dose of 1 mg) and defibrillation, with further dosing guided by clinical response; rewarming with ECMO or CPB (if available) or CPR with active external and alternative internal rewarming

* Hypothermia may be determined clinically on the basis of vital signs with the use of the Swiss staging system.[10] CPB denotes cardiopulmonary bypass, CPR cardiopulmonary resuscitation, and ECMO extracorporeal membrane oxygenation.

† Measurement of body core temperature is helpful but not mandatory. The risk of cardiac arrest increases as the core temperature drops below 32°C and increases substantially if the temperature is less than 28°C.[12,13] To convert values for temperature to degrees Fahrenheit, multiply by 9/5 and add 32.

patient or central venous catheterization), and further cooling.[9,12,35]

Afterdrop is defined as continued core cooling after rescue, which has been documented in artificial cooling experiments or inferred through discrepancies between rectal and core temperatures. With the use of active external and minimally invasive rewarming and concurrent esophageal temperature measurement, afterdrop has not been reported.[15,16,36]

IN-HOSPITAL TREATMENT

In a patient with hypothermia and stable circulation, active external and minimally invasive rewarming is indicated (Table 2),[7,36] as well as treatment of any condition causing secondary hypothermia (Table 1). Given the increased risk of complications, such as hemorrhage or thrombosis, with invasive rewarming methods (e.g., body-cavity lavage, endovascular devices, and extracorporeal heating systems), as well as the absence of evidence that these methods improve the outcome, the best approach may be the use of active external and minimally invasive rewarming.[37] When selecting the rewarming method and rate (Table 3), clinicians should consider accessibility to an appropriate facility, local expertise, resources, and characteristics of the patient. When central venous access is required, it is important to keep the tip of the catheter (and guide wire) far from the heart in order to minimize the risk of arrhythmia.[9]

ECMO or cardiopulmonary bypass should be considered for patients with hypothermia and cardiac instability who do not have a response to medical management. At a core temperature of 28°C (82°F), oxygen consumption and the pulse rate are usually decreased by 50%,[9] but the minimum sufficient circulation has not been defined; therefore, it is not known at what point a patient with cardiac instability should undergo ECMO or cardiopulmonary bypass. The use of ultrasonography and near-infrared spectroscopy to visualize blood flow and assess cerebral oxygenation may assist with these decisions in the future.[38,39]

When signs of life and vital signs are absent (stage HT IV), there is consensus that treatment with ECMO or cardiopulmonary bypass is safe and efficient.[1,2,6-8,12,22,24,33,34,40-42] Among patients treated with ECMO or cardiopulmonary bypass, the rate of survival without neurologic impairment is 47 to 63%.[1,2,33,41] For patients with hypothermia of stage HT IV who are not treated with ECMO or cardiopulmonary bypass, limited data are available, but the survival rate is likely to be less than 37%.[13,16,43] The advantage of ECMO or cardiopulmonary bypass relates to the establishment of blood flow during rewarming. Support with ECMO has resulted in improved outcomes, as compared with traditional cardiopulmonary bypass,[24,41] probably owing to the high incidence of severe pulmonary failure after rewarming, which can be treated more efficiently with ECMO. If ECMO or cardiopulmonary bypass is not avail-

Table 3. Effectiveness of Rewarming Techniques.

Technique	Rewarming Rate	Indication
	°C/hr	
Without cardiac support		
Warm environment and clothing, warm sweet drinks, and active movement[9]	2 (dependent on metabolic rate)*	HT I
Active external and minimally invasive rewarming (warm environment; chemical, electrical, or forced-air heating packs or blankets; and warm parenteral fluids)[3,15-18]	0.1–3.4	HT II or HT III with cardiac stability
Peritoneal dialysis[19]	1–3	Uncertain
Hemodialysis[20]	2–4*	Uncertain
Thoracic lavage[21,22]	3*	HT IV when ECMO or CPB not available
Venovenous ECMO[23]	4*	Uncertain
With cardiac support		
Venoarterial ECMO[24]	6*	HT III with cardiac instability or HT IV
CPB[2]	9*	HT III with cardiac instability or HT IV when ECMO not available

* Value is approximate.

able and transport to a facility with these capabilities is not possible, circulation should be supported with CPR while the patient is rewarmed with a locally available, alternative internal rewarming technique (Table 3).[16,20,21,31] According to case reports, thoracic lavage has restored spontaneous circulation within 2 hours[21] and is a reasonable alternative rewarming technique when ECMO or cardiopulmonary bypass is not available.[7] In patients with a return of spontaneous circulation, multiorgan failure should be expected, and respiratory support with ECMO may be required. Standard management after cardiac arrest is indicated, and some experts recommend 24 hours of therapeutic hypothermia (32 to 34°C [90 to 93°F]), but evidence in support of this approach is lacking. If a patient with cardiac arrest due to hypothermia is rewarmed to a core body temperature that is higher than 32°C and asystole persists, irreversible cardiac arrest is very likely, and termination of CPR should be considered.

MODIFIED VERSUS STANDARD ADVANCED LIFE SUPPORT

The use of vasopressors in animal models of hypothermic cardiac arrest have had mixed results, with a small number of studies showing a benefit.[44] The guidelines of the European Resuscitation Council recommend a modified approach to advanced life support, consisting of up to three defibrillations, with epinephrine withheld until the core temperature is higher than 30°C (86°F) and with the interval between doses doubled until the core temperature is higher than 35°C (95°F).[8] These recommendations conflict with the American Heart Association guidelines, which state, "It may be reasonable to consider administration of a vasopressor during cardiac arrest according to the standard ALS [advanced life support] algorithm concurrently with rewarming strategies."[7] Hence, the administration of up to three doses of medication and defibrillation is likely to be a reasonable approach, with further dosing guided by the clinical response.[45]

SERUM POTASSIUM

Increased serum potassium levels can be caused by hypoxic and traumatic cell death, medications (e.g., depolarizing neuromuscular blockers), and a variety of medical conditions. A severely elevated serum potassium level is associated with nonsurvival and is considered a marker of hypoxia before cooling.[1,33,46] The highest recorded levels of serum potassium in patients with accidental hypothermia who were successfully resuscitated are 11.8 mmol per liter in a 31-month-old child,[42] 9.5 mmol per liter in a 13-year-old child,[47] 7.9 mmol per liter in a 34-year-old adult,[33] and 6.4 mmol per liter in an adult who survived burial in an avalanche.[48]

Some researchers recommend a potassium level

of 12 mmol per liter[49] or 10 mmol per liter[2,4,33,50] as the cutoff above which CPR is considered to be futile, with a cutoff of 8 mmol per liter in adults who have been buried in an avalanche.[7] We recommend that termination of CPR be considered when the potassium level is higher than 12 mmol per liter (Fig. 1), and we recommend consultation with the team providing ECMO or cardiopulmonary bypass when the potassium level is 10 to 12 mmol per liter. When the potassium level is less than 10 mmol per liter, survival without neurologic impairment may be possible, and CPR should be continued until the patient is rewarmed. Unfortunately, a low serum potassium level does not ensure survival.[1,4,7,33] Other biomarkers, such as lactate and pH levels, have been reported to have prognostic significance, although less consistently.[3,4,13]

ACCIDENTAL HYPOTHERMIA IN SPECIAL SITUATIONS

TRAUMA

Trauma, notably shock and cerebrospinal injury, destabilizes thermoregulation[9]; thus, patients with multiple traumas or with central nervous system trauma are prone to hypothermia. Hypothermia increases bleeding and transfusion requirements and may increase mortality.[51,52] Clotting-factor activity and platelet function are reduced with lowered temperature, causing a critical coagulopathy below 34°C (93°F).[53] Blood is warmed before laboratory testing; hence, hypothermia-induced coagulopathy is not measured.[52] Heparin-coated systems for cardiopulmonary bypass, which obviate the need for systemic heparinization, allow the rewarming of patients with severe trauma.[47]

AVALANCHE BURIAL WITHOUT VITAL SIGNS

The maximum reported cooling rate in a person who had been completely buried in an avalanche was 9°C (48°F) per hour.[17,34] With a burial time of less than 35 minutes, life-threatening hypothermia is unlikely, owing to insufficient cooling time, and trauma and hypoxia should be suspected as the cause if vital signs are absent.[7,8,29,46] If the burial time exceeds 35 minutes, the airway is packed with snow, and the patient is asystolic, hypoxia probably preceded hypothermia and CPR is unlikely to be beneficial. However, if the burial time is longer than 35 minutes and the airway is not blocked, severe hypothermia should be suspected and the patient should be treated accordingly (Fig. 1).[8,46,54] The core temperature can be used to estimate the burial time if it is unknown (i.e., a temperature of less than 32°C [90°F] correlates with a burial time of more than 35 minutes).[46]

