CASE REPORT

Acute liver failure and hepatic encephalopathy in exertional heat stroke

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SUMMARY

A 31-year-old man was brought to Accident & Emergency after collapsing during a race. On presentation, the patient had a temperature of 41.7°C (rectal). External cooling was started immediately. The patient was intubated in view of a Glasgow Coma Scale of 7 and was transferred to the intensive therapy unit. Laboratory results revealed an acute kidney injury, rhabdomyolysis, disseminated intravascular coagulopathy and acute liver failure. The patient was encephalopathic, jaundiced and difficult to sedate. His liver function continued to deteriorate with alanine aminotransferase (ALT) levels reaching 9207 U/L. King's Hospital Liver Centre, London was contacted for a possible liver transplant, and they advised an infusion of N-acetylcysteine. The following day liver function tests improved; thus, transplantation was not performed. The patient failed multiple sedation holds and required a tracheostomy. He continued to spike a fever. Despite no source of sepsis being found, the patient remained on broad spectrum antibiotics to cover for any potential infective causes until day 27. After 15 days, the patient's encephalopathy gradually improved. He was weaned off the ventilator and underwent intense physiotherapy. The patient was discharged from hospital one month after admission.

BACKGROUND

Exertional heat stroke (EHS) is a disorder of excessive heat production and inadequate heat dissipation. It is a medical emergency characterised by a high temperature (at least 40°C) and organ dysfunction. It usually occurs in the summer season in unacclimatised individuals who overexert themselves in humid and warm climates. However, it has also been seen in people who are physically fit and heat-acclimatised.¹ It can cause critical injury to all organs including renal, cardiovascular, musculoskeletal and hepatic systems. Mild to moderate liver damage is common in EHS²; rarely a subset of patients has extensive hepatocellular damage leading to acute liver failure.^{3–6}

Despite heat stroke being recognised over 2000 years ago,^{2–8} we still do not understand the complete pathophysiology of this disorder. Unfortunately, in the last 50 years, there has been no real decrease in mortality, which has been quoted as 10%–50%.³ A total of 7%–20% of survivors suffer persistent neurological sequelae.^{3–4}

CASE PRESENTATION

A 31-year-old man, previously a healthy fitness instructor, presented to Accident & Emergency

(A&E) at Mater Dei Hospital in Malta after collapsing during a 15-km obstacle marathon. On the day of the race, the temperature at noon in Malta was recorded as 30°C with 40% humidity. On presentation, the patient was tachypnoeic at 41 breaths per minute and had saturations of 98% on air. He was cardiovascularly unstable with a blood pressure of 68/30 mm Hg and a heart rate of 140 beats per minute. He had a Glasgow Coma Scale (GCS) of 7 (Eyes-2, Verbal-2, Motor-3), and pupils were equal and reactive (3 mm). His temperature was 41.7°C (rectal). In view of his low GCS, the patient was intubated to protect his airway and placed on mechanical ventilation. The patient was immediately cooled using ice packs, fans, paracetamol and bladder irrigation. The nasopharyngeal temperature decreased to 36.7°C within 1 hour of presentation. The patient was admitted to intensive therapy unit (ITU) for further monitoring.

INVESTIGATIONS

Laboratory analysis revealed multiple organ failures with a lactic acidosis (lactate 7.1 mmol/L, pH 7.43, HCO₃⁻ 21.2 mmol/L, base excess -3.4 mmol/L), rhabdomyolysis (creatinine kinase 7482 U/L peaking at 9984 U/L) associated with hyperkalaemia (6.72 mmol/L), acute kidney injury (AKI) (serum creatinine 172 µmol/L, urea 10.4 mmol/L), hepatic injury (bilirubin 51 mmol/L, ALT 3023 U/L) and disseminated intravascular coagulation (DIC) (International Normalised Ratio 1.45, activated partial thromboplastin time 1.29, platelets 56 × 10⁹/L, fibrinogen 1.0 g/L). Initial white cell count (WCC) and C-reactive protein (CRP) were normal.

