MINISTÉRIO DA DEFESA NACIONAL
EXÉRCITO PORTUGUÊS
ACADEMIA MILITAR

Assunto: REFERÊNCIAS BIBLIOGRÁFICAS PARA O CONCURSO ORDINÁRIO PARA INGRESSO NOS **QUADROS PERMANENTES DO QUADRO ESPECIAL DE MEDICINA.**

No âmbito do concurso ordinário para ingresso nos Quadros Permanentes (QP) do Quadro Especial (QEsp) de Medicina (MED) do Exército Português, publicado pelo Aviso n.º 19729/2020 do Diário da República, 2ª série, N.º236 de 04 de dezembro de 2020, cujas normas foram aprovadas por despacho do Chefe do Estado-Maior do Exército (CEME), o General José Nunes da Fonseca, de 10 de novembro de 2020, informa-se que as referências bibliográficas são as abaixo indicadas:

1. **TESTE ESCRITO:**
   - **a. Tema 1:** Suporte Avançado de Vida
     (1) Ref.ª 1: Soar J *et al*; *European Ressuscitation Council Guidelines for Ressuscitation 2015 Section 3. Adult advanced life support*; Ressuscitation; 2015; 95:100-147.
   - **b. Tema 2:** Adaptações a ambientes extremos e Rabdomiólise
     (1) Ref.ª 2a) Norma de Autoridade Técnica 05.02 de 27Mar2017, do Comando do Pessoal, Exército Português: Risco Sanitário e Medidas de Prevenção de Lesões Associadas ao Calor ou Frio em Ambiente Operacional.
     (2) Ref.ª 2b) Bosch X et al; Rhabdomyolysis and Acute Kidney Injur; The New England Journal of Medicine; 2009, 361:62-72.
     (3) Ref.ª 2c) Chavez LO et al; Beyond muscle destruction: a systematic review of rhabdomyolysis for clinical practice; Critical Care; 2016; 20:1.
   - **c. Tema 3:** Traumatologia
     (1) Ref.ª 3a) Dor lombar https://www.orthobullets.com/spine/2034/low-back-pain--introduction
     (2) Ref.ª 3b) Entorse do tornozelo https://www.orthobullets.com/foot-and-ankle/7028/ankle-sprain
     (3) Ref.ª 3c) Artrose da anca https://www.orthobullets.com/recon/5005/hip-osteoarthritis
     (4) Ref.ª 3d) Artrose do joelho https://www.orthobullets.com/recon/12287/knee-osteoarthritis

(5) Ref.ª 3e) Síndrome compartimental
https://www.orthobullets.com/trauma/1064/hand-and-forearm-compartment-syndrome
https://www.orthobullets.com/trauma/1001/leg-compartment-syndrome

(6) Ref.ª 3f) Tendinite
https://www.orthobullets.com/knee-and-sports/3016/quadriceps-tendonitis

(7) Ref.ª 3g) Contusões musculares
https://www.orthobullets.com/knee-and-sports/3103/quadriceps-contusion

(8) Ref.ª 3h) Algoneurodistrofia
https://www.orthobullets.com/basic-science/6095/complex-regional-pain-syndrome-crps

(9) Ref.ª 3i) Fraturas expostas
https://www.orthobullets.com/trauma/1004/open-fractures-management

d. **Tema 4:** Infeciologia e Medicina do Viajante

(1) Ref.ª 4a) Manual de Tuberculose e Micobactérias Não Tuberculosas do Programa Nacional para a Tuberculose; páginas 1-34.

(2) Ref.ª 4b) Malária ou paludismo, Orientação 008/2017 da Direção Geral de Saúde.

(3) Ref.ª 4c) Duração de Terapêutica Antibiótica, Norma I da Direção Geral da Saúde.

(4) Ref.ª 4d) Vacinação contra a Gripe.
Norma 020/2020 - COVID-19: Definição de Caso de COVID-19 - https://www.dgs.pt/normas-orientacoes-e-informacoes/normas-e-circulares-normativas/norma-n-0202020-de-09112020.aspx
Norma nº 004/2020 de 23/03/2020 atualizada a 14/10/2020 - https://www.dgs.pt/normas-orientacoes-e-informacoes/normas-e-circulares-normativas/norma-n-0042020-de-23032020-atualizada-a-141020201.aspx
Norma nº 015/2020 de 24/07/2020 - https://www.dgs.pt/directrizes-da-dgs/normas-e-circulares-normativas/norma-n-0152020-de-24072020-pdf.aspx

(5) Ref.ª 4e) Levy MM et al (2018); The Surviving Sepsis Campaign Bundle: 2018 Update; Critical Care Med; 2018; 46:997-1000.

e. **Tema 5:** Medicina Desportiva

(1) Ref.ª 5a) Molloy J et al; Physical Training Injuries and Interventions for Military Recruits; Military Medicine; 2012; 177, 5:533.

(2) Ref.ª 5b) International Olympic Committee (IOC) Consensus Statement on Relative Energy Deficiency in Sport (RED-S): 2018 Update.

(3) Ref.ª 5c) Casa DJ et al; National Athletic Trainers' Association Position Statement: Exertional Heat Illnesses; Journal of Athletic Training; 2015, 50: 9.

(4) Ref.ª 5d) Meeusen R et al; Prevention, Diagnosis, and Treatment of the Overtraining Syndrome: Joint Consensus Statement of the European College of Sport Science and the American College of Sports Medicine; Medicine & Science in Sports & Exercise; 2012; 13:186-205.

(5) Ref.ª 5e) Sharma S et al; International Recommendations for Electrocardiographic Interpretation in Athletes; The Journal of American College of Cardiology; 2017; 69:1057–75.

(6) Ref.ª 5f) Paterick TE et al; Echocardiography: Profiling of the athlete´s Heart; American Society Echocardiography; 2014; 27:940-8.

(7) Ref.ª 5g) Emery M et al; Sudden Cardiac death in athletes; Journal American Collegue Cardiology HF; 2018; 6:30–40.

2. <u>PROVA PRÁTICA:</u>

a. Ref.ª 1: Soar J et al; European Ressuscitation Council Guidelines for Ressuscitation 2015 Section 3. Adult advanced life support; Ressuscitation; 2015; 95:100-147.

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European Resuscitation Council Guidelines for Resuscitation 2015 Section 3. Adult advanced life support

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Introduction

Adult advanced life support (ALS) includes advanced interventions after basic life support has started and when appropriate an automated external defibrillator (AED) has been used. Adult basic life support (BLS) and use of AEDs is addressed in Section 2. The transition between basic and advanced life support should be seamless as BLS will continue during and overlap with ALS interventions. This section on ALS includes the prevention of cardiac arrest, specific aspects of prehospital ALS, starting in-hospital resuscitation, the ALS algorithm, manual defibrillation, airway management during CPR, drugs and their delivery during CPR, and the treatment of peri-arrest arrhythmias. There are two changes in the presentation of these guidelines since European Resuscitation Council (ERC) Guidelines 2010.[1] There is no longer a separate section on electrical therapies[2] and the ALS aspects are now part of this section. Post-resuscitation care guidelines are presented in a new section (Section 5) that recognises the importance of the final link in the Chain of Survival.[3]

These Guidelines are based on the International Liaison Committee on Resuscitation (ILCOR) 2015 Consensus on Science and Treatment Recommendations (CoSTR) for ALS.[4] The 2015 ILCOR review focused on 42 topics organised in the approximate sequence of ALS interventions: defibrillation, airway, oxygenation and ventilation, circulatory support, monitoring during CPR, and drugs during CPR. For these Guidelines the ILCOR recommendations were supplemented by focused literature reviews undertaken by the ERC ALS Writing Group for those topics not reviewed in the 2015 ILCOR CoSTR. Guidelines were drafted and agreed by the ALS Writing Group members before final approval by the ERC General Assembly and ERC Board.

Summary of changes since 2010 Guidelines

The 2015 ERC ALS Guidelines have a change in emphasis aimed at improved care and implementation of these guidelines in order to improve patient focused outcomes.[5] The 2015 ERC ALS Guidelines do not include any major changes in core ALS interventions since the previous ERC guidelines published in 2010.[1,2] The key changes since 2010 are:

- Continuing emphasis on the use of rapid response systems for care of the deteriorating patient and prevention of in-hospital cardiac arrest.
- Continued emphasis on minimally interrupted high-quality chest compressions throughout any ALS intervention: chest

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compressions are paused briefly only to enable specific interventions. This includes minimising interruptions in chest compressions to attempt defibrillation.
- Keeping the focus on the use of self-adhesive pads for defibrillation and a defibrillation strategy to minimise the preshock pause, although we recognise that defibrillator paddles are used in some settings.
- There is a new section on monitoring during ALS with an increased emphasis on the use of waveform capnography to confirm and continually monitor tracheal tube placement, quality of CPR and to provide an early indication of return of spontaneous circulation (ROSC).
- There are a variety of approaches to airway management during CPR and a stepwise approach based on patient factors and the skills of the rescuer is recommended.
- The recommendations for drug therapy during CPR have not changed, but there is greater equipoise concerning the role of drugs in improving outcomes from cardiac arrest.
- The routine use of mechanical chest compression devices is not recommended, but they are a reasonable alternative in situations where sustained high-quality manual chest compressions are impractical or compromise provider safety.
- Peri-arrest ultrasound may have a role in identifying reversible causes of cardiac arrest.
- Extracorporeal life support techniques may have a role as a rescue therapy in selected patients where standard ALS measures are not successful.

3a – Prevention of in-hospital cardiac arrest

Early recognition of the deteriorating patient and prevention of cardiac arrest is the first link in the chain of survival.[3] Once cardiac arrest occurs, only about 20% of patients who have an in-hospital cardiac arrest will survive to go home.[6,7]

The key recommendations for the prevention of in-hospital cardiac arrest are unchanged since the previous guidance in 2010.[1] We suggest an approach to prevention of in-hospital cardiac arrest that includes staff education, monitoring of patients, recognition of patient deterioration, a system to call for help and an effective response – the chain of prevention.[8]

The problem

Cardiac arrest in patients in unmonitored ward areas is not usually a sudden unpredictable event.[9] Patients often have slow and progressive physiological deterioration, involving hypoxaemia and hypotension that is unnoticed or poorly managed by ward staff.[10–12] The initial cardiac arrest rhythm is usually non-shockable[6,7] and survival to hospital discharge is poor, particularly in patients with preceding signs of respiratory depression or shock.[7,13] Early and effective treatment might prevent some cardiac arrests, deaths and unanticipated ICU admissions. Studies conducted in hospitals with traditional cardiac arrest teams have shown that patients attended by the team but who were found not to have a cardiac arrest, have a high morbidity and mortality.[14–16] Registry data from the US suggests that hospitals with lowest incidence of IHCA also have the highest CA survival.[17]

Nature of the deficiencies in the recognition and response to patient deterioration

These include infrequent, late or incomplete vital signs assessments; lack of knowledge of normal vital signs values; poor design of vital signs charts; poor sensitivity and specificity of 'track and trigger' systems; failure of staff to increase monitoring or escalate care, and staff workload.[18–26] Problems with assessing and treating airway, breathing and circulation abnormalities as well organisational problems such as poor communication, lack of teamwork and insufficient use of treatment limitation plans are not infrequent.[10,27,28]

Education in acute care

Several studies show that medical and nursing staff lack knowledge and skills in acute care,[29–37] e.g. oxygen therapy,[30] fluid and electrolyte balance,[31] analgesia,[32] issues of consent,[33] pulse oximetry,[30,34,35] and drug doses.[36] Staff education is an essential part of implementing a system to prevent cardiac arrest but to date, randomised controlled studies addressing the impact of specific educational interventions are lacking.[37]

In one study, virtually all the improvement in the hospital cardiac arrest rate occurred during the educational phase of implementation of a medical emergency team (MET) system.[38,39] Rapid response teams, such as METs, play a role in educating and improving acute care skills of ward personnel.[37,40] The introduction of specific, objective calling criteria,[41] referral tools[42] and feedback to caregivers[43] has resulted in improved MET use and a significant reduction in cardiac arrests. Another study found that the number of cardiac arrest calls decreased while pre-arrest calls increased after implementing a standardised educational programme[44] in two hospitals[45]; this was associated with a decrease in CA incidence and improved CA survival. Other research suggests that multiprofessional education did not alter the rate of mortality or staff awareness of patients at risk on general wards.[46]

Monitoring and recognition of the critically ill patient

Clinical signs of acute illness are similar whatever the underlying process, as they reflect failing respiratory, cardiovascular and neurological systems. Alterations in physiological variables, singly or in combination are associated with, or can be used to predict the occurrence of cardiac arrest,[12,47–50] hospital death[20,21,51–68] and unplanned ICU admission,[47,66,69,70] and with increasing magnitude and number of derangements the likelihood of death is increased.[18,47,48,63,71–79] Even though abnormal physiology is common on general wards,[80] the measurement and documentation of vital signs is suboptimal.[9,11,22,49,81–83] To assist in the early detection of critical illness, each patient should have a documented plan for vital signs monitoring including which physiological measurements needs no be undertaken and frequency.[24,84]

Many hospitals use early warning scores (EWS) or calling criteria to identify ward patients needing escalation of care,[22,49,82,85–89] and this increases vital signs monitoring.[82,88,89] These calling criteria or 'track and trigger' systems include single-parameter systems, multiple-parameter systems, aggregate weighted scoring systems or combination systems.[90] Aggregate weighted track and trigger systems offer a graded escalation of care, whereas single parameter track and trigger systems provide an all-or-nothing response. Simpler systems may have advantages over more complex ones.[91,92] Nurse concern may also be an important predictor of patient deterioration.[93–95]

The use of an aggregate score based on a number of vital sign abnormalities appears more important than abnormalities in a single criteria.[96,97] Aggregate-weighted scoring systems vary in their performance and in which endpoint they predict.[20,70,98] In older (>65 year) patients, who represent the largest group of IHCA patients,[99] signs of deterioration before cardiac arrest are often blunted, and the predictive value of the Modified Early Warning Score (MEWS) progressively decreases with increasing patient age.[100]

The design of vital signs charts[19,101] or the use of technology[102–104] may have an important role in the detection of

deterioration and the escalation of care, but these require further study. Possible benefits include increased vital signs recording,[105] improved identification of signs of deterioration,[19,101,104] reduced time to team activation[103] and improved patient outcomes.[103,106]

Calling for help and the response to critical illness

Nursing staff and junior doctors often find it difficult to ask for help or escalate treatment as they feel their clinical judgement may be criticised.[107–110] In addition, there is a common belief, especially amongst younger staff, that the patient's primary team should be capable of dealing with problems close to their area of specialty.[110] It is logical that hospitals should ensure all staff are empowered to call for help and also trained to use structured communication tools such as RSVP (reason-story-vital signs-plan)[111] or SBAR (situation-background-assessment-recommendation)[112] tools to ensure effective inter-professional communication. However, recent research suggests that structured communication tools are rarely used in clinical practice.[113]

The response to patients who are critically ill or who are at risk of becoming critically ill is now usually provided by a medical emergency team (MET), rapid response team (RRT), or critical care outreach team (CCOT).[114–117] These replace or coexist with traditional cardiac arrest teams, which typically respond to patients already in cardiac arrest. MET/RRT usually comprise medical and nursing staff from intensive care and general medicine, who respond to specific calling criteria. Any member of the healthcare team can initiate a MET/RRT/CCOT call. In some hospitals, the patient, and their family and friends, are also encouraged to activate the team.[118–120] Team interventions often involve simple tasks such as starting oxygen therapy and intravenous fluids.[121–125] However, *post-hoc* analysis of the MERIT study data suggests that nearly all MET calls required 'critical care-type' interventions.[126] The MET, RRT or CCOT is often also involved in discussions regarding 'do not attempt cardiopulmonary resuscitation' (DNACPR) or end-of-life plans.[127–133] Recently, attempts have been made to develop a screening tool to identify patients at the end of life and quantify the risk of death in order to minimise prognostic uncertainty and avoid potentially harmful and futile treatments.[134]

Studying the effect of the MET/RRT/CCOT systems on patient outcomes is difficult because of the complex nature of the intervention. During the period of most studies of rapid response teams, there has been a major international focus on improving other aspects of patient safety, e.g. hospital acquired infections, earlier treatment of sepsis and better medication management, all of which have the potential to influence patient deterioration and may have a beneficial impact on reducing cardiac arrests and hospital deaths. Most studies on RRT/MET systems to date originate from the USA and Australia and the systems effectiveness in other health care systems in not clear.[135]

A well-designed, cluster-randomised controlled trial of the MET system (MERIT study) involving 23 hospitals[22] did not show a reduction in cardiac arrest rate after introduction of a MET when analysed on an intention-to-treat basis. Both the control and MET groups demonstrated improved outcome compared to baseline. *Post hoc* analysis of the MERIT study showed there was a decrease in cardiac arrest and unexpected mortality rate with increased activation of the MET system.[136] The evidence from predominantly single centre observational studies is inconclusive, with some studies showing reduced numbers of cardiac arrests after MET/RRT implementation[38,41,123,137–159] and some studies failing to show a reduction[121,122,124,125,160–163]. However, systematic reviews, meta-analyses and multicentre studies do suggest that RRT/MET systems reduce rates of cardiopulmonary arrest and lower hospital mortality rates.[164–166] Concern has been expressed about MET activity leading to potential adverse events resulting from staff leaving normal duties to attend MET calls. Research suggests that although MET calls may cause disruption to normal hospital routines and inconvenience to staff, no major patient harm follows.[167]

Appropriate placement of patients

Ideally, the sickest patients should be admitted to an area that can provide the greatest supervision and the highest level of organ support and nursing care. International organisations have offered definitions of levels of care and produced admission and discharge criteria for high dependency units (HDUs) and ICUs.[168,169]

Staffing levels

Hospital staffing tends to be at its lowest during the night and at weekends, which may influence patient monitoring, treatment and outcome. Data from the US National Registry of CPR Investigators shows that survival rates from in-hospital cardiac arrest are lower during nights and weekends.[170] Outcomes for patients admitted to hospital and those discharged from the ICU are worse after hours and at weekends.[171–174] Studies show that higher nurse staffing is associated with lower rates of failure-to-rescue, and reductions in rates of cardiac arrest rates, pneumonia, shock and death.[23,175–177]

Resuscitation decisions

The decision to start, continue and terminate resuscitation efforts is based on the balance between the risks, benefits and burdens these interventions place on patients, family members and healthcare providers. There are circumstances where resuscitation is inappropriate and should not be provided. Consider a 'do not attempt cardiopulmonary resuscitation' (DNACPR) decision when the patient:

- does not wish to have CPR
- is very unlikely to survive cardiac arrest even if CPR is attempted.

There is wide variation in DNACPR decision-making practice throughout Europe particularly with respect to involvement of patients in decision-making.[178–181] Improved knowledge, training and DNACPR decision-making should improve patient care and prevent futile CPR attempts.[182,183] The section on ethics in the ERC Guidelines provides further information.[184]

Guidelines for prevention of in-hospital cardiac arrest

Hospitals should provide a system of care that includes: (a) staff education regarding the signs of patient deterioration and the rationale for rapid response to illness, (b) appropriate, and frequent monitoring of patients' vital signs, (c) clear guidance (e.g. via calling criteria or early warning scores) to assist staff in the early detection of patient deterioration, (d) a clear, uniform system of calling for assistance, and (e) an appropriate and timely clinical response to calls for help.[8] The following strategies may prevent avoidable in-hospital cardiac arrests:

(1) Provide care for patients who are critically ill or at risk of clinical deterioration in appropriate areas, with the level of care provided matched to the level of patient sickness.
(2) Critically ill patients need regular observations: each patient should have a documented plan for vital signs monitoring that identifies which variables need to be measured and the frequency of measurement. Frequency of measurement should relate to the patient's severity of illness, and the likelihood of clinical deterioration and cardiopulmonary arrest.

Recent guidance suggests monitoring of simple physiological variables including pulse, blood pressure, respiratory rate, conscious level, temperature and SpO_2.[24,84]

(3) Use a track and trigger system (either 'calling criteria' or early warning system) to identify patients who are critically ill and, or at risk of clinical deterioration and cardiopulmonary arrest.
(4) Use a patient charting system that enables the regular measurement and recording of vital signs and, where used, early warning scores. The charting system should facilitate easy identification of signs of deterioration.
(5) Have a clear and specific policy that requires a clinical response to abnormal physiology, based on the track and trigger system used. This should include advice on the further clinical management of the patient and the specific responsibilities of medical and nursing staff.
(6) The hospital should have a clearly identified response to critical illness. This may include a designated outreach service or resuscitation team (e.g. MET, RRT system) capable of responding in a timely fashion to acute clinical crises identified by the track and trigger system or other indicators. This service must be available 24 h/day and seven days per week. The team must include staff with the appropriate skills. The patient's primary clinical team should also be involved at an early stage in decision-making.
(7) Train all clinical staff in the recognition, monitoring and management of the critically ill patient. Include advice on clinical management while awaiting the arrival of more experienced staff. Ensure that staff know their role(s) in the rapid response system.
(8) Hospitals must empower staff of all disciplines to call for help when they identify a patient at risk of deterioration or cardiac arrest. Staff should be trained in the use of structured communication tools to ensure effective handover of information between doctors, nurses and other healthcare professions.
(9) Identify patients for whom cardiopulmonary arrest is an anticipated terminal event and in whom CPR is inappropriate, and patients who do not wish to be treated with CPR. Hospitals should have a DNACPR policy, based on national guidance, which is understood by all clinical staff.
(10) Ensure accurate audit of cardiac arrest, deteriorating patients, unexpected deaths and unanticipated ICU admissions using common datasets. Also audit the antecedents and clinical response to these events.

Prevention of sudden cardiac death (SCD) out-of-hospital

Coronary artery disease is the commonest cause of SCD. Non-ischaemic cardiomyopathy and valvular disease account for most other SCD events in older people. Inherited abnormalities (e.g. Brugada syndrome, hypertrophic cardiomyopathy), congenital heart disease, myocarditis and substance abuse are predominant causes in the young.

Most SCD victims have a history of cardiac disease and warning signs, most commonly chest pain, in the hour before cardiac arrest.[185] In patients with a known diagnosis of cardiac disease, syncope (with or without prodrome – particularly recent or recurrent) is an independent risk factor for increased risk of death.[186–196] Chest pain on exertion only, and palpitations associated with syncope only, are associated with hypertrophic cardiomyopathy, coronary abnormalities, Wolff–Parkinson–White, and arrhythmogenic right ventricular cardiomyopathy.

Apparently healthy children and young adults who suffer SCD can also have signs and symptoms (e.g. syncope/pre-syncope, chest pain and palpitations) that should alert healthcare professionals to seek expert help to prevent cardiac arrest.[197–206]

Children and young adults presenting with characteristic symptoms of arrhythmic syncope should have a specialist cardiology assessment, which should include an ECG and in most cases an echocardiogram and exercise test. Characteristics of arrhythmic syncope include: syncope in the supine position, occurring during or after exercise, with no or only brief prodromal symptoms, repetitive episodes, or in individuals with a family history of sudden death. In addition, non-pleuritic chest pain, palpitations associated with syncope, seizures (when resistant to treatment, occurring at night or precipitated by exercise, syncope, or loud noise) and drowning in a competent swimmer should raise suspicion of increased risk. Systematic evaluation in a clinic specialising in the care of those at risk for SCD is recommended in family members of young victims of SCD or those with a known cardiac disorder resulting in an increased risk of SCD.[186,207–211] A family history of syncope or SCD, palpitations as a symptom, supine syncope and syncope associated with exercise and emotional stress are more common in patients with long QT syndrome (LQTS).[212] In older adults[213,214] the absence of nausea and vomiting before syncope and ECG abnormalities is an independent predictor of arrhythmic syncope.

Inexplicable drowning and drowning in a strong swimmer may be due to LQTS or catecholaminergic polymorphic ventricular tachycardia (CPVT).[215] There is an association between LQTS and presentation with seizure phenotype.[216,217]

Guidance has been published for the screening of those at risk of sudden death including the screening of athletes. Screening programmes for athletes vary between countries.[218,219] Identification of individuals with inherited conditions and screening of family members can help prevent deaths in young people with inherited heart disorders.[220–222]

3b – Prehospital resuscitation

This section provides an overview of prehospital resuscitation. Many of the specific issues about prehospital resuscitation are addressed in sections covering ALS interventions, or are generic for both resuscitation for in-hospital and out-of-hospital cardiac arrest.[223] Adult BLS and automated external defibrillation contains guidance on the techniques used during the initial resuscitation of an adult cardiac arrest victim. In addition, many of the specific situations associated with cardiac arrest that are encountered in prehospital resuscitation are addressed in Section 4 – cardiac arrest in special circumstances.[224]

EMS personnel and interventions

There is considerable variation across Europe in the structure and process of emergency medical services (EMS) systems. Some countries have adopted almost exclusively paramedic/emergency medical technician (EMT)-based systems while other incorporate prehospital physicians to a greater or lesser extent. Although some studies have documented higher survival rates after cardiac arrest in EMS systems that include experienced physicians,[225–232] compared with those that rely on non-physician providers,[225,226,233,234] some other comparisons have found no difference in survival between systems using paramedics or physicians as part of the response.[235–237] Well-organised non-physician systems with highly trained paramedics have also reported high survival rates.[238] Given the inconsistent evidence, the inclusion or exclusion of physicians among prehospital personnel responding to cardiac arrests will depend largely on existing local policy.

Whether ALS interventions by EMS improve outcomes is also uncertain. A meta-analysis suggested that ALS care can increase survival in non-traumatic OHCA.[239] However, a recent large

observational study using propensity matching showed survival to hospital discharge and 90 day survival was greater among patients receiving BLS.[240] It is not possible to say whether this is a true difference or the result of unmeasured confounders.

CPR versus defibrillation first for out-of-hospital cardiac arrest

There is evidence that performing chest compressions while retrieving and charging a defibrillator improves the probability of survival.[241] One randomised controlled trial (RCT)[242] found increased ROSC, discharge- and one-year survival in patients with longer arrest times (>5 min). However, we have to keep in mind that this, and a large before-after study from Seattle[243] that showed better outcomes with 90 s of CPR before a shock when the response interval was >4 min), are from a time when 3 stacked-shocks were used and shorter periods of CPR between shocks (1 min). Evidence from five RCTs[242,244–247] and another study[248] suggests that among unmonitored patients with OHCA and an initial rhythm of VF/pVT, there is no benefit in a period of CPR of 90–180 s before defibrillation when compared with immediate defibrillation with CPR being performed while the defibrillator equipment is being applied.

A sub-analysis in one RCT[245] showed no difference in survival to hospital discharge with a prolonged period of CPR (180 s) and delayed defibrillation in patients with a shockable initial rhythm who received bystander CPR. Yet, for those EMS agencies with a higher baseline survival to hospital discharge (defined as >20% for an initial shockable rhythm), 180 s of CPR prior to defibrillation was more beneficial compared with a shorter period of CPR (30–60 s).

EMS personnel should provide high-quality CPR while a defibrillator is retrieved, applied and charged. Defibrillation should not be delayed longer than needed to establish the need for defibrillation and charging. The routine delivery of a pre-specified period of CPR (e.g. 2 or 3 min) before rhythm analysis and a shock is delivered is not recommended.

Termination of resuscitation rules

The 'basic life support termination of resuscitation rule' is predictive of death when applied by defibrillation-only emergency medical technicians.[249] The rule recommends termination when there is no ROSC, no shocks are administered and EMS personnel do not witness the arrest. Several studies have shown external generalisability of this rule.[250–256] More recent studies show that EMS systems providing ALS interventions can also use this BLS rule and therefore termed it the 'universal' termination of resuscitation rule.[251,257,258]

Additional studies have shown associations with futility of certain variables such as no ROSC at scene; non-shockable rhythm; unwitnessed arrest; no bystander CPR, call response time and patient demographics.[259–267]

Termination of resuscitation rules for in-hospital cardiac arrest are less reliable although EMS rules may be useful for those with out-of-hospital cardiac arrest who have ongoing resuscitation in the emergency department.[268–271]

Prospectively validated termination of resuscitation rules can be used to guide termination of prehospital CPR in adults; however, these must be validated in an EMS system similar to the one in which implementation is proposed. Termination of resuscitation rules may require integration with guidance on suitability for extracorporeal CPR (eCPR) or organ donation.[272] Organ donation is specifically addressed in Section 5 – Post-resuscitation care.[273,274]

3c – In-hospital resuscitation

After in-hospital cardiac arrest, the division between BLS and ALS is arbitrary; in practice, the resuscitation process is a continuum and is based on common sense. The public expect that clinical staff can undertake cardiopulmonary resuscitation (CPR). For all in-hospital cardiac arrests, ensure that:

- cardiorespiratory arrest is recognised immediately;
- help is summoned using a standard telephone number;
- CPR is started immediately using airway adjuncts, e.g. a bag mask and, if indicated, defibrillation attempted as rapidly as possible and certainly within 3 min.

The exact sequence of actions after in-hospital cardiac arrest will depend on many factors, including:

- location (clinical/non-clinical area; monitored/unmonitored area);
- training of the first responders;
- number of responders;
- equipment available;
- hospital response system to cardiac arrest and medical emergencies, (e.g. MET, RRT).

Location

Patients who have monitored arrests are usually diagnosed rapidly. Ward patients may have had a period of deterioration and an unwitnessed arrest.[9,11] Ideally, all patients who are at high risk of cardiac arrest should be cared for in a monitored area where facilities for immediate resuscitation are available.

Training of first responders

All healthcare professionals should be able to recognise cardiac arrest, call for help and start CPR. Staff should do what they have been trained to do. For example, staff in critical care and emergency medicine will have more advanced resuscitation skills than staff who are not involved regularly in resuscitation in their normal clinical role. Hospital staff who attend a cardiac arrest may have different levels of skill to manage the airway, breathing and circulation. Rescuers must undertake only the skills in which they are trained and competent.

Number of responders

The single responder must ensure that help is coming. If other staff are nearby, several actions can be undertaken simultaneously.

Equipment available

All clinical areas should have immediate access to resuscitation equipment and drugs to facilitate rapid resuscitation of the patient in cardiopulmonary arrest. Ideally, the equipment used for CPR (including defibrillators) and the layout of equipment and drugs should be standardised throughout the hospital.[275–277] Equipment should be checked regularly, e.g. daily, to ensure its readiness for use in an emergency.

Resuscitation team

The resuscitation team may take the form of a traditional cardiac arrest team, which is called only when cardiac arrest is recognised. Alternatively, hospitals may have strategies to recognise patients at risk of cardiac arrest and summon a team (e.g. MET or RRT) before cardiac arrest occurs. The term 'resuscitation team' reflects the range of response teams. In hospital cardiac arrests are rarely sudden or unexpected. A strategy of recognising patients at risk of cardiac arrest may enable some of these arrests to be prevented, or

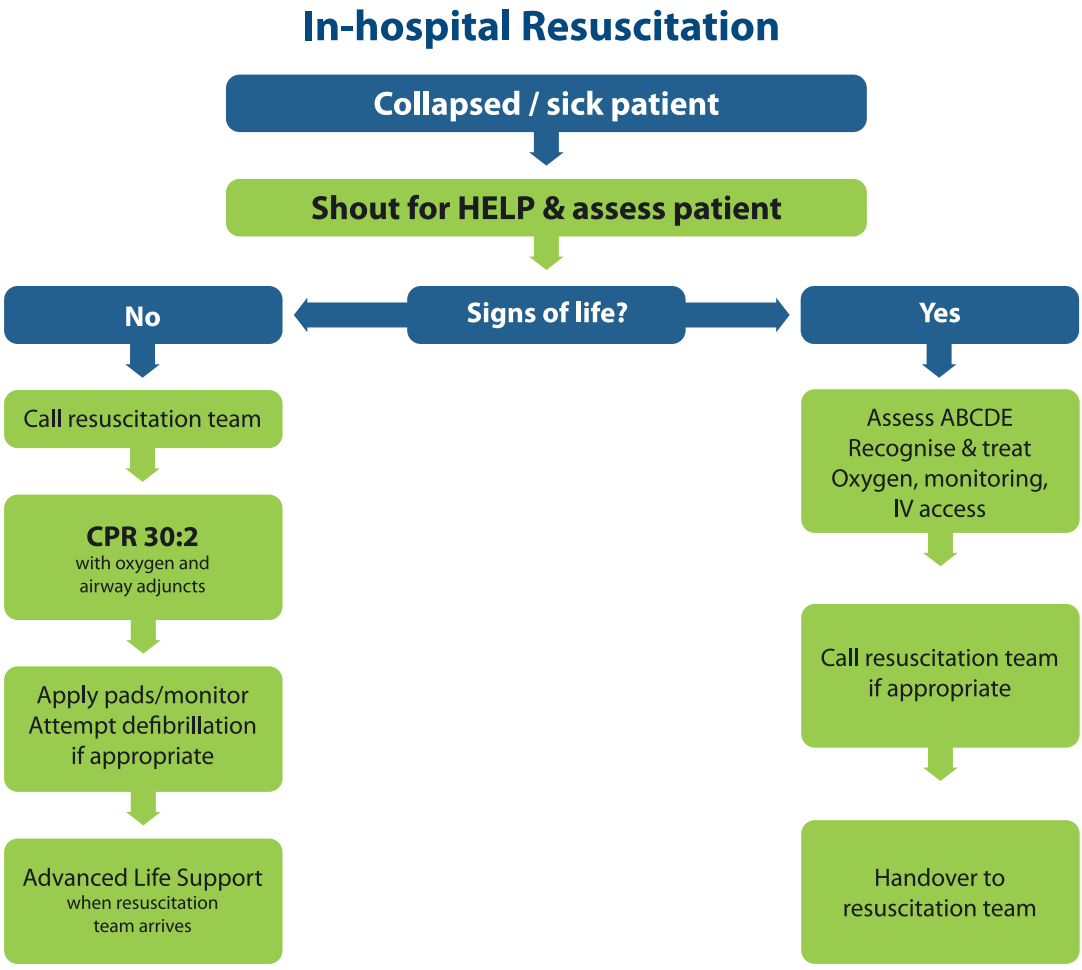


Fig. 3.1. In-hospital resuscitation algorithm. ABCDE – Airway, Breathing Circulation, Disability, Exposure; IV – intravenous; CPR – cardiopulmonary resuscitation

may prevent futile resuscitation attempts in those who are unlikely to benefit from CPR.

Immediate actions for a collapsed patient in a hospital

An algorithm for the initial management of in-hospital cardiac arrest is shown in Fig. 3.1.

- Ensure personal safety.
- When healthcare professionals see a patient collapse or find a patient apparently unconscious in a clinical area, they should first summon help (e.g. emergency bell, shout), then assess if the patient is responsive. Gently shake the shoulders and ask loudly: 'Are you all right?'
- If other members of staff are nearby, it will be possible to undertake actions simultaneously.

The responsive patient

Urgent medical assessment is required. Depending on the local protocols, this may take the form of a resuscitation team (e.g. MET, RRT). While awaiting this team, give oxygen, attach monitoring and insert an intravenous cannula.

The unresponsive patient

The exact sequence will depend on the training of staff and experience in assessment of breathing and circulation. Trained healthcare staff cannot assess the breathing and pulse sufficiently reliably to confirm cardiac arrest.[278–287]

Agonal breathing (occasional gasps, slow, laboured or noisy breathing) is common in the early stages of cardiac arrest and is a sign of cardiac arrest and should not be confused as a sign of life.[288–291] Agonal breathing can also occur during chest compressions as cerebral perfusion improves, but is not indicative of ROSC. Cardiac arrest can cause an initial short seizure-like episode that can be confused with epilepsy.[292,293] Finally changes in skin colour, notably pallor and bluish changes associated with cyanosis are not diagnostic of cardiac arrest.[292]

- Shout for help (if not already)
- Turn the victim on to his back and then open the airway:
- Open airway and check breathing:
  - Open the airway using a head tilt chin lift
  - Keeping the airway open, look, listen and feel for normal breathing (an occasional gasp, slow, laboured or noisy breathing is not normal):
    - Look for chest movement
    - Listen at the victim's mouth for breath sounds
    - Feel for air on your cheek
  - Look, listen and feel for no more than 10 s to determine if the victim is breathing normally.
- Check for signs of a circulation:
  - It may be difficult to be certain that there is no pulse. If the patient has no signs of life (consciousness, purposeful

movement, normal breathing, or coughing), or if there is doubt, start CPR immediately until more experienced help arrives or the patient shows signs of life.
  - Delivering chest compressions to a patient with a beating heart is unlikely to cause harm.[294] However, delays in diagnosing cardiac arrest and starting CPR will adversely effect survival and must be avoided.
  - Only those experienced in ALS should try to assess the carotid pulse whilst simultaneously looking for signs of life. This rapid assessment should take no more than 10 s. Start CPR if there is any doubt about the presence or absence of a pulse.
- If there are signs of life, urgent medical assessment is required. Depending on the local protocols, this may take the form of a resuscitation team. While awaiting this team, give the patient oxygen, attach monitoring and insert an intravenous cannula. When a reliable measurement of oxygen saturation of arterial blood (e.g. pulse oximetry (SpO_2)) can be achieved, titrate the inspired oxygen concentration to achieve a SpO_2 of 94–98%.
- If there is no breathing, but there is a pulse (respiratory arrest), ventilate the patient's lungs and check for a circulation every 10 breaths. Start CPR if there is any doubt about the presence or absence of a pulse.

Starting in-hospital CPR

The key steps are listed here. Supporting evidence can be found in the sections on specific interventions that follow.