DROWNING WITHOUT VITAL SIGNS

Persons who have been submerged in cold water may have a better outcome than those submerged in warm water.[55] If the patient's history indicates immersion in cold water (i.e., the body was exposed to cold water, but the patient was able to breathe) and it is likely that the body cooled before the onset of hypoxia and cardiac arrest (stage HT IV), survival without neurologic impairment may be possible,[40,56] and resuscitation should proceed (Fig. 1). If the history indicates submersion in cold water (i.e., the body was exposed to cold water, and the patient was unable to breathe) before cooling, the outcome may be worse.[1,33] The longest period of submersion that a person has survived without neurologic impairment was 66 minutes in a child who was 2.5 years old (the child's core temperature was 19°C [66°F]).[57]

OUTCOME

The lowest reported core body temperatures in patients with full neurologic recovery are slightly less than 14°C (57°F) in a case of accidental hypothermia[40] and 9°C (48°F) in a case of induced hypothermia.[58] A survey of patients with stage IV hypothermia at one center showed that organ failure was common 24 hours after admission, and among fatal cases of organ failure, the most common cause of death was pulmonary edema.[3] Patients with primary hypothermia and cardiac stability who have been treated with active external and minimally invasive rewarming have a rate of neurologically intact survival of approximately 100%,[16] whereas for patients with cardiac arrest treated with extracorporeal rewarming, the rate is approximately 50%.[1,2,33,41] With cardiac arrest, full recovery may be possible if hypoxia did not precede hypothermia, no serious underlying disease or trauma exists, and extracorporeal rewarming is used.[2,41] To aid in predicting outcomes for unusual presentations, we have provided summary data from important studies of stage III and IV accidental hypothermia in the Supplementary Appendix, available with the full text of this article at NEJM.org.

SUMMARY

Advances in the safety and availability of rewarming techniques have improved the prognosis for patients with hypothermia, especially in the case of patients with cardiac arrest who are treated with extracorporeal rewarming. Patients who have hypothermia without cardiac instability should be rewarmed with active external and minimally invasive rewarming techniques. Patients with cardiac arrest may survive without neurologic impairment if hypothermia was not preceded by a hypoxic event, if there is no serious underlying disease or trauma, and if extracorporeal rewarming is used. For patients with hypothermia and cardiac instability or cardiac arrest, ECMO may be the best treatment currently available and is preferable to cardiopulmonary bypass. Early transport to a facility with the necessary capabilities and selection of an appropriate rewarming technique have the potential to decrease complications and improve survival. Analyses from hypothermia registries and prospective trials are needed to improve treatment strategies.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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CLINICAL PRACTICE

Acute High-Altitude Illnesses

Peter Bärtsch, M.D., and Erik R. Swenson, M.D.

This Journal *feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the authors' clinical recommendations.*

A 45-year-old healthy man wishes to climb Mount Kilimanjaro (5895 m) in a 5-day period, starting at 1800 m. The results of a recent exercise stress test were normal; he runs 10 km 4 or 5 times per week and finished a marathon in less than 4 hours last year. He wants to know how he can prevent becoming ill at high altitude and whether training or sleeping under normobaric hypoxic conditions in the weeks before the ascent would be helpful. What would you advise?

THE CLINICAL PROBLEM

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Persons who are not acclimatized and ascend rapidly to high altitudes are at risk for any of several debilitating and potentially lethal illnesses (Table 1) that occur within the first days after arrival at high altitudes.[1] Traditionally, 2500 m has been used as the threshold for high-altitude illnesses; in rare cases, mild illness occurs in persons who have ascended above 2000 m but below 2500 m.

ACUTE MOUNTAIN SICKNESS

Headache that occurs with an increase in altitude is the cardinal symptom of acute mountain sickness and is usually accompanied by anorexia, nausea, dizziness, malaise, sleep disturbance, or a combination of these symptoms.[2] Acute mountain sickness generally occurs within 6 to 12 hours after a person ascends to 2500 m or higher. Its prevalence and severity increase with increasing altitude. Acute mountain sickness occurs in approximately 10 to 25% of unacclimatized persons who ascend to 2500 m. Symptoms are usually mild at this altitude and have little effect on activity. However, acute mountain sickness occurs in 50 to 85% of unacclimatized persons at 4500 to 5500 m and may be incapacitating.[3-5]

In a retrospective study, major independent risk factors for acute mountain sickness included a history of acute mountain sickness, fast ascent (≥625 m per day above 2000 m), and lack of previous acclimatization (<5 days above 3000 m in the preceding 2 months).[6] A prospective study involving trekkers and climbers who went to altitudes between 4000 and 8848 m showed the same major risk factors for incapacitating acute mountain sickness and other severe altitude illnesses[7] (described below). Other possible risk factors include female sex, an age younger than 46 years, and a history of migraine. Exercise may exacerbate acute mountain sickness, but good physical fitness is not protective.[6-8] Symptoms usually resolve within 1 to 2 days when appropriate measures are taken (see below).

An audio version of this article is available at NEJM.org

HIGH-ALTITUDE CEREBRAL EDEMA

High-altitude cerebral edema is characterized by truncal ataxia, decreased consciousness, and usually mild fever.[2,9] Without appropriate treatment, coma may evolve rapidly, followed by death from brain herniation within 24 hours. Headache

KEY CLINICAL POINTS

ACUTE HIGH-ALTITUDE ILLNESSES

- Acute high-altitude illnesses occur in persons who are not acclimatized during the first days at an altitude of 2500 m or higher, with wide variation in the incidence according to patient characteristics and history.
- Headache is the major symptom of acute mountain sickness. If acute mountain sickness is not treated adequately, it can progress to life-threatening high-altitude cerebral or pulmonary edema.
- High-altitude illnesses can be prevented by ascending 300 to 500 m per day at altitudes above 3000 m and including a rest day every 3 to 4 days.
- Risks of acute mountain sickness and high-altitude cerebral edema are reduced with the use of acetazolamide or dexamethasone; the risk of high-altitude pulmonary edema is reduced with the use of nifedipine, phosphodiesterase-5 inhibitors, or dexamethasone.
- Acute mountain sickness may be treated by a day of rest and nonsteroidal antiinflammatory drugs for headache, but when it is severe, descent or supplemental oxygen is indicated. Dexamethasone is indicated for severe acute mountain sickness or high-altitude cerebral edema, and nifedipine or phosphodiesterase-5 inhibitors are indicated for high-altitude pulmonary edema; treatment with these agents should be followed by descent as soon as possible.

that is poorly responsive to nonsteroidal antiinflammatory drugs (NSAIDs) and vomiting indicate probable progression of acute mountain sickness to high-altitude cerebral edema, but the absence of headache and other symptoms of acute mountain sickness does not rule it out. High-altitude cerebral edema usually develops after at least 2 days at altitudes above 4000 m. The prevalence is estimated to be 0.5 to 1.0% among persons at 4000 to 5000 m.[10] Magnetic resonance imaging in patients with high-altitude cerebral edema shows vasogenic edema[11] and microhemorrhages that are located predominantly in the corpus callosum.[12]

HIGH-ALTITUDE PULMONARY EDEMA

High-altitude pulmonary edema is characterized by loss of stamina, dyspnea, and dry cough with exertion, followed by dyspnea at rest, rales, cyanosis, cough, and pink, frothy sputum.[13] Deterioration in gas exchange also increases the risk of high-altitude cerebral edema. This condition develops 2 or more days after exposure to altitudes above 3000 m and is rare in persons at altitudes below 2500 to 3000 m. The risk increases with increased altitude and faster ascent. For example, the incidence among persons with an unknown history of high-altitude pulmonary edema is 0.2% if they ascend to 4500 m in 4 days and 2% if they ascend to 5500 m in 7 days; the incidence increases to 6% and 15%, respectively, when these altitudes are reached within 1 to 2 days. The risk is further increased among persons with a history of high-altitude pulmonary edema (e.g., the risk of recurrence is 60% among persons who ascend to 4500 m in 2 days).[14] The estimated mortality among persons with untreated high-altitude pulmonary edema is 50%. This disorder is a noncardiogenic pulmonary edema caused by exaggerated hypoxic pulmonary vasoconstriction and abnormally high pulmonary-artery pressure and capillary pressure.[15] These high pressures lead to a noninflammatory and hemorrhagic alveolar capillary leak that secondarily may evoke an inflammatory response.[16]

STRATEGIES AND EVIDENCE

RISK ASSESSMENT

Risk assessment (Table 2) should start with a clinical evaluation directed toward any cardiopulmonary diseases that might worsen during a sojourn involving high altitude. Although a discussion of the effect of altitude in persons with preexisting disease is not within the scope of this article, reviews of this topic are available.[17,18] Given that previous altitude illness is a strong predictor of recurrence, detailed information about the person's history with respect to visits to high-altitude areas, acclimatization before pre-

Table 1. Symptoms, Signs, and Differential Diagnosis of High-Altitude Illnesses.