An echocardiogram done at presentation showed no cardiac abnormalities but did demonstrate a collapsible inferior vena cava. Three litres of crystalloid were given to the patient while in A&E. Sinus rhythm was present on the admission ECG.

In view of the low GCS and one witnessed seizure on admission to ITU, a CT scan of the brain, MRI of the head, MRI angiography of the brain and MRI cerebral venogram were performed, and no abnormalities were seen.

The patient's liver function continued to deteriorate while in ITU. He became clinically jaundiced as bilirubin levels continued to increase reaching a peak of 340 µmol/L 10 days after admission after which they gradually decreased to 78 µmol/L prior to discharge from hospital (29 days after admission). ALT was consistently above 1000 U/L during his ITU stay peaking at 9207 U/L. ALT levels gradually declined to 445 U/L on day 30. Ammonia levels

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Figure 1 Serum CK levels during the patient's admission, peaking at day 13.

were indeterminate because high bilirubin levels interfered with their calculation. Gamma-glutamyl transferase (GGT) remained raised throughout the patient's hospital stay.

The patient developed worsening coagulopathy. Platelets dropped to $33 \times 10^9/L$, and the International Normalised Ratio (INR) increased to 4.5 on day 4. Both parameters remained deranged until day 8 when platelets rose to $192 \times 10^9/L$, and the INR dropped to 1.08.

Common aetiologies for acute liver failure were excluded including negative hepatitis serology (hepatitis A, B, C), negative viral screen (norovirus, astrovirus, rotavirus, cytomegalovirus, Epstein Barr virus, HIV PCR) negative urine toxicology screen (amphetamines, methamphetamines, opiates, cocaine, cannabinoids, 3,4-methylenedioxymethamphetamine), negative serum salicylate and paracetamol levels, negative liver ultrasound for macrovascular abnormalities and negative autoimmune screen (antigastric parietal cell antibody, antimitochondrial antibody, antismooth muscle antibody, liver microsomal antibody). CT liver excluded any anatomical abnormalities in the intrahepatic and extrahepatic biliary tree.

Five days after admission, the CRP started to rise (73 mg/L), peaking at 160 mg/L on day 9. WCC gradually rose to $13.3 \times 10^9/L$. The patient was started on fluconazole and meropenem for broad spectrum antibiotic cover. Blood, urine, sputum, stool as well as mycology cultures were all negative. Because CRP gradually rose over 5 days, a CT of the thorax, abdomen and pelvis was performed, but no sources of sepsis were found.

The patient had persistent agitation despite using multiple sedation protocols. A repeat CT of the brain was performed to rule out any organic causes for the confusion. No abnormalities

were seen. Two EEGs confirmed metabolic encephalopathy. A lumbar puncture could not be performed because of the persistent coagulopathy.

Figures 1–6 display the trends in creatine kinase (CK), liver function (ALT, GTT, bilirubin, INR) and platelets during the patient's admission.

DIFFERENTIAL DIAGNOSIS

EHS was our primary diagnosis because of the patient's neurological involvement with a low GCS and rectal temperature of $41.7^\circ C$. The patient's history—running a marathon in a warm temperate climate—further confirmed our suspicion. The ensuing multiorgan involvement with rhabdomyolysis, AKI, acute liver failure and DIC were all part of the systemic upset caused by the heat stroke.

Other possible causes for the collapse were considered. An echocardiogram was performed to assess for cardiomyopathies such as hypertrophic obstructive cardiomyopathy. However, no abnormalities were detected.

Possible arrhythmias were ruled out with a normal admission ECG and continuous ECG monitoring in ITU.

A drug-induced coma could present similarly; however, the patient was not taking any regular medications and his urine and serum toxicology screens were negative.

A postictal state was considered; however, the patient did not have features of seizures such as incontinence, tongue biting or witnessed fits. The patient was not a known epileptic and did not have a family history of epilepsy. The patient did have a seizure in ITU and was started on levetiracetam; however, this diagnosis would not have accounted for the hyperpyrexia and the eventual systemic upset.

Figure 2 The patient's serum gamma glutamyl transferase levels during admission. Levels remained elevated even after discharge.