- One person starts CPR as others call the resuscitation team and collect the resuscitation equipment and a defibrillator. If only one member of staff is present, this will mean leaving the patient.
- Give 30 chest compressions followed by 2 ventilations.
- Compress to a depth of at least 5 cm but not more than 6 cm.
- Perform chest compressions should be performed at a rate of 100–120 min^{-1}.
- Allow the chest to recoil completely after each compression; do not lean on the chest.
- Minimise interruptions and ensure high-quality compressions.
- Undertaking high-quality chest compressions for a prolonged time is tiring; with minimal interruption, try to change the person doing chest compressions every 2 min.
- Maintain the airway and ventilate the lungs with the most appropriate equipment immediately to hand. Pocket mask ventilation or two-rescuer bag-mask ventilation, which can be supplemented with an oral airway, should be started. Alternatively, use a supraglottic airway device (SGA) and self-inflating bag. Tracheal intubation should be attempted only by those who are trained, competent and experienced in this skill.
- Waveform capnography must be used for confirming tracheal tube placement and monitoring ventilation rate. Waveform capnography can also be used with a bag-mask device and SGA. The further use of waveform capnography to monitor CPR quality and potentially identify ROSC during CPR is discussed later in this section.[295]
- Use an inspiratory time of 1 s and give enough volume to produce a normal chest rise. Add supplemental oxygen to give the highest feasible inspired oxygen as soon as possible.[4]
- Once the patient's trachea has been intubated or a SGA has been inserted, continue uninterrupted chest compressions (except for defibrillation or pulse checks when indicated) at a rate of 100–120 min^{-1} and ventilate the lungs at approximately 10 breaths min^{-1}. Avoid hyperventilation (both excessive rate and tidal volume).
- If there is no airway and ventilation equipment available, consider giving mouth-to-mouth ventilation. If there are clinical reasons to avoid mouth-to-mouth contact, or you are unable to do this, do chest compressions until help or airway equipment arrives. The ALS Writing Group recognises that there can be good clinical reasons to avoid mouth-to-mouth ventilation in clinical settings, and it is not commonly used in clinical settings, but there will be situations where giving mouth-to-mouth breaths could be life-saving.
- When the defibrillator arrives, apply self-adhesive defibrillation pads to the patient whilst chest compressions continue and then briefly analyse the rhythm. If self-adhesive defibrillation pads are not available, use paddles. The use of self-adhesive electrode pads or a 'quick-look' paddles technique will enable rapid assessment of the heart rhythm compared with attaching ECG electrodes.[296] Pause briefly to assess the heart rhythm. With a manual defibrillator, if the rhythm is VF/pVT charge the defibrillator while another rescuer continues chest compressions. Once the defibrillator is charged, pause the chest compressions and then give one shock, and immediately resume chest compressions. Ensure no one is touching the patient during shock delivery. Plan and ensure safe defibrillation before the planned pause in chest compressions.
- If using an automated external defibrillator (AED) follow the AED's audio-visual prompts, and similarly aim to minimise pauses in chest compressions by rapidly following prompts.
- The ALS Writing Group recognises that in some settings where self-adhesive defibrillation pads are not available, alternative defibrillation strategies using paddles are used to minimise the preshock pause.
- The ALS writing group is aware that in some countries a defibrillation strategy that involves charging the defibrillator towards the end of every 2 min cycle of CPR in preparation for the pulse check is used.[297,298] If the rhythm is VF/pVT a shock is given and CPR resumed. Whether this leads to any benefit is unknown, but it does lead to defibrillator charging for non-shockable rhythms.
- Restart chest compressions immediately after the defibrillation attempt. Minimise interruptions to chest compressions. When using a manual defibrillator it is possible to reduce the pause between stopping and restarting of chest compressions to less than 5 s.
- Continue resuscitation until the resuscitation team arrives or the patient shows signs of life. Follow the voice prompts if using an AED.
- Once resuscitation is underway, and if there are sufficient staff present, prepare intravenous cannulae and drugs likely to be used by the resuscitation team (e.g. adrenaline).
- Identify one person to be responsible for handover to the resuscitation team leader. Use a structured communication tool for handover (e.g. SBAR, RSVP).[111,112] Locate the patient's records.
- The quality of chest compressions during in-hospital CPR is frequently sub-optimal.[299,300] The importance of uninterrupted chest compressions cannot be over emphasised. Even short interruptions to chest compressions are disastrous for outcome and every effort must be made to ensure that continuous, effective chest compression is maintained throughout the resuscitation attempt. Chest compressions should commence at the beginning of a resuscitation attempt and continue uninterrupted unless they are paused briefly for a specific intervention (e.g. rhythm check). Most interventions can be performed without interruptions to chest compressions. The team leader should monitor the quality of CPR and alternate CPR providers if the quality of CPR is poor.
- Continuous $ETCO_2$ monitoring during CPR can be used to indicate the quality of CPR, and a rise in $ETCO_2$ can be an indicator of ROSC during chest compressions.[295,301–303]
- If possible, the person providing chest compressions should be changed every 2 min, but without pauses in chest compressions.

3d – ALS treatment algorithm

Introduction

Heart rhythms associated with cardiac arrest are divided into two groups: shockable rhythms (ventricular fibrillation/pulseless ventricular tachycardia (VF/pVT)) and non-shockable rhythms (asystole and pulseless electrical activity (PEA)). The principal difference in the treatment of these two groups of arrhythmias is the need for attempted defibrillation in those patients with VF/pVT. Other interventions, including high-quality chest compressions with minimal interruptions, airway management and ventilation, venous access, administration of adrenaline and the identification and correction of reversible causes, are common to both groups.

Although the ALS cardiac arrest algorithm (Fig. 3.2) is applicable to all cardiac arrests, additional interventions may be indicated for cardiac arrest caused by special circumstances (see Section 4).[224]

The interventions that unquestionably contribute to improved survival after cardiac arrest are prompt and effective bystander basic life support (BLS), uninterrupted, high-quality chest compressions and early defibrillation for VF/pVT. The use of adrenaline has been shown to increase ROSC but not survival to discharge. Furthermore there is a possibility that it causes worse long-term neurological survival. Similarly, the evidence to support the use of advanced airway interventions during ALS remains limited.[4,304–311]

Thus, although drugs and advanced airways are still included among ALS interventions, they are of secondary importance to early defibrillation and high-quality, uninterrupted chest compressions. As an indicator of equipoise for many ALS interventions at the time of writing these guidelines, three large RCTs (adrenaline versus placebo [ISRCTN73485024], amiodarone versus lidocaine versus placebo[312] [NCT01401647] and SGA versus tracheal intubation [ISRCTN No: 08256118]) are currently ongoing.

As with previous guidelines, the ALS algorithm distinguishes between shockable and non-shockable rhythms. Each cycle is broadly similar, with a total of 2 min of CPR being given before assessing the rhythm and where indicated, feeling for a pulse. Adrenaline 1 mg is injected every 3–5 min until ROSC is achieved – the timing of the initial dose of adrenaline is described below. In VF/pVT, a single dose of amiodarone 300 mg is indicated after a total of three shocks and a further dose of 150 mg can be considered after five shocks. The optimal CPR cycle time is not known and algorithms for longer cycles (3 min) exist which include different timings for adrenaline doses.[313]

Duration of resuscitation attempt

The duration of any individual resuscitation attempt should be based on the individual circumstances of the case and is a matter of clinical judgement, taking into consideration the circumstances and the perceived prospect of a successful outcome. If it was considered appropriate to start resuscitation, it is usually considered worthwhile continuing, as long as the patient remains in VF/pVT, or there is a potentially reversible cause than can be treated. The use of mechanical compression devices and extracorporeal CPR techniques make prolonged attempts at resuscitation feasible in selected patients.

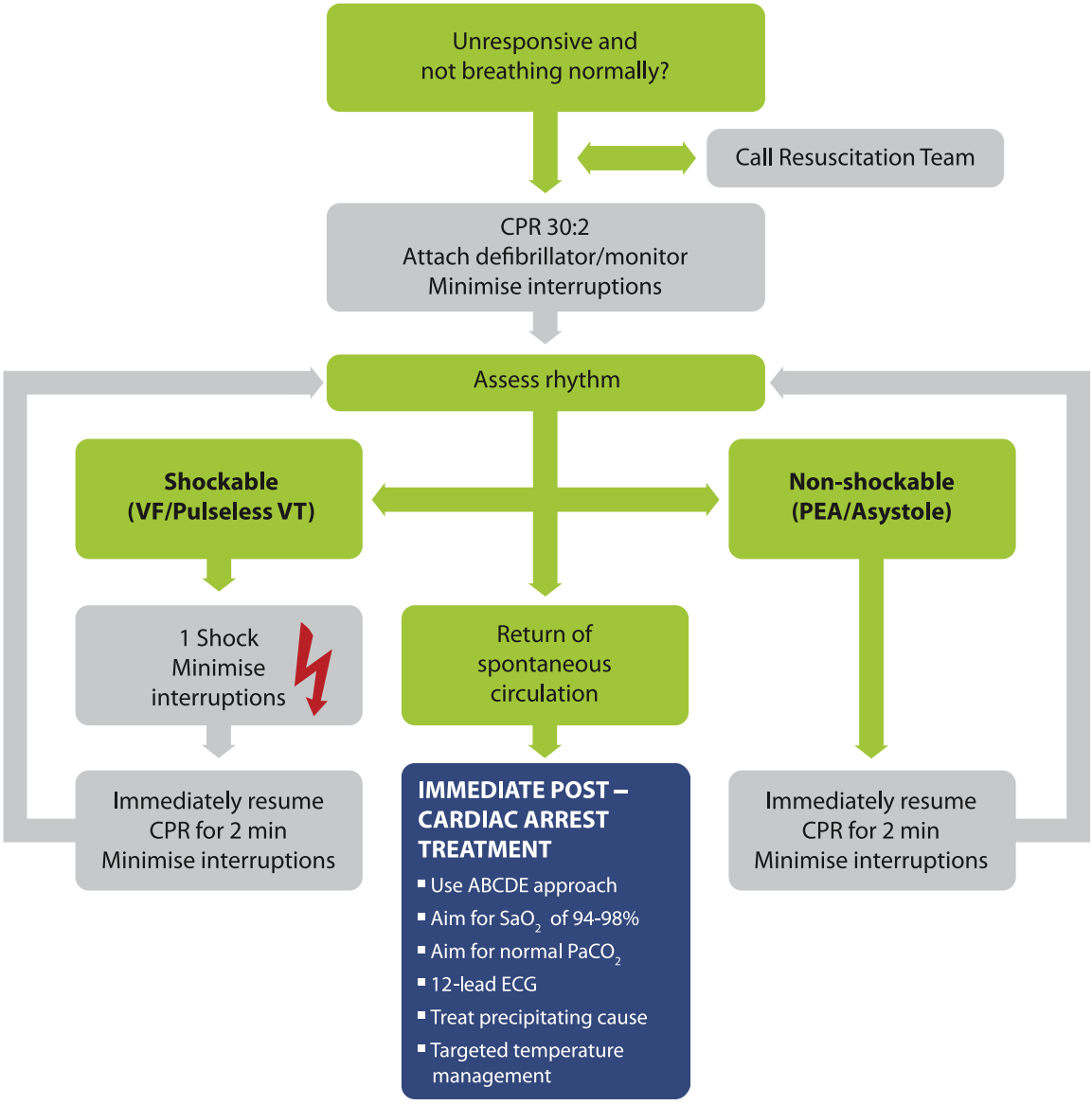
In a large observational study of patients with IHCA, the median duration of resuscitation was 12 min (IQR 6–21 min) in those with ROSC compared with 20 min (IQR 14–30 min) for those with no ROSC.[314] Hospitals with the longest resuscitation attempts (median 25 min [IQR 25–28 min]) had a higher risk-adjusted rate of ROSC and survival to discharge compared with a shorter median duration of resuscitation attempt.[314,315] It is generally accepted that asystole for more than 20 min in the absence of a reversible cause and with ongoing ALS constitutes a reasonable ground for stopping further resuscitation attempts.[316] The ethical principles of starting and stopping CPR are addressed in Section 11, the Ethics of resuscitation and end-of-life decisions.[184]

Shockable rhythms (ventricular fibrillation/pulseless ventricular tachycardia)

The first monitored rhythm is VF/pVT in approximately 20% both for in-hospital[317,7,318,319] and out-of-hospital cardiac arrests.[320] The incidence of VF/pVT may be decreasing,[321–324] and can vary according to bystander CPR rates. Ventricular fibrillation/pulseless ventricular tachycardia will also occur at some stage during resuscitation in about 25% of cardiac arrests with an initial documented rhythm of asystole or PEA.[317,325] Having confirmed cardiac arrest, summon help (including the request for a defibrillator) and start CPR, beginning with chest compressions, with a compression: ventilation (CV) ratio of 30:2. When the defibrillator arrives, continue chest compressions while applying the defibrillation electrodes. Identify the rhythm and treat according to the ALS algorithm.

- If VF/pVT is confirmed, charge the defibrillator while another rescuer continues chest compressions. Once the defibrillator is charged, pause the chest compressions, quickly ensure that all rescuers are clear of the patient and then give one shock.
- Defibrillation shock energy levels are unchanged from the 2010 guidelines.[2] For biphasic waveforms (rectilinear biphasic or biphasic truncated exponential), use an initial shock energy of at least 150 J. For pulsed biphasic waveforms, begin at 120–150 J. The shock energy for a particular defibrillator should be based on the manufacturer's guidance. It is important that those using manual defibrillators are aware of the appropriate energy settings for the type of device used. Manufacturers should consider labelling their manual defibrillators with energy level instructions, but in the absence of this and if appropriate energy levels are unknown, for adults use the highest available shock energy for all shocks. With manual defibrillators it is appropriate to consider escalating the shock energy if feasible, after a failed shock and for patients where refibrillation occurs.[326,327]
- Minimise the delay between stopping chest compressions and delivery of the shock (the preshock pause); even a 5–10 s delay will reduce the chances of the shock being successful.[328–331]
- Without pausing to reassess the rhythm or feel for a pulse, resume CPR (CV ratio 30:2) immediately after the shock, starting with chest compressions to limit the post-shock pause and the total peri-shock pause.[330,331] Even if the defibrillation attempt is successful in restoring a perfusing rhythm, it takes time to establish a post shock circulation[332] and it is very rare for a pulse to be palpable immediately after defibrillation.[333] In one study, after defibrillation attempts, most patients having ALS remained pulseless for over 2 min and the duration of asystole before ROSC was longer than 2 min beyond the shock in as many as 25%.[334] If a shock has been successful immediate resumption of chest compressions does not increase the risk of VF recurrence.[335] Furthermore, the delay in trying to palpate a pulse will further compromise the myocardium if a perfusing rhythm has not been restored.[336]
- Continue CPR for 2 min, then pause briefly to assess the rhythm; if still VF/pVT, give a second shock (150–360 J biphasic). Without pausing to reassess the rhythm or feel for a pulse, resume CPR (CV ratio 30:2) immediately after the shock, starting with chest compressions.
- Continue CPR for 2 min, then pause briefly to assess the rhythm; if still VF/pVT, give a third shock (150–360 J biphasic). Without reassessing the rhythm or feeling for a pulse, resume CPR (CV

Advanced Life Support



DURING CPR

- Ensure high quality chest compressions
- Minimise interruptions to compressions
- Give oxygen
- Use waveform capnography
- Continuous compressions when advanced airway in place
- Vascular access (intravenous or intraosseous)
- Give adrenaline every 3-5 min
- Give amiodarone after 3 shocks

TREAT REVERSIBLE CAUSES

Hypoxia	Thrombosis – coronary or pulmonary
Hypovolaemia	Tension pneumothorax
Hypo-/hyperkalaemia/metabolic	Tamponade – cardiac
Hypothermia/hyperthermia	Toxins

CONSIDER

- Ultrasound imaging
- Mechanical chest compressions to facilitate transfer/treatment
- Coronary angiography and percutaneous coronary intervention
- Extracorporeal CPR

Fig. 3.2. Advanced life support algorithm. CPR – cardiopulmonary resuscitation; VF/Pulseless VT – ventricular fibrillation/pulseless ventricular tachycardia; PEA – pulseless electrical activity; ABCDE – Airway, Breathing Circulation, Disability, Exposure; SaO_2 – oxygen saturation; $PaCO_2$ – partial pressure carbon dioxide in arterial blood; ECG – electrocardiogram.

ratio 30:2) immediately after the shock, starting with chest compressions.
- If IV/IO access has been obtained, during the next 2 min of CPR give adrenaline 1 mg and amiodarone 300 mg.[337]
- The use of waveform capnography may enable ROSC to be detected without pausing chest compressions and may be used as a way of avoiding a bolus injection of adrenaline after ROSC has been achieved. Several human studies have shown that there is a significant increase in end-tidal CO_2 when ROSC occurs.[295,301–303,338,339] If ROSC is suspected during CPR withhold adrenaline. Give adrenaline if cardiac arrest is confirmed at the next rhythm check.
- If ROSC has not been achieved with this 3rd shock, the adrenaline may improve myocardial blood flow and increase the chance of successful defibrillation with the next shock. In animal studies, peak plasma concentrations of adrenaline occur at about 90 s after a peripheral injection and the maximum effect on coronary perfusion pressure is achieved around the same time (70 s).[340] Importantly, high-quality chest compressions are needed to circulate the drug to achieve these times.
- Timing of adrenaline dosing can cause confusion amongst ALS providers and this aspect needs to be emphasised during training.[341] Training should emphasise that giving drugs must not lead to interruptions in CPR and delay interventions such as defibrillation. Human data suggests drugs can be given without affecting the quality of CPR.[305]
- After each 2-min cycle of CPR, if the rhythm changes to asystole or PEA, see 'non-shockable rhythms' below. If a non-shockable rhythm is present and the rhythm is organised (complexes appear regular or narrow), try to feel a pulse. Ensure that rhythm checks are brief, and pulse checks are undertaken only if an organised rhythm is observed. If there is any doubt about the presence of a pulse in the presence of an organised rhythm, immediately resume CPR. If ROSC has been achieved, begin post-resuscitation care.

During treatment of VF/pVT, healthcare providers must practice efficient coordination between CPR and shock delivery whether using a manual defibrillator or an AED. When VF is present for more than a few minutes, the myocardium is depleted of oxygen and metabolic substrates. A brief period of chest compressions will deliver oxygen and energy substrates and increase the probability of restoring a perfusing rhythm after shock delivery.[342] Analyses of VF waveform characteristics predictive of shock success indicate that the shorter the time between chest compression and shock delivery, the more likely the shock will be successful.[342,343] Reduction in the peri-shock pause (the interval between stopping compressions to resuming compressions after shock delivery) by even a few seconds can increase the probability of shock success.[328–331] Moreover, continuing high-quality CPR however may improve the amplitude and frequency of the VF and improve the chance of successful defibrillation to a perfusing rhythm.[344–346]

Regardless of the arrest rhythm, after the initial adrenaline dose has been given, give further doses of adrenaline 1 mg every 3–5 min until ROSC is achieved; in practice, this will be about once every two cycles of the algorithm. If signs of life return during CPR (purposeful movement, normal breathing or coughing), or there is an increase in $ETCO_2$, check the monitor; if an organised rhythm is present, check for a pulse. If a pulse is palpable, start post-resuscitation care. If no pulse is present, continue CPR.

Witnessed, monitored VF/pVT

If a patient has a monitored and witnessed cardiac arrest in the catheter laboratory, coronary care unit, a critical care area or whilst monitored after cardiac surgery, and a manual defibrillator is rapidly available:
- Confirm cardiac arrest and shout for help.
- If the initial rhythm is VF/pVT, give up to three quick successive (stacked) shocks.
- Rapidly check for a rhythm change and, if appropriate, ROSC after each defibrillation attempt.
- Start chest compressions and continue CPR for 2 min if the third shock is unsuccessful.

This three-shock strategy may also be considered for an initial, witnessed VF/pVT cardiac arrest if the patient is already connected to a manual defibrillator. Although there are no data supporting a three-shock strategy in any of these circumstances, it is unlikely that chest compressions will improve the already very high chance of ROSC when defibrillation occurs early in the electrical phase, immediately after onset of VF.

If this initial three-shock strategy is unsuccessful for a monitored VF/pVT cardiac arrest, the ALS algorithm should be followed and these three-shocks treated as if only the first single shock has been given.

The first dose of adrenaline should be given after another 2 shock attempts if VF persists, i.e. Give 3 shocks, then 2 min CPR, then shock attempt, then 2 min CPR, then shock attempt, and then consider adrenaline during this 2 min of CPR. We recommend amiodarone is given after three defibrillation attempts irrespective of whether they are consecutive shocks, or interrupted by CPR and non-shockable rhythms.

Specific guidance concerning the need for resternotomy, and drug timing if the initial stacked shocks are unsuccessful when cardiac arrest occurs after cardiac surgery is addressed in Section 4 – cardiac arrest in special circumstances.[224]

Persistent ventricular fibrillation/pulseless ventricular tachycardia

In VF/pVT persists, consider changing the position of the pads/paddles.[2] Review all potentially reversible causes using the 4 H and 4 T approach (see below) and treat any that are identified. Persistent VF/pVT may be an indication for percutaneous coronary intervention (PCI) – in these cases, a mechanical chest compression device can be used to maintain high-quality chest compressions for transport and PCI.[347] The use of extracorporeal CPR (see below) should also be considered to support the circulation whilst a reversible cause it treated.

Precordial thump

A single precordial thump has a very low success rate for cardioversion of a shockable rhythm.[348–352] Its routine use is therefore not recommended. It may be appropriate therapy only when used without delay whilst awaiting the arrival of a defibrillator in a monitored VF/pVT arrest.[353] Using the ulnar edge of a tightly clenched fist, deliver a sharp impact to the lower half of the sternum from a height of about 20 cm, then retract the fist immediately to create an impulse-like stimulus. There are rare reports of a precordial thump converting a perfusing to a non-perfusing rhythm.[354]

Airway and ventilation

During the treatment of persistent VF, ensure good-quality chest compressions between defibrillation attempts. Consider reversible causes (4 Hs and 4 Ts) and, if identified, correct them. Tracheal intubation provides the most reliable airway, but should be attempted only if the healthcare provider is properly trained and has regular, ongoing experience with the technique. Tracheal intubation must not delay defibrillation attempts. Personnel skilled in advanced airway management should attempt laryngoscopy and intubation without stopping chest compressions; a brief pause in chest compressions may be required as the tube is passed through the vocal cords, but this pause should be less than 5 s. Alternatively, to avoid any interruptions in chest compressions, the intubation attempt

may be deferred until ROSC. No RCTs have shown that tracheal intubation increases survival after cardiac arrest. After intubation, confirm correct tube position and secure it adequately. Ventilate the lungs at 10 breaths min^{-1}; do not hyperventilate the patient. Once the patient's trachea has been intubated, continue chest compressions, at a rate of 100–120 min^{-1} without pausing during ventilation. A pause in the chest compressions causes the coronary perfusion pressure to fall substantially. On resuming compressions, there is some delay before the original coronary perfusion pressure is restored, thus chest compressions that are not interrupted for ventilation (or any reason) result in a substantially higher mean coronary perfusion pressure.

In the absence of personnel skilled in tracheal intubation, a supraglottic airway (SGA) (e.g. laryngeal mask airway, laryngeal tube or i-gel) is an acceptable alternative. Once a SGA has been inserted, attempt to deliver continuous chest compressions, uninterrupted by ventilation.[355] If excessive gas leakage causes inadequate ventilation of the patient's lungs, chest compressions will have to be interrupted to enable ventilation (using a CV ratio of 30:2). Airway interventions for cardiac arrest and the evidence supporting them are described in Section 3f.

Intravenous access and drugs

Peripheral versus central venous drug delivery. Establish intravenous access if this has not already been achieved. Although peak drug concentrations are higher and circulation times are shorter when drugs are injected into a central venous catheter compared with a peripheral cannula,[356] insertion of a central venous catheter requires interruption of CPR and can be technically challenging and associated with complications. Peripheral venous cannulation is quicker, easier to perform and safer. Drugs injected peripherally must be followed by a flush of at least 20 ml of fluid and elevation of the extremity for 10–20 s to facilitate drug delivery to the central circulation.

Intraosseous route. If intravenous access is difficult or impossible, consider the IO route. This is now established as an effective route in adults.[357–365] Intraosseous injection of drugs achieves adequate plasma concentrations in a time comparable with injection through a vein.[366,367] Animal studies suggest that adrenaline reaches a higher concentration and more quickly when it is given intravenously as compared with the intraosseous route, and that the sternal intraosseous route more closely approaches the pharmacokinetic of IV adrenaline.[368] The recent availability of mechanical IO devices has increased the ease of performing this technique.[369] There are a number of intraosseous devices available as well as a choice of insertion sites including the humerus, proximal or distal tibia, and sternum. We have not done a formal review of devices or insertion sites as part of the 2015 Guidelines process. The decision concerning choice of device and insertion site should be made locally and staff adequately trained in its use.

Adrenaline for initial VF/pVT arrest. On the basis of expert consensus, for VF/pVT give adrenaline after the third shock once chest compressions have resumed, and then repeat every 3–5 min during cardiac arrest (alternate cycles). Do not interrupt CPR to give drugs. The use of waveform capnography may enable ROSC to be detected without pausing chest compressions and may be used as a way of avoiding a bolus injection of adrenaline after ROSC has been achieved. If ROSC is suspected during CPR, withhold adrenaline and continue CPR. Give adrenaline if cardiac arrest is confirmed at the next rhythm check.

Despite the widespread use of adrenaline during resuscitation, there is no placebo-controlled study that shows that the routine use of any vasopressor at any stage during human cardiac arrest increases neurologically intact survival to hospital discharge. Further information concerning the role of adrenaline in cardiac arrest is addressed in Section 3g – drugs and fluids during CPR.

Anti-arrhythmic drugs. We recommend that amiodarone should be given after three defibrillation attempts irrespective of whether they are consecutive shocks, or interrupted by CPR, or for recurrent VF/pVT during cardiac arrest. Give amiodarone 300 mg intravenously; a further dose of 150 mg may be given after five defibrillation attempts. Lidocaine 1 mg kg^{-1} may be used as an alternative if amiodarone is not available but do not give lidocaine if amiodarone has been given already. Further information concerning the role of amiodarone in cardiac arrest is addressed in Section 3g – drugs and fluid during CPR.

Non-shockable rhythms (PEA and asystole)

Pulseless electrical activity (PEA) is defined as cardiac arrest in the presence of electrical activity (other than ventricular tachyarrhythmia) that would normally be associated with a palpable pulse.[370] These patients often have some mechanical myocardial contractions, but these are too weak to produce a detectable pulse or blood pressure – this is sometimes described as 'pseudo-PEA' (see below). PEA is often caused by reversible conditions, and can be treated if those conditions are identified and corrected. Survival following cardiac arrest with asystole or PEA is unlikely unless a reversible cause can be found and treated effectively.

If the initial monitored rhythm is PEA or asystole, start CPR 30:2. If asystole is displayed, without stopping CPR, check that the leads are attached correctly. Once an advanced airway has been sited, continue chest compressions without pausing during ventilation. After 2 min of CPR, recheck the rhythm. If asystole is present, resume CPR immediately. If an organised rhythm is present, attempt to palpate a pulse. If no pulse is present (or if there is any doubt about the presence of a pulse), continue CPR.

Give adrenaline 1 mg as soon as venous or intraosseous access is achieved, and repeat every alternate CPR cycle (i.e. about every 3–5 min). If a pulse is present, begin post-resuscitation care. If signs of life return during CPR, check the rhythm and check for a pulse. If ROSC is suspected during CPR withhold adrenaline and continue CPR. Give adrenaline if cardiac arrest is confirmed at the next rhythm check.

Whenever a diagnosis of asystole is made, check the ECG carefully for the presence of P waves, because this may respond to cardiac pacing. There is no benefit in attempting to pace true asystole. In addition, if there is doubt about whether the rhythm is asystole or extremely fine VF, do not attempt defibrillation; instead, continue chest compressions and ventilation. Continuing high-quality CPR however may improve the amplitude and frequency of the VF and improve the chance of successful defibrillation to a perfusing rhythm.[344–346]

The optimal CPR time between rhythm checks may vary according to the cardiac arrest rhythm and whether it is the first or subsequent loop.[371] Based on expert consensus, for the treatment of asystole or PEA, following a 2-min cycle of CPR, if the rhythm has changed to VF, follow the algorithm for shockable rhythms. Otherwise, continue CPR and give adrenaline every 3–5 min following the failure to detect a palpable pulse with the pulse check. If VF is identified on the monitor midway through a 2-min cycle of CPR, complete the cycle of CPR before formal rhythm and shock delivery if appropriate – this strategy will minimise interruptions in chest compressions.

Potentially reversible causes

Potential causes or aggravating factors for which specific treatment exists must be considered during any cardiac arrest. For ease

of memory, these are divided into two groups of four, based upon their initial letter: either H or T. More details on many of these conditions are covered in Section 4 – special circumstances.[224]

The four 'Hs'

Minimise the risk of hypoxia by ensuring that the patient's lungs are ventilated adequately with the maximal possible inspired oxygen during CPR. Make sure there is adequate chest rise and bilateral breath sounds. Using the techniques described in Section 3f, check carefully that the tracheal tube is not misplaced in a bronchus or the oesophagus.

Pulseless electrical activity caused by hypovolaemia is due usually to severe haemorrhage. This may be precipitated by trauma (Section 4),[224] gastrointestinal bleeding or rupture of an aortic aneurysm. Intravascular volume should be restored rapidly with warmed fluid, coupled with urgent surgery to stop the haemorrhage.

Hyperkalaemia, hypokalaemia, hypocalcaemia, acidaemia and other metabolic disorders are detected by biochemical tests (usually by using a blood gas analyser) or suggested by the patient's medical history, e.g. renal failure (Section 4).[224] Intravenous calcium chloride is indicated in the presence of hyperkalaemia, hypocalcaemia and calcium channel-blocker overdose.

Hypothermia should be suspected based on the history such as cardiac arrest associated with drowning (Section 4).[224]

The four 'Ts'

Coronary thrombosis associated with an acute coronary syndrome or ischaemic heart disease is the most common cause of sudden cardiac arrest. An acute coronary syndrome is usually diagnosed and treated after ROSC is achieved. If an acute coronary syndrome is suspected, and ROSC has not been achieved, urgent coronary angiography should be considered when feasible and if required percutaneous coronary intervention. Mechanical chest compression devices and extracorporeal CPR can help facilitate this.

The commonest cause of thromboembolic or mechanical circulatory obstruction is massive pulmonary embolism. The treatment of cardiac arrest with known or suspected pulmonary embolism is addressed in Section 4 including the role of fibrinolysis, surgical or mechanical thrombectomy and extracorporeal CPR.[224]

A tension pneumothorax may be the primary cause of PEA and may be associated with trauma or follow attempts at central venous catheter insertion. The diagnosis is made clinically or by ultrasound. Decompress rapidly by thoracostomy or needle thoracocentesis, and then insert a chest drain. In the context of cardiac arrest from major trauma, consider bilateral thoracostomies for decompression of a suspected tension pneumothorax (Section 4).[224]

Cardiac tamponade is difficult to diagnose because the typical signs of distended neck veins and hypotension are usually obscured by the arrest itself. Cardiac arrest after penetrating chest trauma is highly suggestive of tamponade and is an indication for resuscitative thoracotomy (Section 4).[224] The use of ultrasound will make the diagnosis of cardiac tamponade much more reliable.

In the absence of a specific history, the accidental or deliberate ingestion of therapeutic or toxic substances may be revealed only by laboratory investigations (Section 4).[224] Where available, the appropriate antidotes should be used, but most often treatment is supportive and standard ALS protocols should be followed.

Use of ultrasound imaging during advanced life support

Several studies have examined the use of ultrasound during cardiac arrest to detect potentially reversible causes.[372–374] Although no studies have shown that use of this imaging modality improves outcome, there is no doubt that echocardiography has the potential to detect reversible causes of cardiac arrest. Specific protocols for ultrasound evaluation during CPR may help to identify potentially reversible causes (e.g. cardiac tamponade, pulmonary embolism, hypovolaemia, pneumothorax) and identify pseudo-PEA.[373,375–382] When available for use by trained clinicians, ultrasound may be of use in assisting with diagnosis and treatment of potentially reversible causes of cardiac arrest. The integration of ultrasound into advanced life support requires considerable training if interruptions to chest compressions are to be minimised. A sub-xiphoid probe position has been recommended.[375,381,383] Placement of the probe just before chest compressions are paused for a planned rhythm assessment enables a well-trained operator to obtain views within 10 s.

Absence of cardiac motion on sonography during resuscitation of patients in cardiac arrest is highly predictive of death although sensitivity and specificity has not been reported.[384–387]

Monitoring during advanced life support

There are a number of methods and emerging technologies to monitor the patient during CPR and potentially help guide ALS interventions. These include:

- Clinical signs such as breathing efforts, movements and eye opening can occur during CPR. These can indicate ROSC and require verification by a rhythm and pulse check, but can also occur because CPR can generate a sufficient circulation to restore signs of life including consciousness.[388]
- The use of CPR feedback or prompt devices during CPR is addressed in Section 2 – basic life support.[223] The use of CPR feedback or prompt devices during CPR should only be considered as part of a broader system of care that should include comprehensive CPR quality improvement initiatives [389,390] rather than an isolated intervention.
- Pulse checks when there is an ECG rhythm compatible with an output can be used to identify ROSC, but may not detect pulses in those with low cardiac output states and a low blood pressure.[391] The value of attempting to feel arterial pulses during chest compressions to assess the effectiveness of chest compressions is unclear. A pulse that is felt in the femoral triangle may indicate venous rather than arterial blood flow. There are no valves in the inferior vena cava and retrograde blood flow into the venous system can produce femoral vein pulsations.[392] Carotid pulsation during CPR does not necessarily indicate adequate myocardial or cerebral perfusion.
- ECG monitoring of heart rhythm. Monitoring heart rhythm through pads, paddles or ECG electrodes is a standard part of ALS. Motion artefacts prevent reliable heart rhythm assessment during chest compressions forcing rescuers to stop chest compressions to assess the rhythm, and preventing early recognition of recurrent VF/pVT. Some modern defibrillators have filters that remove artefact from compressions but there are no human studies showing improvements in patient outcomes from their use. We suggest against the routine use of artefact-filtering algorithms for analysis of ECG rhythm during CPR unless as part of a research programme.[393]
- End-tidal carbon dioxide with waveform capnography. The use of waveform capnography during CPR has a greater emphasis in Guidelines 2015 and is addressed in more detail below.
- Blood sampling and analysis during CPR can be used to identify potentially reversible causes of cardiac arrest. Avoid finger prick samples in critical illness because they may not be reliable; instead, use samples from veins or arteries.
- Blood gas values are difficult to interpret during CPR. During cardiac arrest, arterial gas values may be misleading and bear little relationship to the tissue acid-base state.[394] Analysis of central venous blood may provide a better estimation of tissue pH.

Central venous oxygen saturation monitoring during ALS is feasible but its role in guiding CPR is not clear.