Variable	Acute Mountain Sickness	High-Altitude Cerebral Edema	High-Altitude Pulmonary Edema
Symptoms	Headache plus one or more of the following symptoms: nausea, vomiting, dizziness, fatigue, and insomnia. Mild-to-moderate illness: a few symptoms of mild-to-moderate intensity within 6 to 12 hr after exposure to altitudes of ≥2500 m; severe illness: many or all symptoms of severe intensity, usually evolving from mild-to-moderate illness	Moderate-to-severe symptoms of acute mountain sickness	Initial illness: inappropriate dyspnea during exercise, reduced exercise performance, mild fever; advanced illness: orthopnea, pink frothy sputum, drowsiness
Signs	None	Lassitude, truncal ataxia, altered mental status such as drowsiness or loss of consciousness, often mild fever	Tachypnea, arterial oxygen saturation considerably below average value for other persons in climbing group, mild fever, signs of high-altitude cerebral edema with advanced stages
Differential diagnosis	Exhaustion, dehydration, hangover, migraine	Transient ischemic attack or stroke, acute psychosis, intoxication (from carbon monoxide, alcohol, or drugs)	Hyperventilation syndrome, pulmonary embolism, mucus plugging

vious ascents, maximum altitudes for climbing and sleeping, rates of ascent, and any altitude illness should be obtained. The estimation of risk is most reliable for persons with previous rates of ascent and final altitudes that were similar to those planned.

OTHER ASSESSMENTS

The assessment of ventilation in response to exposure to hypoxic conditions at rest or during exercise has been proposed as a means of refining risk prediction for altitude sickness. The increase in ventilation at rest or during exercise while breathing 11.5% oxygen,[19] as well as arterial oxygen saturation after the first 30 minutes of exposure to an altitude of 3000 m or to corresponding normobaric hypoxic conditions,[20] is on average significantly lower in persons who are susceptible to acute altitude sickness than in those who are not. However, considerable overlap between groups classified as susceptible and those classified as not susceptible in a retrospective study[20] and between a group classified as having acute mountain sickness and a group classified as unaffected in a prospective study[19] makes it impossible to define cutoff values that are sufficiently sensitive and specific to be useful in practice. A multivariate analysis of risk factors for severe high-altitude illness[7] showed that the hypoxic ventilatory response and other physiological measurements under hypoxic conditions add little to the discrimination provided by patient characteristics and history (i.e., sex, level of physical activity, rate of previous ascent, and status with respect to previous severe high-altitude illness and migraines).

Persons who are considered to be susceptible to high-altitude pulmonary edema because of two previous episodes of high-altitude pulmonary edema have abnormally high systolic pulmonary-artery pressure (>40 mm Hg) under hypoxic conditions (12% oxygen in ambient air at sea level).[21] In a study of a western European population, exaggerated hypoxic pulmonary-artery pressure was detected in about 10% of study participants,[22] but high-altitude pulmonary edema develops in only 15% of persons with exaggerated hypoxic pulmonary-artery pressure responses who make a rapid ascent (unpublished data). For this reason and because of a very low pretest probability of high-altitude pulmonary edema (e.g., an incidence of 1 to 2% among trekkers to the Mount Everest base camp), measurement of pulmonary-artery pressure under hypoxic conditions cannot be recommended as a means of identifying persons who are susceptible to high-altitude pulmonary edema.

Although athletic persons are more likely to reach the summit than persons who are not athletic,[19] physical fitness appears to have no association[8,19] or at most a modest association[7] with susceptibility to acute mountain sickness and high-altitude pulmonary edema. Thus, an exercise test is not indicated to assess the risk of acute high-altitude illness. Information about the amount and intensity of the person's regular

Table 2. Risk Assessment for Acute High-Altitude Illnesses.*

Risk	Planned Ascent and Clinical History
Low	Slow ascent (≤500 m/day above 2500 m); no history of acute mountain sickness, high-altitude cerebral edema, or high-altitude pulmonary edema with previous exposure to similar altitude; rapid ascent (>500 m/day above 2500 m) for persons who are partially acclimatized (exposure to high altitudes of <3000 m in preceding weeks)
Moderate	Unknown history of acute mountain sickness, high-altitude cerebral edema, or high-altitude pulmonary edema and fast ascent (>500 m/day above 3000 m); unknown history of acute mountain sickness and rapid ascent (ascent to >3000 m in 1 day)
High	Unknown history of acute mountain sickness, high-altitude cerebral edema, or high-altitude pulmonary edema, very rapid ascent (considerably >500 m/day), and high final altitude (>4000 m); history of acute mountain sickness, high-altitude cerebral edema, or high-altitude pulmonary edema with previous exposure to high altitude that is similar to the planned ascent

* All ascent altitudes refer to ascent from the altitude at which the person has slept.

exercise as well as his or her level of athletic performance is helpful in estimating whether there is sufficient reserve to cope with the expected loss of exercise capacity at high altitudes of about 1% for every 100 m above 1500 m.[23] Persons without athletic training should be encouraged to begin regular physical exercise several weeks to months before the planned ascent, particularly when rigorous outdoor activities are planned at high altitudes.

PREVENTION

Nonpharmacologic Approaches

Although data are lacking from prospective studies that systematically assess the influence of the rate of ascent (defined as the gain in altitude between the altitudes at which one sleeps on 2 consecutive nights) on prevention of acute high-altitude illnesses, guidelines for ascents to altitudes above 3000 m[24,25] recommend ascent rates of 300 to 500 m per day and a day of rest every 3 to 4 days (Table 3). However, there are large differences among persons with respect to ascent rates that are not associated with poor outcomes. A person without previous experience in high altitudes should follow the ascent rates recommended by these guidelines. If the planned ascent rate is faster, additional measures, such as acclimatization strategies before the ascent or prophylactic medications, should be considered.

Mountaineering or residence with regular physical activity at altitudes above 3000 m in the weeks preceding a climb to 4500 m is associated with a reduced incidence of acute mountain sickness that is independent of the person's susceptibility to this condition and the rate of ascent.[6] An ascent made after 1 week at an altitude of 2000 m or higher, as compared with an ascent from near sea level, reduces both the incidence and severity of acute mountain sickness at 4300 m by 50%.[26] It has been hypothesized that exposure to normobaric hypoxic conditions before an ascent might provide protection against acute mountain sickness. In double-blind, placebo-controlled trials, however, repeated intermittent exposure to normobaric hypoxia equivalent to an altitude of 2500 to 4500 m for 60 to 90 minutes[27,28] or continuous exposure to normobaric hypoxia equivalent to an altitude of 2500 to 3000 m during 8 hours of sleep on 7 consecutive nights[29] did not significantly reduce the incidence or severity of acute mountain sickness at altitudes of 4300 to 4559 m. On the basis of these data, a recommended strategy to reduce the risk of high-altitude illness is to remain at an altitude between 2000 and 3000 m for about a week[6,26] and to include day hiking or climbing at higher altitudes. This should be done as close in time as possible to the trek or expedition, since it is not known how quickly acclimatization diminishes with time.[30]

Prophylactic Medication

Randomized, placebo-controlled trials have shown a significant reduction in the risk of headache with the use of acetylsalicylic acid at a dose of 320 mg taken three times at 4-hour intervals, starting 1 hour before ascent,[31] or ibuprofen at a dose of 600 mg three times per day,[32,33] starting a few hours before ascent to altitudes between 3480 and 4920 m. Headache is a defining symptom of acute mountain sickness, and the incidence of this condition was reduced in all these trials, which lasted 1 or 2 days only. A risk asso-

Table 3. Prevention of High-Altitude Illnesses.