Figure 3 Serum ALT levels peaked early during admission and gradually returned to normal prior to discharge.

Neuroleptic malignant syndrome can cause rhabdomyolysis, hyperpyrexia and a change in consciousness. However, the patient did not have muscle rigidity, and he was not on any medications that could induce the disorder.

Autoimmune, viral, toxin and drug-induced aetiologies were considered as causes for the patient's acute liver failure as well as structural and vascular abnormalities. Results were all negative as described above.

Sepsis was another possibility; however, based on the patient's history, blood, urine, stool, sputum and mycology cultures being negative, it was unlikely to be the inciting cause. CT of the thorax, abdomen and pelvis did not show any sources of sepsis. A repeat echocardiogram ruled out infective endocarditis.

TREATMENT

Treatment of this patient was supportive throughout. The patient underwent immediate cooling in A&E. External ice packs, paracetamol, urinary bladder washouts, fanning and an external cooling device were used. The patient's rectal temperature dropped from 41.6°C to 38.1°C within 20 minutes of presentation. By 1 hour, the patient's nasopharyngeal temperature was 36.7°C. An antihyperkalaemia regime was started in A&E, and a total of 3 L of crystalloid were administered in view of the hypotension. The patient was intubated and ventilated because of his low GCS. After the fluid resuscitation in A&E, the patient's blood pressure remained stable with mean arterial pressures greater than 65 mm Hg. Vasopressors and inotropes were never needed during the patient's hospital stay.

The patient's creatinine gradually returned to normal after 3 days. Urine output was always greater than 0.5 mL/kg/hour. Renal replacement therapy was not needed.

The patient had a witnessed tonic-clonic seizure while in ITU and was started on sodium valproate, which was eventually changed to levetiracetam in view of the deranged liver function.

Due to the worsening liver function, continuing spiking temperature and rising CRP, on day 6 King's Hospital Liver Centre, London was contacted for advice and potential liver transplantation. They advised starting vitamin B complex, N-acetylcysteine infusion (NAC), meropenem and caspofungin. Liver transplantation was considered; however, it was not performed because liver function tests slowly improved over the next few days (dropping bilirubin and ALT).

External cooling methods were continued because of the patient's persistent hyperpyrexia. To cover for infective causes, meropenem was started which was eventually changed to vancomycin and ceftriaxone. All blood, urine, sputum and stool cultures were negative. CT thorax, abdomen, pelvis did not show any sources of sepsis. CRP started to rise on day 9 and returned to normal on day 18. Antibiotics were continued until day 27 because the patient continued to spike temperature until day 20 (39.1°C, oral).

The patient was sedated with 300 mg/hour of propofol and 1 mg/hour of alfentanil but was agitated when attempting to decrease sedation. In view of the acute liver failure, alfentanil was changed to remifentanil. The propofol infusion needed to be increased to above 4 mg/kg/hour. Concurrently, there was an acute rise in CK on day 12 (figure 1) along with increasing metabolic acidosis which raised the possibility of propofol infusion syndrome. Sedation was therefore switched to remifentanil, clonidine and midazolam, but the patient continued to fail multiple sedation holds. A repeat CT brain revealed no abnormalities.

Figure 4 The patient's serum bilirubin levels during admission.

Figure 5 The patient's INR peaked within the first few days of admission and then gradually normalised.

Two EEGs reported metabolic encephalopathy. On day 14, a surgical tracheostomy was performed.

OUTCOME AND FOLLOW-UP

The patient's encephalopathy gradually improved after 17 days on ITU, and sedation was slowly stopped. The patient was weaned off the ventilator on day 18, placed on trachy mask and eventually decannulated on day 26.

On day 20, the patient was discharged to a medical ward. That evening he spiked a temperature (39.1°C) despite a decreasing CRP and WCC. Ceftriaxone was changed back to meropenem. A repeat transthoracic echocardiogram was performed, and no signs of infective endocarditis were seen. The patient remained afebrile and CRP and WCC continued to drop. Antibiotics were stopped on day 27.