- Invasive cardiovascular monitoring in critical care settings, e.g. continuous arterial blood pressure and central venous pressure monitoring. Invasive arterial pressure monitoring will enable the detection of low blood pressure values when ROSC is achieved. Consider aiming for an aortic diastolic pressure of greater than 25 mmHg during CPR by optimising chest compressions.[395] In practice this would mean measuring an arterial diastolic pressure. Although haemodynamic-directed CPR showed some benefit in experimental studies[396–399] there is currently no evidence of improvement in survival with this approach in humans.[4]
- Ultrasound assessment is addressed above to identify and treat reversible causes of cardiac arrest, and identify low cardiac output states ('pseudo-PEA'). Its use has been discussed above.
- Cerebral oximetry using near-infrared spectroscopy measures regional cerebral oxygen saturation (rSO2) non-invasively.[400–402] This remains an emerging technology that is feasible during CPR. Its role in guiding CPR interventions including prognostication during and after CPR is yet to be established.[403]

Waveform capnography during advanced life support

End-tidal carbon dioxide is the partial pressure of carbon dioxide (CO_2) at the end of an exhaled breath. It reflects cardiac output and pulmonary blood flow, as CO_2 is transported by the venous system to the right side of the heart and then pumped to the lungs by the right ventricle, as well as the ventilation minute volume. During CPR, end-tidal CO_2 values are low, reflecting the low cardiac output generated by chest compression. Waveform capnography enables continuous real time end-tidal CO_2 to be monitored during CPR. It works most reliably in patients who have a tracheal tube, but can also be used with a supraglottic airway device or bag mask. There is currently no evidence that use of waveform capnography during CPR results in improved patient outcomes, although the prevention of unrecognised oesophageal intubation is clearly beneficial. The role of waveform capnography during CPR includes:

- Ensuring tracheal tube placement in the trachea (see below for further details).
- Monitoring ventilation rate during CPR and avoiding hyperventilation.
- Monitoring the quality of chest compressions during CPR. End-tidal CO_2 values are associated with compression depth and ventilation rate and a greater depth of chest compression will increase the value.[404] Whether this can be used to guide care and improve outcome requires further study.[295] (Fig. 3.3)
- Identifying ROSC during CPR. An increase in end-tidal CO_2 during CPR may indicate ROSC and prevent unnecessary and potentially harmful dosing of adrenaline in a patient with ROSC.[295,301,338,339] If ROSC is suspected during CPR withhold adrenaline. Give adrenaline if cardiac arrest is confirmed at the next rhythm check.
- Prognostication during CPR. Lower end-tidal CO_2 values may indicate a poor prognosis and less chance of ROSC.[4] Precise values of end-tidal CO_2 depend on several factors including the cause of cardiac arrest, bystander CPR, chest compression quality, ventilation rate and volume, time from cardiac arrest and the use of adrenaline. Values are higher after an initial asphyxial arrest, with bystander CPR and decline over time after cardiac arrest.[295,302,405] Low end-tidal CO_2 values during CPR have been associated with lower ROSC rates and increased mortality, and high values with better ROSC and survival.[295,406,407] Failure to achieve an end-tidal CO_2 value >1.33 kPa (10 mmHg) after 20 min of CPR is associated with a poor outcome in observational studies.[4] In addition it has been used as a criterion for withholding extracorporeal life support in patients with refractory cardiac arrest.[408] The inter-individual differences and influence of cause of cardiac arrest, the problem with self-fulfilling prophecy in studies, our lack of

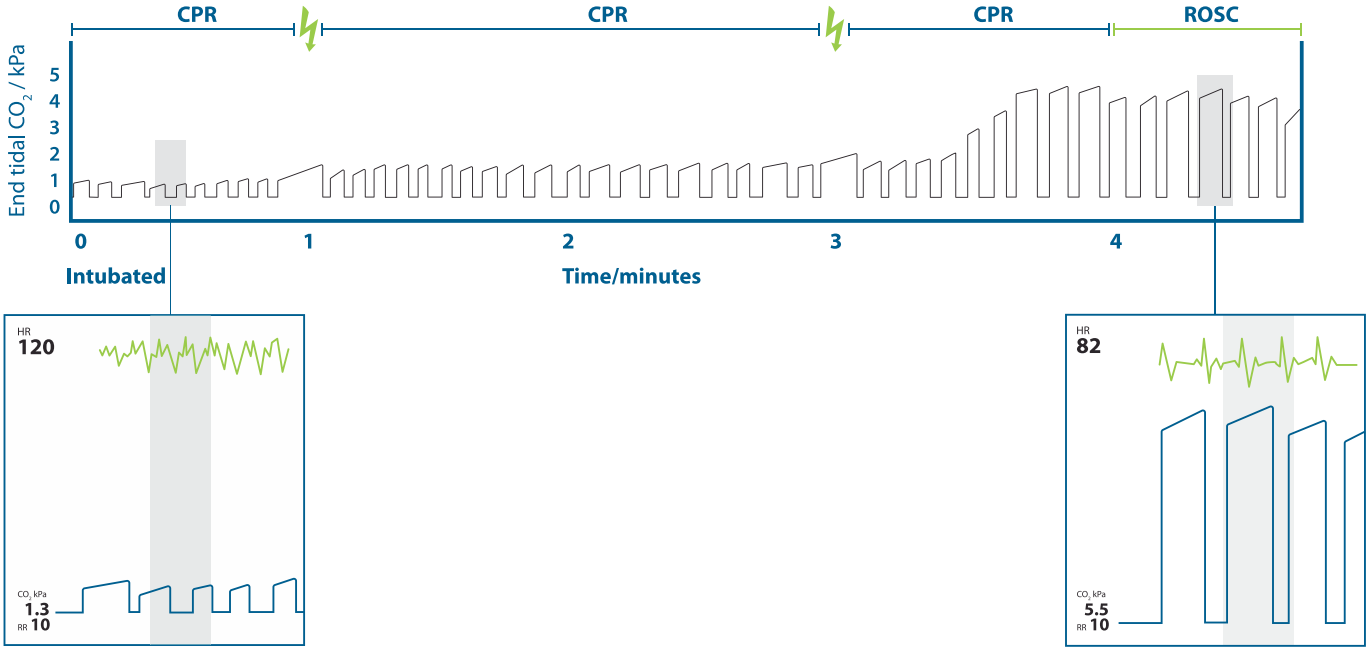


Fig. 3.3. *Waveform capnography* showing changes in the end-tidal carbon dioxide during CPR and after ROSC. The boxes show examples of monitor displays at the times indicated. In this example the patient's trachea is intubated at zero minutes. The patient is then ventilated at 10 breaths min^{-1} and given chest compressions (indicated by CPR) at about two per second. A minute after tracheal intubation, there is pause in chest compressions and ventilation followed by a defibrillation attempt, and chest compressions and ventilation then continue. Higher-quality chest compressions lead to an increased end-tidal carbon dioxide value. There is a further defibrillation attempt after two minutes of chest compressions. There are then further chest compressions and ventilation. There is a significant increase in the end-tidal carbon dioxide value during chest compressions and the patient starts moving and eye opening. Chest compressions are stopped briefly and there is a pulse indicating ROSC. Ventilation continues at 10 breaths min^{-1}. CPR – cardiopulmonary resuscitation; ROSC – return of spontaneous circulation; End tidal CO_2 – end-tidal carbon dioxide; HR – heart rate; RR – respiratory rate.

confidence in the accuracy of measurement during CPR, and the need for an advanced airway to measure end-tidal CO_2 reliably limits our confidence in its use for prognostication. Thus, we recommend that a specific end-tidal CO_2 value at any time during CPR should not be used alone to stop CPR efforts. End-tidal CO_2 values should be considered only as part of a multi-modal approach to decision-making for prognostication during CPR.

Extracorporeal cardiopulmonary resuscitation (eCPR)

Extracorporeal CPR (eCPR) should be considered as a rescue therapy for those patients in whom initial ALS measures are unsuccessful and, or to facilitate specific interventions (e.g. coronary angiography and percutaneous coronary intervention (PCI) or pulmonary thrombectomy for massive pulmonary embolism).[409,410] There is an urgent need for randomised studies of eCPR and large eCPR registries to identify the circumstances in which it works best, establish guidelines for its use and identify the benefits, costs and risks of eCPR.[411,412]

Extracorporeal techniques require vascular access and a circuit with a pump and oxygenator and can provide a circulation of oxygenated blood to restore tissue perfusion. This has the potential to buy time for restoration of an adequate spontaneous circulation, and treatment of reversible underlying conditions. This is commonly called extracorporeal life support (ECLS), and more specifically extracorporeal CPR (eCPR) when used during cardiac arrest. These techniques are becoming more commonplace and have been used for both in-hospital and out-of-hospital despite limited observational data in select patient groups. Observational studies suggest eCPR for cardiac arrest is associated with improved survival when there is a reversible cause for cardiac arrest (e.g. myocardial infarction, pulmonary embolism, severe hypothermia, poisoning), there is little comorbidity, the cardiac arrest is witnessed, the individual receives immediate high-quality CPR, and eCPR is implemented early (e.g. within 1 h of collapse) including when instituted by emergency physicians and intensivists.[413–419] The implementation of eCPR requires considerable resource and training. When compared with manual or mechanical CPR, eCPR has been associated with improve survival after IHCA in selected patients.[413,415] After OHCA outcomes with both standard and eCPR are less favourable.[420] The duration of standard CPR before eCPR is established and patient selection are important factors for success.[409,413,417,419,421–423]

3e – Defibrillation

This section predominantly addresses the use of manual defibrillators. Guidelines concerning the use of an automated external defibrillator (AED) are addressed in Section 2 – Basic Life Support.[223] The defibrillation strategy for the 2015 European Resuscitation Council (ERC) guidelines has changed little from the former guidelines:

- The importance of early, uninterrupted chest compressions remains emphasised throughout these guidelines, together with minimising the duration of pre-shock and post-shock pauses.
- Continue chest compressions during defibrillator charging, deliver defibrillation with an interruption in chest compressions of no more than 5 s and immediately resume chest compressions following defibrillation.
- Self-adhesive defibrillation pads have a number of advantages over manual paddles and should always be used in preference when they are available.
- CPR should be continued while a defibrillator or automated external defibrillator (AED) is retrieved and applied but defibrillation should not be delayed longer than needed to establish the need for defibrillation and charging.
- The use of up to three-stacked shocks may be considered if initial VF/pVT occurs during a witnessed, monitored arrest with a defibrillator immediately available e.g. cardiac catheterisation.
- Although it is recognised that some geographic areas continue to use the older monophasic waveforms, they are not considered in this chapter. When possible, biphasic waveforms should be used in preference to the older monophasic waveform for the treatment of both atrial and ventricular arrhythmias. Defibrillation recommendations in these guidelines apply only to biphasic waveforms. For those using monophasic defibrillators, please refer to Guidelines 2010.[2]
- Defibrillation shock energy levels are unchanged from the 2010 guidelines.[2] For biphasic waveforms (rectilinear biphasic or biphasic truncated exponential), deliver the first shock with an energy of at least 150 J. For pulsed biphasic waveforms, begin at 120–150 J. The shock energy for a particular defibrillator should be based on the manufacturer's guidance. It is important that those using manual defibrillators are aware of the appropriate energy settings for the type of device used. Manufacturers should consider labelling their manual defibrillators with energy level instructions, but in the absence of this and if appropriate energy levels are unknown, for adults use the highest available shock energy for all shocks. With manual defibrillators it is appropriate to consider escalating the shock energy if feasible, after a failed shock and for patients where refibrillation occurs.[326,327]

There are no high-quality clinical studies to indicate the optimal strategies within any given waveform and between different waveforms.[4] Knowledge gaps include the minimal acceptable first-shock energy level; the characteristics of the optimal biphasic waveform; the optimal energy levels for specific waveforms; and the best shock strategy (fixed versus escalating). It is becoming increasingly clear that selected energy is a poor comparator with which to assess different waveforms as impedance-compensation and subtleties in waveform shape result in significantly different transmyocardial current between devices for any given selected energy. The optimal energy levels may ultimately vary between different manufacturers and associated waveforms. Manufacturers are encouraged to undertake high-quality clinical trials to support their defibrillation strategy recommendations.

Strategies for minimising the pre-shock pause

The delay between stopping chest compressions and delivery of the shock (the pre-shock pause) must be kept to an absolute minimum; even 5–10 s delay will reduce the chances of the shock being successful.[328–331,424,425] The pre-shock pause can be reduced to less than 5 s by continuing compressions during charging of the defibrillator and by having an efficient team coordinated by a leader who communicates effectively.[297,426] The safety check to avoid rescuer contact with the patient at the moment of defibrillation should be undertaken rapidly but efficiently. The post shock pause is minimised by resuming chest compressions immediately after shock delivery (see below). The entire process of manual defibrillation should be achievable with less than a 5 s interruption to chest compressions.

Hands-on defibrillation

By allowing continuous chest compressions during the delivery of the defibrillation shock, hands-on defibrillation can minimise peri-shock pause and allow continuation of chest compressions during defibrillation. The benefits of this approach are not proven and further studies are required to assess the safety and efficacy of this technique. A recent study did not observe a benefit when

shocks were delivered without pausing manual or mechanical chest compressions.[427] Standard clinical examination gloves (or bare hands) do not provide a safe level of electrical insulation for hands-on defibrillation.[428]

Safe use of oxygen during defibrillation

In an oxygen-enriched atmosphere, sparking from poorly applied defibrillator paddles can cause a fire and significant burns to a patient.[429–434] The absence of case reports of fires caused by sparking where defibrillation was delivered using self-adhesive defibrillation pads suggests that the latter minimise the risk of electrical arcing and should always be used when possible.

- The risk of fire during attempted defibrillation can be minimised by taking the following precautions:
- Take off any oxygen mask or nasal cannulae and place them at least 1 m away from the patient's chest.
- Leave the ventilation bag connected to the tracheal tube or supraglottic airway, ensuring that there is no residual PEEP remaining in the circuit.
- If the patient is connected to a ventilator, for example in the operating room or critical care unit, leave the ventilator tubing (breathing circuit) connected to the tracheal tube unless chest compressions prevent the ventilator from delivering adequate tidal volumes. In this case, the ventilator is usually substituted by a ventilation bag, which can itself be left connected. If not in use, switch off the ventilator to prevent venting large volumes of oxygen into the room or alternatively connect it to a test lung. During normal use, when connected to a tracheal tube, oxygen from a ventilator in the critical care unit will be vented from the main ventilator housing well away from the defibrillation zone. Patients in the critical care unit may be dependent on positive end expiratory pressure (PEEP) to maintain adequate oxygenation; during cardioversion, when the spontaneous circulation potentially enables blood to remain well oxygenated, it is particularly appropriate to leave the critically ill patient connected to the ventilator during shock delivery.

The technique for electrode contact with the chest

The techniques described below aim to place external defibrillation electrodes (self-adhesive pads) in an optimal position using techniques that minimise transthoracic impedance.

Electrode position

No human studies have evaluated the electrode position as a determinant of ROSC or survival from VF/pVT. Transmyocardial current during defibrillation is likely to be maximal when the electrodes are placed so that the area of the heart that is fibrillating lies directly between them (i.e. ventricles in VF/pVT, atria in AF). Therefore, the optimal electrode position may not be the same for ventricular and atrial arrhythmias.

More patients are presenting with implantable medical devices (e.g. permanent pacemaker, implantable cardioverter defibrillator (ICD)). Medic alert bracelets are recommended for these patients. These devices may be damaged during defibrillation if current is discharged through electrodes placed directly over the device.[435,436] Place the electrode away from the device (at least 8 cm) or use an alternative electrode position (anterior–lateral, anterior–posterior) as described below.[435]

Placement for ventricular arrhythmias and cardiac arrest. Place electrodes (either pads or paddles) in the conventional sternal–apical position. The right (sternal) electrode is placed to the right of the sternum, below the clavicle. The apical paddle is placed in the left mid-axillary line, approximately level with the V6 ECG electrode. This position should be clear of any breast tissue.[437] It is important that this electrode is placed sufficiently laterally. Other acceptable pad positions include

- Placement of each electrode on the lateral chest walls, one on the right and the other on the left side (bi-axillary).
- One electrode in the standard apical position and the other on the right upper back.
- One electrode anteriorly, over the left precordium, and the other electrode posteriorly to the heart just inferior to the left scapula.

It does not matter which electrode (apex/sternum) is placed in either position. The long axis of the apical paddle should be orientated in a cranio-caudal direction to minimise transthoracic impedance.[438]

Placement for atrial arrhythmias. Atrial fibrillation is maintained by functional re-entry circuits anchored in the left atrium. As the left atrium is located posteriorly in the thorax, electrode positions that result in a more posterior current pathway may theoretically be more effective for atrial arrhythmias. Although some studies have shown that antero-posterior electrode placement is more effective than the traditional antero-apical position in elective cardioversion of atrial fibrillation,[439,440] the majority have failed to demonstrate any clear advantage of any specific electrode position.[441–444] Efficacy of cardioversion may be less dependent on electrode position when using biphasic impedance-compensated waveforms.[443–445] The following electrode positions all appear safe and effective for cardioversion of atrial arrhythmias:

- Traditional antero-apical position.
- Antero-posterior position (one electrode anteriorly, over the left precordium, and the other electrode posteriorly to the heart just inferior to the left scapula).

Respiratory phase

Transthoracic impedance varies during respiration, being minimal at end-expiration. If possible, defibrillation should be attempted at this phase of the respiratory cycle. Positive end expiratory pressure (PEEP) increases transthoracic impedance and should be minimised during defibrillation. Auto-PEEP (gas trapping) may be particularly high in asthmatics and may necessitate higher than usual energy levels for defibrillation.[446]

Fibrillation waveform analysis

It is possible to predict, with varying reliability, the success of defibrillation from the fibrillation waveform.[342,343,447–467] If optimal defibrillation waveforms and the optimal timing of shock delivery can be determined in prospective studies, it should be possible to prevent the delivery of unsuccessful high energy shocks and minimise myocardial injury. This technology is under active development and investigation but current sensitivity and specificity is insufficient to enable introduction of VF waveform analysis into clinical practice.

CPR versus defibrillation as the initial treatment

This aspect has been dealt with in detail above in 4b – prehospital resuscitation. Rescuers should provide high-quality CPR while a defibrillator is retrieved, applied and charged. Do not delay defibrillation longer than needed to establish the need for defibrillation and charging. The routine delivery of a pre-specified period of CPR (e.g. 2 or 3 min) before rhythm analysis and a shock is delivered is not recommended.

One shock versus three stacked shock sequence

In 2010, it was recommended that when defibrillation was required, a single shock should be provided with immediate resumption of chest compressions after the shock.[468,469] This recommendation was made for two reasons. Firstly in an attempt to minimise peri-shock interruptions to chest compressions and secondly because it was felt that with the greater efficacy of biphasic shocks, if a biphasic shock failed to defibrillate, a further period of chest compressions could be beneficial.

Studies since 2010 have not shown that any specific shock strategy is of benefit for any survival end-point.[470,471] There is no conclusive evidence that a single shock strategy is of benefit for ROSC or recurrence of VF compared with three stacked shocks, but in view of the evidence suggesting that outcome is improved by minimising interruptions to chest compressions, we continue to recommend single shocks for most situations.

When defibrillation is warranted, give a single shock and resume chest compressions immediately following the shock. Do not delay CPR for rhythm reanalysis or a pulse check immediately after a shock. Continue CPR (30 compressions: 2 ventilations) for 2 min until rhythm reanalysis is undertaken and another shock given (if indicated). Even if the defibrillation attempt is successful, it takes time until the post shock circulation is established[332] and it is very rare for a pulse to be palpable immediately after defibrillation.[333] Patients can remain pulseless for over 2 min and the duration of asystole before ROSC can be longer than 2 min in as many as 25% of successful shocks.[334]

If a patient has a monitored and witnessed cardiac arrest in the catheter laboratory, coronary care unit, a critical care area or whilst monitored after cardiac surgery, and a manual defibrillator is rapidly available:

- Confirm cardiac arrest and shout for help.
- If the initial rhythm is VF/pVT, give up to three quick successive (stacked) shocks.
- Rapidly check for a rhythm change and if appropriate ROSC after each defibrillation attempt.
- Start chest compressions and continue CPR for 2 min if the third shock is unsuccessful.

This three-shock strategy may also be considered for an initial, witnessed VF/pVT cardiac arrest if the patient is already connected to a manual defibrillator. Although there are no data supporting a three-shock strategy in any of these circumstances, it is unlikely that chest compressions will improve the already very high chance of ROSC when defibrillation occurs early in the electrical phase, immediately after onset of VF.

Waveforms

Biphasic waveforms, are now well established as a safe and effective waveform for defibrillation. Biphasic defibrillators compensate for the wide variations in transthoracic impedance by electronically adjusting the waveform magnitude and duration to ensure optimal current delivery to the myocardium, irrespective of the patient's size (impedance compensation). There are two main types of biphasic waveform: the biphasic truncated exponential (BTE) and rectilinear biphasic (RLB). A pulsed biphasic waveform is also in clinical use, in which the current rapidly oscillates between baseline and a positive value before inverting in a negative pattern. It may have a similar efficacy as other biphasic waveforms, but the single clinical study of this waveform was not performed with an impedance compensating waveform, which is used in the commercially available product.[472,473]

We recommend that a biphasic waveform is used for cardioversion of both atrial and ventricular arrhythmias in preference to a monophasic waveform. We place a high value on the reported higher first shock success rate for termination of fibrillation with a biphasic waveform, the potential for less post shock myocardial dysfunction and the existing 2010 Guidelines.[1,2,468,469] We acknowledge that many emergency medical services (EMS) systems and hospitals continue to use older monophasic devices. For those using monophasic defibrillators, please refer to Guidelines 2010.[2]

Energy levels

Defibrillation requires the delivery of sufficient electrical energy to defibrillate a critical mass of myocardium, abolish the wavefronts of VF and enable restoration of spontaneous synchronised electrical activity in the form of an organised rhythm. The optimal energy for defibrillation is that which achieves defibrillation whilst causing the minimum of myocardial damage.[474] Selection of an appropriate energy level also reduces the number of repetitive shocks, which in turn limits myocardial damage.[475]

Optimal energy levels for defibrillation are unknown. The recommendations for energy levels are based on a consensus following careful review of the current literature. Although delivered energy levels are selected for defibrillation, it is the transmyocardial current flow that achieves defibrillation. Current correlates well with successful defibrillation and cardioversion.[476] Defibrillation shock energy levels are unchanged from the 2010 guidelines.[2]

First shock

Relatively few studies have been published in the past five years on which to refine the 2010 guidelines. There is no evidence that one biphasic waveform or device is more effective than another. First shock efficacy of the BTE waveform using 150–200 J has been reported as 86–98%.[477–481] First shock efficacy of the RLB waveform using 120 J is up to 85%.[327] First shock efficacy of a new pulsed biphasic waveform at 130 J showed a first shock success rate of 90%.[472] Two studies have suggested equivalence with lower and higher starting energy biphasic defibrillation.[482,483] Although human studies have not shown harm (raised biomarkers, ECG changes, ejection fraction) from any biphasic waveform up to 360 J,[482,484] several animal studies have suggested the potential for harm with higher energy levels.[485–488]

The initial biphasic shock should be no lower than 120 J for RLB waveforms and at least 150 J for BTE waveforms. Ideally, the initial biphasic shock energy should be at least 150 J for all waveforms. Manufacturers should display the effective waveform dose range on the face of the biphasic defibrillator. If the rescuer is unaware of the recommended energy settings of the defibrillator, use the highest setting for all shocks.

Second and subsequent shocks

The 2010 guidelines recommended either a fixed or escalating energy strategy for defibrillation. Several studies demonstrated that although an escalating strategy reduces the number of shocks required to restore an organised rhythm compared with fixed-dose biphasic defibrillation, and may be needed for successful defibrillation,[326,489] rates of ROSC or survival to hospital discharge are not significantly different between strategies.[482,483] Conversely, a fixed-dose biphasic protocol demonstrated high cardioversion rates (>90%) with a three-shock fixed dose protocol but the small number of cases did not exclude a significant lower ROSC rate for recurrent VF.[490] Several in-hospital studies using an escalating shock energy strategy have demonstrated improvement in cardioversion rates (compared with fixed dose protocols) in non-arrest

rhythms with the same level of energy selected for both biphasic and monophasic waveforms.[491–496]

Animal studies, case reports and small case series have documented the use of two defibrillators to deliver a pair of shocks at the same time ('dual sequential defibrillation') to patients in refractory shockable states.[497–501] Given the very limited evidence, the routine use of dual sequential defibrillation' cannot be recommended.

There remains no evidence to support either a fixed or escalating energy protocol, although an escalating protocol may be associated with a lower incidence of refibrillation (see below). Both strategies are acceptable; however, if the first shock is not successful and the defibrillator is capable of delivering shocks of higher energy it is reasonable to increase the energy for subsequent shocks.

Recurrent ventricular fibrillation (refibrillation). Refibrillation is common and occurs in the majority of patients following initial first-shock termination of VF. Refibrillation was not specifically addressed in 2010 guidelines. Distinct from refractory VF, defined as 'fibrillation that persists after one or more shocks', recurrence of fibrillation is usually defined as 'recurrence of VF during a documented cardiac arrest episode, occurring after initial termination of VF while the patient remains under the care of the same providers (usually out-of-hospital).' Two studies showed termination rates of subsequent refibrillation were unchanged when using fixed 120 J or 150 J shock protocols respectively,[490,502] but a larger study showed termination rates of refibrillation declined when using repeated 200 J shocks, unless an increased energy level (360 J) was selected.[326] In a retrospective analysis, termination rate of VF into a pulse generating rhythm was higher if the VF appeared after a pulse generating rhythm, than after PEA or asystole.[503]

In view of the larger study suggesting benefit from higher subsequent energy levels for refibrillation,[326] we recommend that if a shockable rhythm recurs after successful defibrillation with ROSC, and the defibrillator is capable of delivering shocks of higher energy it is reasonable to increase the energy for subsequent shocks.

Other related defibrillation topics

Cardioversion

If electrical cardioversion is used to convert atrial or ventricular tachyarrhythmias, the shock must be synchronised to occur with the R wave of the electrocardiogram rather than with the T wave: VF can be induced if a shock is delivered during the relative refractory portion of the cardiac cycle.[504] Synchronisation can be difficult in VT because of the wide-complex and variable forms of ventricular arrhythmia. Inspect the synchronisation marker carefully for consistent recognition of the R wave. If needed, choose another lead and/or adjust the amplitude. If synchronisation fails, give unsynchronised shocks to the unstable patient in VT to avoid prolonged delay in restoring sinus rhythm. Ventricular fibrillation or pulseless VT requires unsynchronised shocks. Conscious patients require anaesthesia or sedation, and analgesia before attempting synchronised cardioversion.

Atrial fibrillation. Optimal electrode position has been discussed previously, but anterolateral and anteroposterior are both acceptable positions.[443] Biphasic waveforms are more effective than monophasic waveforms for cardioversion of AF[493,494,505,506]; and cause less severe skin burns.[507] More data are needed before specific recommendations can be made for optimal biphasic energy levels and different biphasic waveforms. Biphasic rectilinear and biphasic truncated exponential waveform show similar high efficacy in the elective cardioversion of atrial fibrillation.[508] Commencing at high energy levels has not shown to result in more successful cardioversion rates compared to lower energy levels.[494,509–514] An initial synchronised shock of 120–150 J, escalating if necessary is a reasonable strategy based on current data.

Atrial flutter and paroxysmal supraventricular tachycardia. Atrial flutter and paroxysmal SVT generally require less energy than atrial fibrillation for cardioversion.[513] Give an initial shock of 70–120 J biphasic. Give subsequent shocks using stepwise increases in energy.[476]

Ventricular tachycardia. The energy required for cardioversion of VT depends on the morphological characteristics and rate of the arrhythmia.[515] Ventricular tachycardia with a pulse responds well using biphasic energy levels of 120–150 J for the initial shock. Consider stepwise increases if the first shock fails to achieve sinus rhythm.[515]

Pacing

Consider pacing in patients with symptomatic bradycardia refractory to anti-cholinergic drugs or other second line therapy. Immediate pacing is indicated especially when the block is at or below the His-Purkinje level. If transthoracic pacing is ineffective, consider transvenous pacing. Whenever a diagnosis of asystole is made, check the ECG carefully for the presence of P waves because this will likely respond to cardiac pacing. The use of epicardial wires to pace the myocardium following cardiac surgery is effective and discussed elsewhere. Do not attempt pacing for asystole unless P waves are present; it does not increase short or long-term survival in- or out-of-hospital.[516–524] For haemodynamically unstable, conscious patients with bradyarrhythmias, percussion pacing as a bridge to electrical pacing may be attempted, although its effectiveness has not been established.[525,526]

Implantable cardioverter defibrillators

Implantable cardioverter defibrillators (ICDs) are becoming increasingly common as the devices are implanted more frequently as the population ages. They are implanted because a patient is considered to be at risk from, or has had, a life-threatening shockable arrhythmia and are usually embedded under the pectoral muscle below the left clavicle (in a similar position to pacemakers, from which they cannot be immediately distinguished). More recently, extravascular devices can be implanted subcutaneously in the left chest wall, with a lead running to the left of the sternum.

On sensing a shockable rhythm, an ICD will discharge approximately 40 J (approximately 80 J for subcutaneous devices) through an internal pacing wire embedded in the right ventricle. On detecting VF/pVT, ICD devices will discharge no more than eight times, but may reset if they detect a new period of VF/pVT. Patients with fractured ICD leads may suffer repeated internal defibrillation as the electrical noise is mistaken for a shockable rhythm; in these circumstances, the patient is likely to be conscious, with the ECG showing a relatively normal rate. A magnet placed over the ICD will disable the defibrillation function in these circumstances.

Discharge of an ICD may cause pectoral muscle contraction in the patient, and shocks to the rescuer have been documented.[527] In view of the low energy levels discharged by conventional ICDs, it is unlikely that any harm will come to the rescuer, but minimising contact with the patient whilst the device is discharging is prudent. Surface current from subcutaneous ICDs is currently under investigation. Cardioverter and pacing function should always be re-evaluated following external defibrillation, both to check the device itself and to check pacing/defibrillation thresholds of the device leads.

Pacemaker spikes generated by devices programmed to unipolar pacing may confuse AED software and emergency personnel,

and may prevent the detection of VF.[528] The diagnostic algorithms of modern AEDs can be insensitive to such spikes.

3f – Airway management and ventilation

Introduction

The optimal strategy for managing the airway has yet to be determined. Several observational studies have challenged the premise that advanced airway interventions (tracheal intubation or supraglottic airways) improve outcomes.[529] Options for airway management and ventilation during CPR include: no airway and no ventilation (compression-only CPR), compression-only CPR with the airway held open (with or without supplementary oxygen), mouth-to-mouth breaths, mouth-to-mask, bag-mask ventilation with simple airway adjuncts, supraglottic airways (SGAs), and tracheal intubation (inserted with the aid of direct laryngoscopy or videolaryngoscopy, or via a SGA). In practice a combination of airway techniques will be used stepwise during a resuscitation attempt.[530] The best airway, or combination of airway techniques will vary according to patient factors, the phase of the resuscitation attempt (during CPR, after ROSC), and the skills of rescuers.[311] A stepwise approach to airway and ventilation management using a combination of techniques is therefore suggested. Compression-only CPR and use of ventilation during basic life support is addressed in Section 2 – Basic Life Support.[223]

Patients requiring resuscitation often have an obstructed airway, usually secondary to loss of consciousness, but occasionally it may be the primary cause of cardiorespiratory arrest. Prompt assessment, with control of the airway and ventilation of the lungs, is essential. This will help to prevent secondary hypoxic damage to the brain and other vital organs. Without adequate oxygenation it may be impossible to achieve ROSC. These principles may not apply to the witnessed primary cardiac arrest in the vicinity of a defibrillator; in this case, the priority is immediate defibrillation.

Airway obstruction

Causes of airway obstruction

Obstruction of the airway may be partial or complete. It may occur at any level, from the nose and mouth down to the trachea. In the unconscious patient, the commonest site of airway obstruction is at the soft palate and epiglottis.[531,532] Obstruction may also be caused by vomit or blood (regurgitation of gastric contents or trauma), or by foreign bodies. Laryngeal obstruction may be caused by oedema from burns, inflammation or anaphylaxis. Upper airway stimulation may cause laryngeal spasm. Obstruction of the airway below the larynx is less common, but may arise from excessive bronchial secretions, mucosal oedema, bronchospasm, pulmonary oedema or aspiration of gastric contents.

Recognition of airway obstruction

Airway obstruction can be subtle and is often missed by healthcare professionals, let alone by laypeople. The 'look, listen and feel' approach is a simple, systematic method of detecting airway obstruction.

- Look for chest and abdominal movements.
- Listen and feel for airflow at the mouth and nose.

In partial airway obstruction, air entry is diminished and usually noisy. Inspiratory stridor is caused by obstruction at the laryngeal level or above. Expiratory wheeze implies obstruction of the lower airways, which tend to collapse and obstruct during expiration. In a patient who is making respiratory efforts, complete airway obstruction causes paradoxical chest and abdominal movement, often described as 'see-saw' breathing. During airway obstruction, other accessory muscles of respiration are used, with the neck and the shoulder muscles contracting to assist movement of the thoracic cage.

Basic airway management

There are three manoeuvres that may improve the patency of an airway obstructed by the tongue or other upper airway structures: head tilt, chin lift, and jaw thrust.

Head tilt and chin lift

The rescuer's hand is placed on the patient's forehead and the head gently tilted back; the fingertips of the other hand are placed under the point of the patient's chin, which is lifted gently to stretch the anterior neck structures.[533–538]

Jaw thrust

Jaw thrust is an alternative manoeuvre for bringing the mandible forward and relieving obstruction by the soft palate and epiglottis. The rescuer's index and other fingers are placed behind the angle of the mandible, and pressure is applied upwards and forwards. Using the thumbs, the mouth is opened slightly by downward displacement of the chin.

Airway management in patients with suspected cervical spine injury

When there is a risk of cervical spine injury, establish a clear upper airway by using jaw thrust or chin lift in combination with manual in-line stabilisation (MILS) of the head and neck by an assistant.[539,540] If life-threatening airway obstruction persists despite effective application of jaw thrust or chin lift, add head tilt in small increments until the airway is open; establishing a patent airway takes priority over concerns about a potential cervical spine injury.

Adjuncts to basic airway techniques

Despite a total lack of published data on the use of nasopharyngeal and oropharyngeal airways during CPR, they are often helpful, and sometimes essential, to maintain an open airway, particularly when resuscitation is prolonged. The position of the head and neck is maintained to keep the airway aligned. Oropharyngeal and nasopharyngeal airways overcome backward displacement of the soft palate and tongue in an unconscious patient, but head tilt and jaw thrust may also be required.

Oropharyngeal airways. Oropharyngeal airways are available in sizes suitable for the newborn to large adults. An estimate of the size required is obtained by selecting an airway with a length corresponding to the vertical distance between the patient's incisors and the angle of the jaw. The most common sizes are 2, 3 and 4 for small, medium and large adults, respectively.

Nasopharyngeal airways. In patients who are not deeply unconscious, a nasopharyngeal airway is tolerated better than an oropharyngeal airway. The nasopharyngeal airway may be life saving in patients with clenched jaws, trismus or maxillofacial injuries, when insertion of an oral airway is impossible. The tubes are sized in millimetres according to their internal diameter and the length increases with diameter. Sizes of 6–7 mm are suitable for adults.

Oxygen during CPR

During CPR, give the maximal feasible inspired oxygen concentration. A self-inflating bag can be connected to a facemask, tracheal tube or supraglottic airway (SGA). Without supplementary oxygen,

the self-inflating bag ventilates the patient's lungs with ambient air (21% oxygen). The delivered oxygen concentration can be increased to about 85% by using a reservoir system and attaching oxygen at a flow 10 l min^{-1}. There are no data to indicate the optimal arterial blood oxygen saturation (SaO_2) during CPR, and no trials comparing different inspired oxygen concentrations. In one observational study of patients receiving 100% inspired oxygen via a tracheal tube during CPR, a higher measured PaO_2 value during CPR was associated with ROSC and hospital admission.[541] The worse outcomes associated with a low PaO_2 during CPR could however be an indication of illness severity. Animal data and observational clinical data indicate an association between high SaO_2 after ROSC and worse outcome (Section 5 – Post-resuscitation care).[273,542–544]

After ROSC, as soon as arterial blood oxygen saturation can be monitored reliably (by blood gas analysis and/or pulse oximetry), titrate the inspired oxygen concentration to maintain the arterial blood oxygen saturation in the range of 94–98%. Avoid hypoxaemia, which is also harmful – ensure reliable measurement of arterial oxygen saturation before reducing the inspired oxygen concentration. This is addressed in further detail in Section 5 – post resuscitation care.[273]

Suction

Use a wide-bore rigid sucker (Yankauer) to remove liquid (blood, saliva and gastric contents) from the upper airway. Use the sucker cautiously if the patient has an intact gag reflex; pharyngeal stimulation can provoke vomiting.

Choking

The initial management of foreign body airway obstruction (choking) is addressed in Section 2 – basic life support.[223] In an unconscious patient with suspected foreign body airway obstruction if initial basic measures are unsuccessful use laryngoscopy and forceps to remove the foreign body under direct vision. To do this effectively requires training.

Ventilation

Advanced Life Support providers should give artificial ventilation as soon as possible for any patient in whom spontaneous ventilation is inadequate or absent. Expired air ventilation (rescue breathing) is effective, but the rescuer's expired oxygen concentration is only 16–17%, so it must be replaced as soon as possible by ventilation with oxygen-enriched air. The pocket resuscitation mask is similar to an anaesthetic facemask, and enables mouth-to-mask ventilation. It has a unidirectional valve, which directs the patient's expired air away from the rescuer. The mask is transparent so that vomit or blood from the patient can be seen. Some masks have a connector for the addition of oxygen. When using masks without a connector, supplemental oxygen can be given by placing the tubing underneath one side and ensuring an adequate seal. Use a two-hand technique to maximise the seal with the patient's face.

High airway pressures can be generated if the tidal volume or inspiratory flow is excessive, predisposing to gastric inflation and subsequent risk of regurgitation and pulmonary aspiration. The risk of gastric inflation is increased by:

- malalignment of the head and neck, and an obstructed airway;
- an incompetent oesophageal sphincter (present in all patients with cardiac arrest);
- a high airway inflation pressure.

Conversely, if inspiratory flow is too low, inspiratory time will be prolonged and the time available to give chest compressions is reduced. Deliver each breath over approximately 1 s, giving a volume that corresponds to normal chest movement; this represents a compromise between giving an adequate volume, minimising the risk of gastric inflation, and allowing adequate time for chest compressions. During CPR with an unprotected airway, give two ventilations after each sequence of 30 chest compressions.

Inadvertent hyperventilation during CPR is common. While this increased intrathoracic pressure[545] and peak airway pressures[546] in small case series in humans, a carefully controlled animal experiment revealed no adverse effects.[547] We suggest a ventilation rate of 10 min^{-1} during continuous chest compressions with an advanced airway based on very limited evidence.[4]

Self-inflating bag

The self-inflating bag can be connected to a facemask, tracheal tube or supraglottic airway (SGA). Without supplementary oxygen, the self-inflating bag ventilates the patient's lungs with ambient air (21% oxygen). The delivered oxygen concentration can be increased to about 85% by using a reservoir system and attaching oxygen at a flow 10 l min^{-1}.

Although a bag-mask enables ventilation with high concentrations of oxygen, its use by a single person requires considerable skill. When used with a face mask, it is often difficult to achieve a gas-tight seal between the mask and the patient's face, and to maintain a patent airway with one hand while squeezing the bag with the other. Any significant leak will cause hypoventilation and, if the airway is not patent, gas may be forced into the stomach.[548,549] This will reduce ventilation further and greatly increase the risk of regurgitation and aspiration.[550] The two-person technique for bag-mask ventilation is preferable. Several recent observational studies and a meta-analysis have documented better outcomes with use of bag-mask ventilation compared with more advanced airways (SGA or tracheal tube).[529,551–554] However, these observation studies are subject to significant bias caused by confounders such as advanced airways not being required in those patients who achieve ROSC and awaken early.