Method	Description
Acclimatization before exposure	Sojourning several days at intermediate altitudes at or above 2000 m (staging), hiking or climbing on day tours above 3000 m, or both
Slow ascent	Ascent rate of 300–500 m/day above 2500–3000 m, with a day of rest every 3–4 days; appropriate treatment of early symptoms of acute mountain sickness for prevention of severe high-altitude disease
Drugs for prevention of acute mountain sickness, high-altitude cerebral edema, or both	
Moderate risk	Acetazolamide, 125 mg twice/day; if there are side effects with or contraindications to acetazolamide, dexamethasone, 4 mg twice/day, can be used
High risk	Acetazolamide, 250 mg two or three times/day (three times/day recommended for rapid ascent, though efficacy uncertain); dexamethasone, 4 mg three times/day, if acetazolamide has unacceptable side effects or is contraindicated
Drugs for prevention of high-altitude pulmonary edema in persons with history of this condition	
First line	Nifedipine, 30 mg of slow-release formulation twice/day
Second line	Phosphodiesterase-5 inhibitors (e.g., tadalafil, 10 mg twice/day) or dexamethasone, 8 mg twice/day
Third line	Inhaled salmeterol (125 μg twice/day) appears to be less effective than other options and may cause tremor and tachycardia in some persons with this dose

ciated with these medications is gastrointestinal bleeding, which may be increased at high altitudes,[34] but studies were not powered to assess this risk.[31-33]

When risk assessment indicates a high probability of the development of acute mountain sickness (Table 2), acetazolamide is recommended. In a large, prospective, observational study, the use of acetazolamide was associated with a 44% reduction in the risk of severe high-altitude illnesses.[7] A meta-analysis of randomized trials of various doses of acetazolamide initiated before ascent likewise showed a significantly reduced risk of acute mountain sickness; the authors of this meta-analysis concluded that the lowest effective dose for prevention is 125 mg twice per day.[35] This dose has been shown to be effective in reducing the incidence of acute mountain sickness associated with rapid ascent from a baseline altitude of 1600 to 4300 m[36] or during further ascent to 4900 m among trekkers who have ascended to 4200 m without illness.[37] However, a study that showed acute mountain sickness in more than 50% of persons who received acetazolamide at a dose of 250 mg twice per day during a rapid ascent of Mount Kilimanjaro (5895 m in 5 days)[38] suggested that low-to-moderate doses may be inadequate with more rapid ascents and higher final altitudes; it is not known whether higher doses are more effective in persons at these altitudes. Acetazolamide should be started 1 day before the ascent and discontinued after 2 days at the final altitude or during the descent. A meta-analysis showed that acral paresthesias occurred in 35 to 90% of persons receiving acetazolamide, and polyuria occurred with the first several doses in 8 to 55%, with distaste for carbonated beverages in 4 to 14%.[35] Nausea and tiredness developed in about 20% of persons who received 250 mg of acetazolamide three times per day at low altitudes.[39] Thus, testing for side effects of the drug before the ascent might be useful to avoid confusion of a side effect with a symptom of acute mountain sickness. If side effects occur, the person should be advised not to use this prophylactic agent.

If there is a contraindication to acetazolamide or if it has intolerable side effects, an alternative is dexamethasone at a dose of 4 mg two or three times per day. In a randomized, placebo-controlled trial, dexamethasone was associated with a significant reduction in the incidence and severity of acute mountain sickness among persons who ascended to 2700 m.[40] Several smaller randomized trials, including one head-to-head trial,[39] have also shown these results at 4300 to 4570 m, with a magnitude of effect similar to that of acetazolamide.[10] Given the potential adverse effects of dexamethasone (e.g., hyperglycemia, adrenal suppression, and psychosis), its use for pre-

Table 4. Treatment of Acute High-Altitude Illnesses.

Treatment	Acute Mountain Sickness	High-Altitude Cerebral Edema	High-Altitude Pulmonary Edema
General measures	Mild to moderate: day of rest, descend 500–1000 m if no improvement with day of rest Severe: descend as soon as possible to lowest possible altitude; administer oxygen at a rate of 2–4 liters/min or with the use of hyperbaric bag until descent or evacuation possible	Descend as soon as possible to lowest possible altitude; administer oxygen at a rate of 2–4 liters/min or with the use of hyperbaric bag until descent or evacuation possible	Descend as soon as possible to lowest possible altitude; administer oxygen at a rate of 2–4 liters/min or with the use of hyperbaric bag until descent or evacuation possible
Drugs	Mild to moderate: nonsteroidal anti-inflammatory drugs, antiemetic agents, acetazolamide (125–250 mg twice/day) to enhance acclimatization Severe: intravenous, intramuscular, or oral dexamethasone, 8 mg, followed by 4 mg every 6 hr	Intravenous, intramuscular, or oral dexamethasone, 8 mg, followed by 4 mg every 6 hr	Nifedipine, 60–80 mg of slow-release formulation/24 hr in several doses
Measures after recovery	Reascent possible when recovery is complete without use of drugs, except for acetazolamide; consider acetazolamide, 250 mg twice/day, during reascent	Reascent possible with complete recovery after discontinuation of dexamethasone; consider acetazolamide, 250 mg twice/day, during reascent	Reascent possible when symptoms have resolved and oxygenation at rest and during exercise is normal for altitude without supplemental oxygen; continue nifedipine, 60 mg of slow-release formulation/day

vention of acute mountain sickness should be limited to persons with unequivocal indications, and it should be administered for less than 1 week.

Since there appears to be a continuum from acute mountain sickness to high-altitude cerebral edema, drugs that prevent the first condition will probably also reduce the risk of the second one. However, systematic data are lacking to confirm this theory.

Small randomized trials involving persons with a history of high-altitude pulmonary edema have shown that the risk of recurrence can be reduced with the use of medications that lower the high pulmonary-artery pressure that is typical in susceptible persons. Nifedipine in a slow-release formulation at a dose of 30 mg twice per day,[41] tadalafil (a phosphodiesterase-5 inhibitor) at a dose of 10 mg twice per day, and dexamethasone at a dose of 8 mg twice per day[42] appear to be similarly effective in lowering pulmonary-artery pressure and reducing the incidence of high-altitude pulmonary edema from approximately 70% to approximately 10% or less. Although it has not been compared directly with these agents, inhaled salmeterol, a long-acting β_2-agonist, at a high dose of 5 puffs (125 μg) twice per day, appears to be less effective; in a placebo-controlled trial, it was associated with a reduction in the incidence of high-altitude pulmonary edema from 74% to 33%.[43]

TREATMENT

The treatment of mild-to-moderate acute mountain sickness (Table 4) generally consists of a day of rest, NSAIDs for headache, and possibly antiemetic drugs. One small, placebo-controlled, crossover trial showed that ibuprofen reduced headache significantly in affected persons.[44] Treatment with oxygen and acetazolamide may also facilitate more rapid recovery, although there are only limited data from randomized trials to support the benefit of acetazolamide in persons in whom acute mountain sickness has already developed.[45] In remote areas, a descent of 500 to 1000 m is indicated if symptoms of acute mountain sickness persist despite a day of rest and symptomatic treatment. If descent is not possible because of logistical constraints or the person's condition, improvement sufficient to allow descent can be achieved with one or a combination of the following interventions: administration of dexamethasone at a dose of 4 to 8 mg every 6 hours,[46] provision of supplemental oxygen (2 to 4 liters per minute), or treatment in a manually pressurized, body-length, portable hyperbaric bag.[47]

Immediate descent is lifesaving when severe symptoms suggest the onset of high-altitude cerebral edema or high-altitude pulmonary edema. In persons with high-altitude pulmonary edema, pulmonary-artery pressure should be lowered by means of supplemental oxygen (2 to

4 liters per minute), descent to a lower altitude, or pulmonary vasodilators (of which only nifedipine has been tested in a prospective study, which was uncontrolled).[48] Anecdotal reports describe a benefit of phosphodiesterase-5 inhibitors for the treatment of high-altitude pulmonary edema, but they do not provide support for the use of dexamethasone.[49] Although descent to a lower altitude is the primary goal for the management of high-altitude pulmonary edema in remote areas, allowing a fully conscious person with mild-to-moderate high-altitude pulmonary edema to remain in a mountainous resort area is reasonable when supplemental oxygen and oral pulmonary vasodilators can be provided under the supervision of a local physician or in an emergency facility.[50] There is no role for diuretics in the treatment of high-altitude pulmonary edema.