On day 29, NAC was stopped because ALT dropped to less than 500 U/L as advised by King's hospital. The patient underwent an intense physiotherapy regimen to regain muscle mass. He was discharged from hospital on day 31.

DISCUSSION

There are multiple heat-related disorders including heat syncope, heat cramps, heat exhaustion and heat stroke. The latter occurs when core body temperature increases with a failing thermoregulatory system.⁹ Rectal temperature should be greater than 40.6°C.^{10 11} Heat stroke can be divided into exertional or classical heat stroke. EHS occurs in previously healthy individuals who exercise in normally hot or humid environments. Classical heat stroke occurs during heat waves with the elderly being the most vulnerable.^{11 12}

Strict body temperature regulation is vital to avoid cellular and enzymatic damage. This range is normally between 36.5°C to 37.5°C. The autonomic nervous system controls body temperature by comparing afferent and efferent inputs to a particular set point. The response is both autonomic and behavioural.¹³ Currently, it is believed that heat stroke is due to thermoregulatory failure that causes hyperthermia and ultimately a systemic inflammatory response syndrome (SIRS). This can cause multi-organ failure thought to be due to both direct thermal injury and SIRS.¹⁰

This case describes the development of severe acute liver failure in a previously healthy individual as a result of EHS. It also highlights the susceptibility of highly fit and athletic individuals to heat stroke in relatively temperate weather conditions.

There are multiple risk factors for developing EHS. Environmental risks include high ambient temperatures with high humidity as well as lack of acclimatisation and vigorous exercise.⁹ The temperature in Malta was 30°C with 40% humidity on the day of the race, which increased our patient's risk of EHS. Female gender seems to be a protective factor for unknown reasons. Other risk factors include recent alcohol consumption, lack of sleep, food or water, current upper respiratory tract infections/febrile illnesses, obesity and drugs such as anticholinergics, diuretics, antihistamines, beta-blockers, MDMA and amphetamines.⁹

Our patient did report in retrospect having mild coryzal type symptoms on the day of the race. He denied any fitness enhancing drugs except for consuming an energy gel. These gels are used for energy supplementation for sports activities. Recent increases in football heatstroke fatalities may in part be

Figure 6 The patient's platelet count during admission. Levels dropped early on in the disease process.

attributable to or aggravated by the use of dietary supplements. Evidence has been found that amphetamine derivatives and ergogenic aids such as creatine may contribute to subclinical dehydration and heatstroke in predisposed individuals.¹⁴ The use of synthetic or 'natural' stimulants may be particularly dangerous during exertion. Stimulants increase the rate of cellular metabolism which leads to a rise in metabolic heat production. They concurrently cause vasoconstriction and decrease the body's ability for thermoregulation.¹⁵

Hepatic injury in EHS is caused by direct thermal injury and decreased splanchnic perfusion. The latter occurs because of shunting of blood to the peripheries. Liver damage in the majority of cases is asymptomatic and reversible.² About 5% of patients with EHS have fulminant hepatic failure that can be fatal.¹⁶

Neurological impairment is a key feature of heat stroke.¹⁷ Patients present with an array of dysfunctions with different durations including lethargy, delirium, encephalopathy, coma and seizures.¹² Neurological impairment is thought to be due to heatstroke-induced metabolic changes, cerebral oedema and ischaemia.¹⁸ Sedation proved difficult in our patient because he was young and fit and because of his hepatic encephalopathy. The central nervous system is more sensitive to sedative drugs in patients with liver disease.¹⁹ The liver can compensate for up to 90% parenchymal damage¹⁹; however, with severe liver failure, lack of drug metabolism can cause several problems. The time intervals and infusion rates usually need to be reduced. Drugs with short durations of action should be used. Some drugs such as remifentanyl and propofol undergo extrahepatic metabolism and thus may be preferable for sedation.²⁰ Propofol is metabolised into inactive products; consequently, accumulation is not a concern in liver or renal failure. Midazolam accumulates in liver failure and is thus best avoided. In addition, our patient developed an AKI, and the ensuing uraemic encephalopathy exaggerates sedative properties. Renal clearance of drugs is reduced prolonging their effects and thus compounding the problem of sedation choice.