Once a tracheal tube or a SGA has been inserted, ventilate the lungs at a rate of 10 breaths min^{-1} and continue chest compressions without pausing during ventilations. The laryngeal seal achieved with a SGA may not be good enough to prevent at least some gas leaking when inspiration coincides with chest compressions. Moderate gas leakage is acceptable, particularly as most of this gas will pass up through the patient's mouth. If excessive gas leakage results in inadequate ventilation of the patient's lungs, chest compressions will have to be interrupted to enable ventilation, using a compression–ventilation ratio of 30:2.

Passive oxygen delivery

In the presence of a patent airway, chest compressions alone may result in some ventilation of the lungs.[555] Oxygen can be delivered passively, either via an adapted tracheal tube (Boussignac tube),[556,557] or with the combination of an oropharyngeal airway and standard oxygen mask with non-rebreather reservoir.[558] In theory, a SGA can also be used to deliver oxygen passively but this has yet to be studied. One study has shown higher neurologically favourable survival with passive oxygen delivery (oral airway and oxygen mask) compared with bag-mask ventilation after out-of-hospital VF cardiac arrest, but this was a retrospective analysis and is subject to numerous confounders.[558] Until further data are available, passive oxygen delivery without ventilation is not recommended for routine use during CPR.

Alternative airway devices

The tracheal tube has generally been considered the optimal method of managing the airway during cardiac arrest.[309] There is evidence that, without adequate training and experience, the incidence of complications, such as unrecognised

oesophageal intubation (2.4–17% in several studies involving paramedics)[559–563] and dislodgement, is unacceptably high.[564] Prolonged attempts at tracheal intubation are harmful; the cessation of chest compressions during this time will compromise coronary and cerebral perfusion. Several alternative airway devices have been used for airway management during CPR. There are published studies on the use during CPR of the Combitube, the classic laryngeal mask airway (cLMA), the laryngeal tube (LT), the i-gel, and the LMA Supreme (LMAS) but none of these studies have been powered adequately to enable survival to be studied as a primary endpoint; instead, most researchers have studied insertion and ventilation success rates. The SGAs are easier to insert than a tracheal tube and,[565] unlike tracheal intubation, can generally be inserted without interrupting chest compressions.[566]

There are no data supporting the routine use of any specific approach to airway management during cardiac arrest. The best technique is dependent on the precise circumstances of the cardiac arrest and the competence of the rescuer. It is recognised that during cardiac arrest a stepwise approach to airway management is commonly used, which implies that multiple devices may be used during a single resuscitation attempt.

Laryngeal mask airway (LMA)

The original LMA (classic LMA [cLMA]), which is reusable, has been studied during CPR, but none of these studies has compared it directly with the tracheal tube. Although the cLMA remains in common use in elective anaesthetic practice, it has been superseded by several 2nd generation SGAs that have more favourable characteristics, particularly when used for emergency airway management.[567] Most of these SGAs are single use and achieve higher oropharyngeal seal pressures than the cLMA, and some incorporate gastric drain tubes.

Combitube

The Combitube is a double-lumen tube introduced blindly over the tongue, and provides a route for ventilation whether the tube has passed into the oesophagus. There are many studies of the Combitube in CPR and successful ventilation was achieved in 79–98% of patients.[568–576] Two RCTs of the Combitube versus tracheal intubation for out-of-hospital cardiac arrest showed no difference in survival.[575,576] Use of the Combitube is waning and in many parts of the world it is being replaced by other devices such as the LT.

Laryngeal tube

The laryngeal tube (LT) was introduced in 2001; it is known as the King LT airway in the United States. After just 2 h of training, nurses successfully inserted a laryngeal tube and achieved ventilation in 24 of 30 (80%) of OHCAs.[577] In five observational studies, a disposable version of the laryngeal tube (LT-D) was inserted successfully by prehospital personnel in 85–100% of OHCAs (number of cases ranged from 92 to 347).[578–582] Although some studies are supportive of the use of the LT during cardiac arrest several other studies have reported that insertion problems are common; these include problems with positioning and leakage.[580,583]

i-gel

The cuff of the i-gel is made of thermoplastic elastomer gel and does not require inflation; the stem of the i-gel incorporates a bite block and a narrow oesophageal drain tube. It is very easy to insert, requiring only minimal training and a laryngeal seal pressure of 20–24 cmH_2O can be achieved.[584,585] The ease of insertion of the i-gel and its favourable leak pressure make it theoretically very attractive as a resuscitation airway device for those inexperienced in tracheal intubation. In observational studies insertion success rates for the i-gel were 93% ($n = 98$) when used by paramedics for OHCA[586] and 99% ($n = 100$) when used by doctors and nurses for IHCA.[587]

LMA supreme (LMAS). The LMAS is a disposable version of the Proseal LMA, which is used in anaesthetic practice. In an observational study, paramedics inserted the LMAS successfully and were able to ventilate the lungs of 33 (100%) cases of OHCA.[588]

Tracheal intubation

There is insufficient evidence to support or refute the use of any specific technique to maintain an airway and provide ventilation in adults with cardiopulmonary arrest. Despite this, tracheal intubation is perceived as the optimal method of providing and maintaining a clear and secure airway.[309] It should be used only when trained personnel are available to carry out the procedure with a high level of skill and confidence. A systematic review of randomised controlled trials (RCTs) of tracheal intubation versus alternative airway management in acutely ill and injured patients identified just three trials[589]: two were RCTs of the Combitube versus tracheal intubation for out-of-hospital cardiac arrest,[575,576] which showed no difference in survival. The third study was a RCT of prehospital tracheal intubation versus management of the airway with a bag-mask in children requiring airway management for cardiac arrest, primary respiratory disorders and severe injuries.[590] There was no overall benefit for tracheal intubation; on the contrary, of the children requiring airway management for a respiratory problem, those randomised to intubation had a lower survival rate that those in the bag-mask group.

The perceived advantages of tracheal intubation over bag-mask ventilation include: enabling ventilation without interrupting chest compressions[591]; enabling effective ventilation, particularly when lung and/or chest compliance is poor; minimising gastric inflation and therefore the risk of regurgitation; protection against pulmonary aspiration of gastric contents; and the potential to free the rescuer's hands for other tasks. Use of the bag-mask is more likely to cause gastric distension that, theoretically, is more likely to cause regurgitation with risk of aspiration. However, there are no reliable data to indicate that the incidence of aspiration is any more in cardiac arrest patients ventilated with bag-mask versus those that are ventilated via tracheal tube.

The perceived disadvantages of tracheal intubation over bag-valve-mask ventilation include:

- The risk of an unrecognised misplaced tracheal tube – in patients with out-of-hospital cardiac arrest the reliably documented incidence ranges from 0.5% to 17%: emergency physicians–0.5%;[592] paramedics – 2.4%,[559] 6%,[560,561] 9%,[562] 17%.[563]
- A prolonged period without chest compressions while intubation is attempted – in a study of prehospital intubation by paramedics during 100 cardiac arrests the total duration of the interruptions in CPR associated with tracheal intubation attempts was 110 s (IQR 54–198 s; range 13–446 s) and in 25% the interruptions were more than 3 min.[593] Tracheal intubation attempts accounted for almost 25% of all CPR interruptions.
- A comparatively high failure rate. Intubation success rates correlate with the intubation experience attained by individual paramedics.[594] Rates for failure to intubate are as high as 50% in prehospital systems with a low patient volume and providers who do not perform intubation frequently.[595,596]
- Tracheal intubation is a difficult skill to acquire and maintain. In one study, anaesthesia residents required about 125 intubations in the operating room setting before they were able to achieve and intubation success rate of 95%.[597]

Only one study has prospectively compared tracheal intubation with insertion of a SGA in OHCA and this was a feasibility study that is not powered to show differences in survival.[530] A secondary analysis of the North American Resuscitation Outcomes Consortium (ROC) PRIMED study that compared tracheal intubation (n = 8487) with SGAs (LT, Combitube, or LMA; n = 1968) showed that successful tracheal intubation was associated with increased neurologically favourable survival to hospital discharge (adjusted OR 1.40, 95% CI 1.04–1.89) when compared with successful SGA insertion.[598] In a Japanese OHCA study, tracheal intubation (n = 16,054) was compared with the LMA (n = 34,125) and the oesophageal obturator airway (n = 88,069) over a 3-year period.[599] Adjusted ORs for favourable one-month survival were lower for the LMA (0.77, 95% CI 0.64–0.94) and the oesophageal obturator airway (0.81, 95% CI 0.68–0.96) in comparison with tracheal intubation. Even though the data from these two observational studies are risk-adjusted, it is likely that hidden confounders account for the findings.

Healthcare personnel who undertake prehospital intubation should do so only within a structured, monitored programme, which should include comprehensive competency-based training and regular opportunities to refresh skills. Rescuers must weigh the risks and benefits of intubation against the need to provide effective chest compressions. The intubation attempt may require some interruption of chest compressions but, once an advanced airway is in place, ventilation will not require interruption of chest compressions. Personnel skilled in advanced airway management should be able to undertake laryngoscopy without stopping chest compressions; a brief pause in chest compressions will be required only as the tube is passed through the vocal cords. Alternatively, to avoid any interruptions in chest compressions, the intubation attempt may be deferred until ROSC[558,600]; this strategy is being studied in a large prehospital randomised trial.[601] The intubation attempt should interrupt chest compressions for less than 5 s; if intubation is not achievable within these constraints, recommence bag-mask ventilation. After intubation, tube placement must be confirmed and the tube secured adequately.

Videolaryngoscopy

Videolaryngoscopes are being used increasingly in anaesthetic and critical care practice.[602,603] In comparison with direct laryngoscopy, they enable a better view of the larynx and improve the success rate of intubation. Preliminary studies indicate that use of videolaryngoscopes improve laryngeal view and intubation success rates during CPR[604–606] but further data are required before recommendations can be made for wider use during CPR.

Confirmation of correct placement of the tracheal tube

Unrecognised oesophageal intubation is the most serious complication of attempted tracheal intubation. Routine use of primary and secondary techniques to confirm correct placement of the tracheal tube should reduce this risk.

Clinical assessment. Primary assessment includes observation of chest expansion bilaterally, auscultation over the lung fields bilaterally in the axillae (breath sounds should be equal and adequate) and over the epigastrium (breath sounds should not be heard). Clinical signs of correct tube placement (condensation in the tube, chest rise, breath sounds on auscultation of lungs, and inability to hear gas entering the stomach) are not reliable. The reported sensitivity (proportion of tracheal intubations correctly identified) and specificity (proportion of oesophageal intubations correctly identified) of clinical assessment varies: sensitivity 74–100%; specificity 66–100%.[592,607–610]

Secondary confirmation of tracheal tube placement by an exhaled carbon dioxide or oesophageal detection device should reduce the risk of unrecognised oesophageal intubation but the performance of the available devices varies considerably. Furthermore, none of the secondary confirmation techniques will differentiate between a tube placed in a main bronchus and one placed correctly in the trachea.

Oesophageal detector device. The oesophageal detector device creates a suction force at the tracheal end of the tracheal tube, either by pulling back the plunger on a large syringe or releasing a compressed flexible bulb. Air is aspirated easily from the lower airways through a tracheal tube placed in the cartilage-supported rigid trachea. When the tube is in the oesophagus, air cannot be aspirated because the oesophagus collapses when aspiration is attempted. The oesophageal detector device may be misleading in patients with morbid obesity, late pregnancy or severe asthma or when there are copious tracheal secretions; in these conditions the trachea may collapse when aspiration is attempted. Detection of correct placement of a tracheal tube during CPR has been documented in five observational studies[561,611–614] that included 396 patients, and in one randomised study[615] that included 48 patients.[4] The pooled specificity was 92% (95% CI 84–96%), the pooled sensitivity was 88% (95% CI 84–192%), and the false positive rate was 0.2% (95% CI, 0–0.6%). One observational study showed no statistically significant difference between the performance of a bulb (sensitivity 71%, specificity 100%) and a syringe (sensitivity 73%, specificity 100%) type oesophageal detection devices in the detection of tracheal placement of a tracheal tube.[615]

Thoracic impedance. There are smaller changes in thoracic impedance with oesophageal ventilations than with ventilation of the lungs.[616–618] Changes in thoracic impedance may be used to detect ventilation[619] and oesophageal intubation[591,620] during cardiac arrest. It is possible that this technology can be used to measure tidal volume during CPR. The role of thoracic impedance as a tool to detect tracheal tube position and adequate ventilation during CPR is undergoing further research but is not yet ready for routine clinical use.

Ultrasound for tracheal tube detection. Three observational studies including 254 patients in cardiac arrest have documented the use of ultrasound to detect tracheal tube placement.[621–623] The pooled specificity was 90% (95% CI 68–98%), the sensitivity was 100% (95% CI 98–100%), and the FPR was 0.8% (95% CI 0.2–2.6%).

Carbon dioxide detectors. Carbon dioxide (CO_2) detector devices measure the concentration of exhaled carbon dioxide from the lungs. The persistence of exhaled CO_2 after six ventilations indicates placement of the tracheal tube in the trachea or a main bronchus.[592] Confirmation of correct placement above the carina will require auscultation of the chest bilaterally in the mid-axillary lines. Broadly, there three types of carbon dioxide detector device:

(1) Disposable colorimetric end-tidal carbon dioxide ($ETCO_2$) detectors use a litmus paper to detect CO_2, and these devices generally give readings of purple ($ETCO_2$ < 0.5%), tan ($ETCO_2$ 0.5–2%) and yellow ($ETCO_2$ > 2%). In most studies, tracheal placement of the tube is considered verified if the tan colour persists after a few ventilations. Seven observational studies[592,614,624–628] including 1119 patients have evaluated the diagnostic accuracy of colorimetric CO_2 devices in cardiac arrest patients.[4] The specificity was 97% (95% CI 84–99%), the sensitivity was 87% (95% CI 85–89%), and the FPR was 0.3% (0–1%). Although colorimetric CO_2 detectors identify placement in patients with good perfusion quite well, these devices are less accurate than clinical assessment in cardiac arrest patients

because pulmonary blood flow may be so low that there is insufficient exhaled carbon dioxide. Furthermore, if the tracheal tube is in the oesophagus, six ventilations may lead to gastric distension, vomiting and aspiration.

(2) Non-waveform electronic digital $ETCO_2$ devices generally measure $ETCO_2$ using an infrared spectrometer and display the results with a number; they do not provide a waveform graphical display of the respiratory cycle on a capnograph. Five studies of these devices for identification of tracheal tube position in cardiac arrest document 70–100% sensitivity and 100% specificity.[592,609,614,627,629,630]

(3) End-tidal CO_2 detectors that include a waveform graphical display (capnographs) are the most reliable for verification of tracheal tube position during cardiac arrest. Two studies of waveform capnography to verify tracheal tube position in victims of cardiac arrest demonstrate 100% sensitivity and 100% specificity in identifying correct tracheal tube placement.[592,631] One observational study showed that the use of waveform capnography compared with no waveform capnography in 153 critically-ill patients (51 with cardiac arrest) decreased the occurrence of unrecognised oesophageal intubation on hospital arrival from 23% to 0% (OR 29; 95% CI 4–122).[631] Three observational studies with 401 patients[592,607,613] and one randomised study[615] including 48 patients showed that the specificity for waveform capnography to detect correct tracheal placement was 100% (95% CI 87–100%). The sensitivity was 100% in one study when waveform capnography was used in the pre-hospital setting immediately after intubation, and oesophageal intubation was less common than the average (1.5%).[592,607] The sensitivity was between 65% to 68% in the other three studies when the device was used in OHCA patients after intubation in the emergency department (ED).[607,613,615] The difference may be related to prolonged resuscitation with compromised or non-existent pulmonary blood flow. Based on the pooled sensitivity/specificity from these studies and assumed oesophageal intubation prevalence of 4.5%, the false positive rate (FPR) of waveform capnography was 0% (95% CI 0–0.6%).

Based on the available data, the accuracy of colorimetric CO_2 detectors, oesophageal detector devices and non-waveform capnometers does not exceed the accuracy of auscultation and direct visualisation for confirming the tracheal position of a tube in victims of cardiac arrest. Waveform capnography is the most sensitive and specific way to confirm and continuously monitor the position of a tracheal tube in victims of cardiac arrest and must supplement clinical assessment (auscultation and visualisation of tube through cords). Waveform capnography will not discriminate between tracheal and bronchial placement of the tube – careful auscultation is essential. Existing portable monitors make capnographic initial confirmation and continuous monitoring of tracheal tube position feasible in almost all settings, including out-of-hospital, emergency department and in-hospital locations where intubation is performed.

The ILCOR ALS Task Force recommends using waveform capnography to confirm and continuously monitor the position of a tracheal tube during CPR in addition to clinical assessment (strong recommendation, low quality evidence). Waveform capnography is given a strong recommendation as it may have other potential uses during CPR (e.g. monitoring ventilation rate, assessing quality of CPR). The ILCOR ALS Task Force recommends that if waveform capnography is not available, a non-waveform carbon dioxide detector, oesophageal detector device or ultrasound in addition to clinical assessment is an alternative (strong recommendation, low quality evidence).

Cricoid pressure

The routine use of cricoid pressure in cardiac arrest is not recommended. If cricoid pressure is used during cardiac arrest, the pressure should be adjusted, relaxed or released if it impedes ventilation or intubation.

In non-arrest patients cricoid pressure may offer some measure of protection to the airway from aspiration but it may also impede ventilation or interfere with intubation. The role of cricoid pressure during cardiac arrest has not been studied. Application of cricoid pressure during bag-mask ventilation reduces gastric inflation.[632–635]

Studies in anaesthetised patients show that cricoid pressure impairs ventilation in many patients, increases peak inspiratory pressures and causes complete obstruction in up to 50% of patients depending on the amount of cricoid pressure (in the range of recommended effective pressure) that is applied.[632,633,636–641]

Securing the tracheal tube

Accidental dislodgement of a tracheal tube can occur at any time, but may be more likely during resuscitation and during transport. The most effective method for securing the tracheal tube has yet to be determined; use either conventional tapes or ties, or purpose-made tracheal tube holders.

Cricothyroidotomy

Occasionally it will be impossible to ventilate an apnoeic patient with a bag-mask, or to pass a tracheal tube or alternative airway device. This may occur in patients with extensive facial trauma or laryngeal obstruction caused by oedema or foreign material. In these circumstances, delivery of oxygen through a needle or surgical cricothyroidotomy may be life-saving. A tracheostomy is contraindicated in an emergency, as it is time consuming, hazardous and requires considerable surgical skill and equipment.

Surgical cricothyroidotomy provides a definitive airway that can be used to ventilate the patient's lungs until semi-elective intubation or tracheostomy is performed. Needle cricothyroidotomy is a much more temporary procedure providing only short-term oxygenation. It requires a wide-bore, non-kinking cannula, a high-pressure oxygen source, runs the risk of barotrauma and can be particularly ineffective in patients with chest trauma. It is also prone to failure because of kinking of the cannula, and is unsuitable for patient transfer. In the 4th National Audit Project of the UK Royal College of Anaesthetists and the Difficult Airway Society NAP4, 60% of needle cricothyroidotomies attempted in the intensive care unit (ICU), and elsewhere, failed.[642] In contrast, all surgical cricothyroidotomies achieved access to the trachea. While there may be several underlying causes, these results indicate a need for more training in surgical cricothyroidotomy and this should include regular manikin-based training using locally available equipment.[643]

Summary of airway management for cardiac arrest

The ILCOR ALS Task Force has suggested using either an advanced airway (tracheal intubation or SGA) or a bag-mask for airway management during CPR.[4] This very broad recommendation is made because of the total absence of high quality data to indicate which airway strategy is best.

The type of airway used may depend on the skills and training of the healthcare provider. In comparison with bag-mask ventilation and use of a SGA, tracheal intubation requires considerably more training and practice and may result in unrecognised oesophageal intubation and increased hands-off time. A bag-mask, a SGA and a tracheal tube are frequently used in the same patient as part of a stepwise approach to airway management but this has not been formally assessed. Patients who remain comatose after initial

resuscitation from cardiac arrest will ultimately require tracheal intubation regardless of the airway technique used during cardiac arrest. Anyone attempting tracheal intubation must be well trained and equipped with waveform capnography. In the absence of these prerequisites, consider use of bag-mask ventilation and/or an SGA until appropriately experience and equipped personnel are present.

There are very few data relating to airway management during in-hospital cardiac arrest and it is necessary to extrapolate from data derived from out-of-hospital cardiac arrest. On this basis, the principles discussed above apply equally to in-hospital cardiac arrest.

3g – Drugs and fluids for cardiac arrest

This topic is divided into: drugs used during the management of a cardiac arrest; anti-arrhythmic drugs used in the peri-arrest period; other drugs used in the peri-arrest period; and fluids. Every effort has been made to provide accurate information on the drugs in these guidelines, but literature from the relevant pharmaceutical companies will provide the most up-to-date data.

There are three groups of drugs relevant to the management of cardiac arrest that were reviewed during the 2015 Consensus Conference: vasopressors, anti-arrhythmics and other drugs.[4] The systematic reviews found insufficient evidence to comment on critical outcomes such as survival to discharge and survival to discharge with good neurological outcome with either vasopressors or anti-arrhythmic drugs. There was also insufficient evidence to comment on the best time to give drugs to optimise outcome. Thus, although drugs are still included among ALS interventions, they are of secondary importance to high-quality uninterrupted chest compressions and early defibrillation. As an indicator of equipoise regarding the use of drugs during ALS, two large RCTs (adrenaline versus placebo [ISRCTN73485024], and amiodarone versus lidocaine versus placebo[312] [NCT01401647] are currently ongoing.

Vasopressors

Despite the continued widespread use of adrenaline and the use of vasopressin during resuscitation in some countries, there is no placebo-controlled study that shows that the routine use of any vasopressor during human cardiac arrest increases survival to hospital discharge, although improved short-term survival has been documented.[305,306,308] The primary goal of CPR is to re-establish blood flow to vital organs until the restoration of spontaneous circulation. Despite the lack of data from cardiac arrest in humans, vasopressors continue to be recommended as a means of increasing cerebral and coronary perfusion pressure during CPR.

Adrenaline (epinephrine) versus no adrenaline

One randomised, placebo-controlled trial on patients with out-of-hospital cardiac arrest from all rhythms showed that administration of standard-dose adrenaline was associated with significantly higher rates of prehospital ROSC (relative risk [RR] 2.80 [95% CI 1.78–4.41], $p < 0.00001$) and survival to hospital admission (RR 1.95 [95% CI 1.34–2.84], $p = 0.0004$) when compared to placebo.[308] There was no difference in survival to hospital discharge (RR 2.12 [95% CI 0.75–6.02], $p = 0.16$) or good neurological outcome, defined as Cerebral Performance Categories (CPC) 1 or 2 (RR 1.73, [95% CI 0.59–5.11], $p = 0.32$). The trial, however, was stopped early and included only 534 subjects.

Another trial randomised 851 patients with out-of-hospital cardiac arrest to receive advanced life support with or without intravenous drug administration. Results of this trial showed that administration of intravenous drugs was associated with significantly higher rates of prehospital ROSC (40% vs. 25%; $p < 0.001$) and admission to hospital (43% vs. 29%; $p < 0.001$).[305] However, the rates of survival to hospital discharge did not differ (10.5 vs.9.2; $p = 0.61$). The effect on ROSC was most prominent and only significant in the non-shockable group.[305] In a post-hoc analysis comparing patients who were given adrenaline vs. not given adrenaline, the OR of being admitted to hospital was higher with adrenaline, but the likelihood of being discharged from hospital alive and surviving with favourable neurological outcome was reduced [OR for adrenaline vs. no-adrenaline were 2.5 (95% CI 1.9–3.4), 0.5 (95% CI 0.3–0.8) and 0.4 (95% CI 0.2–0.7) respectively].[644]

A series of observational studies on large cohorts of out-of-hospital cardiac arrest patients have compared the outcomes of patients who were administered adrenaline with those of patients who did not receive adrenaline. Adjustments were made using logistic regression and propensity matching. A study conducted in Japan which included a total of 417,188 patients (13,401 of whom were propensity-matched) showed that use of prehospital adrenaline was significantly associated with increased odds of ROSC before hospital arrival (adjusted OR 2.36 [95% CI 2.22–2.50]) but decreased chance of survival (0.46 [95%CI 0.42–0.51]) and good functional outcome (0.31 [95% CI 0.26–0.36]) at one month after the arrest.[645] Conversely, another Japanese study conducted on 11,048 propensity-matched, bystander-witnessed arrests showed that prehospital administration of adrenaline was associated with significantly higher rates of overall survival and, for patients with non-shockable rhythms, it was also associated with significantly higher odds of neurologically intact survival (adjusted OR 1.57 [95% CI 1.04–2.37]).[646] However, the absolute increase of neurologically intact survival in this last group of patients was minimal (0.7% vs. 0.4%). Finally, in a recent study in France on 1556 cardiac arrest patients who achieved ROSC and were admitted to hospital, administration of adrenaline was associated with significantly lower odds of neurologically intact survival.[647]

There is an increasing concern about the potential detrimental effects of adrenaline. While its alpha-adrenergic, vasoconstrictive effects cause systemic vasoconstriction, which increases macrovascular coronary and cerebral perfusion pressures, its beta-adrenergic actions (inotropic, chronotropic) may increase coronary and cerebral blood flow, but with concomitant increases in myocardial oxygen consumption, ectopic ventricular arrhythmias (particularly when the myocardium is acidotic), transient hypoxaemia from pulmonary arteriovenous shunting, impaired microcirculation,[648] and worse post-cardiac arrest myocardial dysfunction.[649,650] Experimental evidence suggests that epinephrine also impairs cerebral microcirculation.[651] In retrospective secondary analyses, adrenaline use is associated with more rhythm transitions during ALS, both during VF[652] and PEA.[325]

Two systematic reviews of adrenaline for OHCA indicate rates of ROSC are increased with adrenaline but good long-term survival (survival to discharge and neurological outcome) is either no better, or worse.[653,654]

The optimal dose of adrenaline is not known, and there are no human data supporting the use of repeated doses. In fact, increasing cumulative dose of epinephrine during resuscitation of patients with asystole and PEA is an independent risk factor for unfavourable functional outcome and in-hospital mortality.[655]

Our current recommendation is to continue the use of adrenaline during CPR as for Guidelines 2010. We have considered the benefit in short-term outcomes (ROSC and admission to hospital) and our uncertainty about the benefit or harm on survival to discharge and neurological outcome given the limitations of the observational studies.[4,653,654] We have decided not to change current practice until there is high-quality data on long-term outcomes. Dose response and placebo-controlled efficacy trials are needed to evaluate the use of adrenaline in cardiac arrest. We are aware of an ongoing randomised study of adrenaline vs.

placebo for OHCA in the UK (PARAMEDIC 2: The Adrenaline Trial, ISRCTN73485024).

Adrenaline (epinephrine) versus vasopressin

The potentially deleterious beta-effects of adrenaline have led to exploration of alternative vasopressors. Vasopressin is a naturally occurring antidiuretic hormone. In very high doses it is a powerful vasoconstrictor that acts by stimulation of smooth muscle V1 receptors. Vasopressin has neither chronotropic nor inotropic effects on the heart. In comparison with adrenaline it has a longer half-life (10–20 min vs. 4 min) and it is potentially more effective during acidosis.[656,657] Vasopressin has been proposed as an alternative to adrenaline in cardiac arrest, based on the finding that its levels were significantly higher in successfully resuscitated patients than in patients who died.[658] However, a trial comparing up to four doses of either 40 IU vasopressin or 1 mg adrenaline every 5–10 min in patients with out of hospital cardiac arrest did not demonstrate any significant difference in terms of survival to hospital discharge or neurological outcome between the two study arms.[659] This trial had serious methodological issues and included a small number of patients.

A series of randomised controlled trials[660–664] demonstrated no difference in outcomes (ROSC, survival to discharge, or neurological outcome) with vasopressin versus adrenaline as a first line vasopressor in cardiac arrest. Other studies comparing adrenaline alone or in combination with vasopressin also demonstrated no difference in ROSC, survival to discharge or neurological outcome.[665–667] There are no alternative vasopressors that provide survival benefit during cardiac arrest resuscitation when compared with adrenaline.

We suggest vasopressin should not be used in cardiac arrest instead of adrenaline. Those healthcare professionals working in systems that already use vasopressin may continue to do so because there is no evidence of harm from using vasopressin when compared to adrenaline.[4]

Steroids

Two studies suggest that a bundled regimen of adrenaline, vasopressin and methylprednisolone improved survival after in-hospital cardiac arrest. In a single-centre randomised, placebo-controlled trial in patients with in-hospital cardiac arrest, a combination of vasopressin 20 IU and adrenaline 1 mg per CPR cycle for the first 5 CPR cycles *plus* methylprednisolone 40 mg at the first CPR cycle *plus* hydrocortisone 300 mg in case of post-resuscitation shock was associated with significantly higher rates of ROSC (39/48 [81%] vs. 27 of 52 [52%]; $p = 0.003$) and survival to hospital discharge (9 [19%] vs. 2 [4%]; $p = 0.02$) than conventional treatment.[668] These results were confirmed by a subsequent three-centre trial including a total of 300 patients from the same group of investigators.[669] This last trial also showed significantly higher odds of survival with good neurological outcome (CPC = 1–2) (OR 3.28, 95% CI 1.17–9.20; $p = 0.02$).

The population in these studies had very rapid advanced life support, a high incidence of asystolic cardiac arrest and low baseline survival compared to other in-hospital studies. Thus the findings of these studies are not generalisable to all cardiac arrests and we suggest that steroids are not used routinely for cardiac arrest.[4]

Adrenaline

Indications. Adrenaline is:

- the first drug used in cardiac arrest of any cause: it is included in the ALS algorithm for use every 3–5 min of CPR (alternate cycles).
- preferred in the treatment of anaphylaxis (Section 4).[224]
- a second-line treatment for cardiogenic shock.

Dose during CPR. During cardiac arrest, the initial IV/IO dose of adrenaline is 1 mg. There are no studies showing improvement in survival or neurological outcomes with higher doses of adrenaline for patients in refractory cardiac arrest.[4]

Following ROSC, even small doses of adrenaline (50–100 μg) may induce tachycardia, myocardial ischaemia, VT and VF. Once a perfusing rhythm is established, if further adrenaline is deemed necessary, titrate the dose carefully to achieve an appropriate blood pressure. Intravenous doses of 50 μg are usually sufficient for most hypotensive patients.

Use. Adrenaline is available most commonly in two dilutions:

- 1 in 10,000 (10 ml of this solution contains 1 mg of adrenaline)
- 1 in 1000 (1 ml of this solution contains 1 mg of adrenaline).

Both these dilutions are used routinely in Europe.

Anti-arrhythmics

As with vasopressors, the evidence that anti-arrhythmic drugs are of benefit in cardiac arrest is limited. No anti-arrhythmic drug given during human cardiac arrest has been shown to increase survival to hospital discharge, although amiodarone has been shown to increase survival to hospital admission.[670,671] Despite the lack of human long-term outcome data, the balance of evidence is in favour of the use anti-arrhythmic drugs for the management of arrhythmias in cardiac arrest. There is an ongoing trial comparing amiodarone to lidocaine and to placebo designed and powered to evaluate for functional survival.[312]

Amiodarone

Amiodarone is a membrane-stabilising anti-arrhythmic drug that increases the duration of the action potential and refractory period in atrial and ventricular myocardium. Atrioventricular conduction is slowed, and a similar effect is seen with accessory pathways. Amiodarone has a mild negative inotropic action and causes peripheral vasodilation through non-competitive alpha-blocking effects. The hypotension that occurs with intravenous amiodarone is related to the rate of delivery and is due more to the solvent (Polysorbate 80 and benzyl alcohol), which causes histamine release, rather than the drug itself.[672] A premixed formulation of intravenous amiodarone (PM101) that does not contain Polysorbate 80 and uses a cyclodextrin to maintain amiodarone in the aqueous phase is available in the United States.[673]

Following three initial shocks, amiodarone in shock-refractory VF improves the short-term outcome of survival to hospital admission compared with placebo[670] or lidocaine.[671] Amiodarone also appears to improve the response to defibrillation when given to humans or animals with VF or haemodynamically unstable ventricular tachycardia.[674–678] There is no evidence to indicate the optimal time at which amiodarone should be given when using a single-shock strategy. In the clinical studies to date, the amiodarone was given if VF/pVT persisted after at least three shocks. For this reason, and in the absence of any other data, amiodarone 300 mg is recommended if VF/pVT persists after three shocks.

Indications. Amiodarone is indicated in:

- refractory VF/pVT
- haemodynamically stable ventricular tachycardia (VT) and other resistant tachyarrhythmias (Section 11).

Dose during CPR. We recommend that an initial intravenous dose of 300 mg amiodarone, diluted in 5% glucose (or other suitable solvent) to a volume of 20 ml (or from a pre-filled syringe) should

be given after three defibrillation attempts irrespective of whether they are consecutive shocks, or interrupted by CPR, or for recurrent VF/pVT during cardiac arrest. A further dose of 150 mg may be given after five defibrillation attempts. Amiodarone can cause thrombophlebitis when injected into a peripheral vein; use a central vein if a central venous catheter is *in situ* but, if not, use a large peripheral vein or the IO route followed by a generous flush.

Clinical aspects of use. Amiodarone may paradoxically be arrhythmogenic, especially if given concurrently with drugs that prolong the QT interval. However, it has a lower incidence of pro-arrhythmic effects than other anti-arrhythmic drugs under similar circumstances. The major acute adverse effects from amiodarone are hypotension and bradycardia in patients with ROSC, and can be treated with fluids and/or inotropic drugs. The side effects associated with prolonged oral use (abnormalities of thyroid function, corneal microdeposits, peripheral neuropathy, and pulmonary/hepatic infiltrates) are not relevant in the acute setting.

Lidocaine

Lidocaine is recommended for use during ALS when amiodarone is unavailable.[671] Lidocaine is a membrane-stabilising anti-arrhythmic drug that acts by increasing the myocyte refractory period. It decreases ventricular automaticity, and its local anaesthetic action suppresses ventricular ectopic activity. Lidocaine suppresses activity of depolarised, arrhythmogenic tissues while interfering minimally with the electrical activity of normal tissues. Therefore, it is effective in suppressing arrhythmias associated with depolarisation (e.g. ischaemia, digitalis toxicity) but is relatively ineffective against arrhythmias occurring in normally polarised cells (e.g. atrial fibrillation/flutter). Lidocaine raises the threshold for VF.

Lidocaine toxicity causes paraesthesia, drowsiness, confusion and muscular twitching progressing to convulsions. It is considered generally that a safe dose of lidocaine must not exceed 3 mg kg^{-1} over the first hour. If there are signs of toxicity, stop the infusion immediately; treat seizures if they occur. Lidocaine depresses myocardial function, but to a much lesser extent than amiodarone. The myocardial depression is usually transient and can be treated with intravenous fluids or vasopressors.

Indications. Lidocaine is indicated in refractory VF/pVT (when amiodarone is unavailable).

Dose. When amiodarone is unavailable, consider an initial dose of 100 mg (1–1.5 mg kg^{-1}) of lidocaine for VF/pVT refractory to three shocks. Give an additional bolus of 50 mg if necessary. The total dose should not exceed 3 mg kg^{-1} during the first hour.

Clinical aspects of use. Lidocaine is metabolised by the liver, and its half-life is prolonged if the hepatic blood flow is reduced, e.g. in the presence of reduced cardiac output, liver disease or in the elderly. During cardiac arrest normal clearance mechanisms do not function, thus high plasma concentrations may be achieved after a single dose. After 24 h of continuous infusion, the plasma half-life increases significantly. Reduce the dose in these circumstances, and regularly review the indication for continued therapy. Lidocaine is less effective in the presence of hypokalaemia and hypomagnesaemia, which should be corrected immediately.

Magnesium

We recommend magnesium is not routinely used for the treatment of cardiac arrest. Studies in adults in and out of hospital have failed to demonstrate any increase in the rate of ROSC when magnesium is given routinely during CPR.[679–684]

Magnesium is an important constituent of many enzyme systems, especially those involved with ATP generation in muscle. It plays a major role in neurochemical transmission, where it decreases acetylcholine release and reduces the sensitivity of the motor endplate. Magnesium also improves the contractile response of the stunned myocardium, and limits infarct size by a mechanism that has yet to be fully elucidated.[685] The normal plasma range of magnesium is 0.8–1.0 mmol l^{-1}.

Hypomagnesaemia is often associated with hypokalaemia, and may contribute to arrhythmias and cardiac arrest. Hypomagnesaemia increases myocardial digoxin uptake and decreases cellular Na^+/K^+-ATP-ase activity. In patients with hypomagnesaemia, hypokalaemia, or both digitalis may become cardiotoxic even with therapeutic digitalis levels. Magnesium deficiency is not uncommon in hospitalised patients and frequently coexists with other electrolyte disturbances, particularly hypokalaemia, hypophosphataemia, hyponatraemia and hypocalcaemia.

Give an initial intravenous dose of 2 g (4 ml (8 mmol)) of 50% magnesium sulphate); it may be repeated after 10–15 min. Preparations of magnesium sulphate solutions differ among European countries.

Clinical aspects of use. Hypokalaemic patients are often hypomagnesaemic. If ventricular tachyarrhythmias arise, intravenous magnesium is a safe, effective treatment. Magnesium is excreted by the kidneys, but side effects associated with hypermagnesaemia are rare, even in renal failure. Magnesium inhibits smooth muscle contraction, causing vasodilation and a dose-related hypotension, which is usually transient and responds to intravenous fluids and vasopressors.

Calcium

Calcium plays a vital role in the cellular mechanisms underlying myocardial contraction. There is no data supporting any beneficial action for calcium after most cases of cardiac arrest[686–691]; conversely, other studies have suggested a possible adverse effect when given routinely during cardiac arrest (all rhythms).[692,693] High plasma concentrations achieved after injection may be harmful to the ischaemic myocardium and may impair cerebral recovery. Give calcium during resuscitation only when indicated specifically, i.e. in pulseless electrical activity caused by:

- hyperkalaemia
- hypocalcaemia
- overdose of calcium channel-blocking drugs.