AREAS OF UNCERTAINTY

Since high-altitude cerebral edema and high-altitude pulmonary edema occur infrequently in remote areas, rigorous data are lacking to guide their management. Although numerous trials provide support for the use of acetazolamide for prophylaxis against acute mountain sickness, the appropriate dosage for persons planning an ascent to higher altitudes (above 4500 to 5000 m) or a rapid ascent is uncertain; data are lacking from randomized trials comparing dexamethasone with high doses of acetazolamide in these circumstances. The magnitude and duration of a reduced risk of acute mountain sickness associated with various forms of exposure to high altitudes before an ascent remain unclear.

GUIDELINES

Our recommendations are generally concordant with the guidelines of the Wilderness Medical Society for the prevention and treatment of high-altitude illnesses.[45]

CONCLUSIONS AND RECOMMENDATIONS

The person described in the vignette has planned a rapid ascent of Mount Kilimanjaro (5895 m over a period of 5 days). In addition to the need for region-specific prophylaxis against infectious disease such as malaria, he should be advised that his plan involves a 40% risk of the development of acute mountain sickness that would be severe enough to prevent him from reaching the peak, as well as a small risk of high-altitude pulmonary edema or high-altitude cerebral edema. To improve his chances of staying relatively symptom-free and reaching the summit, we would recommend that he spend several days hiking and living at intermediate altitudes of 2000 to 3000 m near his home before departure; consider climbing Mount Meru, a 4500-m neighboring peak, in 3 or 4 days before ascending Mount Kilimanjaro; or plan a flexible timetable to allow additional stops at intermediate altitudes according to his clinical condition. Since randomized trials have shown no significant reduction in the incidence of high-altitude illness with athletic training in hypoxic conditions, such training should not be recommended, but we would encourage regular endurance training, since good aerobic performance will help to make mountaineering less strenuous. There are currently no reliable tests to predict susceptibility to high-altitude illnesses during an ascent. If acclimatization before the ascent or a slower ascent rate is not possible, we would recommend that prophylaxis with acetazolamide, at a dose of 250 mg two or three times per day, be initiated at the mountain base after testing for side effects of the drug at home. However, the efficacy of acetazolamide for particularly high and fast climbs such as this one is uncertain. It would be reasonable to provide the patient with dexamethasone for use as rescue medication during descent, if severe acute mountain sickness or high-altitude cerebral edema develops suddenly, and he should be advised not to delay the descent, if it is indicated.

Anyone climbing to a high altitude should be educated about high-altitude illnesses and the steps that should be taken if symptoms develop. Good sources of information include www.ismmed.org and www.medex.org.uk. Steps include resting for a day if acute mountain sickness develops and descending if there is no improvement in symptoms with the use of NSAIDs and antiemetic agents within 1 day, and descending immediately at the first appearance of symptoms or signs of high-altitude pulmonary edema or high-altitude cerebral edema.

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Extreme Physiology & Medicine

COMMENTARY

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Faculty of Prehospital Care, Royal College of Surgeons Edinburgh guidance for medical provision for wilderness medicine

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Abstract

To support leaders and those involved in providing medical care on expeditions in wilderness environments, the Faculty of Pre-Hospital Care (FPHC) of The Royal College of Surgeons of Edinburgh convened an expert panel of leading healthcare professionals and expedition providers. The aims of this panel were to: (1) provide guidance to ensure the best possible medical care for patients within the geographical, logistical and human factor constraints of an expedition environment. (2) Give aspiring and established expedition medics a 'benchmark' of skills they should meet. (3) Facilitate expedition organisers in selecting the most appropriate medical cover and provider for their planned activity. A system of medical planning is suggested to enable expedition leaders to identify the potential medical risks and their mitigation. It was recognised that the scope of practice for wilderness medicine covers elements of primary healthcare, pre-hospital emergency medicine and preventative medicine. Some unique competencies were also identified. Further to this, the panel recommends the use of a matrix and advisory expedition medic competencies relating to the remoteness and medical threat of the expedition. This advice is aimed at all levels of expedition medic, leader and organiser who may be responsible for delivering or managing the delivery of remote medical care for participants. The expedition medic should be someone equipped with the appropriate medical competencies, scope of practice and capabilities in the expedition environment and need not necessarily be a qualified doctor. *In addition to providing guidance regarding the clinical competencies required of the expedition medic*, the document provides generic guidance and signposting to the more pertinent aspects of the role of expedition medic.

Keywords: Expedition, Risk assessment, Medical planning, Wilderness medicine, Austere environment

Background

The Oxford English dictionary defines an expedition as "a journey undertaken by a group of people with a particular purpose". This definition highlights the broad scope of expeditions and de facto, expedition medical planning. Medical care provided in an austere environment is often referred to as "wilderness medicine". This was described by Backer and was defined by its remoteness, physiology, need for improvisation and dependence upon clinical examination and judgement [1]. The scope of this guidance is intended to cover the planning and competencies that facilitate the understanding of the challenges described by Backer and therefore the delivery of good quality clinical care.

The practice of wilderness medicine occurs in many environments and this document is not intended to provide specific advice to specialist expeditions (e.g. deep cave exploration or pioneering extreme new routes in the mountains). The concept of competencies in pre-hospital care has previously been described [2] and *competent individuals are those deemed* to have the "ability to apply knowledge, understanding and skills" to perform to an accepted standard. The competencies discussed consider

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pre-hospital and primary care skills relevant to medical providers on expeditions in remote areas with some consideration of more specialist environments.

Death and serious injury or illness on expeditions is thankfully rare. Aside from extreme sports in the wilderness, the risks faced by participants on a well-planned expedition are equivalent to those faced by an active person living in the UK. For example, road traffic accidents cause approximately 50 % of unexpected deaths on expeditions per annum [3]. Anderson and Johnson [4] reviewed the data from 246 expeditions with 1263 medical problems (gastrointestinal disease 30 %, medical problems 21 %, orthopaedic problems 19 %, environmental problems 14 %) and a 10 % evacuation rate. More recent published data reviewed charity expeditions over a 5-year period provided by one company. Overall 1564 incidents were reported during 42,482 expedition days. 94 % of the incidents reported were minor and 1 % severe giving a risk of a severe injury or condition of 0.47 per 1000 participant days [5]. Even on potentially high threat expeditions to Denali in Alaska, medical incidents were rare with only 3.5 % of 24,079 climbers requesting medical assistance and only 15 % of these requiring evacuation by the National Park Service [6]. It is worth bearing such figures in mind when planning an expedition, and considering the relatively low prevalence of problems, whilst being mindful of the potentially higher impact should they occur. In addition to medical provision the expedition medic will be responsible for the dental health of participants as well as environmental health. Dental problems, in particular, present a potential burden to the expedition with one expedition reporting 50/309 (16.5 %) of expedition members suffering dental symptoms potentially treatable with a simple dental first aid kit [7].

This document not only provides guidance on the clinical competencies required of the expedition medic but also on other pertinent aspects of the role such as medical planning, risk management, human factors, clinical governance and medical kits.

Methods

An initial meeting was convened by the FPHC. Members were invited based on their contribution to wilderness medicine in terms of research, teaching, military experience or were selected as representatives of UK-based expedition providers. It was identified that the competencies required for wilderness medicine were wide ranging and evidence for what skills and interventions are required was lacking. For this reason, the panel elected to use the existing FPHC competency framework and adapted it (based on expert opinion) for wilderness medicine use. Members of the panel were then selected to undertake literature reviews and to author specific parts of this consensus document.

The key drivers to any medical plan are:

1. The degree of remoteness of the potential incident.
2. The medical threat—the likelihood of a medical incident occurring.

Remoteness was considered as the time taken to *access* advanced medical care defined in varying ways depending on the injury or illness. For the purposes of this document, it is a facility where a doctor, basic diagnostics, pharmacy, etc., are available and the injury or illness can be managed in a timely and definitive manner. It is accepted that this definition is flexible, as definitive care could potentially be delivered within a well-equipped and appropriately staffed expedition setup and is dependent on the presenting condition.