Management of these patients adheres to the basic airway, breathing, circulation algorithm. Rapid cooling is desirable. It has been demonstrated that dropping the body temperature to less than 38.9°C within 30 minutes of presentation improves survival.¹² Some authors refer to this time period as the 'golden half-hour'.²¹ Duration and severity of hyperthermia affect outcome.^{22 23} Cooling can take the form of cold/ice-water immersion, fanning the patient to increase evaporative heat losses and body cooling devices. There is no consensus as to which technique is more effective in reducing the temperature. Critics of water immersion point out that it is uncomfortable for the patient, can interfere with resuscitation and can cause shivering and cutaneous vasoconstriction, all of which are detrimental to cooling.²⁴ Those that advocate immersion argue that cooling occurs faster because of a greater temperature gradient. Also, it does not require special equipment.²⁵ Body-cooling units work by accelerating evaporative losses. Some claim they are two to three times more effective than water immersion.²⁶ If a body-cooling unit is not available, tepid sponging and fans to keep the patient 'wet and windy' is acceptable.²⁷ Gastric lavage, intraperitoneal dialysis, extracorporeal circulation and cold intravenous fluids are alternatives to increase heat dissipation.²⁸ Antipyretics work by inhibiting pyrogens that act on the hypothalamic set-point; thus, antipyretic effects in EHS are controversial.^{9 21}

Sufficient volume resuscitation is necessary on admission; if the patient is hypotensive, initial treatment should be with intravenous crystalloids. In acute liver failure, patients are at risk of

hypoglycaemia. Continuous glucose monitoring is vital. Enteral protein in the range of 1.0–1.5 g/kg/day is needed because of high-energy expenditure.²⁹ Coagulation should be monitored regularly. Prophylactic plasma transfusions are not necessary unless there is a risk of haemorrhage. If prophylactic plasma is administered, this might confound INR trends, which are important prognostic markers for acute liver failure.^{29 30}

Currently there are no validated prognostic tools to predict survival and to indicate when a patient will need orthotopic liver transplant. Many patients with acute liver failure secondary to

Patient's perspective

The day of the race I woke up at 6 am. I had my usual breakfast of three rice cakes, peanut butter, raspberry jam, a banana, coffee and just two glasses of water as I didn't want to feel heavy while running. I drove myself to the venue and started my warm up. Everything seemed normal for me that morning except that my nose was a bit blocked, and I was sneezing a few times. But I wasn't very concerned. Just before starting the race, I took one packet of gel supplement for runners.

The race started. My race mate and I took fourth and fifth position. I was leading at first. After 1 km, there was an 8 m high jump into a water obstacle. I jumped in first and my mate second. As I jumped into the water I started feeling strange but nothing alarming. Next there was a 5 m hill. As I climbed up the hill, I remember turning to see where my mate was and shouted at him to hurry up as we needed to catch up with the first two runners. As soon as I turned back onto the track, everything seemed to have gone black in front of me.

The next thing that I remember was that I was closed somewhere where I couldn't move. I was shouting, 'please, please let me go from here. I don't belong here. I want to go back'. I was shouting for a long time. Then I was in a lot of different strange and scary dreams where someone always wanted to kill me but there were also people who wanted to help me to get out of those dreams. As soon as I would get out of one dream I would go to another where I was always trying to save myself from people who wanted to kill me.

When I woke up from the coma, I didn't know who I was or where I was. It was a hard period for me. People were talking in a language that I was familiar with but didn't know. Once I asked a nurse where she was from and she said Malta. I said, 'ok I know that place. I had lived there for 8 years'. I couldn't move and speak much. Sleep was difficult because I was having nightmares and because of persistent cramps in my stomach.

I couldn't remember that I had a wife, and when I finally did, I accused her of selling my body for some experiments. I wasn't very kind to her every time I saw her. I was so angry and confused until one day my good friend and doctor Mr C explained what really had happened to me 3 weeks before. It was very hard for me to believe, but as time went by, the story started to make sense. What was most shocking to me was that after things went blank, I actually continued running another 8 km through obstacles. At one point I was even leading the race!