The initial dose of 10 ml 10% calcium chloride (6.8 mmol Ca^{2+}) may be repeated if necessary. Calcium can slow the heart rate and precipitate arrhythmias. In cardiac arrest, calcium may be given by rapid intravenous injection. In the presence of a spontaneous circulation give it slowly. Do not give calcium solutions and sodium bicarbonate simultaneously by the same route to avoid precipitation.

Buffers

Cardiac arrest results in combined respiratory and metabolic acidosis because pulmonary gas exchange ceases and cellular metabolism becomes anaerobic. The best treatment of acidaemia in cardiac arrest is CPR. During cardiac arrest, arterial gas values may be misleading and bear little relationship to the tissue acid-base state[394]; analysis of central venous blood may provide a better estimation of tissue pH. Bicarbonate causes generation of carbon dioxide, which diffuses rapidly into cells. It has the following effects.

- It exacerbates intracellular acidosis.
- It produces a negative inotropic effect on ischaemic myocardium.
- It presents a large, osmotically active, sodium load to an already compromised circulation and brain.
- It produces a shift to the left in the oxygen dissociation curve, further inhibiting release of oxygen to the tissues.

Mild acidaemia causes vasodilation and can increase cerebral blood flow. Therefore, full correction of the arterial blood pH may theoretically reduce cerebral blood flow at a particularly critical time. As the bicarbonate ion is excreted as carbon dioxide via the lungs, ventilation needs to be increased.

Several animal and clinical studies have examined the use of buffers during cardiac arrest. Clinical studies using Tribonate® [694] or sodium bicarbonate as buffers have failed to demonstrate any advantage.[694–701] Two studies have found that EMS systems using sodium bicarbonate earlier and more frequently had significantly higher ROSC and hospital discharge rates and better long-term neurological outcome.[702,703]. Animal studies have generally been inconclusive, but some have shown benefit in giving sodium bicarbonate to treat cardiovascular toxicity (hypotension, cardiac arrhythmias) caused by tricyclic antidepressants and other fast sodium channel blockers (Section 4).[224,704,705] Giving sodium bicarbonate routinely during cardiac arrest and CPR or after ROSC is not recommended. Consider sodium bicarbonate for:

- life-threatening hyperkalaemia
- cardiac arrest associated with hyperkalaemia
- tricyclic overdose.

Give 50 mmol (50 ml of an 8.4% solution) or 1 mmol kg^{-1} of sodium bicarbonate intravenously. Repeat the dose as necessary, but use acid/base analysis (either arterial, central venous or marrow aspirate from IO needle) to guide therapy. Severe tissue damage may be caused by subcutaneous extravasation of concentrated sodium bicarbonate. The solution is incompatible with calcium salts as it causes the precipitation of calcium carbonate.

Fibrinolysis during CPR

Fibrinolytic drugs may be used when pulmonary embolism is the suspected or known cause of cardiac arrest. Thrombus formation is a common cause of cardiac arrest, most commonly due to acute myocardial ischaemia following coronary artery occlusion by thrombus, but occasionally due to a dislodged venous thrombus causing a pulmonary embolism. The use of fibrinolytic drugs to break down coronary artery and pulmonary artery thrombus has been the subject of several studies. Fibrinolytics have also been demonstrated in animal studies to have beneficial effects on cerebral blood flow during cardiopulmonary resuscitation,[706,707] and a clinical study has reported less anoxic encephalopathy after fibrinolytic therapy during CPR.[708]

Several studies have examined the use of fibrinolytic therapy given during non-traumatic cardiac arrest unresponsive to standard therapy.[709–715] and some have shown non-significant improvements in survival to hospital discharge,[709,712] and greater ICU survival.[708] A small series of case reports also reported survival to discharge in three cases refractory to standard therapy with VF or PEA treated with fibrinolytics.[716] Conversely, two large clinical trials[717,718] failed to show any significant benefit for fibrinolytics in out-of-hospital cardiac arrest unresponsive to initial interventions.

Results from the use of fibrinolytics in patients suffering cardiac arrest from suspected pulmonary embolism have been variable. A meta-analysis, which included patients with pulmonary embolism as a cause of the arrest, concluded that fibrinolytics increased the rate of ROSC, survival to discharge and long-term neurological function.[719] Several other studies have demonstrated an improvement in ROSC and admission to hospital or the intensive care unit, but not in survival to neurologically intact hospital discharge.[709–712,714,715,720–723]

Although several relatively small clinical studies[709,710,712,721] and case series[708,716,724–726] have not demonstrated any increase in bleeding complications with thrombolysis during CPR in non-traumatic cardiac arrest, a recent large study[718] and meta-analysis[719] have shown an increased risk of intracranial bleeding associated with the routine use of fibrinolytics during non-traumatic cardiac arrest. Successful fibrinolysis during cardiopulmonary resuscitation is usually associated with good neurological outcome.[719,721,722]

Fibrinolytic therapy should not be used routinely in cardiac arrest. Consider fibrinolytic therapy when cardiac arrest is caused by proven or suspected acute pulmonary embolism. Following fibrinolysis during CPR for acute pulmonary embolism, survival and good neurological outcome have been reported in cases requiring in excess of 60 min of CPR. If a fibrinolytic drug is given in these circumstances, consider performing CPR for at least 60–90 min before termination of resuscitation attempts.[727–729] Ongoing CPR is not a contraindication to fibrinolysis. Treatment of pulmonary embolism is addressed in Section 4 including the role of extracorporeal CPR, and surgical or mechanical thrombectomy.[224]

Intravenous fluids

Hypovolaemia is a potentially reversible cause of cardiac arrest. Infuse fluids rapidly if hypovolaemia is suspected. In the initial stages of resuscitation there are no clear advantages to using colloid, so use balanced crystalloid solutions, Hartmann's solution or 0.9% sodium chloride. Avoid glucose, which is redistributed away from the intravascular space rapidly and causes hyperglycaemia, and may worsen neurological outcome after cardiac arrest.[730–738]

Whether fluids should be infused routinely during cardiac arrest is controversial. There are no published human studies specifically aimed to evaluate the advantages of routine fluid use compared to no fluids during normovolaemic cardiac arrest. Three animal studies show that the increase in right atrial pressure produced by infusion of fluids during CPR decreases coronary perfusion pressure,[739–741] and another animal study[742] shows that the coronary perfusion pressure rise with adrenaline during CPR is not improved with the addition of a fluid infusion. In a clinical trial which randomised patients to rapid prehospital cooling, accomplished by infusing up to 2 L of 4 °C normal saline immediately after ROSC, the incidence of re-arrest and pulmonary oedema on first chest X-ray was significantly higher in the intervention group.[743] This was not confirmed by a similar study in which patients received a median of 1 L of cold saline before hospital admission.[744] Results of a further study on rapid prehospital cooling (NCT01173393) are awaited.

One animal study shows that hypertonic saline improves cerebral blood flow during CPR.[745] However, one small clinical study[746] and one randomised trial[747] have not shown any benefit with hypertonic fluid during CPR. One retrospective matched pair analysis of a German OHCA registry showed that use of hypertonic saline with 6% hydroxyethyl starch was associated with increased rates of survival to hospital admission.[748] However there are concerns regarding the use of colloids and starch solutions in particular in critically ill patients.[749]

Ensure normovolaemia, but in the absence of hypovolaemia, infusion of an excessive volume of fluid is likely to be harmful.[750] Use intravenous fluid to flush peripherally injected drugs into the central circulation.

3h – CPR techniques and devices

At best, standard manual CPR produces coronary and cerebral perfusion that is just 30% of normal.[751] Several CPR techniques and devices aim to improve haemodynamics and survival when used by trained providers in selected cases. However, the success of any technique or device depends on the education and training of the rescuers and on resources (including personnel). In the hands of some groups, novel techniques and adjuncts may be better than standard CPR. However, a device or technique which provides good quality CPR when used by a highly trained team or in a test setting may show poor quality and frequent interruptions when used in an uncontrolled clinical setting.[752] It is prudent that rescuers are well-trained and that if a circulatory adjunct is used, a programme of continuous surveillance be in place to ensure that use of the adjunct does not adversely affect survival. Although manual chest compressions are often performed very poorly,[753–755] no adjunct has consistently been shown to be superior to conventional manual CPR.

Mechanical chest compression devices

Providing high-quality manual chest compressions can be challenging and there is evidence that CPR quality deteriorates with time. Automated mechanical chest compression devices may enable the delivery of high quality compressions especially in circumstances where this may not be possible with manual compressions – CPR in a moving ambulance where safety is at risk, prolonged CPR (e.g. hypothermic arrest), and CPR during certain procedures (e.g. coronary angiography or preparation for extracorporeal CPR).[347,390,414,756–761] Data from the US American CARES (Cardiac Arrest Registry to Enhance Survival) registry shows that 45% of participating EMS services use mechanical devices.[762]

Since Guidelines 2010 there have been three large RCTs enrolling 7582 patients that have shown no clear advantage from the routine use of automated mechanical chest compression devices for OHCA.[763–765] Ensuring high-quality chest compressions with adequate depth, rate and minimal interruptions, regardless of whether they are delivered by machine or human is important.[766,767] In addition mechanical compressions usually follow a period of manual compressions.[768] The transition from manual compressions to mechanical compressions whilst minimising interruptions to chest compression and avoiding delays in defibrillation is therefore an important aspect of using these devices.

We suggest that automated mechanical chest compression devices are not used routinely to replace manual chest compressions. We suggest that automated mechanical chest compression devices are a reasonable alternative to high-quality manual chest compressions in situations where sustained high-quality manual chest compressions are impractical or compromise provider safety.[4] Interruptions to CPR during device deployment should be avoided. Healthcare personnel who use mechanical CPR should do so only within a structured, monitored programme, which should include comprehensive competency-based training and regular opportunities to refresh skills.

The experience from the three large RCTs suggests that use of mechanical devices requires initial and on-going training and quality assurance to minimise interruptions in chest compression when transitioning from manual to mechanical compressions and preventing delays in defibrillation. The use of training drills and 'pit-crew' techniques for device deployment are suggested to help minimise interruptions in chest compression.[769–771]

Our recommendation is generic for automated chest compression devices. Although there may be some device specific differences, they have not been directly compared in RCTs, and the three large RCTs[763–765] did not suggest a difference between the two most studied devices [the AutoPulse (Zoll Circulation, Chelmsford, Massachusetts, USA) and LUCAS-2 (Physio-Control Inc/Jolife AB, Lund, Sweden)] for critical and important patient outcomes when compared with the use of manual chest compressions alone.[4]

Information concerning the routine use of mechanical devices for IHCA is limited.[772] One small RCT of 150 IHCA patients showed improved survival with mechanical chest compressions delivered by a piston device [Thumper 1007 CCV device (Michigan Instruments, Grand Rapids, Michigan, USA)] when compared with manual compressions (OR 2.81, 95% CI 1.26–6.24).[773]

Lund University cardiac arrest system (LUCAS) CPR

The LUCAS delivers chest compression and active decompression through a piston system with suction cup. The current model is a battery driven device that delivers 100 compressions min^{-1} to a depth of 40–50 mm. There have been two large RCTs of the LUCAS device since the 2010 Guidelines.[764,765]

The LINC (LUCAS in cardiac arrest) RCT included 2589 adult OHCA patients and compared a modified CPR algorithm, which included mechanical chest compressions with a standard resuscitation algorithm which included manual chest compressions.[764] In the intention to treat analysis, there was no improvement in the primary outcome of 4-h survival (mechanical CPR 23.6% vs. manual CPR 23.7%, treatment difference −0.05%, 95% CI 3.3–3.2%; $p > 0.99$), 1 month survival (survival: 8.6% vs. 8.5%, treatment difference 0.16%, 95% CI 2.0–2.3%) and favourable neurological survival (8.1% vs. 7.3%, treatment difference 0.78%, 95% CI 1.3–2.8%). A follow-up study reported that patients who received LUCAS CPR were more likely to sustain injury (OR 3.4, 95% CI 1.55–7.31%), including rib fractures (OR 2.0, 95% CI 1.11–3.75%).[774]

The PaRAMeDIC trial (Prehospital Randomised Assessment of a Mechanical Compression Device) trial was cluster RCT that randomised ambulance vehicles to LUCAS or control and included 4471 patients (1652 LUCAS, 2819 manual chest compressions).[765] The intention-to-treat analysis found no improvement in the primary outcome of 30-day survival (LUCAS CPR 6% vs. manual CPR 7%, adjusted OR 0.86, 95% CI 0.64–1.15). Survival with a favourable neurological outcome at three months was lower amongst patients randomised to LUCAS CPR (5% vs. 6%, adjusted OR 0.72, 95% CI 0.52–0.99). In addition, in patients with VF/pVT, there was a lower 30-day survival with LUCAS CPR (OR 0.71, 95% CI 0.52–0.98). Delays in attempted defibrillation caused by device deployment may have caused this.

A meta-analysis of the three LUCAS RCTs that included 7178 patients with OHCA was included in the PARAMEDIC publication.[764,765,775] and reported similar initial and long-term survival (survived event OR 1.00, 95% CI 0.90–1.11; survival to discharge/30-days OR 0.96, 95% CI 0.80–1.15). Meta-analysis from the two larger RCTs noted significant heterogeneity ($I^2 = 69\%$) but no overall difference in neurological outcomes between LUCAS and manual chest compressions (random effects model OR 0.93, 95% CI 0.64–1.33).[764,765]

Load-distributing band CPR (AutoPulse)

The load-distributing band (LDB) is a battery-powered device consisting of a large backboard and a band that encircles the patient's chest. Compressions are delivered at a rate of 80 min^{-1} by tightening of the band. The evidence from clinical trials considered for the LDB in 2010 was conflicting. Evidence from one OHCA multi-centre RCT showed no improvement in 4-h survival and worse neurological outcome with LDB-CPR.[776] A further study showed lower odds of 30-day survival (OR 0.4) but subgroup analysis showed an increased rate of ROSC in LDB-CPR treated patients.[777] Non-randomised trials reported increased rates of sustained ROSC,[778,779] increased survival to discharge following

OHCA[779] and improved haemodynamics following failed resuscitation from in-hospital cardiac arrest.[780]

A recent large RCT showed similar outcomes for LDB and manual CPR.[763] The CIRC (Circulation Improving Resuscitation Care) trial, an equivalence RCT, randomised 4753 adult OHCA patients to the LDB or manual chest compressions. After a predefined adjustment for covariates and multiple interim analyses the adjusted OR was 1.06 (95% CI 0.83–1.37) and within the pre-defined region of equivalence for the primary outcome of survival to discharge (manual CPR vs. LDB CPR 11.0% vs. 9.4%). Good neurological survival to hospital discharge was similar (mechanical CPR 44.4% vs. manual CPR 48.1%, adjusted OR 0.80, 95% CI 0.47–1.37).

Open-chest CPR

Open-chest CPR produces better coronary perfusion coronary pressure than standard CPR and may be indicated for patients with cardiac arrest caused by trauma,[781] in the early postoperative phase after cardiothoracic surgery[782,783] (see Section 4 – special circumstances[224]) or when the chest or abdomen is already open (transdiaphragmatic approach), for example, in trauma surgery.[784]

Active compression-decompression CPR (ACD-CPR)

ACD-CPR is achieved with a hand-held device equipped with a suction cup to lift the anterior chest actively during decompression. Decreasing intrathoracic pressure during the decompression phase increases venous return to the heart and increases cardiac output and subsequent coronary and cerebral perfusion pressures during the compression phase.[785–788] Results of ACD-CPR have been mixed. In some clinical studies ACD-CPR improved haemodynamics compared with standard CPR,[786,788–790] but in another study it did not.[791] In three randomised studies,[790,792,793] ACD-CPR improved long-term survival after out-of-hospital cardiac arrest; however, in five other randomised studies, ACD-CPR made no difference to outcome.[794–798] The efficacy of ACD-CPR may be highly dependent on the quality and duration of training.[799]

A meta-analysis of 10 trials of out-of-hospital cardiac arrest and two of in-hospital cardiac arrest showed no early or late survival benefit to ACD-CPR over conventional CPR[234,800] and this is confirmed by another recent meta-analysis.[801] Two post-mortem studies have shown more rib and sternal fractures after ACD-CPR compared with conventional CPR,[802,803] but another found no difference.[804]

Impedance threshold device (ITD)

The impedance threshold device (ITD) is a valve that limits air entry into the lungs during chest recoil between chest compressions; this decreases intrathoracic pressure and increases venous return to the heart. When used with a cuffed tracheal tube and active compression–decompression (ACD),[805–807] the ITD is thought to act synergistically to enhance venous return during active decompression. The ITD has also been used during conventional CPR with a tracheal tube or facemask.[808] If rescuers can maintain a tight face-mask seal, the ITD may create the same negative intrathoracic pressure as when used with a tracheal tube.[808]

An RCT of the ITD with standard CPR compared to standard CPR alone with 8718 OHCA patients failed to show any benefit with ITD use in terms of survival and neurological outcome.[809] We therefore recommend that the ITD is not used routinely with standard CPR.

Two RCTs did not show a benefit in terms of survival to hospital discharge of the ITD with active compression decompression CPR when compared with active compression decompression CPR alone.[805,810]

Results of a large trial of a combination of ITD with active compression decompression CPR (ACD CPR) compared to standard CPR was reported in two publications. The primary publication reported the results from 2470 patients with OHCA[811] whereas the secondary publication reported results from those with non-traumatic cardiac arrest ($n = 27380$).[812] This study did detect a statistically significant difference in neurologically favourable survival at discharge, and survival at 12 months but no difference for survival to discharge and neurologically favourable survival at 12 months.[4] After consideration of the number needed to treat a decision was made not to recommend the routine use of the ITD and ACD.[4]

3i – Peri-arrest arrhythmias

The correct identification and treatment of arrhythmias in the critically ill patient may prevent cardiac arrest from occurring or reoccurring after successful initial resuscitation. The treatment algorithms described in this section have been designed to enable the non-specialist ALS provider to treat the patient effectively and safely in an emergency; for this reason, they have been kept as simple as possible. If patients are not acutely ill there may be several other treatment options, including the use of drugs (oral or parenteral) that will be less familiar to the non-expert. In this situation there will be time to seek advice from cardiologists or other senior doctors with the appropriate expertise.

More comprehensive information on the management of arrhythmias can be found at www.escardio.org.

Principles of treatment

The initial assessment and treatment of a patient with an arrhythmia should follow the ABCDE approach. Key elements in this process include assessing for adverse signs; oxygen if indicated and guided by pulse oximetry; obtaining intravenous access, and establishing monitoring (ECG, blood pressure, SpO_2). Whenever possible, record a 12-lead ECG; this will help determine the precise rhythm, either before treatment or retrospectively. Correct any electrolyte abnormalities (e.g. K^+, Mg^{2+}, Ca^{2+}). Consider the cause and context of arrhythmias when planning treatment.

The assessment and treatment of all arrhythmias addresses two factors: the condition of the patient (stable versus unstable), and the nature of the arrhythmia. Anti-arrhythmic drugs are slower in onset and less reliable than electrical cardioversion in converting a tachycardia to sinus rhythm; thus, drugs tend to be reserved for stable patients without adverse signs, and electrical cardioversion is usually the preferred treatment for the unstable patient displaying adverse signs.

Adverse signs

The presence or absence of adverse signs or symptoms will dictate the appropriate treatment for most arrhythmias. The following adverse factors indicate a patient who is unstable because of the arrhythmia.

1. Shock – this is seen as pallor, sweating, cold and clammy extremities (increased sympathetic activity), impaired consciousness (reduced cerebral blood flow), and hypotension (e.g. systolic blood pressure < 90 mmHg).
2. Syncope – loss of consciousness, which occurs as a consequence of reduced cerebral blood flow
3. Heart failure – arrhythmias compromise myocardial performance by reducing coronary artery blood flow. In acute situations this is manifested by pulmonary oedema (failure of the

left ventricle) and/or raised jugular venous pressure, and hepatic engorgement (failure of the right ventricle).

4. Myocardial ischaemia – this occurs when myocardial oxygen consumption exceeds delivery. Myocardial ischaemia may present with chest pain (angina) or may occur without pain as an isolated finding on the 12-lead ECG (silent ischaemia). The presence of myocardial ischaemia is especially important if there is underlying coronary artery disease or structural heart disease because it may cause further life-threatening complications including cardiac arrest.

Treatment options

Having determined the rhythm and the presence or absence of adverse signs, the options for immediate treatment are categorised as:

1. Electrical (cardioversion, pacing).
2. Pharmacological (anti-arrhythmic (and other) drugs).

Tachycardias

If the patient is unstable

If the patient is unstable and deteriorating, with any of the adverse signs and symptoms described above being caused by the tachycardia, attempt synchronised cardioversion immediately (Fig. 3.4). In patients with otherwise normal hearts, serious signs and symptoms are uncommon if the ventricular rate is <150 beats min^{-1}. Patients with impaired cardiac function or significant comorbidity may be symptomatic and unstable at lower heart rates. If cardioversion fails to restore sinus rhythm and the patient remains unstable, give amiodarone 300 mg intravenously over 10–20 min and re-attempt electrical cardioversion.

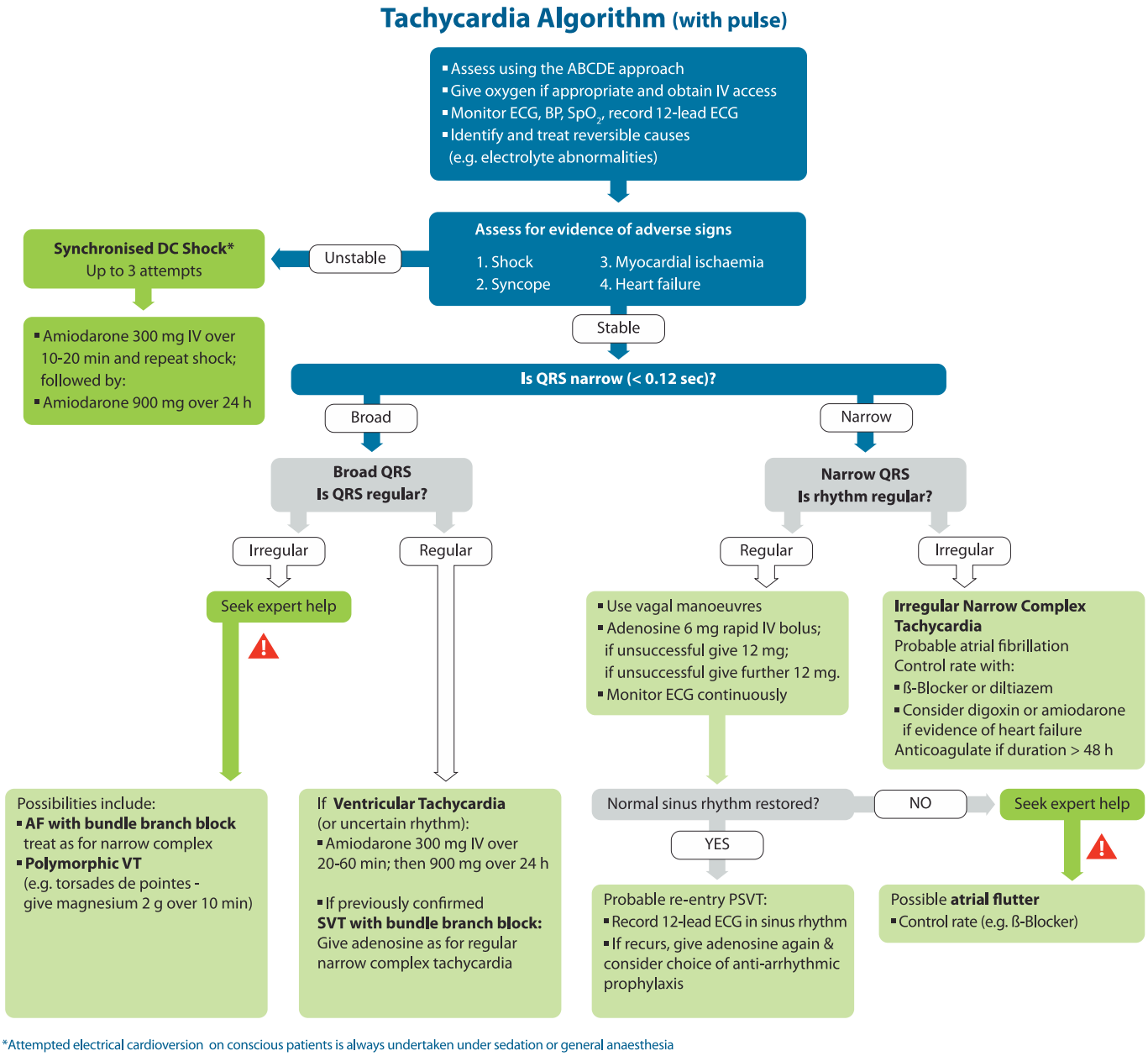


Fig. 3.4. Tachycardia algorithm. ABCDE – Airway, Breathing Circulation, Disability, Exposure; IV – intravenous; SpO_2 – oxygen saturation measured by pulse oximetry; BP – blood pressure; ECG – electrocardiogram; DC – direct current; AF – atrial fibrillation; VT – ventricular tachycardia; SVT – supraventricular tachycardia; PSVT – paroxysmal supraventricular tachycardia.

The loading dose of amiodarone can be followed by an infusion of 900 mg over 24 h.

Repeated attempts at electrical cardioversion are not appropriate for recurrent (within hours or days) paroxysms (self-terminating episodes) of atrial fibrillation. This is relatively common in critically ill patients who may have ongoing precipitating factors causing the arrhythmia (e.g. metabolic disturbance, sepsis). Cardioversion does not prevent subsequent arrhythmias. If there are recurrent episodes, treat them with drugs.

Synchronised electrical cardioversion. If electrical cardioversion is used to convert atrial or ventricular tachyarrhythmias, the shock must be synchronised with the R wave of the ECG rather than with the T wave.[813] By avoiding the relative refractory period in this way, the risk of inducing ventricular fibrillation is minimised. Conscious patients must be anaesthetised or sedated before synchronised cardioversion is attempted. For a broad-complex tachycardia and AF, start with 120–150 J biphasic and increase in increments if this fails. Atrial flutter and paroxysmal supraventricular tachycardia (SVT) will often convert with lower energies: start with 70–120-J biphasic.

If the patient is stable

If the patient with tachycardia is stable (no adverse signs or symptoms) and is not deteriorating, pharmacological treatment may be possible. Evaluate the rhythm using a 12-lead ECG and assess the QRS duration. If the QRS duration is greater than 0.12 s (3 small squares on standard ECG paper) it is classified as a broad complex tachycardia. If the QRS duration is less than 0.12 s it is a narrow complex tachycardia.

All anti-arrhythmic treatments – physical manoeuvres, drugs, or electrical treatment – can also be pro-arrhythmic, so that clinical deterioration may be caused by the treatment rather than lack of effect. The use of multiple anti-arrhythmic drugs or high doses of a single drug can cause myocardial depression and hypotension. This may cause a deterioration of the cardiac rhythm. Expert help should be sought before using repeated doses or combinations of anti-arrhythmic drugs.

Broad-complex tachycardia

Broad-complex tachycardias are usually ventricular in origin. Although broad-complex tachycardias may be caused by supraventricular rhythms with aberrant conduction, in the unstable patient in the peri-arrest context assume they are ventricular in origin. In the stable patient with broad-complex tachycardia, the next step is to determine if the rhythm is regular or irregular.

Regular broad complex tachycardia. A regular broad-complex tachycardia is likely to be ventricular tachycardia or SVT with bundle branch block. If there is uncertainty about the source of the arrhythmia, give intravenous adenosine (using the strategy described below) as it may convert the rhythm to sinus and help diagnose the underlying rhythm.

Stable ventricular tachycardia can be treated with amiodarone 300 mg intravenously over 20–60 min followed by an infusion of 900 mg over 24 h. Specialist advice should be sought before considering alternatives treatments such as procainamide, nifekalant or sotalol.

Irregular broad complex tachycardia. Irregular broad complex tachycardia is most likely to be AF with bundle branch block. Another possible cause is AF with ventricular pre-excitation (Wolff–Parkinson–White (WPW) syndrome). In this case there is more variation in the appearance and width of the QRS complexes than in AF with bundle branch block. A third possible cause is polymorphic VT (e.g. torsade de pointes), although this rhythm is relatively unlikely to be present without adverse features.

Seek expert help with the assessment and treatment of irregular broad-complex tachyarrhythmia. If treating AF with bundle branch block, treat as for AF (see below). If pre-excited AF (or atrial flutter) is suspected, avoid adenosine, digoxin, verapamil and diltiazem. These drugs block the AV node and cause a relative increase in pre-excitation – this can provoke severe tachycardias. Electrical cardioversion is usually the safest treatment option.

Treat torsades de pointes VT immediately by stopping all drugs known to prolong the QT interval. Correct electrolyte abnormalities, especially hypokalaemia. Give magnesium sulphate 2 g, intravenously over 10 min. Obtain expert help, as other treatment (e.g. overdrive pacing) may be indicated to prevent relapse once the arrhythmia has been corrected. If adverse features develop (which is usual), arrange immediate synchronised cardioversion. If the patient becomes pulseless, attempt defibrillation immediately (cardiac arrest algorithm).

Narrow-complex tachycardia

The first step in the assessment of a narrow complex tachycardia is to determine if it is regular or irregular.

The commonest regular narrow-complex tachycardias include:

- sinus tachycardia;
- AV nodal re-entry tachycardia (AVNRT, the commonest type of SVT);
- AV re-entry tachycardia (AVRT), which is associated with Wolff–Parkinson–White (WPW) syndrome;
- atrial flutter with regular AV conduction (usually 2:1).

Irregular narrow-complex tachycardia is most commonly AF or sometimes atrial flutter with variable AV conduction ('variable block').

Regular narrow-complex tachycardia.

Sinus tachycardia. Sinus tachycardia is a common physiological response to a stimulus such as exercise or anxiety. In a sick patient it may be seen in response to many stimuli, such as pain, fever, anaemia, blood loss and heart failure. Treatment is almost always directed at the underlying cause; trying to slow sinus tachycardia will make the situation worse.

AVNRT and AVRT (paroxysmal SVT). AVNRT is the commonest type of paroxysmal SVT, often seen in people without any other form of heart disease and is relatively uncommon in a peri-arrest setting.[814] It causes a regular narrow-complex tachycardia, often with no clearly visible atrial activity on the ECG. Heart rates are usually well above the typical range of sinus rates at rest (60–120 beats min^{-1}). It is usually benign, unless there is additional co-incidental structural heart disease or coronary disease.

AV re-entry tachycardia (AVRT) is seen in patients with the WPW syndrome and is also usually benign unless there happens to be additional structural heart disease. The common type of AVRT is a regular narrow-complex tachycardia, also often having no visible atrial activity on the ECG.

Atrial flutter with regular AV conduction (often 2:1 block). Atrial flutter with regular AV conduction (often 2:1 block) produces a regular narrow-complex tachycardia in which it may be difficult to see atrial activity and identify flutter waves with confidence, so it may be indistinguishable initially from AVNRT and AVRT. When atrial flutter with 2:1 block or even 1:1 conduction is accompanied by bundle branch block, it produces a regular broad-complex tachycardia that will usually be very difficult to distinguish from VT. Treatment of this rhythm as if it were VT will usually be effective, or will lead to slowing of the ventricular response and identification of the rhythm. Most typical atrial flutter has an atrial rate of

about 300 beats min^{-1}, so atrial flutter with 2:1 block tends to produce a tachycardia of about 150 beats min^{-1}. Much faster rates are unlikely to be due to atrial flutter with 2:1 block.

Treatment of regular narrow complex tachycardia. If the patient is unstable with adverse features caused by the arrhythmia, attempt synchronised electrical cardioversion. It is reasonable to give adenosine to an unstable patient with a regular narrow-complex tachycardia while preparations are made for synchronised cardioversion; however, do not delay electrical cardioversion if the adenosine fails to restore sinus rhythm. In the absence of adverse features, proceed as follows.

- Start with vagal manoeuvres[814]: carotid sinus massage or the Valsalva manoeuvre will terminate up to a quarter of episodes of paroxysmal SVT. Carotid sinus massage stimulates baroreceptors, which increase vagal tone and reduces sympathetic drive, which slows conduction via the AV node. Carotid sinus massage is given by applying pressure over the carotid artery at the level of the cricoid cartilage. Massage the area with firm circular movements for about 5 s. If this does not terminate the arrhythmia, repeat on the opposite side. Avoid carotid massage if a carotid bruit is present: rupture of an atheromatous plaque could cause cerebral embolism and stroke. A Valsalva manoeuvre (forced expiration against a closed glottis) in the supine position may be the most effective technique. A practical way of achieving this without protracted explanation is to ask the patient to blow into a 20 ml syringe with enough force to push back the plunger. Record an ECG (preferably multi-lead) during each manoeuvre. If the rhythm is atrial flutter, slowing of the ventricular response will often occur and demonstrate flutter waves.
- If the arrhythmia persists and is not atrial flutter, use adenosine. Give 6 mg as a rapid intravenous bolus. Record an ECG (preferably multi-lead) during each injection. If the ventricular rate slows transiently but the arrhythmia then persists, look for atrial activity such as atrial flutter or other atrial tachycardia and treat accordingly. If there is no response to adenosine 6 mg, give a 12 mg bolus; if there is no response, give one further 12 mg-bolus. This strategy will terminate 90–95% of supraventricular arrhythmias.
- Successful termination of a tachyarrhythmia by vagal manoeuvres or adenosine indicates that it was almost certainly AVNRT or AVRT. Monitor the patients for further rhythm abnormalities. Treat recurrence either with further adenosine or with a longer-acting drug with AV nodal-blocking action (e.g. diltiazem or verapamil).
- If adenosine is contraindicated or fails to terminate a regular narrow-complex tachycardia without demonstrating that it is atrial flutter, give a calcium channel blocker (e.g. verapamil or diltiazem).

Irregular narrow-complex tachycardia

An irregular narrow-complex tachycardia is most likely to be AF with an uncontrolled ventricular response or, less commonly, atrial flutter with variable AV block. Record a 12-lead ECG to identify the rhythm. If the patient is unstable with adverse features caused by the arrhythmia, attempt synchronised electrical cardioversion as described above. The European Society of Cardiology provides detailed guidelines on the management of AF: www.escardio.org.

If there are no adverse features, treatment options include:

- rate control by drug therapy
- rhythm control using drugs to encourage chemical cardioversion
- rhythm control by electrical cardioversion
- treatment to prevent complications (e.g. anticoagulation).

Obtain expert help to determine the most appropriate treatment for the individual patient. The longer a patient remains in AF, the greater is the likelihood of atrial clot developing. In general, patients who have been in AF for more than 48 h should not be treated by cardioversion (electrical or chemical) until they have received full anticoagulation or absence of atrial clot has been shown by transoesophageal echocardiography. If the clinical scenario dictates that cardioversion is required and the duration of AF is greater than 48 h (or the duration is unknown) discuss anticoagulation, choice of agent, and duration with a cardiologist.

If the aim is to control heart rate, the drugs of choice are beta-blockers and diltiazem. Digoxin and amiodarone may be used in patients with heart failure.

If the duration of AF is less than 48 h and rhythm control is considered appropriate, chemical cardioversion may be attempted. Seek expert help and consider, flecainide, propafenone, or ibutilide. Amiodarone (300 mg intravenously over 20–60 min followed by 900 mg over 24 h) may also be used but is less effective. Electrical cardioversion remains an option in this setting and will restore sinus rhythm in more patients than chemical cardioversion.

Seek expert help if any patient with AF is known or found to have ventricular pre-excitation (WPW syndrome). Avoid using adenosine, diltiazem, verapamil or digoxin in patients with pre-excited AF or atrial flutter, as these drugs block the AV node and cause a relative increase in pre-excitation.

Bradycardia

A bradycardia is defined as a heart rate of <60 beats min^{-1}. Bradycardia can have cardiac causes (e.g. myocardial infarction; myocardial ischaemia; sick sinus syndrome), non-cardiac causes (e.g. vasovagal response, hypothermia; hypoglycaemia; hypothyroidism, raised intracranial pressure) or be caused by drug toxicity (e.g. digoxin; beta blockers; calcium channel blockers).

Bradycardias are caused by reduced sinoatrial node firing or failure of the atrial–ventricular conduction system. Reduced sinoatrial node firing is seen in sinus bradycardia (caused by excess vagal tone), sinus arrest, and sick sinus syndrome. Atrioventricular (AV) blocks are divided into first, second, and third degrees and may be associated with multiple medications or electrolyte disturbances, as well as structural problems caused by acute myocardial infarction and myocarditis. A first-degree AV block is defined by a prolonged P-R interval (>0.20 s), and is usually benign. Second-degree AV block is divided into Mobitz types I and II. In Mobitz type I, the block is at the AV node, is often transient and may be asymptomatic. In Mobitz type II, the block is most often below the AV node at the bundle of His or at the bundle branches, and is often symptomatic, with the potential to progress to complete AV block. Third-degree heart block is defined by AV dissociation, which may be permanent or transient, depending on the underlying cause.

Initial assessment

Assess the patient with bradycardia using the ABCDE approach. Consider the potential cause of the bradycardia and look for the adverse signs. Treat any reversible causes of bradycardia identified in the initial assessment. If adverse signs are present start to treat the bradycardia. Initial treatments are pharmacological, with pacing being reserved for patients unresponsive to pharmacological treatments or with risks factors for asystole (Fig. 3.5).