For the purposes of discussing the required medical competencies, three measures of remoteness from advanced medical care were considered:

1. Time 1: less than 4 h away.
2. Time 2: 4–12 h away.
3. Time 3: more than 12 h away.

These timelines were considered alongside the levels of medical threat that take into account the demographics of the group, the location and the planned activity.

1. Low—such as young, fit group trekking in foothills of Atlas Mountains, Morocco.
2. Medium—such as vehicle borne overland expedition across Eastern Africa with diverse middle aged group.
3. High—such as a ski mountaineering in remote area of Greenland or a medically unscreened group doing charity trek up Mt Kilimanjaro.

Using this model, two main assumptions were made, firsty that time is based on typical estimated travelling time, e.g. summer rather than winter and not worse case. However, planning should take into account a range of travel time most likely to be encountered. Secondly, specific competencies will be dictated by environment (cold, high, hot or any unusual endemic diseases identified by the medical plan).

Priorities for care and evacuation, and therefore competencies for each, could then be agreed upon and are summarised as;

- Less than 4 h: emergency field care.
- 4–12 h: commence definitive treatment in the field.
- 12 h plus: prolonged field care.

A suggested level of expedition medic could then be made considering the medical threat and remoteness (Fig. 1). Levels of healthcare provider have previously been established by the FPHC [8].

In summary, these equate to:

- Level D—a non-health care professional with a nationally recognised first aid certificate, caring for patients as a secondary role (such as an expedition leader).
- Level G—a registered healthcare professional working in the expedition environment (such as a junior doctor, nurse or paramedic).
- Level H—an advanced wilderness medicine practitioner (such as a senior doctor with expedition experience).

Once the level of expedition medic has been decided, the competency framework at "Appendix 1" should be used in conjunction with an expedition risk assessment. The competency framework covers most types of expedition—clearly, if the proposed itinerary does not include altitude or diving exposure then those specific competencies will not be required of the expedition medic.

Furthermore, it was recognised by the panel that additional personal skills and attributes may influence who is selected to be the expedition medic. Some of these are discussed within this document.

Medical planning

The expedition medical plan depends on a fundamental understanding of the risks which are specific to each expedition. Risk assessments are often based on personal experience (or lack of it) and anecdote.

Iserson [9] identified 10 key stages in planning for an extended expedition in a remote location;

1. Optimise workers' fitness.
2. Anticipate treatable problems.
3. Stock appropriate medications.
4. Provide appropriate equipment.
5. Provide adequate logistical support.
6. Provide adequate medical communications.
7. Know the environmental limitations on patient access and evacuation.
8. Use qualified providers.
9. Arrange knowledgeable and timely consultations.
10. Establish and distribute rationale administrative rules.

An additional key planning stage not included in this original list is knowledge of the planned destination and prevention of illness and problems associated with this area, e.g. malaria, snake envenomation.

All this should be put in place before an expedition leaves to mitigate risk. However, there has to be an acceptance that the provision of medical care in a remote location is inherently challenging and likely to be lacking if measured against what would be available in a developed world healthcare setting.

Understanding the expedition population's medical needs is fundamental. The support for an expedition of extremely fit experienced mountaineers will be different to that for a charitable trek following similar terrain. Published data can inform estimates of the frequency of likely illnesses, such as altitude illness [4, 10, 11]. Medication and equipment scales can then be decided upon. Providing adequate equipment for unlikely events but with serious consequences is more difficult. Unfortunately, the reality of medicine in remote areas is that severe illness and injury is often non-survivable. In Snowdonia, North Wales, a retrospective data set of 1100 cases brought to the emergency department concluded "there is little or no scope to save any additional lives from trauma in the mountains of Snowdonia" [11].

Communications, logistical support and evacuation routes are all crucial to medical planning. These factors need to be considered along with the nature of the activity to decide on the medical skills required of the provider. With the improvements in global communications and ability to send images, worldwide expert support for management of conditions such as frostbite can be accessed from remote locations. Such links should be established and tested before an expedition leaves as part of the medical plan where possible.

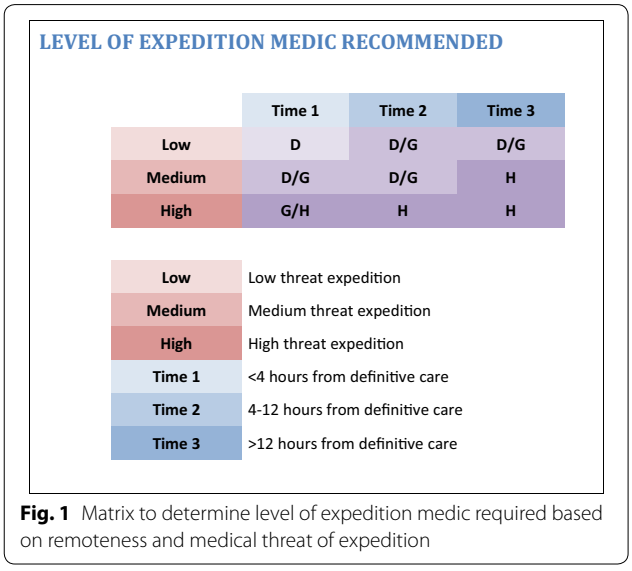

Fig. 1 Matrix to determine level of expedition medic required based on remoteness and medical threat of expedition

Consideration should be given to medical plans in the absence of the lead expedition medic, i.e. small groups operating from one base location or climbers split across different camps. Diagnostic algorithms for likely conditions such as heat illness or altitude sickness can be placed with medical kits as well as protocols for administration of emergency medication. The lead expedition medic will often be able to communicate emergency medical advice over radio or satellite phone to remote teams, however, algorithms should be robust enough for independent use in emergent situations. The role of expedition medic will include briefing these teams in usage of emergency medical treatments. There is no suggested guidance on the ratio of medics to participants required on an expedition but should be considered on a case-by-case basis in the planning phase.

Medical planning relies on the ability to assess the likelihood of adverse medical events. This is dependent on published data to detect the underlying rate of injury such as discussed above. It is therefore important that, wherever practicable, the incidence of medical problems during expeditions are well recorded and accessible. This is now facilitated by a range of open access journals or online resources.

The purpose of this guideline is to inform best practice and inform expedition planning. It does not seek to provide a mandated framework beyond which none should go. It is accepted that the degree to which the guidelines are implemented may legitimately vary with the nature of the expedition.

Clinical governance in wilderness medicine

Clinical governance is the framework used to maintain and improve standards of medical care, in which 'organisations are accountable for continuously improving the quality of their services and safeguarding high standards of care…' [12].

There are several domains to clinical governance that all have a part to play in an expedition setting:

- Risk management.
- Continuing professional development.
- Evidence based and effective clinical care.
- Audit.
- Patient satisfaction.

These features remain applicable during the pre-expedition, expedition, and post-expedition phases and should not be viewed as optional simply because a practitioner is working outside the health system of the UK. Participants in an expedition should have care provided by someone working within an appropriate scope of practice.

Responsibility for clinical governance rests with both the expedition medic and the expedition organisers. For instance, the organisation must ensure that it carefully selects the expedition medic, that it provides them with timely and accurate information about the participants and the nature of the expedition and that it encourages a culture of openness through the sharing of [medical] risk assessments and post-expedition [medical] reports. The expedition medic is responsible for maintaining their own personal and medical competencies, for precise and robust documentation and for the safe usage and maintenance of medical kit and equipment. Both are responsible for reporting identified problems of any nature and recording these in such a way that incidents can be learned from and mitigated against in the future. Clinical audit should be encouraged.

It is good practice to have a contract between the expedition medic and organisation. An example of such is the UIAA's Model Contract for Health Care on Trekking and Expeditions [13].

Other factors that the expedition medic and expedition organisers should agree on are listed:

- Provision of medical kit and supply/resupply.
- Work place and distant supervision of expedition medics.
- Responsibility for arranging the provision of specialist medical advice.
- Security and ownership of confidential medical information.
- Responsibility for development and use of Medical Standard Operating Procedures.
- Standardised medical record keeping.

The liability for providing adequate medical care for all expedition members ultimately lies with the expedition organisers. In addition, all Level G and H practitioners should discuss any proposed expedition with their professional indemnifiers.

Risk management

Pre-emptive risk management is essential for managing safety while on expeditions. An understanding of the terms used in risk management is needed to manage risk appropriately.