Four months down the line, I have gained my weight back at 85 kg again (I left hospital at 65 kg), and I am leading a normal life. I am back at work and doing my training regularly five times a week including heavy weights. The only residual problem I have is related to my vision where sometimes I see things a bit blurred especially moving objects.

EHS have been successfully managed conservatively.²¹ 61.5% of patients treated conservatively in one study recovered spontaneously.⁶ Prognostic indicators are unpredictable; thus, indications for transplantation are non-specific for this disorder. Discussion with a transplant centre should occur early. Patient outcomes after transplant have been disappointing. Four patients have been reported to have received a liver transplant with only one surviving for more than 1 year.^{5 6 16 31 32}

Our patient continued to spike temperature for almost 2 weeks while in ITU, and this was associated with a rising CRP. King's College Hospital advised that the patient remain on antibiotics for a possible infection despite cultures always being negative. However, heat stroke has many similarities to a sepsis syndrome.⁸ In order to facilitate heat loss, blood is redistributed from the splanchnic circulation to the periphery. This physiological change can cause gut ischaemia, which allows bacterial endotoxin translocation.^{12 33} These endotoxins induce an inflammatory response with increased levels of tumour necrosis factor, interleukins 1, 2, 6 and 8, platelet-activating factor, vasoactive amines and arachidonic acid metabolites.^{33 34} This inflammatory response along with the direct thermal injury is responsible for the multiorgan dysfunction and thermal changes in heat stroke.³³ Hyperthermia reduces blood brain barrier integrity, which raises the possibility of gastrointestinal bacterial endotoxaemia causing some of the neurological dysfunction. Animal models have shown antibiotics improve survival in heatstroke.³⁵

Superimposed infection is a common comorbid condition in heat stroke. It has been suggested that proinflammatory cytokines generated from a previous infection can deactivate cellular protective mechanisms from extreme temperatures.³⁶ Heatstroke can predispose a patient to early infection because of heat-induced altered immune status, bacterial translocation and endotoxaemia.³⁷ There are reported cases of heat stroke in cool weather occurring in well-trained athletes who had a viral infection a week prior to the event.³⁸ Our patient reported mild coryzal symptoms prior to the race. Clinicians should be suspicious of an underlying infection in adults presenting with heat stroke with no other precipitating factors.³⁹

Acute liver failure increases a patient's susceptibility to infections because of impaired leucocyte, macrophage and complement function.⁴⁰ Infection risk increases with indwelling lines, catheters and tubes in the critically ill. Microbial infections have been documented in up to 80% of patients.⁴¹ Negative outcomes are seen in patients with acute liver failure with sepsis. Bacteraemia and SIRS are associated with worsening of

hepatic encephalopathy, coagulopathy and renal failure.^{42–44} It has been reported that infective organisms in patients with acute liver failure were bacterial in 80% of cases and fungal in 32%.⁴⁵ Thus, antibiotic and antifungal prophylaxis is seen in most centres managing patients with acute liver failure.²⁹ A fungal infection should be strongly suspected in a patient with unresponsive fever, leucocytosis, deteriorating neurological status after initial improvement and presence of AKI.⁴⁶ Since our patient had acute liver failure with continuing hyperpyrexia and a rising CRP, King's College Hospital advised starting empirically an antifungal.