Pharmacological treatment

If adverse signs are present, give atropine 500 μg, intravenously and, if necessary, repeat every 3–5 min to a total of 3 mg. Doses of atropine of less than 500 μg, paradoxically, may cause further slowing of the heart rate.[815] In healthy volunteers a dose of 3 mg produces the maximum achievable increase in resting heart

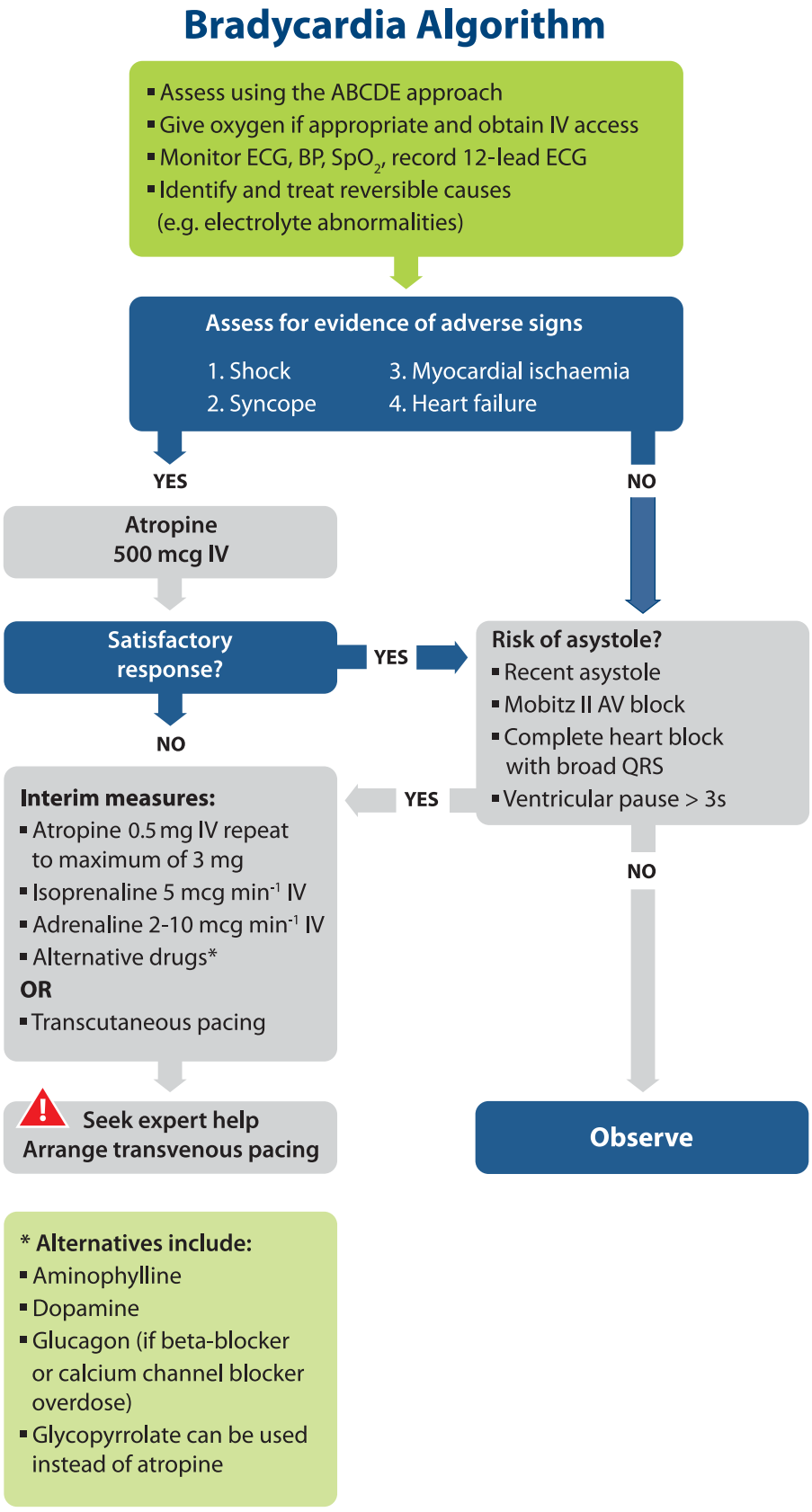


Fig. 3.5. Bradycardia algorithm. ABCDE – Airway, Breathing Circulation, Disability, Exposure; IV – intravenous; SpO_2 – oxygen saturation measured by pulse oximetry; BP – blood pressure; ECG – electrocardiogram; AV – atrioventricular.

rate.[816] Use atropine cautiously in the presence of acute coronary ischaemia or myocardial infarction; increased heart rate may worsen ischaemia or increase the zone of infarction.

If treatment with atropine is ineffective, consider second line drugs. These include isoprenaline (5 μg min^{-1} starting dose), adrenaline (2–10 μg min^{-1}) and dopamine (2–10 μg kg^{-1} min^{-1}). Theophylline (100–200 mg slow intravenous injection) should be considered if the bradycardia is caused by inferior myocardial infarction, cardiac transplant or spinal cord injury. Consider giving intravenous glucagon if beta-blockers or calcium channel blockers are a potential cause of the bradycardia. Do not give atropine to patients with cardiac transplants – it can cause a high-degree AV block or even sinus arrest.[817]

Pacing

Initiate transcutaneous pacing immediately if there is no response to atropine, or if atropine is unlikely to be effective.

Transcutaneous pacing can be painful and may fail to produce effective mechanical capture. Verify mechanical capture and reassess the patient's condition. Use analgesia and sedation to control pain, and attempt to identify the cause of the bradyarrhythmia.

If atropine is ineffective and transcutaneous pacing is not immediately available, fist pacing can be attempted while waiting for pacing equipment. Give serial rhythmic blows with the closed fist over the left lower edge of the sternum to pace the heart at a physiological rate of 50–70 beats min^{-1}.

Seek expert help to assess the need for temporary transvenous pacing. Temporary transvenous pacing should be considered if there are is a history of recent asystole; Mobitz type II AV block; complete (third-degree) heart block (especially with broad QRS or initial heart rate < 40 beats min^{-1}) or evidence of ventricular standstill of more than 3 s.

Antiarrhythmic drugs

Adenosine

Adenosine is a naturally occurring purine nucleotide. It slows transmission across the AV node but has little effect on other myocardial cells or conduction pathways. It is highly effective for terminating paroxysmal SVT with re-entrant circuits that include the AV node (AVNRT). In other narrow-complex tachycardias, adenosine will reveal the underlying atrial rhythms by slowing the ventricular response. It has an extremely short half-life of 10–15 s and, therefore, is given as a rapid bolus into a fast running intravenous infusion or followed by a saline flush. The smallest dose likely to be effective is 6 mg (which is outside some current licences for an initial dose) and, if unsuccessful this can be followed with up to two doses each of 12 mg every 1–2 min. Patients should be warned of transient unpleasant side effects, in particular nausea, flushing, and chest discomfort. Adenosine is not available in some European countries, but adenosine triphosphate (ATP) is an alternative. In a few European countries neither preparation may be available; verapamil is probably the next best choice. Theophylline and related compounds block the effect of adenosine. Patients receiving dipyridamole or carbamazepine, or with denervated (transplanted) hearts, display a markedly exaggerated effect that may be hazardous. In these patients, or if injected into a central vein, reduce the initial dose of adenosine to 3 mg. In the presence of WPW syndrome, blockage of conduction across the AV node by adenosine may promote conduction across an accessory pathway. In the presence of supraventricular arrhythmias this may cause a dangerously rapid ventricular response. In the presence of WPW syndrome, rarely, adenosine may precipitate atrial fibrillation associated with a dangerously rapid ventricular response.

Amiodarone

Intravenous amiodarone has effects on sodium, potassium and calcium channels as well as alpha- and beta-adrenergic blocking properties. Indications for intravenous amiodarone include:

- Control of haemodynamically stable monomorphic VT, polymorphic VT and wide-complex tachycardia of uncertain origin.
- Paroxysmal SVT uncontrolled by adenosine, vagal manoeuvres or AV nodal blockade;
- to control rapid ventricular rate due to accessory pathway conduction in pre-excited atrial arrhythmias. In patients with pre-excitation and AF, digoxin, non-dihydropyridine calcium channel antagonists, or intravenous amiodarone should not be administered as they may increase the ventricular response and may result in VF.[818,819]
- Unsuccessful electrical cardioversion.

Give amiodarone, 300 mg intravenously, over 10–60 min depending on the circumstances and haemodynamic stability of the patient. This loading dose is followed by an infusion of 900 mg over 24 h. Additional infusions of 150 mg can be repeated as necessary for recurrent or resistant arrhythmias to a maximum manufacturer-recommended total daily dose of 2 g (this maximum licensed dose varies between different countries). In patients with severely impaired heart function, intravenous amiodarone is preferable to other anti-arrhythmic drugs for atrial and ventricular arrhythmias. Major adverse effects from amiodarone are hypotension and bradycardia, which can be prevented by slowing the rate of drug infusion. The hypotension associated with amiodarone is caused by vasoactive solvents (Polysorbate 80 and benzyl alcohol). An aqueous formulation of amiodarone does not contain these solvents and causes no more hypotension than lidocaine.[677] Whenever possible, intravenous amiodarone should be given via a central venous catheter; it causes thrombophlebitis when infused into a peripheral vein. In an emergency it can be injected into a large peripheral vein.

Calcium channel blockers: verapamil and diltiazem

Verapamil and diltiazem are calcium channel blocking drugs that slow conduction and increase refractoriness in the AV node. Intravenous diltiazem is not available in some countries. These actions may terminate re-entrant arrhythmias and control ventricular response rate in patients with a variety of atrial tachycardias. Indications include:

- stable regular narrow-complex tachycardias uncontrolled or unconverted by adenosine or vagal manoeuvres;
- to control ventricular rate in patients with AF or atrial flutter and preserved ventricular function.

The initial dose of verapamil is 2.5–5 mg intravenously given over 2 min. In the absence of a therapeutic response or drug-induced adverse event, give repeated doses of 5–10 mg every 15–30 min to a maximum of 20 mg. Verapamil should be given only to patients with narrow-complex paroxysmal SVT or arrhythmias known with certainty to be of supraventricular origin. The administration of calcium channel blockers to a patient with ventricular tachycardia may cause cardiovascular collapse.

Diltiazem at a dose of 250 μg kg^{-1} intravenously, followed by a second dose of 350 μg kg^{-1}, is as effective as verapamil. Verapamil and, to a lesser extent, diltiazem may decrease myocardial contractility and critically reduce cardiac output in patients with severe LV dysfunction. For the reasons stated under adenosine (above), calcium channel blockers are considered harmful when given to patients with AF or atrial flutter associated with pre-excitation (WPW) syndrome.

Beta-adrenergic blockers

Beta-blocking drugs (atenolol, metoprolol, labetalol (alpha- and beta-blocking effects), propranolol, esmolol) reduce the effects of circulating catecholamines and decrease heart rate and blood pressure. They also have cardioprotective effects for patients with acute coronary syndromes. Beta-blockers are indicated for the following tachycardias:

- narrow-complex regular tachycardias uncontrolled by vagal manoeuvres and adenosine in the patient with preserved ventricular function;
- to control rate in AF and atrial flutter when ventricular function is preserved.

The intravenous dose of atenolol ($beta_1$) is 5 mg given over 5 min, repeated if necessary after 10 min. Metoprolol ($beta_1$) is given in doses of 2–5 mg at 5-min intervals to a total of 15 mg. Propranolol ($beta_1$ and $beta_2$ effects), 100 $\mu g\,kg^{-1}$, is given slowly in three equal doses at 2–3-min intervals.

Intravenous esmolol is a short-acting (half-life of 2–9 min) $beta_1$-selective beta-blocker. It is given as an intravenous loading dose of 500 $\mu g\,kg^{-1}$ over 1 min, followed by an infusion of 50–200 $\mu g\,kg^{-1}\,min^{-1}$.

Side effects of beta-blockade include bradycardia, AV conduction delay and hypotension. Contraindications to the use of beta-adrenergic blocking drugs include second- or third-degree heart block, hypotension, severe congestive heart failure and lung disease associated with bronchospasm.

Magnesium

Magnesium is the first line treatment for polymorphic ventricular tachycardia (torsades de pointes) and ventricular or supraventricular tachycardia associated with hypomagnesaemia. It may also reduce ventricular rate in atrial fibrillation. Give magnesium sulphate 2 g (8 mmol) over 10 min. This can be repeated once if necessary.

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	Normas de Autoridade Técnica **NAT 05.00**	**Exemplar nº** **Pag 1 de 19** **27Mar2017**
Assunto:	**RISCO SANITÁRIO E MEDIDAS DE PREVENÇÃO DE LESÕES ASSOCIADAS AO CALOR OU FRIO EM AMBIENTE OPERACIONAL**	
Referência (s):	a) CARTER III, Robert et al; Epidemiology of Hospitalizations and Deaths from Heat Illness in soldiers. Medicine & Science in Sports Exercice- 2005 Aug;37(8):1338-44 b) PHINNEY, LLOYD T.; GARDNER et al, Long-term follow-up after exertional heat illness during recruit training; Medicine & Science in Sports & Exercise:September 2001 - Volume 33 - Issue 9 - pp 1443-1448; c) TB MED507/AFPAM 48-152- HEAT STRESS CONTROL and HEAT CASUALTY MANAGEMENT – HEADQUARTERS, DEPARTMENT OF ARMY and AIR FORCE d) RTO TECHNICAL REPORT / TR-HFM-187, Management of Heat and Cold Stress Guidance to NATO Medical Personnel, December 2013 e) NATO - AJMEDP-4 / 30 May 2011 f) NATO - AJMEDP-6 / NOV 2015 g) NATO - AJMEDP-3/ MAY 2015 h) NATO - STANAG 2122 / NOV 2011 i) Preventing Heat Injuries, The Commanders´Guide , Marines Corps j) Casa, DJ et al; National Athletic Trainers' Association Position Statement: Exertional Heat Illnesses; J Athl Train. 2015 Aug 18 k) Medical Evaluation for Exposure Extremes: Heat - Riana R. et al; WILDERNESS & ENVIRONMENTAL MEDICINE, 26, S69–S75 (2015). l) Stacey M, Woods D, Ross D*, et al* Heat illness in military populations: asking the right questions for research; *Journal of the Royal Army Medical Corps* 2014; 160:121-124. m) PHINNEY, LLOYD T.; GARDNER et al, Long-term follow-up after exertional heat illness during recruit training; Medicine & Science in Sports & Exercise: September 2001 - Volume 33 - Issue 9 - pp 1443-1448 n) MF Bergeron, R Bahr et al; International Olympic Committee consensus statement on thermoregulatory and altitude challenges for high-level athletes; Br J Sports Med 2012;46:11 770-779 o) A commander´s Guide to Climatic Injury – JSP 539 – Climatic Illness and Injury in the armed Forces- UK	

1. GENERALIDADES E CONCEITOS

a. As tropas especiais (Comandos, Operações Especiais e Tropas Para-quedistas) em ambiente de formação, treino ou missão podem encontrar *stress* associado a temperaturas elevadas ou baixas sendo necessário manusear este fator com sucesso de forma a manter o potencial de combate;

b. É importante compreender que as alterações da temperatura (associadas ao exercício ou naturais) condicionam de forma relevante a atividade física,

individual do militar e consequentemente da sua unidade. Pode condicionar a diminuição da *performance* física e psíquica como levar eventualmente a incidentes ou morte;

c. Da revisão do estado de arte e das publicações no âmbito na medicina operacional e medicina aplicada ao desporto no que diz respeito a este tema verifica-se o seguinte:

(1) Relativamente a lesões causadas por alta temperatura / lesão por calor:

(a) As lesões associadas ao calor representam 30-40% dos incidentes, demonstrando a sua relevância epidemiológica;

(b) Do ponto de vista epidemiológico, o número de hospitalizações e mortes associadas a lesão por calor tem vindo aumentar de forma linear na última década;

(c) Existe uma relação entre incidentes associados a lesão por calor e tempo de serviço. Sendo que quanto menor for o tempo de serviço maior será a probabilidade de lesão associada ao calor. A falta de treino, a menor preparação e a menor aclimatização foram os fatores encontrados para esta maior probabilidade;

(d) A síndrome de agressão térmica, compreende um espectro de severidade com os seguintes graus: *rash* térmico, queimadura, cãibras, exaustão por calor e golpe de calor;

(e) São conhecidos quatro grupos de fatores de risco para lesão associada ao calor, são eles: fatores individuais, fatores ambientais, medicação/substâncias de abuso e patologias crónicas. Dentro destes quatro grupos importa destacar:

1. Fatores individuais: idade, obesidade, baixa *performance* física, falta de aclimatização e desidratação;

2. Fatores ambientais: elevada temperatura ambiente, elevada humidade, falta de fluxo de ar e ausência de abrigo/sombra;

3. Medicação e substâncias de abuso: álcool, anfetaminas, laxantes (…).

(f) As lesões associadas ao calor no seu variado espectro podem ser minoradas com ações preventivas, tais como:

1. Uso de equipamento leve e largo;

2. Contemplar no plano um processo de aclimatização progressivo;

3. Evitar exercício intenso durante horas de temperatura elevada;

4. Manter níveis de hidratação adequados ao exercício e clima.

(g) Em ambiente operacional a prevenção da lesão associada ao calor deve ser considerada pela equipa de saúde, instrutor e instruendo;

(h) Existem atualmente ferramentas que permitem estratificar o risco ambiental associado a calor em ambiente de instrução. O índice WBGT (*wet bulb globe temperature*), é calculado através dos níveis de humidade, radiação solar, velocidade do vento e temperatura, Este índice permite determinar a quantidade de exercício que pode/deve ser realizado em ambiente quente;

(i) Esta protocolado pela NATO, através de *guidelines* os tempos de instrução/descanso e hidratação em função do valor de índice de WBGT.

(2) Relativamente a lesões causadas por baixa temperatura / lesão pelo frio:

(a) A exposição de militares a ambiente frio, representa um fator de risco acrescido em ambiente operacional/treino. Especialmente se não forem tomadas as devidas precauções;

(b) As lesões provocadas por baixas temperaturas podem ser de diversos tipos:

1. Hipotermia: surge quando a temperatura central corporal é inferior aos 35ºC. Pode ser considerada leve, moderada ou severa;

2. Lesões por frio a temperaturas > 0ºC. (pé de trincheira);

3. Lesões por frio a temperaturas < 0ºC (sinais precoces de queimadura/queimadura pelo frio);

4. Outras lesões associadas a ambiente frio (intoxicação por CO, queimaduras solares, cegueira da neve, exacerbações respiratórias).

(c) A perda de calor através da pele para o ambiente envolvente é influenciada por diversos fatores:

1. Temperatura do ar;

2. Velocidade do vento;

3. Humidade; Radiação solar;

4. Equipamento/fardamento.

(d) O suor não evaporado pode-se acumular nas roupas e formar cristais de gelo, acentuado ainda mais a perda de calor;

(e) O ar frio nas vias respiratórias aumenta a perda de água através da respiração, especialmente durante o exercício físico;

(f) A base da prevenção para lesão associada ao frio, reside no conhecimento, pelos militares envolvidos, dos fatores risco;

(g) Os fatores de risco descritos na literatura dividem-se em:

1. Ambientais: temperatura do ar, vento, precipitação, imersão e altitude;

2. Missão: intensidade, duração, disponibilidade de abrigo adequado, fardamento e alimentação;

3. Individuais: forma física, composição corporal, fadiga acumulada, género, antecedentes de saúde/hábitos e desidratação.

(h) O consumo energético individual aumenta com a diminuição da temperatura. Em ambiente operacional/tático o gasto pode rondar as 4400Kcal/dia e com incremento da intensidade pode superar as 6000Kcal/dia;

(i) A implementação de hidratação de acordo com o grau de atividade física exigido é fundamental. Pelo que se deve garantir o reabastecimento e disponibilidade de fluidos ao militar;

(j) É necessário implementar um processo de reavaliação constante dos fatores de risco, para que se faça um ajuste proporcional das medidas preventivas;

(k) O cálculo do risco faz-se através do "*Wind-chill temperature index*". Este correlaciona a temperatura do ar em graus Celsius com a velocidade do vento em km/h, determinando o stress

ambiental provocado por frio. Este índex usa como referência a face de humanos como área exposta;

(l) O exercício físico em ambiente frio usualmente mantém ou aumenta a temperatura corporal dado a produção de calor ser maior que a perda;

(m) A atividade física ao frio durante a precipitação/imersão pode não ser suficiente para manter a temperatura corporal, dado que a água leva a aumento a perda de calor 7-10 vezes;

(n) As baixas temperaturas influenciam a destreza manual e mental dos indivíduos expostos. Podendo condicionar decisivamente o cumprimento da missão, quando não são tomadas medidas preventivas em função do risco;

(o) A hipotermia resulta da diminuição da temperatura corporal <35ºC e é caracterizada por tremor severo, letargia, dificuldade em trabalhar e confusão mental. A hipotermia severa é uma condição ameaçadora de vida caracterizada por inconsciência, diminuição e ausência de pulso, diminuição da frequência respiratória e ausência de tremor.

2. FINALIDADE

Definir regras e procedimentos que devem ser adotados quanto à gestão de risco sanitário no âmbito das lesões causadas pelo frio ou calor em ambiente operacional.

3. ÂMBITO

A presente norma interessa a todas as U/E/O do Exército e militares com funções de comando, e em particular às tropas especiais (Comandos, Operações Especiais e Para-quedistas), por forma a identificar fatores de *stress* associados a temperaturas elevadas ou baixas.

4. EXECUÇÃO

a. Alta temperatura / Lesão por calor:

(1) Processo de Aclimatização:

(a) Este processo é uma adaptação fisiológica ao calor e deve compreender um período mínimo de 2 semanas de exposição progressiva ao calor / exercício intenso;

(b) Esta adaptação permite otimizar a performance/desempenho do militar. Verifica-se aumento do volume plasmático, aumento da sudorese e diminuição do limiar para o seu início, aumento de capacidade máxima de vasodilatação cutânea, diminuição da concentração de eletrólitos no suor, diminuição da frequência cardíaca para um mesmo esforço físico exigido, aumenta níveis de aldosterona com consequente diminuição da excreção urinária de sódio/retenção de volume e diminui temperatura central e cutânea.

(c) Após a aclimatização inicial esta mantém-se até um mês, mesmo com a exposição a ambientes opostos (climas mais frios);

(d) Assim sendo este processo deve ser desenvolvido, na fase preparatória, segundo as seguintes premissas:

1. Exposição ao calor mínima de 2h/dia em exercício de endurance cardiovascular;

2. Deve existir uma gradação crescente do exercício físico / intensidade, até se atingir o nível pretendido para desempenho da missão/prova;

3. Deve ser feita monitorização da ingestão hídrica durante todo o processo de aclimatização, com o objetivo de garantir um elevado estado de hidratação do militar;

4. É necessário manter os níveis de hidratação para uma aclimatização efetiva;

5. A aclimatização diminui a concentração de sódio perdida por litro de suor;

6. Concluído o processo de aclimatização deverá existir manutenção da *performance* física atingida – através de exercício regular, respeitando os níveis anteriormente exigidos.

(e) O processo de aclimatização não permite diminuir as necessidades de hidratação;

(f) Não é um processo para diminuir a quantidade de água disponível a cada militar;

(g) Pretende é aumentar a capacidade de um indivíduo resistir ao stress térmico provocado pelas condições/exercício de forma a prevenir as lesões associados ao calor.

(2) Fardamento e Material:

(a) Relevou-se importante adequar a indumentária ao ambiente no qual decorre a missão/treino.

(b) Deve ser considerado a quantidade de fluxo de ar / quantidade de suor absorvido pela farda de forma a otimizar a libertação de calor;

(c) Assim sendo deve se ter em atenção as seguintes premissas:

1. A indumentária deve ser leve e larga;

2. Deve ser aplicado protetor solar, se for o caso, nas áreas expostas ao sol;

3. A quantidade de material atribuído a cada militar deve ter em atenção as condições climatéricas/nível de intensidade exigido.

(3) Cálculo de risco:

(a) As forças NATO utilizam a medida WBGT para quantificar o risco de stress associado ao calor em ambiente tático;

(b) O WBGT é um índex empírico usado para determinar de acordo com o risco a quantidade de atividade física tolerada e os níveis de necessários de aporte de fluidos de forma a maximizar a *performance* militar e diminuir os incidentes durante atividade;

(c) O WBGT, em ambiente exterior, é calculado de acordo com a seguinte fórmula:

WBGT = 0,7 (temperatura bolbo húmido) + 0,2 (temperatura) + 0,1 (humidade)

(d) O valor calculado de WBGT irá definir o risco associado à prática de atividade física em relação à probabilidade de lesão por calor;

(e) Em função do valor encontrado a atividade terá de respeitar diferentes ciclos de trabalho/descanso, diferentes níveis de re-hidratação e podendo ser a atividade adiada/cancelada se não estiverem reunidas condições de segurança;

(f) É possível verificar na seguinte tabela 1 o risco por categorias em função do valor encontrado de WBGT.

(4) Hidratação:

(a) A hidratação é uma necessidade operacional para o sucesso da missão;

(b) É adequado providenciar quantidade de água necessária para que seja mantida o nível de saúde e prontidão de cada militar;

(c) A desidratação é uma das maiores ameaças em ambiente operacional;

(d) A intensidade do exercício físico, o stress ambiental, o equipamento e indumentária aumentam as perdas de água pelo corpo levando a desidratação;

(e) Assim sendo deve se ter em atenção as seguintes premissas:

1. A sensação de sede não é um bom orientador do estado de hidratação;

2. Não se deve implementar restrição hídrica. A restrição hídrica não promove a capacidade de resistir à diminuição da disponibilidade de água;

3. A monitorização do status de hidratação pode ser feita indiretamente pela coloração da urina e peso do militar;

4. A hidratação deve ter em conta três fases: Pré-hidratação, Hidratação durante o exercício e pós-exercício;

5. De forma a rentabilizar a performance do militar o reforço da hidratação pré atividades de alta intensidade é essencial;

6. Deve ser evitada a restrição de água, sendo que a quantidade máxima que se pode disponibilizar é 1,5l/h até 12l/dia. Sendo a média 1,2l/h.

7. Deve ser promovido o hábito de hidratação voluntária do militar, antes de este sentir sede, e não de forma reativa a esta.

(f) Na tabela 1 é possível encontrar a título demonstrativo de orientações de re-hidratação utilizadas por forças NATO.

(5) Tempos exercício / descanso:

(a) O planeamento do horário de trabalho deve ser ter em atenção o ambiente no qual se desenvolver, a intensidade física necessária e a situação militar em causa;

(b) É necessário que quem planeia e quem executa a ação reconheça que é necessário contemplar descanso proporcional à atividade pedida – de acordo com as recomendações NATO;

(c) Importa ressalvar que em ambiente de instrução por vezes o planeamento contempla horas de exercício exigente intercalado com exercício moderado/leve para cumprir o plano formativo;

(d) Nestes casos a experiência do comandante/instrutor é importante para compreender que não deve levar a sua levar a sua unidade a trabalhar no ritmo demasiado elevado que origine lesões associadas ao calor, mas também não deve aligeirar demasiado a intensidade pondo em risco o cumprimento da missão;

(e) Os tempos de descanso assim como o tempo de exercício são bem definidos na seguinte tabela:

Tabela 1 – Cálculo Risco/Hidratação/Tempo exercício -descanso

Categoria de calor	Index WBGT, C°	Trabalho/Exercício Ligeiro		Trabalho/Exercício Moderado		Trabalho/Exercício Pesado	
		Trabalho ou Exercício/ Descanso (min)	Ingestão de água (ml/hr)	Trabalho ou Exercício/ Descanso (min)	Ingestão de água (ml/hr)	Trabalho ou Exercício/ Descanso (min)	Ingestão de água (ml/hr)
1	26°-27,9°	SL	500	SL	750	40/20 min	750
2 (verde)	28°-28,9°	SL	500	50/10 min	750	30/30 min	1000
3 (amarelo)	29°-30,9°	SL	750	40/20 min	750	30/30 min	1000
4 (vermelho)	31°-31,9°	SL	750	30/30 min	750	20/40 min	1000
5 (preto)	> 32°	50/10 min	1000	20/40 min	1000	10/50 min	1000

Legenda 1

- **Exercício Ligeiro** - Caminhar em superfície dura a 4km/H, com menos de 13,6 kg de material individual de combate; Manutenção da arma; Prova de Tiro regular.
- **Exercício Moderado** - Patrulhas, Caminhar em areia a 4km/h sem material de combate.
- **Exercício Pesado** - Caminhar na areia a 4km/h com material de combate; Treino de técnicas de assalto.

Nota: Tempos indicativos, calculados em função do risco definido pela WBGT e tem níveis de hidratação estipulados

(f) Na tabela abaixo, pode-se visualizar algumas recomendações elaboradas por federações desportivas em função do risco calculado pelo WBGT:

WBGT (ºC)	Organização	Tipo de atletas	Recomendações
32.3	ACSM	Indivíduos de baixo risco, em forma e aclimatizados	Limiar de participação
32.2	ITF	Tenistas juniores e em cadeiras de rodas	Suspenção imediata da partida
32.2	WTA	Tenistas femininas	Suspenção imediata da partida
32.0	FIFA	Jogadores de futebol	Intervalo adicional de 30 a 75minutos
30.1	ACSM	Indivíduos de alto risco, não treinadados e não aclimatizados	Limiar de participação
30.1	ITF-WTA	Tenistas femininas juniores	Intervalo de 10minutos entre o 2ª e o 3ª set
30.1	ITF	Tenistas em cadeiras de rodas	Suspenção da partida no final desse set
28.0	ITF	Tenistas em cadeiras de rodas	Intervalo de 15minutos entre o 2ª e o 3ª set
28.0	Open da Australia	Tenistas	Intervalo de 10minutos entre o 2ª e o 3ª set
21.0	Maratonas no hemisfério norte	Corredores em eventos de multidão	Cancelar o envento

(6) Reposição de fluidos e de eletrólitos:

(a) A hidratação é um ponto fulcral na manutenção do potencial do combatente e do seu bem-estar;

(b) A reposição de água simples é fulcral, assim como, de eletrólitos, que ajudarão na manutenção da homeostase corporal, pelo que se deve ter em atenção as seguintes premissas:

1. Está comprovado, por estudos distintos de que não se treina a capacidade adaptativa para baixas ingestões hídricas;

2. O próprio militar deve ter em atenção o nível de hidratação: através da coloração e volume de urina, para além do peso corporal (sem roupa) pré e pós atividade física (sabendo que a perda de 1Kg é aproximadamente igual à perda de 1L);

3. A coloração da urina é uma forma indireta de avaliar a desidratação. Sendo que segundo a escala na lateral, quando mais escura for a cor na urina (mais concentrada) maior será a necessidade de re-hidratação;

4. A ausência de urina, deve ser interpretada como suspeita e como necessidade também de re-hidratação;



5. A partir da coloração urinária correspondente ao nível 3 considera-se como um estado de desidratação severa, pelo que está recomendado reiniciar hidratação imediata;

6. Deve ser fornecida água para repor o volume de suor perdido, bem como, implementar escalas de hidratação e monitorização dessa ingestão;

7. O militar usualmente beberá grande quantidade de água no decorrer das refeições, dado também a ingestão alimentar incrementar o consumo de água;

8. Adicionalmente às refeições deve ser fornecido quantidade de sal para a retenção da água ingerida;

9. Durante a atividade operacional excecional poderão ser exigidos níveis de alta intensidade de trabalho, pelo que em função do ambiente e equipamento pode ser aumentada a necessidade de água até limite máximo diário de 12l/dia;

10. Deve estar calculada as necessidades de sódio e água diárias de cada unidade e incorporadas no plano de reabastecimento;

11. O Gasto Energético deve ser tido em consideração aquando da estimativa da quantidade de água necessária.

As taxas metabólicas para unidades militares no terreno usualmente estão compreendidas entre 3,500 a 5,000 kcal/dia;

Necessidades diárias de água e sódio baseados na variação da WBGT e do gasto energético de moderado (3,500Kcal) a elevado (5,500Kcal)

WBGT	3,500Kcal	5,500Kcal
10ºC	3 litros 2 gramas	6 litros 4 gramas
20ºC	5 litros 3 gramas	10 litros 6 gramas
30ºC	6 litros 4 gramas	14 litros 8 gramas

12. A tabela anterior estima as necessidades de um militar após o período de aclimatização consoante o gasto energético estimado e assumindo uma concentração de sódio no suor de 0,6g/l;

13. Relativamente ao tipo de bebida que deve ser ingerida:

a. Exposição ao calor, inferior a 90min: água natural fresca (15-20ºC);

b. Exposição ao calor, entre 90min e 240min: bebida isotónica açucarada fresca (com uma concentração não superior a 8% ou 2 colheres de açúcar por litro)

c. Exposição ao calor, superior a 240min: bebida isotónica açucarada (concentração não superior a 8% ou 2 colheres de açúcar por litro) suplementada com 1 colher de chá de sal por litro.

14. Não devem ser utilizadas fórmulas de re-hidratação comerciais para desidratação por diarreia, dadas as necessidades específicas de sais serem distintas

b. Baixa temperatura / Lesão por frio:

(1) Exposição em ambientes húmidos:

(a) A água possui condutividade superior ao ar, acelera a perda de calor até 25 vezes mais;

(b) As perdas de calor estão relacionadas com a temperatura da água assim como com o nível de imersão a que é sujeito um determinado indivíduo;

(c) A seguinte tabela serve como orientação para evitar episódios de hipotermia, referindo o número máximo de horas a que se pode submeter um indivíduo a imersão em função da temperatura água e nível de imersão.

Temperatura da água	Imersão até ao tornozelo	Imersão até ao joelho	Imersão até à cintura
10-13ºC	7 horas Com precipitação 3,5 horas	5 horas Com precipitação 2,5 horas	1,5 horas Com precipitação 1 hora
13-16ºC	8 horas Com precipitação 4 horas	7 horas Com precipitação 3,5 horas	2 horas Com precipitação 1,5 hora
16-19ºC	9 horas Com precipitação 4,5 horas	8 horas Com precipitação 4 horas	3,5 horas Com precipitação 2,5 horas
19-21ºC	12 horas Com precipitação 6 horas	12 horas Com precipitação 6 horas	8 horas Com precipitação 5 horas
> 21ºC	> 12 horas	> 12 horas	> 6 horas

1. Os valores são indicativos de uma população em geral;

2. Deve-se ter especial atenção aos indivíduos com fatores de risco individuais (nomeadamente: gordura corporal, antecedentes pessoais etc.);

3. O militar deve assegurar o acondicionamento prévio de mudas de roupa e saco cama de modo a garantir que estes permaneçam secos e em condições de utilização após a imersão.

(2) Fardamento e Material:

(a) É importante adequar a indumentária ao ambiente no qual decorre a missão/treino;

(b) O fardamento molhado leva a perda de potencial de isolamento e aumentando assim a perda de calor;

(c) Pelo que, se recomenda o seguinte:

1. O fardamento para ambientes frios, deve incluir proteção para frio, chuva e neve. Baseando-se em dois princípios

fundamentais: diferentes camadas e manutenção de fardamento/material seco;

2. É importante referir, que este método permite ajustar as camadas ao tipo de ambiente e de atividade;

3. As camadas denominam-se por:

a. Interna: Contacto direto com a pele, devendo ser de *polyester* ou *polypropileno* - materiais que não absorvem o suor, transmite antes às camadas seguintes

b. Média: É a primeira camada e isolamento devendo ser de *polyester* que mimetize polar;

c. Externa: Deve ser semipermeável, o que permite ao suor evaporação e ao mesmo tempo proteger contravento e chuva. A existência de "fendas axilares" é importante pois permite ajustar o nível de ventilação sob a referida camada, potenciado a libertação de suor.

4. Poderão ser adicionadas ou removidas camadas para que o militar se sinta mais confortável. (em função da sudação e inversamente à velocidade do vento e aumento do frio);

5. Durante a prática de exercício previsto, devem ser retiradas camadas de forma a impedir que o militar tenha sudação aumentada. Da mesma forma que após exercício devem ser repostas/adicionadas camadas;

6. De forma minimizar as perdas de calor pela cabeça, deverá ser incutido o uso de chapéus de inverno e *balaclava*;

7. Similarmente está recomendado uso de luvas, devendo idealmente o militar ter disponível sempre um par de luvas seco para troca;

8. O uso do modelo de luvas "*mittens*" promovem uma maior proteção individual, apesar de estas comprometerem a destreza manual;

9. No que diz respeito aos pés, deverão ser usadas duas camadas de meias:

a. A primeira **(meia interna)** deve ser de *polypropileno* ou *nylon*, para desta forma permitir a passagem de suor para camada seguinte;

b. A **meia externa** deverá ser de lã pura ou mistura, para absorver o suor do pé. As meias não deverão ser demasiado justas, pois podem comprometer a circulação. As botas deverão ser de um tamanho superior ao habitualmente usado de forma a comportar estas duas camadas.