A threat is something that can cause harm. This may be harm to an individual, to property or to the expedition itself. For example malaria may constitute a threat to an individual, theft is a risk to property and a hurricane may represent a threat to all three. The result of the threat is the consequence of that occurrence.

Likelihood: This is the chance of a threat occurring. For example, acute mountain sickness (AMS) is a threat to

which climbers in Scotland will not be exposed. However, for the Himalayan mountaineer, AMS is a threat to which he or she is vulnerable.

The likelihood multiplied by the consequences gives an index of the threat [14]. The assessment of the threat must take place within the context of the expedition. With this context comes the important concept of residual risk. Residual risk describes the risks that remain despite mitigation attempts. For example, while driving a car, a driver may mitigate the risks of crashing by ensuring the car is roadworthy, not driving at night and not exceeding the speed limit. However, the threat of error by another driver causing an accident is difficult to mitigate. This is known as a residual risk.

Once a threat has been assessed and is deemed to be above the threshold of risk for an expedition steps may be taken to reduce the impact of the threat. There are three main ways to mitigate risk:

1. Remove or diminish the threat.
2. Reduce the exposure to the threat.
3. Take measures to reduce the impact of the threat.

For example, an expedition to the Honduran jungle may consider the threat of envenomation by snakebite. The threat may be diminished by ensuring everyone on the expedition wears boots. The exposure to the threat can be reduced by running a teaching session about the snake habitat and how to avoid coming into contact with snakes. The impact could be reduced by ensuring timely evacuation is available to a facility where appropriate care is available. These measures may change an unacceptable risk into a risk accepted by the expedition.

Risk assessment should be carried out at three levels; generic risk assessment for the activity, a daily risk assessment documented for the activity and local conditions and then dynamic risk assessment during the course of the activity.

Incidents that cause harm should be documented, as should 'near misses'. This will aid future expeditions in building an evidence base of hazards and mitigation strategies. Expedition providers have a legal responsibility for the safety of both paying clients (under Package Travel Regulations 1992) and staff, including any locally employed *staff* (Employer's Liability). Thorough risk assessment is key to providing both physical and legal protection for both staff and clients.

Medical threats and mitigation

Expeditions to remote areas are, by their very nature, complex and normal medical risk assumptions and mitigation may not apply.

The experiential evidence backed up by limited published evidence suggest serious incidents on expeditions are unusual [3–6]. Most medical conditions or injuries seen during expeditions can be managed by a competent expedition medic with basic skills. However, incidents in the wilderness environment are compounded by a number of factors;

- The incident occurs in a different location to the expedition medic.
- The casualty may be travelling alone (e.g. between camps in a jungle or on a mountain).
- The casualty may not have the means, capacity or capability to identify their location.
- The casualty may not have the means, capacity or capability to communicate and request help.
- Bad weather/night/visibility/poor communications may hinder the realisation that someone is missing, that a medical incident has occurred and therefore delay any response.

Good medical screening can reduce, but not eliminate, the medical risks to an expedition and should be an essential part of any medical planning. Consideration should be given to who has access to this medically confidential information and whether a certificate and disclosure from the participants' medical practitioner may be required. In addition to screening, education as to the likely hazards is a key part of reducing the medical risks on an expedition. It should be borne in mind that participants often fail to disclose key medical information and this only comes to light once the expedition starts. Participants should be medically risk assessed again if new information becomes available.

On many expeditions it may be impossible, impractical or unreasonable (as it would fundamentally change the character of the expedition) to provide the highest level of medical care and participants should be sufficiently well informed to accept this risk. Suitable planning and development of guidelines and protocols for management of likely hazards is an important part of medical planning and may remove the need for a medical professional on an expedition.

Human factors

Human factors refer to the non-clinical aspects of wilderness medicine. It is important to recognise that the role of the expedition medic goes beyond the simple provision of medical care. They often form part of the leadership team, with all the associated responsibilities that this entails.

In the best case, the expedition medic is an independent experienced professional who puts the health and

safety of the participants above the objectives of the expedition. For every trip, the expectations and requirements of the expedition medic, from the participants, expedition leaders and the organisers will be subtly different. On occasions, they may even be a source of conflict.

Therefore, the expedition medic does not merely require appropriate clinical skills to deliver care in a wilderness setting but should have the personal skills to work within a team and the technical skills to be able to live comfortably in that environment. A deficiency in any part of the clinical–personal–technical triad will render the expedition medic less effective.

Personal skills

Personal/interpersonal skills do not always come naturally yet are a vital part of being a functioning, respected team member. The manner in which one employs these 'soft' skills will vary depending on the expedition. For example, interaction with a group of ultra-marathon athletes will differ considerably from an inexperienced charity clientele group. The following areas should be considered:

- Communication skills and self-awareness.
- Teamwork.
- Leadership.
- Decision making.
- Coping with fatigue and stress.

The ability to communicate and interact successfully with a team whilst living alongside them is incredibly important, particularly when fostering therapeutic relationships. The expedition medic must be aware of subtle differences in 'sense of humour', the need for compassion even with the trivial and regularly reflect on the need to adapt. Instructions or advice should be clear and unambiguous for those to whom they are directed. The expedition medic will often spend the majority of their time as an equal team colleague and friend. It is important to ensure boundaries are well defined and it is clear to participants when there is a swap to the "medic role".

Leadership styles vary greatly. The expedition medic should be capable of adapting their leadership skills to the needs and requirements of the group. Clear demarcation of roles, responsibilities and decision-making frameworks should be clarified before departure thus minimising the potential for conflict during times of increased stress. Both expedition leader and medic require clarity of jurisdiction, not only during a medical incident/s, but also in a situation where failure to intervene pre-emptively may result in harm.

Decision making on expedition carries with it far more responsibility than purely arriving at a treatable diagnosis. The decisions made will have consequences varying from temporary cessation of activities to permanent casualty evacuation, with all the associated logistical, financial and emotional implications.

The demands placed on the expedition medic have the potential to exceed any other expedition participant. Expedition medics should be prepared to carry out a full day's expedition activities and then face the possibility of providing the full range of expedition healthcare, irrespective of the time of day or night, including a complex casualty evacuation. Mental resilience and physical fitness are important, as stressors on expedition are many and varied. They include clinical pressures associated with independent/autonomous decision making, stressors of living in a close-knit community or the difficulties of just living and surviving in uncomfortable surroundings with reduced communication with home.

Expedition skills

The expedition medic will need a range of skills specific to the expedition objectives. These skills are beyond the scope of this document.

Real-life examples of the impact of personal or expedition skill deficiencies can be found at "Appendix 2".

Medical kit

Designing and gathering a fit-for-purpose medical kit is frequently overlooked by expedition planners but it is a multifaceted and time-consuming job. It must be clear whose responsibility it will be to provide and pay for medical kit and it must be checked regularly for acceptable quality, including for damage, stock level and out-of-date contents. Meticulous labelling, organisation of the kit and a contents spreadsheet are of paramount importance.

The expedition medic must have knowledge of the indications and side effects of each medication carried, this will depend on the level of medical provider, but any provider must be competent dispensing or administering those medications and be familiar with the identification and timely treatment of any complications occurring. All expedition medics should have access to reference material in this regard. For example, the British National Formulary (BNF) is available electronically as an App.

Medical kits should be bespoke to the expedition in question. Their composition will vary based on team composition, demographics and number of participants as well as destination and the duration of the trip. Kits should reflect the likely illness and injury patterns of the planned activities and to some extent, the level and skills of the expedition medic. Published surveys suggest that first responder medical kits tend to be well equipped to support trauma but less well equipped for medical

emergencies [15]. It should also be remembered that the majority of medical presentations on expeditions are not high-level trauma or medical emergencies and medical kits should reflect this by including medications and equipment for treating simple illness and injuries.

Comprehensive advice on provision of medical kits is beyond the scope of this publication. Broad areas for consideration are listed below.

1. A medical kit should be dictated by the medical plan and wilderness environment.
2. Medications (unlike dressings) cannot be improvised and expeditions need to have adequate supplies of trustworthy medications.
3. Import and export restrictions for medications vary between countries.
4. Medications that have a variety of uses should be taken.
5. Practitioners should be aware of expedition members with drug allergies or on regular medications and be aware of any interactions these may have.
6. Group medical kits should be appropriately and securely stored.
7. Ensure adequate means of diluting and administering drugs are available.
8. Individuals should have a personal first aid kit on their person at all times.
9. If travelling in areas with high incidence of HIV or hepatitis consider carrying sterile needles, etc.