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REFERENCES

- Capacchione JF, Muldoon SM. The relationship between exertional heat illness, exertional rhabdomyolysis, and malignant hyperthermia. *Anesth Analg* 2009;109:1065–9.
- Hassanein T, Razack A, Gavalier JS, et al. Heatstroke: its clinical and pathological presentation, with particular attention to the liver. *Am J Gastroenterol* 1992;87:1382–9.
- Feller RB, Wilson JS. Hepatic failure in fatal exertional heatstroke. *Aust N Z J Med* 1994;24:69.
- Ichai C, Clais JF, Hyvernat H, et al. [Fatal acute liver failure: a rare complication of exertion-induced heat stroke]. *Ann Fr Anesth Reanim* 1997;16:64–7.
- Berger J, Hart J, Millis M, et al. Fulminant hepatic failure from heat stroke requiring liver transplantation. *J Clin Gastroenterol* 2000;30:429–31.
- Hadad E, Ben-Ari Z, Heled Y, et al. Liver transplantation in exertional heat stroke: a medical dilemma. *Intensive Care Med* 2004;30:1474–8.
- Dio Cocceianus C, Heinemann W, Roman History (Cary E. & Foster HB trans). VI. London, 1914:269–71. Book LIII. <https://ia802701.us.archive.org/3/items/diosromanhistry06cassuoft/diosromanhistry06cassuoft.pdf>. (accessed 1 May 2018).
- Bouchama A. Heatstroke: a new look at an ancient disease. *Intensive Care Med* 1995;21:623–5.
- Bricknell MC. Heat illness—a review of military experience (Part 1). *J R Army Med Corps* 1995;141:157–66.
- Bouchama A, amp;Knöchel JP, stroke H. *The New England Journal of Medicine* 2002;25:1978–88.
- Shahid MS, Hatle L, Mansour H, et al. Echocardiographic and Doppler study of patients with heatstroke and heat exhaustion. *Int J Card Imaging* 1999;15:279–85.
- Dematte JE, O'Mara K, Buescher J, et al. Near-fatal heat stroke during the 1995 heat wave in Chicago. *Ann Intern Med* 1998;129:173–81.
- Buggy DJ. Thermoregulation CAW. *British Journal of Anaesthesia* 2000;84:615–28.
- Bailes JE, Cantu RC, Day AL. The neurosurgeon in sport: awareness of the risks of heatstroke and dietary supplements. *Neurosurgery* 2002;51:283–8.
- O'Connor FG. Dietary supplements and warfighters: a challenge for military providers. *Mil Med* 2012;177:1448–9.
- Knöchel JP, Reed G. Disorders of heat regulation. *Clinical Disorders of Fluid and Electrolyte Metabolism* 1994:1549–90.
- Alzeer AH, Al-Arifi A, Warsy AS, et al. Nitric oxide production is enhanced in patients with heat stroke. *Intensive Care Med* 1999;25:58–62.
- Boersma LV, Leyten QH, Meijer JW, et al. Cerebral hemorrhage complicating exertional heat stroke. *Clin Neurol Neurosurg* 1998;100:112–5.
- Short TG. Pharmacokinetics GT. pharmacodynamics and drug monitoring in acute illness. *British Medical Bulletin* 1998;55:653–61.
- Burns AM, Shelly MP, Park GR. The use of sedative agents in critically ill patients. *Drugs* 1992;43:507–15.
- Casa DJ, Armstrong LE, Kenny GP, et al. Exertional heat stroke: new concepts regarding cause and care. *Curr Sports Med Rep* 2012;11:115–23.
- Hunt PAF, Smith JE, Illness H. *Journal of the Royal Army Medical Corps* 2005;151:234–42.
- Smith JE. Cooling methods used in the treatment of exertional heat illness. *Br J Sports Med* 2005;39:503–7.
- Graham BS. Features and Outcomes of Classic Heat Stroke. *Ann Intern Med* 1999;130:613.

Learning points

- ▶ Heat stroke is a medical emergency.
- ▶ Mortality is high.
- ▶ Decreasing core body temperature to below 38.9°C within 30 min of presentation improves survival.
- ▶ Heat stroke can lead to multiorgan dysfunction.
- ▶ Management is rapid cooling and multiorgan support.
- ▶ Mild liver derangement is common but acute liver failure is rare.
- ▶ Orthotopic liver transplantation is a possible treatment option; however, conservative management has demonstrated better outcomes.
- ▶ Early discussion with a transplant centre is important.
- ▶ Hepatic encephalopathy in young patients makes sedation challenging.