10. O militar deverá mudar periodicamente de meias, nunca permanecendo com o mesmo par mais de doze horas;

11. O uso de polainas é vantajoso para impedir que a neve entre nas botas;

12. O militar não deve dormir de botas, permitindo assim que o pé respire e seque. Devendo aproveitar este tempo, para colocar as botas e as meias a secar durante a noite;

13. O modelo de bota a usar deve ser indicado para ambientes táticos frios;

14. Os sacos cama tipo patrulha estão preparados para temperaturas até 2ºC, sendo que os especiais para frio conferem proteção até aos -20ºC. A combinação destes dois modelos poderá fornecer proteção até aos menos -34ºC;

15. Todo o equipamento deve ser sacudido e limpo regularmente para que a sujidade não obstrua os poros e comprometa a sua funcionalidade

(3) Queimadura por frio:

(a) A queimadura por frio é caracterizada por congelamento do tecido corporal, em áreas mais suscetíveis como as extremidades: dedos das mãos, pés, orelhas e nariz;

(b) O treino para este tipo de ambiente tático não é suficiente, sendo sempre necessário que a aprendizagem seja feita de forma empírica pelo militar ao longo do cumprimento da missão;

(c) Pelo que se aconselha o seguinte:

1. Implementação de programa de auto e hetero-vigilância para reconhecer sinais de queimadura precoce, nomeadamente das extremidades corporais (dedos das mãos e pés; orelhas, bochechas e nariz);
2. O comandante deve criar um ambiente de a vontade para o militar reportar superiormente as referia lesões;
3. A probabilidade de queimadura por frio é definida pelo *índex Wind-Chill Temperature*;
4. Quando o index Wind-chill é < 3 existe grande probabilidade de se verificar congelamento de dedos dos pés;
5. Devem sempre ser usadas luvas no contacto com o equipamento. A título de exemplo, manusear arma sem luvas pode levar a queimadura por frio em segundos;
6. Evitar derramar líquidos na pele ou nas roupas;
7. Não deve ser usada camuflagem facial abaixo de valores de temperatura que condicionem congelamento;
8. Manter a face e orelhas protegidas, usando a *balaclava*;
9. Manter meias limpas e secas, e evitar o uso de calçado apertado;
10. O militar não deve usar o ar expirado como forma de aquecimento de mãos, pois o ar expirado conte vapor de água que posteriormente pode congelar;
11. O militar deve "desmochilar" regularmente de forma aumentar a circulação, diminuído a possibilidade de lesão por frio.

(d) O risco de lesão associada ao frio é dado pelo valor de WCTI, que relaciona o valor de temperatura com a velocidade do vento – como se pode verificar na tabela seguinte:

O *Wind-Chill Temperature Index* em ºC: combinando a temperatura do ar e a velocidade do vento.
As cores indicam o tempo após o qual surgirem queimaduras pelo frio na superfície cutânea da face exposta.

Temperatura do ar (ºC)

Velocidade do vento (Km/h)	5	0	-5	-10	-15	-20	-25	-30	-35	-40	-45	-50
5	4	-2	-7	-13	-19	-24	-30	-36	-41	-47	-53	-58
10	3	-3	-9	-15	-21	-27	-33	-39	-45	-51	-57	-63
15	2	-4	-11	-17	-23	-29	-35	-41	-48	-54	-60	-66
20	1	-5	-12	-18	-24	-30	-37	-43	-49	-56	-62	-68
25	1	-6	-12	-19	-25	-32	-38	-44	-51	-57	-64	-70
30	0	-6	-13	-20	-26	-33	-39	-46	-52	-59	-65	-72
35	0	-7	-14	-20	-27	-33	-40	-47	-53	-60	-66	-73
40	-1	-7	-14	-21	-27	-34	-41	-48	-54	-61	-68	-74
45	-1	-8	-15	-21	-28	-35	-42	-48	-55	-62	-69	-75
50	-1	-8	-15	-22	-29	-35	-42	-49	-56	-63	-69	-76
55	-2	-8	-15	-22	-29	-36	-43	-50	-57	-63	-70	-77
60	-2	-9	-16	-23	-30	-36	-43	-50	-57	-64	-71	-78
65	-2	-9	-16	-23	-30	-37	-44	-51	-58	-65	-72	-79
70	-2	-9	-16	-23	-30	-37	-44	-51	-58	-65	-72	-80
75	-3	-10	-17	-24	-31	-38	-45	-52	-59	-66	-73	-80
80	-3	-10	-17	-24	-31	-38	-45	-52	-60	-67	-74	-81

Risco baixo de queimadura pelo frio para a generalidade das pessoas
Risco aumentado de queimadura pelo frio para a generalidade das pessoas em 10-30min de exposição
Risco elevado de queimadura pelo frio para a generalidade das pessoas em 5-10min de exposição
Risco elevado de queimadura pelo frio para a generalidade das pessoas em 2-5min de exposição
Risco elevado de queimadura pelo frio para a generalidade das pessoas em menos de 2 min de exposição

(e) Em função do risco calculado existem recomendações gerais, pela doutrina NATO. Podem ser encontradas na tabela abaixo:

Risco de queimadura pelo frio			
Baixo	**Aumentado**	**Elevado (5-10min)**	**Muito elevado (2-5min)**
Aumentar a auto e hetero-vigilância	Auto e hetero-vigilância obrigatória a cada 20-30min	Auto e hetero-vigilância obrigatória a cada 10min	Auto e hetero-vigilância obrigatória a cada 5min
Usar camadas de fardamento adequadas e protecção do vento; induir cabeça, mãos, pés e face	Usar camadas de fardamento adequadas e protecção do vento; induir cabeça, mãos, pés e face	Usar camadas de fardamento adequadas e protecção do vento; induir cabeça, mãos, pés e face	Usar camadas de fardamento adequadas e protecção do vento; induir cabeça, mãos, pés e face
Cobrir a superfície cutânea exposta se possível.	Cobrir a superfície cutânea exposta se possível	Cobrir a superfície cutânea exposta se possível	Cobrir a superfície cutânea exposta se possível
Usar barreira para o vapor e o modelo de botas aqueadas para baixas temperaturas	Usar barreira para o vapor e o modelo de botas aqueadas para baixas temperaturas	Usar barreira para o vapor e o modelo de botas aqueadas para baixas temperaturas	Usar barreira para o vapor e o modelo de botas aqueadas para baixas temperaturas
Evitar suar	Evitar suar	Evitar suar	Evitar suar
	Providenciar instalações com aquecimento	Providenciar instalações com aquecimento	Providenciar instalações com aquecimento
		Grupos de trabalho com no mínimo 2 elementos	Grupos de trabalho com no mínimo 2 elementos
		Não exposição cutânea	Não exposição cutânea
		Manter-se activo	Manter-se activo
			Estar preparado para modificar as actividades dado o risco
			Encurtar a duração das activiades ao máximo

(4) Lesões por frio com temperaturas > 0ºC (Pé de trincheira / úlcera necrótica pé):

(a) Este tipo de lesões surge nas exposições entre os 0ºC e os 15ºC;

(b) Essencialmente, associadas a um ambiente húmido e à inatividade. (mais frequente nas operações defensivas);

(c) Este tipo de lesões é caracterizado por ausência de sensibilidade e edema do tecido corporal afetado por exposição prolongada a frio húmido;

(d) Assim aconselha-se o seguinte, para evitar este tipo de lesões:

1. Manter as mãos e os pés limpos e secos;

2. Mudar assim que possível para luvas e meias secas, sempre que molhados;

3. Promover a rotatividade de militares, bem como promover atividade física em espaços confinados;

4. Secar as botas e forro pelo menos uma vez por dia;

5. Usar polainas, de forma a manter a neve/gelo fora das botas. As polainas feitas com membranas semipermeáveis permitem evaporação do suor.

(5) "Cegueira da neve":

(a) A luz é intensificada pela reflexão das ondas luminosas na superfície de neve ou de água e há exposição a radiação ultravioleta por vezes sem qualquer proteção ocular;

(b) Pode provocar lesões na córnea e conjuntiva;

(c) Pelo que se aconselha, o uso de óculos de sol com protetor lateral, o que deve ser considerado um elemento de proteção individual do militar.

(6) Hidratação:

(a) Mesmo com baixas temperaturas a reposição adequada de fluidos de acordo com grau de intensidade física é fundamental;

(b) A manutenção de níveis de hidratação é considerada uma necessidade operacional;

(c) Assim aconselha-se o seguinte:

1. Esta hidratação deve ser feita, idealmente, às refeições;

2. O fornecimento de bebidas quentes estimula a hidratação do militar, assim como, promove a elevação da moral;

3. As refeições aumentam o consumo de água e devem garantir o aporte mineral de sais;

4. Deve existir um planeamento detalhado dos reabastecimentos;

5. Cada combatente deverá garantir que o conteúdo do seu cantil / *camelback* não congela:

a. Para tal deverá transporta-los entre as camadas de roupa;

b. Evitar contentores de metal;

c. Não expor estes diretamente ao meio exterior.

6. Em caso de necessidade extrema, deverá ser planeada a purificação/descongelar da neve ou gelo como fonte de água;

7. A ingestão de neve não descongelada / não purificada acarreta elevados riscos para o militar;

8. A semelhança do que acontece em ambiente quentes, é da responsabilidade do militar a monitorização do grau de hidratação através da frequência e coloração urinária.

O Ajudante-General do Exército

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REVIEW ARTICLE

CURRENT CONCEPTS

Rhabdomyolysis and Acute Kidney Injury

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Rhabdomyolysis — literally, the dissolution of striped (skeletal) muscle — is characterized by the leakage of muscle-cell contents, including electrolytes, myoglobin, and other sarcoplasmic proteins (e.g., creatine kinase, aldolase, lactate dehydrogenase, alanine aminotransferase, and aspartate aminotransferase) into the circulation. Massive necrosis, which is manifested as limb weakness, myalgia, swelling, and, commonly, gross pigmenturia without hematuria, is the common denominator of both traumatic and nontraumatic rhabdomyolysis.[1,2] Acute kidney injury is a potential complication of severe rhabdomyolysis, regardless of whether the rhabdomyolysis is the result of trauma or some other cause, and the prognosis is substantially worse if renal failure develops. In contrast, in less severe forms of rhabdomyolysis or in cases of chronic or intermittent muscle destruction — a condition sometimes called hyperCKemia — patients usually present with few symptoms and no renal failure. We review the pathophysiological characteristics and management of acute kidney injury associated with rhabdomyolysis.

There are eight commonly reported categories of rhabdomyolysis (Table 1). Exogenous agents that can be toxic to muscles, especially alcohol, illicit drugs, and lipid-lowering agents, are common nontraumatic causes. Recurrent episodes of rhabdomyolysis are often a sign of an underlying defect in muscle metabolism.[1,3,4]

Acute rhabdomyolysis occasionally develops in patients with structural myopathies when they are performing strenuous exercise, are under anesthesia, have taken drugs that are toxic to muscles, or have viral infections.[1] When a diagnosis of acute rhabdomyolysis is suspected, histochemical, immunohistochemical, and mitochondrial respiration studies performed on a muscle-biopsy specimen may yield a specific diagnosis. It is important to wait several weeks or months after the clinical event to perform a biopsy, because the results of a biopsy will typically be uninformative at an early stage. Thus, the specimen may appear normal or show no specific findings other than necrosis during and early after the acute episode of rhabdomyolysis (Fig. 1).[2,5]

The mechanisms involved in the pathogenesis of rhabdomyolysis are direct sarcolemmic injury (e.g., trauma) or depletion of ATP within the myocyte, leading to an unregulated increase in intracellular calcium.[6,7] Sarcoplasmic calcium is strictly regulated by a series of pumps, channels, and exchangers that maintain low levels of calcium when the muscle is at rest and allow the increase that is necessary for actin–myosin binding and muscle contraction. Depletion of ATP impairs the function of these pumps, resulting in a persistent increase in sarcoplasmic calcium that leads to persistent contraction and energy depletion and the activation of calcium-dependent neutral proteases and phospholipases; the result is the eventual destruction of myofibrillar, cytoskeletal, and membrane proteins, followed by lysosomal digestion of fiber contents. Ultimately, the myofibrillar network breaks down, resulting in disintegration of the myocyte.[2] In the case of patients with rhabdomy-

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Table 1. Major Categories and Commonly Reported Causes of Rhabdomyolysis.

Category	Commonly Reported Cause
Trauma	Crush syndrome
Exertion	Strenuous exercise, seizures, alcohol withdrawal syndrome
Muscle hypoxia	Limb compression by head or torso during prolonged immobilization or loss of consciousness,* major artery occlusion
Genetic defects	Disorders of glycolysis or glycogenolysis, including myophosphorylase (glycogenosis type V), phosphofructokinase (glycogenosis type VII), phosphorylase kinase (glycogenosis type VIII), phosphoglycerate kinase (glycogenosis type IX), phosphoglycerate mutase (glycogenosis type X), lactate dehydrogenase (glycogenosis type XI) Disorders of lipid metabolism, including carnitine palmitoyl transferase II, long-chain acyl-CoA dehydrogenase, short-chain L-3-hydroxyacyl-CoA dehydrogenase, medium-chain acyl-CoA dehydrogenase, very-long-chain acyl-CoA dehydrogenase, medium-chain 3-ketoacyl-CoA, thiolase† Mitochondrial disorders, including succinate dehydrogenase, cytochrome *c* oxidase, coenzyme Q10 Pentose phosphate pathway: glucose-6-phosphate dehydrogenase Purine nucleotide cycle: myoadenylate deaminase
Infections‡	Influenza A and B, coxsackievirus, Epstein–Barr virus, primary human immunodeficiency virus, legionella species *Streptococcus pyogenes, Staphylococcus aureus* (pyomyositis), clostridium
Body-temperature changes	Heat stroke, malignant hyperthermia, malignant neuroleptic syndrome, hypothermia
Metabolic and electrolyte disorders	Hypokalemia, hypophosphatemia, hypocalcemia, nonketotic hyperosmotic conditions, diabetic ketoacidosis
Drugs and toxins	Lipid-lowering drugs (fibrates, statins), alcohol, heroin, cocaine
Idiopathic (sometimes recurrent)	

* Rhabdomyolysis from this cause is associated with a crush syndrome–like mechanism.
† CoA denotes coenzyme A.
‡ In most cases, the mechanism is unclear.

olysis caused by trauma, additional injury results from ischemia reperfusion and inflammation by neutrophils that infiltrate damaged muscle.[8]

EPIDEMIOLOGY OF MYOGLOBINURIA-INDUCED ACUTE KIDNEY INJURY

Acute kidney injury associated with myoglobinuria is the most serious complication of both traumatic and nontraumatic rhabdomyolysis, and it may be life-threatening. Acute kidney injury as a complication of rhabdomyolysis is quite common, representing about 7 to 10% of all cases of acute kidney injury in the United States.[4,9] The true incidence of acute kidney injury in rhabdomyolysis is difficult to establish owing to varying definitions and clinical scenarios. The reported incidence ranges from 13% to approximately 50%.[9-11] In a study by Melli et al. involving 475 hospitalized patients with rhabdomyolysis, the incidence of acute kidney injury was 46%.[10] Although rhabdomyolysis from any cause can lead to acute kidney injury, in this study, the incidence of acute kidney injury was higher among persons who used illicit drugs or abused alcohol and among persons who had undergone trauma than among persons with muscle disease, and the incidence was particularly high among persons with more than one recognized causal factor.[10]

The outcome of rhabdomyolysis is usually good provided that there is no renal failure. Nevertheless, mortality data vary widely according to the study population and setting and the number and severity of coexisting conditions. In a study in which the incidence of vasculopathy leading to rhabdomyolysis as a result of limb ischemia was high, the overall mortality was 32%.[12] In contrast, the study by Melli et al. of hospitalized patients, in whom the abuse of illicit drugs and alcohol was the most frequently identified cause of rhabdomyolysis, showed a mortality of 3.4% among patients with acute kidney injury.[10] Among patients in the intensive care unit, the mortality has been reported to be 59% when acute kidney injury is present and 22% when it is not present.[13,14] Long-term survival among patients with rhabdomyolysis and acute kidney injury is reported to be close to 80%, and the majority of patients with rhabdomyolysis-induced acute kidney injury recover renal function.[14]

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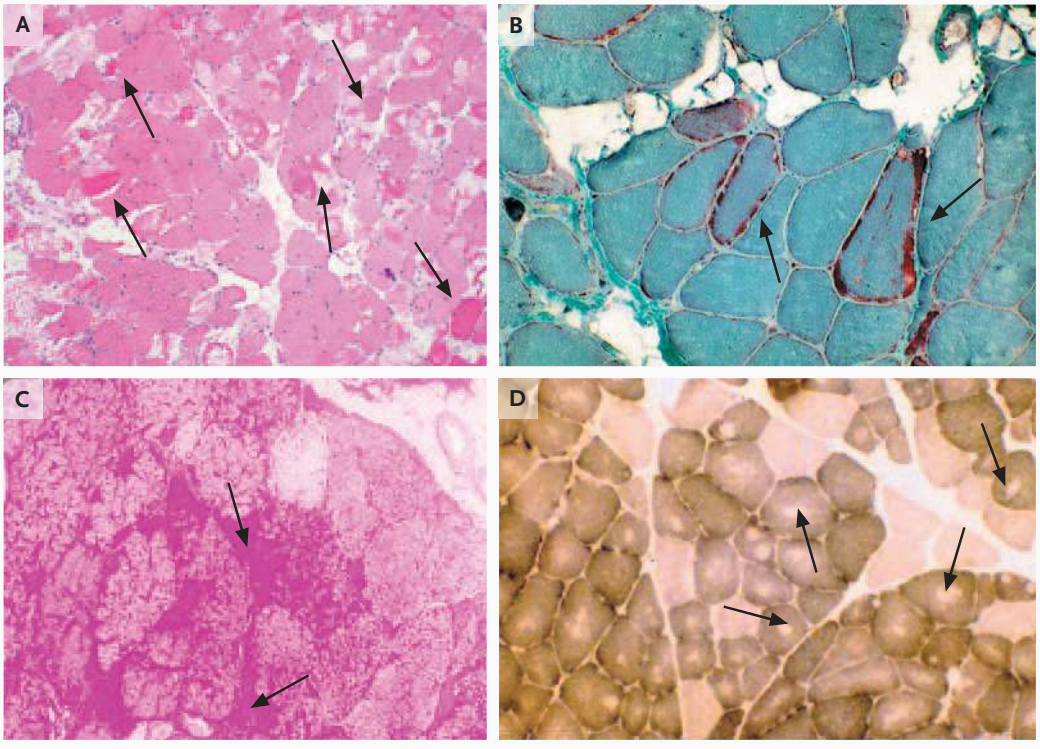

Figure 1. Histopathological Findings in Frozen Muscle-Tissue Specimens from Patients with Rhabdomyolysis.

Panel A shows massive muscle necrosis (arrows) in a patient with statin-related rhabdomyolysis (hematoxylin and eosin). This histologic feature would be similar in every case of rhabdomyolysis, irrespective of the cause. Panel B shows the typical ragged-red fibers (arrows) in a muscle-biopsy specimen from a patient with mitochondrial myopathy that was obtained 3 months after an episode of severe rhabdomyolysis. The mitochondrial dysfunction was confirmed by a mitochondrial respiratory chain–based assay (Gomori's trichrome). Panel C shows periodic acid–Schiff (PAS)–positive material (arrows) in some muscle fibers in a case of McArdle's disease. The biopsy was performed a few months after the patient's recovery from recurrent rhabdomyolysis (PAS stain). Panel D shows a muscle-biopsy specimen from a patient with central core disease. The specimen was obtained after the patient's recovery from malignant hyperthermia. Abundant central cores can be seen (arrows) (NADH–tetrazolium reductase stain).

PATHOGENESIS OF MYOGLOBIN-INDUCED ACUTE KIDNEY INJURY

Myoglobinuria occurs only in the context of rhabdomyolysis. Myoglobin is a dark red 17.8-kDa protein that is freely filtered by the glomerulus, enters the tubule epithelial cell through endocytosis, and is metabolized. It appears in the urine only when the renal threshold of 0.5 to 1.5 mg of myoglobin per deciliter is exceeded and is grossly visible as reddish-brown ("tea-colored") urine when serum myoglobin levels reach 100 mg per deciliter[15]; therefore, not all cases of rhabdomyolysis are associated with myoglobinuria.

Although the exact mechanisms by which rhabdomyolysis impairs the glomerular filtration rate are unclear, experimental evidence suggests that intrarenal vasoconstriction, direct and ischemic tubule injury, and tubular obstruction all play a role (Fig. 2).[16] Myoglobin becomes concentrated along the renal tubules, a process that is enhanced by volume depletion and renal vasoconstriction, and it precipitates when it interacts with the Tamm–Horsfall protein, a process favored by acidic urine.[17] Tubule obstruction occurs principally at the level of the distal tubules, and direct tubule cytotoxicity occurs mainly in the proximal tubules.

Myoglobin seems to have no marked nephrotoxic effect in the tubules unless the urine is acidic. Myoglobin is a heme protein; it contains iron, as ferrous oxide (Fe^{2+}), which is necessary for the binding of molecular oxygen. However, molecular oxygen can promote the oxidation of Fe^{2+} to ferric oxide (Fe^{3+}), thus generating a hydroxyl radical. This oxidative potential is counter-

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acted by effective intracellular antioxidant molecules. However, cellular release of myoglobin leads to uncontrolled leakage of reactive oxygen species, and free radicals cause cellular injury. It has been suggested that heme and free iron–driven hydroxyl radicals are critical mediators of tubule damage owing to the protective effects of deferoxamine (an iron chelator) and glutathione.[18] More recently, it has been shown that myoglobin itself can exhibit peroxidase-like enzyme activity that leads to uncontrolled oxidation of biomolecules, lipid peroxidation, and the generation of isoprostanes.[19]

Renal vasoconstriction is a characteristic feature of rhabdomyolysis-induced acute kidney injury and is the result of various combinations of several mechanisms. First, intravascular volume depletion due to fluid sequestration within damaged muscle promotes homeostatic activation of the renin–angiotensin system, vasopressin, and the sympathetic nervous system. Second, experimental studies have shown that there are additional vascular mediators in the reduction of renal blood flow, including endothelin-1, thromboxane A_2, tumor necrosis factor α; and F_2-isoprostanes[9,20]; a deficit in the vasodilator nitric oxide, which can be attributed to the scavenging effect of myoglobin in the renal microcirculation, has also been shown to be a mediator in the reduction in renal blood flow.[16] Collectively, these vascular mediators appear to be locally stimulated by oxidant injury and leukocyte-mediated inflammation as a result of the endothelial dysfunction that is common to other forms of acute kidney injury.[21]

RENAL MANIFESTATIONS OF RHABDOMYOLYSIS

Patients with acute rhabdomyolysis usually present with pigmented granular casts, reddish-brown urine supernatant, and markedly raised serum creatine kinase. There is no defined threshold value of serum creatine kinase above which the risk of acute kidney injury is markedly increased. A very weak correlation between the peak creatine kinase value and the incidence of acute kidney injury or peak serum creatinine has been reported.[10,11,22] The risk of acute kidney injury in rhabdomyolysis is usually low when creatine kinase levels at admission are less than 15,000 to 20,000 U per liter.[12,13,23] Although acute kidney injury may be associated with creatine kinase values as low as 5000 U per liter, this usually occurs when coexisting conditions such as sepsis, dehydration, and acidosis are present.[11] For example, in patients with chronic myopathies such as muscular dystrophies and inflammatory myopathies, acute kidney injury seldom develops unless a superimposed event is present. Patients with these chronic myopathies, on the other hand, may have moderately raised concentrations of plasma myoglobin but not overt myoglobinuria.[24] Myoglobinuria can be inferred if urinary dipstick testing shows a positive result for blood when there are no red cells in the sediment. This false positive result for blood occurs because the dipstick test is unable to distinguish between myoglobin and hemoglobin. The test has a sensitivity of 80% for the detection of rhabdomyolysis.[10] Other causes of pigmented urine should be taken into consideration (Table 2).[25] Myoglobin is the true pathogenic factor in rhabdomyolysis-induced acute kidney injury but is seldom measured directly in urine or plasma. Serum myoglobin levels peak well before serum creatine kinase levels, and serum myoglobin has a rapid and unpredictable metabolism, which functions partly through the kidney but mainly outside the kidney (probably through the liver or spleen).[26] Therefore, measurement of serum myoglobin has a low sensitivity for the diagnosis of rhabdomyolysis.[27]

Acute kidney injury associated with rhabdomyolysis often leads to a more rapid increase in plasma creatinine than do other forms of acute kidney injury. However, this finding may reflect the overrepresentation of young, muscular men among patients with rhabdomyolysis rather than increased creatinine or creatine release from injured muscle.[14,28,29] Similarly, a low ratio of blood urea nitrogen to creatinine is often seen in patients with rhabdomyolysis. Rhabdomyolysis-induced acute kidney injury frequently causes oliguria and occasionally causes anuria.

Another characteristic feature of rhabdomyolysis-induced acute kidney injury that is different from the manifestation of other forms of acute tubular necrosis is the frequent, but not universal, presence of a low fractional excretion of sodium (<1%), perhaps reflecting the primacy of preglomerular vasoconstriction and tubular occlusion rather than tubular necrosis.[30] The fractional excretion of sodium is a measurement of the percentage of filtered sodium that is excreted in the urine, and low levels in patients with acute kidney injury are an indication of the relative

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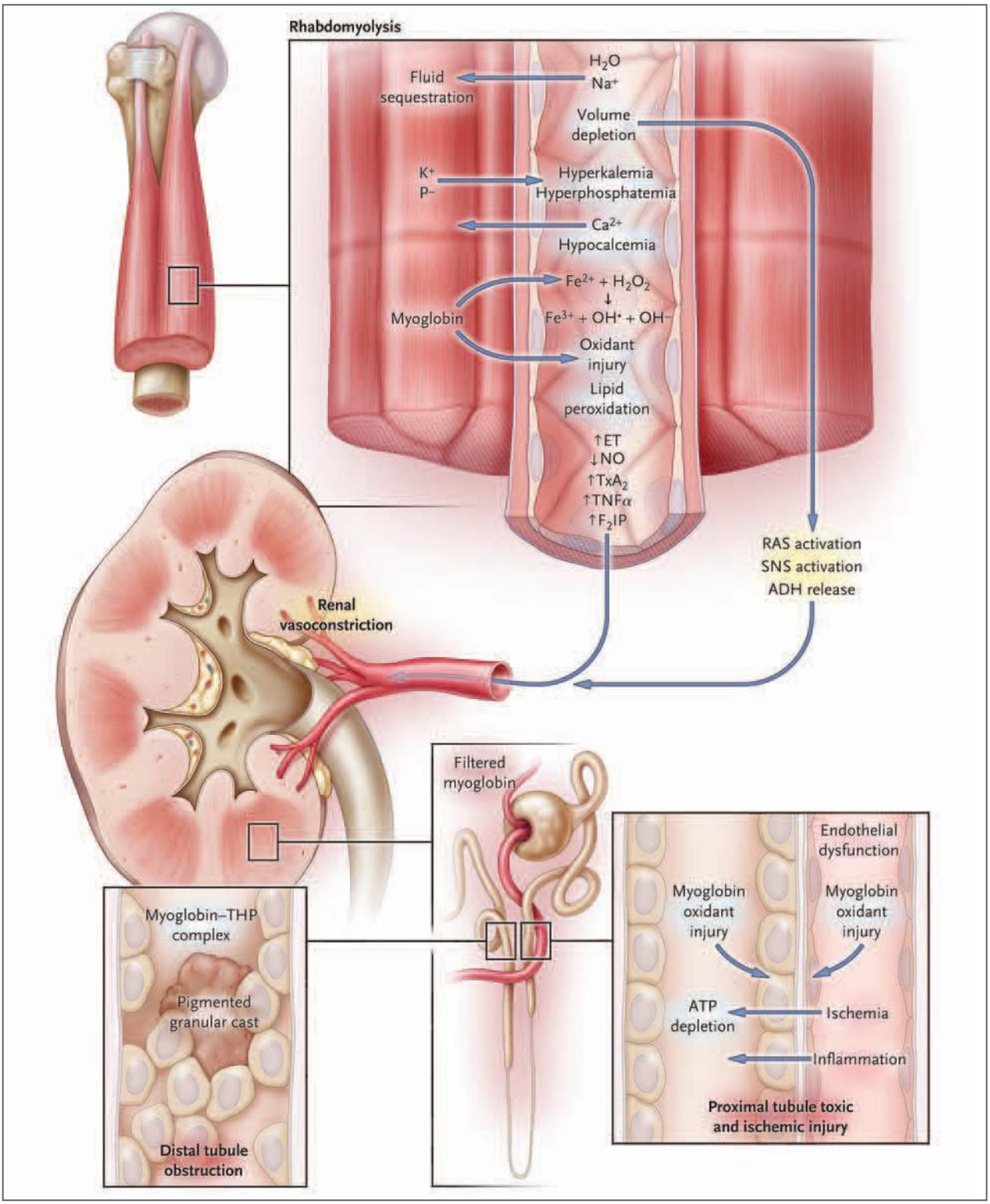

integrity of tubular functions. However, when ischemic or toxic acute tubular necrosis is established, both urinary sodium and the fractional excretion of sodium are raised.

Electrolyte abnormalities that occur as a result of the release of cellular components often accompany and determine the severity of rhabdomyolysis-induced acute kidney injury. Because

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Table 2. Causes and Macroscopic Features of Red and Brown Urine.

Cause	Results of Test for Blood in Fresh Urine*	Sediment†‡	Supernatant‡
Hematuria	+ to ++++	Red	Yellow
Myoglobinuria	+ to ++++	Normal	Red to brown
Hemoglobinuria	+ to ++++	Normal	Red to brown
Porphyria	Negative	Normal	Red
Bile pigments	Negative	Normal	Brown
Food and drugs§	Negative	Normal	Red to brown

* Urine was tested with the use of a dipstick test. This is a semiquantitative test of the number of erythrocytes per microliter. Results range from + (5 to 10 erythrocytes per microliter) to ++++ (approximately 250 erythrocytes per microliter).
† Normal refers to white or yellow in color, unremarkable in the absence of cells, crystals, or cylinders.
‡ The sediment and supernatant were examined after centrifugation of 10 to 15 ml of urine at 1500 to 3000 rpm for 5 minutes.
§ Food and drugs that can cause red urine include beets, blackberries, rhubarb, food coloring, fava beans, phenolphthalein, rifampin, doxorubicin, deferoxamine, chloroquine, ibuprofen, and methyldopa. Those that can cause brown urine include levodopa, metronidazole, nitrofurantoin, iron sorbitol, chloroquine, and methyldopa.

they may precede the acute kidney injury, electrolyte levels should be measured as soon as rhabdomyolysis is diagnosed. The electrolyte abnormalities that can occur with rhabdomyolysis include hyperkalemia (which can be rapidly increasing), hyperphosphatemia, hyperuricemia, high anion-gap metabolic acidosis, and hypermagnesemia mainly when renal failure is present.[4,15,22,31] High levels of phosphate can bind to calcium, and deposition of calcium–phosphate complexes in soft tissues can occur. In addition, hyperphosphatemia inhibits 1α-hydroxylase, thus limiting the formation of calcitriol (1,25-dihydroxyvitamin D_3), the active form of vitamin D. Hyperkalemia is an early manifestation of rhabdomyolysis, and serum potassium can occasionally reach life-threatening levels both in patients with severe traumatic rhabdomyolysis and in those with nontraumatic rhabdomyolysis.[15,31] Hyperuricemia is also usually present owing to the liberation of nucleosides from injured muscle and can contribute to renal tubule obstruction since uric acid is insoluble and may precipitate in acidic urine.

Hypocalcemia is a common complication of rhabdomyolysis and usually results from calcium entering the ischemic and damaged muscle cells and from the precipitation of calcium phosphate with calcification in necrotic muscle. Hypercalcemia associated with recovery of renal function is unique to rhabdomyolysis-induced acute kidney injury and results from the mobilization of calcium that was previously deposited in muscle, the normalization of hyperphosphatemia, and an increase in calcitriol.[32]

Figure 2 (facing page). Pathophysiological Mechanisms in Rhabdomyolysis-Induced Acute Kidney Injury.

Fluid sequestration in injured muscle induces volume depletion and consequent activation of the sympathetic nervous system (SNS), antidiuretic hormone (ADH), and the renin–angiotensin system (RAS), all of which favor vasoconstriction and renal salt and water conservation. In addition, myoglobin-induced oxidative injury increases vasoconstrictors and decreases vasodilators. Kidney injury results from a combination of ischemia due to renal vasoconstriction, direct tubular toxicity mediated by myoglobin-associated oxidative injury (inset, lower right), tubular damage due to ischemia, and distal tubule obstruction due to precipitation of the Tamm–Horsfall protein–myoglobin complex (inset, lower left) in addition to sloughed tubular cells forming cellular cast. As in acute kidney injury due to other causes, endothelial dysfunction and local inflammation contribute to tissue damage and organ dysfunction. ET denotes endothelin, F_2 IP F_2 isoprostanes, NO nitric oxide, THP Tamm–Horsfall protein, TNF-α tumor necrosis factor α, TxA_2 thromboxane A_2, and VC vasoconstriction.

TREATMENT AND PREVENTION

Patients with rhabdomyolysis that is associated with acute kidney injury usually present with a clinical picture of volume depletion that is due to the sequestration of water in injured muscles. Therefore, the main step in managing the condition (Table 3) remains the early, aggressive repletion of fluids; patients often require about 10 liters of fluid per day,[31] with the amount administered depending on the severity of the rhabdomyolysis.[33] There are no randomized trials that have evaluated fluid repletion in patients with the crush syndrome resulting from injuries sus-

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Table 3. Steps in the Prevention and Treatment of Rhabdomyolysis-Induced Acute Kidney Injury.

Check for extracellular volume status, central venous pressure, and urine output.*
Measure serum creatine kinase levels. Measurement of other muscle enzymes (myoglobin, aldolase, lactate dehydrogenase, alanine aminotransferase, and aspartate aminotransferase) adds little information relevant to the diagnosis or management.
Measure levels of plasma and urine creatinine, potassium and sodium, blood urea nitrogen, total and ionized calcium, magnesium, phosphorus, and uric acid and albumin; evaluate acid–base status, blood-cell count, and coagulation.
Perform a urine dipstick test and examine the urine sediment.
Initiate volume repletion with normal saline promptly at a rate of approximately 400 ml per hour (200 to 1000 ml per hour depending on the setting and severity), with monitoring of the clinical course or of central venous pressure.
Target urine output of approximately 3 ml per kilogram of body weight per hour (200 ml per hour).
Check serum potassium level frequently.
Correct hypocalcemia only if symptomatic (e.g., tetany or seizures) or if severe hyperkalemia occurs.
Investigate the cause of rhabdomyolysis.
Check urine pH. If it is less than 6.5, alternate each liter of normal saline with 1 liter of 5% dextrose plus 100 mmol of bicarbonate. Avoid potassium and lactate-containing solutions.
Consider treatment with mannitol (up to 200 g per day and cumulative dose up to 800 g). Check for plasma osmolality and plasma osmolal gap. Discontinue if diuresis (>20 ml per hour) is not established.
Maintain volume repletion until myoglobinuria is cleared (as evidenced by clear urine or a urine dipstick testing result that is negative for blood).
Consider renal-replacement therapy if there is resistant hyperkalemia of more than 6.5 mmol per liter that is symptomatic (as assessed by electrocardiography), rapidly rising serum potassium, oliguria (<0.5 ml of urine per kilogram per hour for 12 hours), anuria, volume overload, or resistant metabolic acidosis (pH <7.1).

* In the case of the crush syndrome (e.g., earthquake, building collapse), institute aggressive volume repletion promptly before evacuating the patient.

tained in a disaster such as an earthquake. However, most, if not all, reports show that patients in whom acute kidney injury developed had a longer delay in receiving supportive therapy than did patients in whom acute kidney injury did not develop (Table 4).[8,23,31,33,39] Therefore, early, aggressive volume repletion is crucial in patients with the crush syndrome.[34,35]

Although the need for volume repletion is established, the composition of the fluid used for repletion remains controversial. Some investigators recommend administering sodium bicarbonate, which results in an alkaline urine, as first proposed by Bywaters and Beall,[8,39,40] whereas others argue against this approach and favor normal or 0.45% saline solution.[15] The three empirical advantages of alkalinization that have been noted are based on studies in animal models of rhabdomyolysis. First, it is known that precipitation of the Tamm–Horsfall protein–myoglobin complex is increased in acidic urine.[17] Second, alkalinization inhibits reduction–oxidation (redox) cycling of myoglobin and lipid peroxidation in rhabdomyolysis, thus ameliorating tubule injury.[41] Third, it has been shown that metmyoglobin induces vasoconstriction only in an acidic medium in the isolated perfused kidney.[42] The principal, and probably the only, disadvantage of alkalinization is the reduction in ionized calcium, which can exacerbate the symptoms of the initial hypocalcemic phase of rhabdomyolysis.

The clinical benefits of alkalinization as compared with simple volume repletion are not firmly established. Comparative studies usually have small sample sizes and show a combination of measures (e.g., alkalinization plus mannitol) that preclude an analysis of the effectiveness of the particular single measure[34-38] (Table 4). In one study, renal outcomes did not differ significantly between patients treated with bicarbonate plus mannitol and those treated with saline alone, although peak serum creatine kinase values were below 5000 U per liter, a finding indicating that the degree of injury was mild, making treatment effect difficult to appreciate.[36] In the largest study of patients who had undergone trauma (2083 patients), rhabdomyolysis developed in 85% of the patients, and administration of bicarbonate plus mannitol did not prevent renal failure, the need for dialysis, or death in the sample as a whole, although the results suggested that it might be beneficial in patients with peak creatine kinase

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Table 4. Comparative Studies on Preventive and Therapeutic Regimens in Rhabdomyolysis.