These points are expanded in "Appendix 3".

Cardiopulmonary resuscitation in the wilderness environment

The decision whether to attempt resuscitation or not in the event of cardio-respiratory arrest in the wilderness is a complex one and requires a pragmatic and realistic decision-making process. Resuscitation efforts and extrication may take place in hazardous terrain and in extreme meteorological conditions. Additionally, resources may be very limited, and there may be multiple casualties amongst who these resources must be shared. Multiple casualty emergencies may fit the definition criteria for a major incident and appropriate Major Incident Medical Management systems may need to be applied in a wilderness setting to effectively utilise available resources.

In 2012, Paal et al. [16] published a position paper to establish scientifically supported guidelines under which cardiopulmonary resuscitation (CPR) could be terminated during mountain rescue. This guidance was subsequently adopted as a formal recommendation by the International Commission for Alpine Rescue (ICAR/CISA) and it is applicable both to medical and non-medical personnel.

As the same principles apply both to organised rescue in the mountains and to wilderness expeditions in terms of decision-making algorithms. The aim of these guidelines is to reduce unnecessary CPR, diminish risk to expedition members or rescuers, apportion limited human and material resources effectively and to identify special circumstances where extended CPR may be indicated.

These circumstances permit the termination of CPR in a patient with unwitnessed loss of vital signs in the wilderness:

1. No return of spontaneous circulation during 20 min of CPR.

AND

2. No special circumstance (see below) warranting extended CPR.

AND

3. When professional medical support is available, either that no shock is advised by an Automated External Defibrillator (AED) at any time, or that only asystole is observed by electrocardiogram (ECG) monitoring.

Special circumstances are hypothermia, lightning strike and submersion (drowning). With these, prolonged CPR may be associated with a good neurological outcome and functional recovery.

Conclusion

The role of an expedition medic can fall to either medically qualified professionals or to others providing medical care in addition to their primary duty. It is important to recognise that the role of expedition medic is multifaceted and requires an extensive skill set in addition to suitable underpinning medical knowledge and skills. Expedition medical planning should enable all these aspects to be considered so that appropriate personnel are selected and medical threats recognised and mitigated against.

Additional file

Additional file 1. Expedition medic competencies.

Abbreviations
AED: automated external defibrillator; AMS: acute mountain sickness; BNF: British National Formulary; CPR: cardiopulmonary resuscitation; ECG: electrocardiogram; FPHC: Faculty of prehospital care of the Royal College of Surgeons of Edinburgh; ICAR: International Commission for Alpine Rescue; UIAA: International Climbing and Mountaineering Federation (Union International des Associations d'Alpinisme).

Authors' contributions
All authors contributed to the FPHC working group in expedition medical capability and contributed to the manuscript. JH chaired the working group, ND collated authors' initial drafts, AM and HP drafted the final manuscript and AM, HP, JH, ND edited the final version of the manuscript. RJ, MW, TH-W, JR drafted the human factors, threats and medical planning sections, NH and DL drafted the personal skills section, BL contributed to the dental and medical kit sections, ND, JH, SD, DH, EH, SH, DL and NH drafted the competency matrix, PD drafted the section on CPR. All listed authors reviewed and revised the final version of the manuscript. All authors read and approved the final manuscript.

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Competing interests
A number of the authors have affiliations to commercial medical training providers but none view this as a conflict of interest in contributing to these guidelines.

Appendix 1

The FPHC competencies are available as an additional file please see Additional file 1.

Appendix 2

This appendix includes examples of where the expedition medic without the appropriate personal or expedition skills could potentially put themselves and others at risk. These examples are based on the real-life experiences of those on the panel.

1. The expedition medic has never been to altitude and therefore has a lack of environmental experience. As a result is unable to cope with working at altitude and is less effective in providing medical care. Eventually falls prey to altitude illness and has to be evacuated to definitive medical care. The group is left without the originally intended medical care.
2. Expedition medic is required to independently arrive at a casualty in a remote environment. The expedition medic is not competent in navigating and fails to arrive at the casualty. The expedition medic potentially becomes a lost person and requires additional resources to mount a search and rescue effort.
3. Expedition medic lacks situational awareness and as a result becomes targeted by assailants at a market place in a foreign country. They are attacked and robbed of possessions. The expedition medic is psychologically affected for the duration of the expedition and is less effective in providing care with potential long-term health implications.
4. Expedition medic does not have experience in camp craft and lacks necessary personal admin skills. The expedition medic is late each morning in properly organising own equipment. As a result is not ready when the rest of group is ready and either the expedition is delayed or the group is left without the intended medical care until later.
5. A commercial television production taking expedition naive individuals to a hostile environment and filming the outcome. Production aims are to stress individuals physically, socially and mentally whilst filming results. Production company staff have limited understanding of both risk and consequence of harm in the expedition environment and as such encourage risky activities. Intervention by the expedition medic to mitigate risk is frowned upon as this reduces 'story potential'. These issues will be predicted by experienced expedition medics and mitigated for.
6. Expedition medic is required to treat a casualty on more technical terrain. Expedition medic does not have sufficient technical skills such as appropriate rope work to move competently over technical terrain. They become stranded as a result and require rescuing.
7. A production company wish to film a sequence where a presenter is attempting to recover a vehicle trapped in soft sand. Expedition porters are placing rocks and sand ladders in front of spinning wheels whilst the presenter is positioned behind the vehicle at great risk of being hit by flying debris. An astute and experienced medic with identify a significant risk of injury to the presenter and intervene promptly.

The above examples can happen to anyone even with sound non-medical skills and experience in the wilderness environment. However, expedition medics that have the required operational capability reduce any risk.

Appendix 3

This annex composes some of the lessons identified from the experience of the panel with regard to preparing an expedition medical kit.

1. Know your environment and adapt the team medical kit accordingly. For example, for tropical environments where the risk of infection is high, take broad spectrum antibiotics, a malarial detection kit (with high sensitivity) and stand-by treatment. For high altitude environments, include medications following the most recent guidance in the treatment of acute mountain sickness, high altitude pulmonary and cerebral oedema.
2. You cannot improvise medications. Dressings and splints can be improvised whereas medications cannot be. You cannot guarantee the quality of medications bought in many countries so whilst they may be easily available, they may not be as efficacious.
3. Know the import and export restrictions for countries. Know the Medicines Health and Regulatory Agency (MHRA) scheduling of different drugs and the restrictions that this imposes. Be aware of the restrictions imposed by other countries; for example, drugs such as codeine are robustly regulated in the Middle Eastern countries. The FCO website is a useful resource for more details of restrictions for individual countries.
4. Take medications with more than one use. For example, codeine has analgesic, antitussive and anti diarrhoeal properties so is extremely versatile. Antibiotics such as co-amoxiclav and azithromycin have broad spectrums of cover so can be used to treat a wide range of infection.
5. Beware of interactions between medicines in the medical kit. For example, ciprofloxacin and ibuprofen in combination can reduce the seizure threshold so make epileptics more prone to seize. Be aware what regular medications are being taken by group members and compile the group medical kit accordingly.
6. Choose the most appropriate container for the medical kit. Be aware that in a tropical environment, the medical kit will need to be stored in a damp proof, sealable container.
7. Ensure that all participants have their own personal medical kits containing basic medical supplies such as blister prevention and treatment, simple analgesia, dressings and a plentiful supply of their own regular medication.
8. Be aware that certain medications used for intramuscular injection have specific diluents. For example, ceftriaxone for intramuscular injection uses 1 % lignocaine for reconstitution and injection. This is particularly important for groups where the medic is not confident or unable to achieve intravenous cannulation.
9. If travelling to regions of the world with a high incidence of HIV, consider taking a set of sterile needles and cannulae in the event that a participant requires local hospital admission.
10. Remember that other issues not normally associated with developed world medicine will fall to the expedition medic. For example, issues with contact lenses and hearing aids. Contact lenses can be problematic on expedition. The risk of keratitis is greater in contact lens wearers. Ensure all participants that plan to wear contact lenses take their glasses in addition. Ensure that anyone with a hearing aid takes spare batteries and that you and they know how to change them. If participants travel with specific pieces of equipment to manage their condition, consider asking for a demonstration on usage before the trip, for example, an insulin pump. A plan for dealing with failure of equipment (e.g. insulin pump) should be in place.

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