- 25 Gaffin SL, Gardner JW, Flinn SD. Cooling methods for heatstroke victims. *Ann Intern Med* 2000;132:678.
- 26 Weiner JS, Khogali M. A physiological body-cooling unit for treatment of heat stroke. *Lancet* 1980;1:507–9.
- 27 Slovis CM. Features and outcomes of classic heat stroke. *Ann Intern Med* 1999;130:614.
- 28 Akhtar MJ, al-Nozha M, al-Harhi S, et al. Electrocardiographic abnormalities in patients with heat stroke. *Chest* 1993;104:411–4.
- 29 Bernal W, Wendon J, failure Aliver *New England Journal of Medicine* 2013;369:2525–34.
- 30 Lee WM, Larson AM, Stravitz RT. AASLD Position Paper: the management of acute liver failure update 2011. *The American Association for the Study of Liver Diseases* 2011 http://www.aasld.org/sites/default/files/guideline_documents/alfenhanced.pdf (Accessed: May 2018).
- 31 Saissy JM. Liver transplantation in a case of fulminant liver failure after exertion. *Intensive Care Med* 1996;22:831.
- 32 Takahashi K, Chin K, Ogawa K, et al. Living donor liver transplantation with noninvasive ventilation for exertional heat stroke and severe rhabdomyolysis. *Liver Transpl* 2005;11:570–2.
- 33 Knochel JP. Exertional heat stroke-pathophysiology of heat stroke. In: Hopkins PM, Ellis FR, eds. *Hyperthermic and Hypermetabolic Disorders*. Cambridge: Cambridge University Press, 1996:42–62.
- 34 Hammami MM, Bouchama A, Al-Sedairy S, et al. Concentrations of soluble tumor necrosis factor and interleukin-6 receptors in heatstroke and heatstress. *Crit Care Med* 1997;25:1314–9.
- 35 Bynum G, Brown J, Dubose D, et al. Increased survival in experimental dog heatstroke after reduction of gut flora. *Aviat Space Environ Med* 1979;50:816–9.
- 36 Sonna LA, Wenger CB, Flinn S, et al. Exertional heat injury and gene expression changes: a DNA microarray analysis study. *J Appl Physiol* 2004;96:1943–53.
- 37 Sithinamsuwan P, Piyavechviratana K, Kitthaweesin T, et al. Exertional heatstroke: early recognition and outcome with aggressive combined cooling—a 12-year experience. *Mil Med* 2009;174:496–502.
- 38 Roberts WO. Exertional heat stroke during a cool weather marathon: a case study. *Med Sci Sports Exerc* 2006;38:1197–203.
- 39 Wijerathne BTB, Pilapitiya SD, Vijitharan V, et al. Exertional heat stroke in a young military trainee: is it preventable? *Mil Med Res* 2016;3:1–4.
- 40 Antoniadis CG, Berry PA, Wendon JA, et al. The importance of immune dysfunction in determining outcome in acute liver failure. *J Hepatol* 2008;49:845–61.
- 41 Rolando N, Philpott-Howard J, Williams R. Bacterial and fungal infection in acute liver failure. *Semin Liver Dis* 1996;16:389–402.
- 42 Vaquero J, Polson J, Chung C, et al. Infection and the progression of hepatic encephalopathy in acute liver failure. *Gastroenterology* 2003;125:755–64.
- 43 Kumar R, Shalimar, Sharma H, et al. Persistent hyperammonemia is associated with complications and poor outcomes in patients with acute liver failure. *Clin Gastroenterol Hepatol* 2012;10:925–31.
- 44 Hadem J, Tacke F, Bruns T, et al. Acute Liver Failure Study Group Germany, Etiologies and outcomes of acute liver failure in Germany. *Clinical Gastroenterology and Hepatology* 2012;10:664–9.
- 45 Rolando N, Harvey F, Brahm J, et al. Fungal infection: a common, unrecognised complication of acute liver failure. *J Hepatol* 1991;12:1–9.
- 46 Shalimar. Antibiotics in Acute Liver Failure (ALF). *J Clin Exp Hepatol* 2015;5:95–7.

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