Study	Study Design	Patient Group	No. in Sample	Therapeutic Strategy	Outcome in Patients with Acute Kidney Injury
Shimazu et al.[34]	Retrospective	Patients with the crush syndrome	14	Late vs. early initiation of therapy; high (>10 liters for 48 hours) vs. low volume of hydration	Better if therapy initiated early; high volume of hydration better
Gunal et al.[35]	Retrospective	Patients with the crush syndrome	16	Early vs. late treatment with normal saline followed immediately by bicarbonate	Better if treatment initiated early
Homsi et al.[36]	Retrospective	Patients in the intensive care unit	24	Normal saline vs. normal saline plus bicarbonate and mannitol	No difference
Brown et al.[37]	Retrospective	Patients with trauma	2083	Normal saline vs. bicarbonate plus mannitol	No difference
Cho et al.[38]	Prospective, randomized	Patients with intoxication from doxylamine	28	Ringer's lactate vs. normal saline; bicarbonate if urine pH is <6.5	No effect on peak creatine kinase level or recovery with Ringer's lactate as compared with normal saline; more bicarbonate needed with normal saline than with Ringer's lactate

values of more than 30,000 U per liter.[37] In a randomized, prospective trial of fluid repletion with Ringer's lactate as compared with normal saline in patients with rhabdomyolysis attributed to doxylamine intoxication, 28 patients were randomly assigned to receive one of the solutions.[38] Sodium bicarbonate was added in both groups if the urine pH was less than 6.5 after 12 hours of aggressive volume repletion. Peak creatine kinase levels were less than 10,000 U per liter, and it appears that acute kidney injury did not develop in any of the patients, although these data were not reported. Whatever the real, consistent benefits of urine alkalinization in patients with rhabdomyolysis, there is evidence that massive infusion of normal saline alone can contribute to metabolic acidosis, mainly owing to the dilution of serum bicarbonate with a solution relatively high in chloride ions, generating hyperchloremic metabolic acidosis with observed reductions in serum pH of as much as 0.30 units.[43] Therefore, administration of both normal saline and sodium bicarbonate seems to be a reasonable approach when fluid is being replenished in patients with rhabdomyolysis, especially patients with metabolic acidosis (Table 3). If sodium bicarbonate is used, urine pH and serum bicarbonate, calcium, and potassium levels should be monitored, and if the urine pH does not rise after 4 to 6 hours of treatment or if symptomatic hypocalcemia develops, alkalinization should be discontinued and hydration continued with normal saline.

The use of diuretics remains controversial, but it is clear that it should be restricted to patients in whom the fluid repletion has been achieved. Mannitol may have several benefits: as an osmotic diuretic, it increases urinary flow and the flushing of nephrotoxic agents through the renal tubules; as an osmotic agent, it creates a gradient that extracts fluid that has accumulated in injured muscles and thus improves hypovolemia; finally, it is a free-radical scavenger.[4,8,20] Most data on the action of mannitol come from studies in animals, which collectively show that the protective effect of mannitol may be attributable to its osmotic diuretic action rather than to the other mechanisms.[44] No randomized, controlled trial has supported the evidence-based use of mannitol, and some clinical studies suggest no beneficial effects.[36,37] In addition, high accumulated doses of mannitol (>200 g per day or accumulated doses of >800 g) have been associated with acute kidney injury due to renal vasoconstriction and tubular toxicity, a condition known as osmotic nephrosis.[45,46] However, many experts continue to suggest that mannitol should be used to prevent and treat rhabdomyolysis-induced acute kidney injury and relieve compartmental pressure.[20,45-47] During the time mannitol is being administered, plasma osmolality and the osmolal gap (i.e., the difference between the measured and calculated serum osmolality) should be monitored frequently and therapy discontinued if adequate diuresis is not achieved or if the osmolal gap rises above 55 mOsm per kilogram.[46] Loop

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Table 5. Approach to the Management of Hyperkalemia (Serum Potassium ≥5.5 mmol per Liter) in Rhabdomyolysis.

Check for potassium levels every 4 hours in cases of severe rhabdomyolysis (creatine kinase level >60,000 to 80,000 U per liter) or suspected systemic toxin. Treat rapidly rising potassium levels aggressively.
Obtain an electrocardiogram and check for severe manifestations (QRS interval widening, small P waves, severe arrhythmias thought to be caused by high levels of potassium). Consider cardiac monitoring and admission to an intensive care unit if the potassium level is higher than 6 mmol per liter, if there are abnormalities on the electrocardiogram, or if rhabdomyolysis is severe, with rapidly rising potassium.
Check for plasma calcium levels. Hypocalcemia seriously aggravates the adverse electrical effects of hyperkalemia.
If the electrocardiogram shows severe irregularities, administer calcium chloride or calcium gluconate by intravenous infusion. Consider slow continuous infusion if hypocalcemia is present. Anticipate possible hypercalcemia in late rhabdomyolysis. Do not mix with bicarbonate solutions.
If potassium level is higher than 6 mmol per liter, shift potassium into cells. Serum potassium will be lowered approximately 10 to 30 minutes after the following measures are performed, and the effect will last for 2 to 6 hours.
Administer insulin and glucose by means of a slow intravenous push; monitor glucose with the use of fingerstick testing.
Administer a β_2-adrenergic agonist such as albuterol, 10 to 20 mg in 4 ml of normal saline by inhalation of aerosol over 10 minutes. Do not use as a single measure; combine with glucose and insulin for additive effect.
Administer sodium bicarbonate if the patient has acidemia. This treatment may worsen the manifestations of hypocalcemia, and the efficacy is not as consistent as that with insulin and glucose or albuterol. Do not use as a single measure.
Remove potassium from the body with the use of either resins or dialysis as indicated; the use of diuretics is optional.
Administer cation-exchange resin (sodium polystyrene sulfonate) orally or as a retention enema (avoid sorbitol in such cases and avoid after surgery).
Perform hemodialysis if the above measures fail or if severe renal failure or severe hyperkalemia develops. Consider hemodialysis when rhabdomyolysis is associated with marked tissue breakdown and rapidly rising serum potassium levels. Check serum potassium levels 4 hours after hemodialysis, since a rebound increase can occur. Previous measures of potassium shift into cells may decrease the efficiency of hemodialysis with respect to removal of potassium.
Administer loop diuretics such as furosemide, but only after the patient's fluid level has been expanded.

diuretics also increase urinary flow and may decrease the risk of myoglobin precipitation, but no study has shown a clear benefit in patients with rhabdomyolysis. Therefore, loop diuretics in rhabdomyolysis-induced acute kidney injury should be used in the same manner as that recommended in acute kidney injury that is due to other causes.[47,48]

The electrolyte abnormalities associated with rhabdomyolysis-induced acute kidney injury must be treated promptly; the correction of hyperkalemia, which occurs very early in the course of the disease, is especially important (Table 5).[49] Agents that cause a shift of potassium from the extracellular to the intracellular space (e.g., hypertonic glucose and bicarbonate) are effective only temporarily, and the only means of removing potassium from the body is diuresis (effective kaliuresis), the use of intestinal potassium binders, or dialysis.[4,8,9,15] In contrast, early hypocalcemia should not be treated unless it is symptomatic or unless severe hyperkalemia is present. Calcium-containing chelators should be used with caution to treat hyperphosphatemia, since the calcium load could increase the precipitation of calcium phosphate in injured muscle.[4,8,9,15]

When acute kidney injury is severe enough to produce refractory hyperkalemia, acidosis, or volume overload, renal-replacement therapy is indicated, principally with intermittent hemodialysis, which can correct electrolyte abnormalities rapidly and efficiently.[8,9,47] Conventional hemodialysis does not remove myoglobin effectively owing to the size of the protein and is therefore usually mandated by renal indications. However, owing to the pathogenic role of myoglobin in rhabdomyolysis-induced acute kidney injury, preventive extracorporeal elimination has been studied. Although plasmapheresis has been shown to have no effect on outcomes or on the myoglobin burden of the kidneys,[50] continuous venovenous hemofiltration or hemodiafiltration has shown some efficacy in removing myoglobin, principally with the use of super high-flux filters and high volumes of ultrafiltration (convection).[51] However, the evidence is mainly from isolated case reports, and the effect on outcomes is unknown. In addition, some studies have shown that the half-life of serum myoglobin does not differ significantly between patients who are treated conservatively and those who receive continuous venovenous hemodiafiltration.[27] Until randomized studies are performed, preventive hemofiltration cannot be recommended.

The use of antioxidants and free-radical scav-

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engers (e.g., pentoxifylline, vitamin E, and vitamin C) may be justified in the treatment or prevention of myoglobinuric acute kidney injury,[8,52] as suggested by small case series, case reports, and various experimental studies of myoglobinuria, but controlled studies evaluating their efficacy are lacking.

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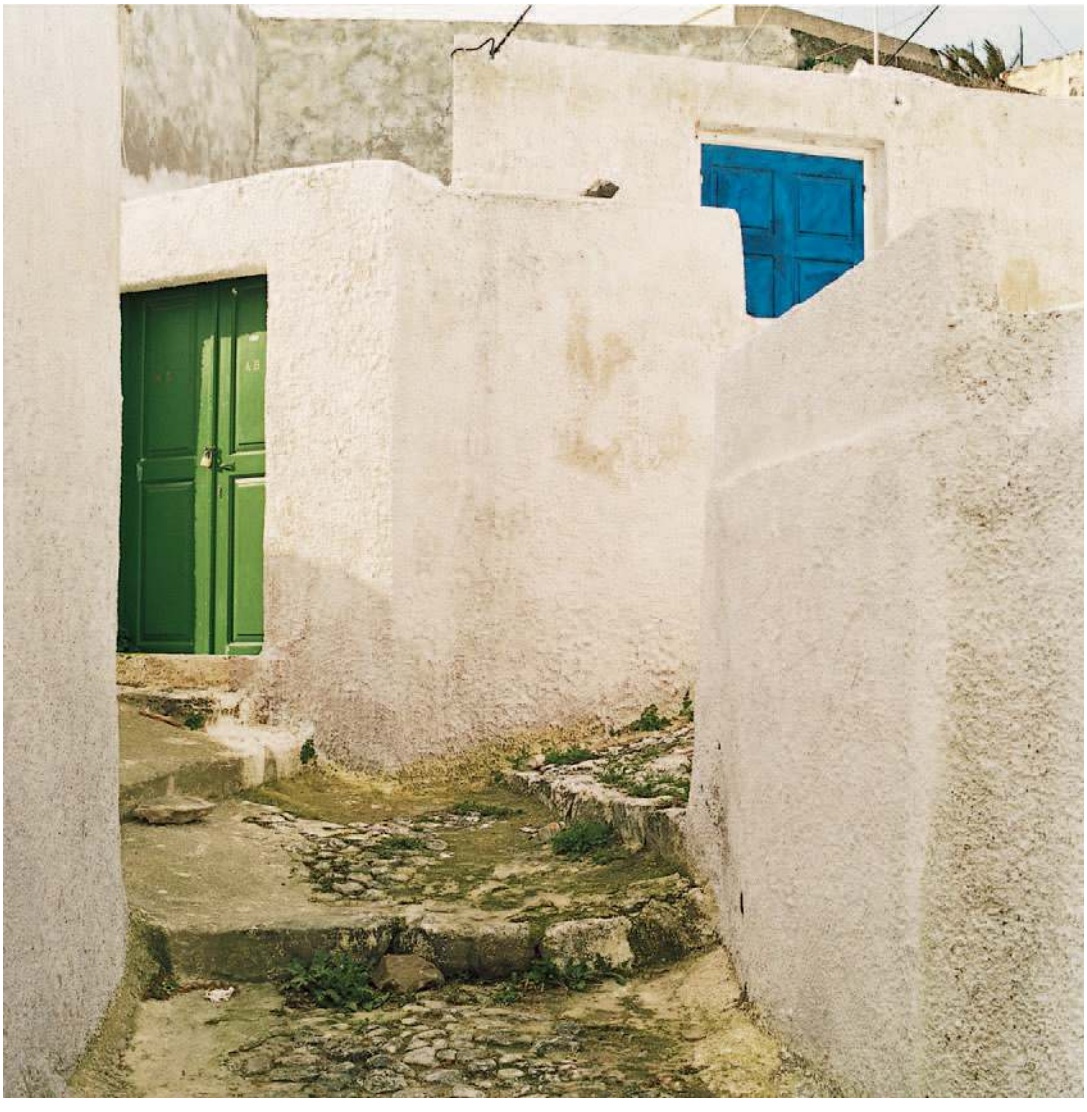

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Critical Care

REVIEW Open Access

Beyond muscle destruction: a systematic review of rhabdomyolysis for clinical practice

Luis O. Chavez[1], Monica Leon[2], Sharon Einav[3,4] and Joseph Varon[5*]

Abstract

Background: Rhabdomyolysis is a clinical syndrome that comprises destruction of skeletal muscle with outflow of intracellular muscle content into the bloodstream. There is a great heterogeneity in the literature regarding definition, epidemiology, and treatment. The aim of this systematic literature review was to summarize the current state of knowledge regarding the epidemiologic data, definition, and management of rhabdomyolysis.

Methods: A systematic search was conducted using the keywords "rhabdomyolysis" and "crush syndrome" covering all articles from January 2006 to December 2015 in three databases (MEDLINE, SCOPUS, and ScienceDirect). The search was divided into two steps: first, all articles that included data regarding definition, pathophysiology, and diagnosis were identified, excluding only case reports; then articles of original research with humans that reported epidemiological data (e.g., risk factors, common etiologies, and mortality) or treatment of rhabdomyolysis were identified. Information was summarized and organized based on these topics.

Results: The search generated 5632 articles. After screening titles and abstracts, 164 articles were retrieved and read: 56 articles met the final inclusion criteria; 23 were reviews (narrative or systematic); 16 were original articles containing epidemiological data; and six contained treatment specifications for patients with rhabdomyolysis.

Conclusion: Most studies defined rhabdomyolysis based on creatine kinase values five times above the upper limit of normal. Etiologies differ among the adult and pediatric populations and no randomized controlled trials have been done to compare intravenous fluid therapy alone versus intravenous fluid therapy with bicarbonate and/or mannitol.

Keywords: Rhabdomyolysis, Acute kidney injury, Myoglobinuria, Myopathy

Background

Rhabdomyolysis is a clinical entity characterized by the destruction of skeletal muscle with resultant release of intracellular enzymatic content into the bloodstream that leads to systemic complications [1, 2]. The classic presentation of this condition is muscle pain, weakness, dark tea-colored urine (pigmenturia), and a marked elevation of serum creatine kinase (CK) five to ten times above the upper limit of normal serum levels [3]. The global incidence of rhabdomyolysis remains unknown but several population risk groups have been identified (i.e., morbid obese patients, chronic users of lipid-lowering drugs, post-operative patients) [4–6].

The term "crush syndrome" is usually used to describe muscle destruction after direct trauma, injury, or compression [7]. It was first described in 1941, when Bywaters and coworkers established a relationship between muscle necrosis and a brown pigment found by autopsy in the renal tubules of patients buried for several hours during a bomb attack in London [8]. Man-made and natural disasters comprise the majority of cases of crush syndrome-associated rhabdomyolysis with development of life-threatening complications to this day [7].

Acute kidney injury (AKI) is the most common systemic complication of rhabdomyolysis. It occurs at an incidence ranging between 10 and 55 % and is associated

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with a poor outcome, particularly in the presence of multiple organ failure [9]. Therefore, preservation of renal function with intravenous (IV) fluid therapy remains the cornerstone of rhabdomyolysis treatment [10]. The importance of rapid initiation of IV fluid therapy in the management of patients with rhabdomyolysis was first documented by Ron and coworkers in 1984 [11]; among the seven patients treated with fluids on-site during a disaster, none developed AKI. This finding received further support in additional studies suggesting that prompt IV fluid administration is associated with better patient outcome [12–14].

No guidelines for the management of rhabdomyolysis are available; nor have any randomized controlled trials of treatment been conducted. Recommendations for fluid therapy in rhabdomyolysis have yet to be established in terms of fluid type, volume, and time of initiation. Management of rhabdomyolysis is currently based on observations from retrospective studies, case reports, and case series which describe diverse and often parallel medical treatments for this syndrome and for its most common complication, AKI [10, 15].

Most of the current knowledge is based on historical data and has been unchanged for more than a decade. Therefore, the aim of this review is to summarize the literature published in the past 10 years (2006–2015) to update the definition, etiological classification, pathophysiology, diagnosis, epidemiology (e.g., risk factors, population and subgroup incidence, common etiologies, and morbidity and mortality), and treatment of rhabdomyolysis in humans.

Methods

Information sources

Two authors (LOC and ML) independently searched the medical literature published in three databases (MEDLINE, SCOPUS, and ScienceDirect) for articles that included in their title or abstract the keywords "rhabdomyolysis" or "crush syndrome". The search covered all articles from January 2006 to December 2015; we selected this period to increase knowledge and provide an updated review based on the existing literature from the past 10 years. All types of articles, including reviews (narrative and systematic), randomized controlled trials (RCTs), case-control cohorts, case series, and case reports were screened for relevant content. Abstracts from the selected articles were read and, if considered eligible for further review, the complete article was obtained.

Search approach

Data collection and extraction were divided into two steps. The first step was intended to identify the articles with data relevant for extraction regarding definition, pathophysiology, and diagnosis of rhabdomyolysis. In order to qualify for inclusion the article was to contain any information regarding the following: definition, etiological classification, pathophysiology, or diagnosis of rhabdomyolysis.

The second step was intended to identify original research articles that included data regarding the epidemiology (e.g., risk factors, population and subgroup incidence, common etiologies, and morbidity and mortality) or treatment of rhabdomyolysis. To this end we searched MEDLINE using the keywords noted above ("rhabdomyolysis" or "crush syndrome") and added a filter selecting "humans" in the "Species" field. We selected for inclusion only original research articles which contained specifics of human epidemiological data or treatment. Excluded were articles referring to treatment of rhabdomyolysis-induced AKI only, case reports, and laboratory investigations of rhabdomyolysis. Repeated publications and articles not in English or Spanish were also excluded. Figure 1 shows a flowchart for study selection.

Data collection

Controversies regarding article eligibility for data extraction were resolved by a third author (JV). The references from the selected articles that had been retrieved were also screened for additional possible references. After determining the relevance of each paper, the articles were divided into several files according to their topic relevance (definition, etiology and epidemiology, pathophysiology, diagnosis, and treatment). There was no limit to the number of files an article could appear in. Finally, the data from each topic file were summarized. No additional statistical analysis was performed.

Results

The two searches generated 5632 articles overall. After screening the titles of all these articles, only 286 potentially relevant articles remained. The abstracts of these articles were screened and only 164 articles contained information relevant to the topic files. These 164 complete articles were retrieved and read. Only 56 articles met final inclusion criteria; single case reports and articles published in a language different from English or Spanish were excluded. This systematic review includes reference to 23 reviews (narrative or systematic) which include information regarding definition, etiological classification, pathophysiology, and diagnosis of rhabdomyolysis. It also includes reference to 16 original articles which met inclusion criteria for epidemiological data extraction and six original articles which met inclusion criteria for treatment. Table 1 lists the original articles that included data on risk factors, etiology, and epidemiology of rhabdomyolysis. Table 2 lists the original

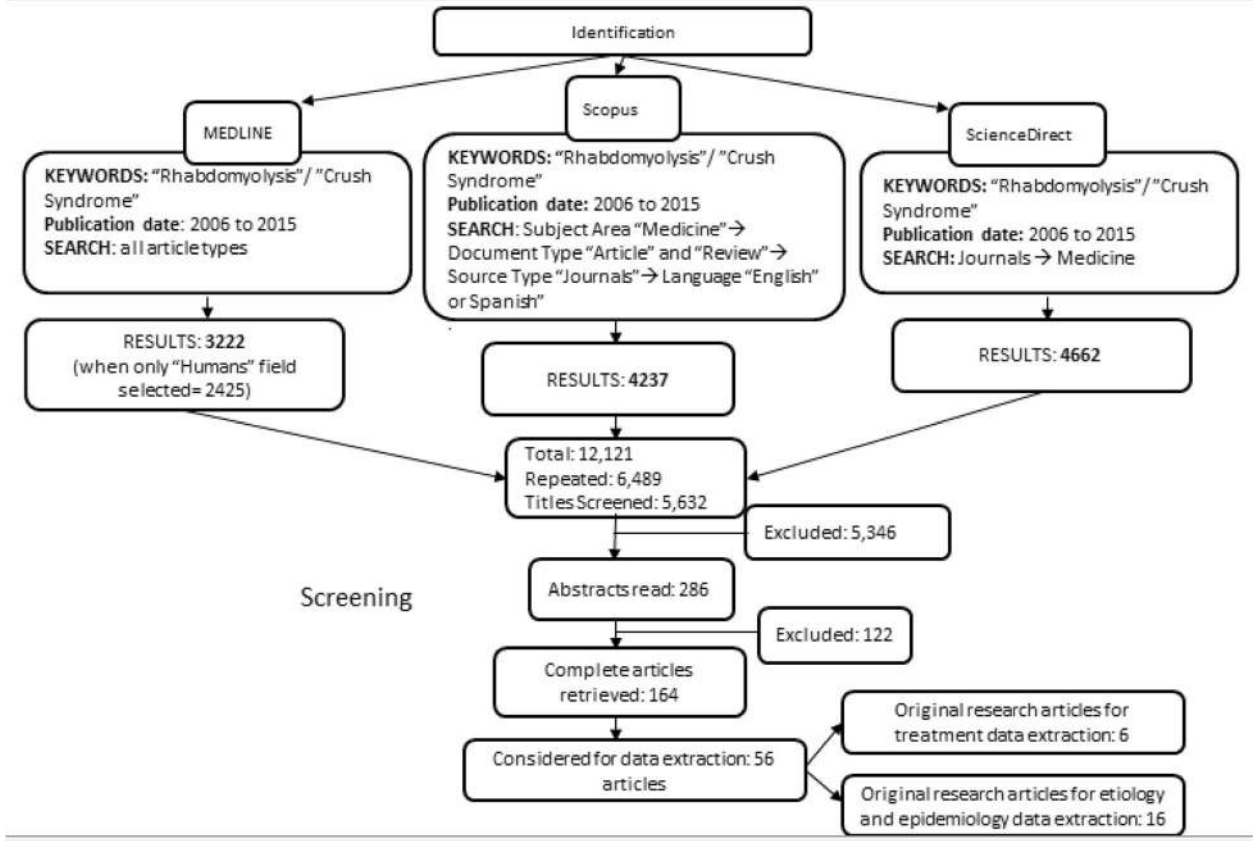

Fig. 1 Flowchart for study selection

articles that included data on treatment specifications for rhabdomyolysis.

Data synthesis

Definition

The clinical studies were very heterogeneous with regard to the definition of rhabdomyolysis; although most authors diagnosed rhabdomyolysis based on CK levels five times the upper limit of normal levels (>1000 U/L), others used alternative criteria for diagnosis (Table 1) [16–31]. In the clinical setting, symptoms were not usually taken into consideration when defining rhabdomyolsysis; however, the most commonly included ones were muscle pain and muscle weakness while the presence of dark urine was not used to define this entity in most studies [16, 18, 21]. When rhabdomyolysis is associated with the use of lipid-lowering drugs (statins, fibrates, or a combination of both), the CK level cutoff is considered ten times the upper limit of normal [30, 32, 33]. The definition of severity of rhabdomyolysis varied among studies, some defining "severe rhabdomyolysis" based on different CK cutoff values (>5000 U/L up to >15,000 U/L) [26, 34].

Epidemiology and etiology

Many cases of rhabdomyolysis are not detected and the incidence of this clinical entity has been reported only in subgroups of populations at risk [5, 6, 9, 35]. Rhabdomyolysis is more frequent among males, African-Americans, patients <10 and >60 years old, and in people with a body mass index exceeding 40 kg/m^2 [5, 6].

The causes of rhabdomyolysis have been classified differently by several authors. Zimmerman and Shen [36] used a classification based on their mechanism of injury (hypoxic, physical, chemical, and biologic). Other authors described alternative classifications such as physical/non-physical, exertional/non-exertional, and acquired/inherited [2, 37–39]. Table 3 distinguishes rhabdomyolysis according to acquired and inherited causes and includes some examples of the most common etiologies reported in the medical literature. Causes of rhabdomyolysis are also different depending on the age; trauma, drugs, and infections are the most commonly reported in adults [19, 24, 26] while trauma, viral infections, drugs, and exercise etiologies prevail in children [16, 27–29].

Muscle toxicity due to several drugs may arise either by a direct mechanism or through drug interactions [23, 40].

Table 1 Studies with epidemiological data

Article	Type of study	Type of patients	RM definition	Etiologies	Risk factors	Patients with RM	Comments
Mannix et al. 2006 [16]	RS	Pediatric patients in the ED	CK level >1000 IU/L	Viral myositis, trauma, connective tissue disease	NA	RM = 191	Most common reported symptoms were muscle pain and fever. AKI developed in only nine patients
Lagandre et al. 2006 [17]	POS	49 bariatric post-operative patients	CK level >1000 IU/L	NA	Surgical time >4 h, diabetes, BMI >40 kg/m^2	RM = 13	Type of surgeries performed were gastric banding or bypass
De Oliveira et al. 2009 [18]	POS	22 bariatric post-operative patients	An increase >5× the upper limit of the normal CK level	NA	Prolonged surgical duration	RM = 17	Clinical neuromuscular symptoms occurred in 45 % of patients
Linares et al. 2009 [19]	RS	Hospitalized patients	CK levels >5000 IU/L	Recreational drugs and alcohol, trauma, compression, shock and statin use	NA	RM = 106	The authors suggest that RM should be defined using CK levels above 10–25 times the upper limit of normal. AKI developed in 52 patients
Youssef et al. 2010 [20]	POS	23 bariatric post-operative patients	Post-operative CK levels >1000 IU/L	NA	BMI >56 kg/m_2	RM = 7	Factors such as sex, age, and length of surgery were not good predictors of RM
Alpers et al. 2010 [21]	RS	Patients in military training	Muscle pain, weakness, or swelling over <7 days with a CK >5× the upper limit of normal	Exertional RM	NA	RM = 177	Authors comment that exertional RM is associated with lower incidence of AKI
Bache et al. 2011 [22]	RS	76 burn patients in the ICU	"Late-onset" RM: CK >1000 U/L, 1 week or more after burn episode	NA	Sepsis, nephrotoxic drugs, hypokalemia	"Late-onset" RM = 7	Authors suggest measuring CK in all patients with the risk factors described in burn patients to initiate prompt treatment
Oshima 2011 [23]	RS	Cases of drug-related RM	NA	Drug use	<10 year olds, weight less than 50 kg	RM = 8610	Lipid lowering drugs were most frequently reported as the associated drugs
Herraez Garcia et al. 2012 [24]	RS	Adult hospitalized patients	CK level of 5× upper limit (975 UI/L)	Trauma, sepsis, immobility	Elder patients and male sex	RM = 449	No relationship was found between CK levels and AKI development or mortality
El-Abdellati et al. 2013 [25]	RS	1769 ICU patients	CK level >1000 U/L	Prolonged surgery, trauma, ischemia, infections	Surgical duration >6 h, resuscitation, compartment syndrome	RM = 342	The authors found a correlation between CK levels and the development of AKI

Table 1 Studies with epidemiological data *(Continued)*

Rodriguez et al. 2013 [26]	RS	Acute-care hospital patients	Severe RM: >5000 IU/L	Immobilization, illicit drug abuse, infections, trauma	NA	Severe RM = 126	More than half of the patients developed AKI. Variables associated with poor outcome were hypoalbuminemia, metabolic acidosis, and decreased prothrombin time
Chen et al. 2013 [27]	RS	Pediatric patients in the ED	CK levels >1000 IU/	Infection, trauma, exercise	NA	RM = 37	Common symptoms were muscle pain and weakness. Dark urine reported in 5.4 % of patients
Talving et al. 2013 [28]	RS	Pediatric trauma patients	NA	Trauma	NA	RM = 521	AKI occurred in 70 patients. The authors concluded that a CK level ≥3000 was an independent risk factor for developing AKI
Grunau et al. 2014 [29]	RS	Patients in the ED	CK levels >1000 U/L	Illicit drug use, infections, trauma	NA	RM = 400	AKI developed in 151 patients; 18 patients required hemodialysis
van Staa et al. 2014 [30]	RS	641,703 statin users	CK levels 10× the upper limit of normal	Statin drug use	Drug–drug interaction	Reported with RM = 59 CK >10× = 182	The incidence of RM in this cohort of statin users was very low
Pariser et al. 2015 [31]	RS	1,016,074 patients with a major urologic surgery	NA	NA	Diabetes, chronic kidney disease, obesity, bleeding, age and male sex	RM = 870	Surgeries associated with RM were nephrectomy (radical or partial) and radical cystectomy

Abbreviations: *AKI* acute kidney injury, *BMI* body mass index, *CK* creatine kinase, *ED* emergency department, *ICU* intensive care unit, *NA* not available, *POS* prospective observational study, *RM* rhabdomyolysis, *RS* retrospective study

Table 2 Studies included with treatment details

Article	Type of study	Population	IV fluid	Bicarbonate/mannitol	Rate of AKI and need for RRT
Altintepe et al. 2007 [55]	CS	*N* = 9	Fluid type used 5 % dextrose and 0.45 NS. 4–8 L of IV fluid daily	40 mEq $NaHCO_3$ and 50 mL of 20 % mannitol mixed with 1 L of IV fluid (0.45 % NaCl and 5 % dextrose) They targeted a urine pH above or equal 6.5	2 patients (28.6 %) developed AKI Patients received hemodialysis due to hyperkalemia
Cho et al. 2007 [56]	PS	*N* = 28	Fluid therapy consisted of lactated Ringer's solution (13 patients) versus NS (15 patients) (the authors concluded that LR was more useful than NS) IV fluid rate 400 mL/h	Bicarbonate was used to achieve urine pH ≥6.5 in the patients with NS IV fluid	No patient developed AKI
Talaie et al. 2008 [51]	RS	*N* = 156	Fluid therapy given 1–8 L in the first 24 h (mean IV fluid 3.2 L/24 h)	Bicarbonate was given to 115 patients	30 patients (28.6 %) developed AKI
Zepeda-Orozco et al. 2008 [57]	RS	*N* = 28	36 % of the patients received saline infusion (20 mL/kg) in the first 24 h	79 % of patients received sodium bicarbonate IV fluid	11 patients (39.2) developed AKI 7 patients with CK levels >5000 U/L required RRT
Sanadgol et al. 2009 [58]	CS	*N* = 31	0.45 % NS	15 mEqL NaHC03 mixed with IV fluid Alkaline IV solution 3–5× more than maintenance rate was used	8 patients (25.8 %) developed AKI
Iraj et al. 2011 [34]	PS	*N* = 638	Authors recommend >6 L/day in severe RM and ≥3 L/day IV fluid in moderate RM to decrease the incidence of AKI	NA	134 patients (21 %) developed AKI 110 patients required RRT

Abbreviations: *AKI* acute kidney injury, *CS* case series, *IV* intravenous, *NA* not available, *NS* normal saline, *PS* prospective study, *RM* rhabdomyolysis, *RRT* renal replacement therapy, *RS* retrospective study

A retrospective study of 8610 cases of drug-associated rhabdomyolysis reported to the US Food and Drug Administration (FDA) from 2004 to 2009 found that simvastatin, atorvastatin, and rosuvastatin were most frequently suspected and accounted for 3945 cases (45 %) [23]. Statin drugs all have the potential to cause muscle damage in a dose-dependent manner, although they vary in several characteristics. Simvastatin, atorvastatin, and lovastatin are metabolized by CYP3A4 (the most common cytochrome P_{450} isozyme), which necessarily leads to competition with other drugs for metabolism, increasing statin blood levels and predisposing to toxicity [41]. Rosuvastatin and fluvastatin are metabolized by the CYP2A9 isozyme and therefore carry less risk of drug interaction [41]. Some degree of muscle toxicity is experienced by 0.08–10 % of patients being treated with statins alone or in combination with other lipid-lowering drugs [6, 32, 33]. However, less than 1 % have significant elevation of serum CK levels [30].

The number of rhabdomyolysis cases associated with surgery seems to have been increasing over recent years [5, 17]. Several related risk factors include extended length of surgery and comorbidities such as obesity and diabetes [17, 25, 31]. As the length of surgery increases, so does the time spent in immobility, raising the likelihood of secondary tissue compression and ischemia. Drugs used for anesthesia (propofol, barbiturates, benzodiazepines, and opiates) have also been associated with rhabdomyolysis [35].

Pathophysiology

Regardless of the cause of rhabdomyolysis, the pathophysiology of muscle destruction follows a common pathway. The muscle cell is affected either by direct cell membrane destruction or by energy depletion [9]. Free ionized calcium enters the intracellular space and activates proteases and apoptosis pathways [2]. Production of reactive oxygen species (ROS) leads to mitochondrial dysfunction and ultimately to cell death [2, 37].

Muscle cell calcium homeostasis is normally maintained by transmembrane proteins (i.e., channels, pumps), most of which are energy-dependent [42]. When energy (in the form of ATP) depletes, ATPase pump dysfunction is accompanied by an increase in intracellular Na^+ concentration, activating the $2Na^+/Ca^{2+}$ exchanger in order to correct ionic abnormalities [38]. The parallel secondary increase in intracellular calcium activates proteases such as the phospholipase A2 (PLA2) enzyme, which destroys both cellular and mitochondrial membranes [2, 37]. Figure 2 illustrates the cascade of events leading to muscle cell lysis.

Table 3 Rhabdomyolysis etiology classification [2, 25–27, 44]

Type	Cause	Examples
Acquired	Trauma	"Crush syndrome"
	Exertion	Intense muscle activity, energy depletion, electrolyte imbalance
	Ischemia	Immobilization, compression, thrombosis
	Illicit drugs	Cocaine, heroin, LSD
	Alcohol	Acute or chronic consumption
	Drugs	Dose-dependent, multiple interactions
	Infections	Bacterial, viral, parasitic
	Extreme temperatures	Hyperthermia, hypothermia, neuroleptic malignant syndrome
	Endocrinopathies	Hyper/hypo-thyroidism, diabetic complications
	Toxins	Spider bites, wasp stings, snake venom
Inherited	Metabolic myopathies	Glycogen storage, fatty acid, mitochondrial disorders
	Structural myopathies	Dystrophinopathy, dysferlinopathy
	Channel related gene mutations	RYR1 gene mutation, SCN4A gene mutation
	Others	Lipin-1 gene mutation, sickle-cell disease, "benign exertional rhabdomyolysis"

Following muscle cell necrosis, release of cytotoxic intracellular components causes capillary injury and leads to third-spacing of fluids [3]. Edema, ischemia, and cell necrosis cause additional metabolic acidosis and electrolyte abnormalities, perpetuating the vicious cycle of cell death [36].

Mechanisms of AKI

Rhabdomyolysis-associated AKI may be induced through several mechanisms, including hypovolemia, myoglobinuria, and metabolic acidosis (Fig. 3) [9, 43].

During muscle destruction, intracellular fluid is first leaked then sequestered in extracellular spaces. This depletes the intravascular volume and activates the renin–angiotensin–aldosterone system, decreasing renal blood flow [2, 9]. Release of myoglobin, the oxygen-carrier protein of the muscle, into the systemic circulation exerts a cytotoxic effect on the nephron both directly and through its compounds. The free iron released after myoglobin breakdown in the kidney reacts with hydrogen peroxide compounds (Fenton reaction), generating ROS which damage renal tubular integrity [42]. A second mechanism of kidney injury is lipid peroxidation: lipid membrane components in the kidney react with the ferryl form of myoglobin, a process called redox cycling [42]. The presence of metabolic acidosis potentiates myoglobin nephrotoxicity by promoting cast formation and tubular obstruction, particularly in the distal convoluted tubules [3].

Besides myoglobin, uric acid is also released from necrotic muscle. Uric acid forms deposits of crystals in an acidic environment, further contributing to tubular obstruction [44]. A similar pathophysiology is observed in tumor-lysis syndrome: cell damage and substance release with subsequent AKI [45].

Diagnosis

The classic symptoms associated with rhabdomyolysis include severe muscle pain, weakness, and the presence of dark tea-colored urine, which are highly suggestive of the diagnosis [3]. Patients may also present with oliguria or even anuria [27]. Systemic circulation of intracellular muscle components can yield additional non-specific symptoms. Cardiovascular symptoms may stem from the associated electrolyte abnormalities (i.e., potassium, calcium, phosphate) and may range from cardiac dysrhythmias to cardiac arrest [10]. Patients may be hyperventilating due to pain if they are awake and agitated or hypoventilating if rhabdomyolysis was drug-induced or due to trauma [19, 28]. Drug-induced syndromes associated with rhabdomyolysis (neuroleptic malignant syndrome and malignant hyperthermia) are characterized by muscle rigidity, hyperthermia, and metabolic acidosis [10, 35].

Laboratory work-up

Serum CK levels gradually increase during the first 12 h of rhabdomyolysis, peak within 3–5 days, and return to baseline during the following 6–10 days [39]. Clinicians often use serum CK levels exceeding five times the upper limit of normal for diagnosing rhabdomyolysis [18, 21, 24].

Urinalysis can detect the presence of myoglobin when it exceeds 0.3 mg/L in serum [2]. The heme molecule reacts in a urine dipstick but this method cannot distinguish between a positive result due to the presence of hemoglobin or myoglobin [37]. Myoglobinuria can be considered when a patient has a reactive heme test positive for blood but the microscopic exam reveals only few red blood cells in the urine [38]. The urine pH tends to be acidic and it often contains detectable levels of protein [2, 3].

Serum CK levels have traditionally been considered the best predictor of AKI [25, 46]. However, Baeza-Trinidad and coworkers [47] recently conducted a retrospective study of 522 patients with rhabdomyolysis in which both initial CK and creatinine levels were recorded. In this study, the initial CK level was not a predictor of AKI [47]. Serum myoglobin has also been used as a predictor of AKI; Premru and coworkers [48] found that >15 mg/L of myoglobin in the blood was highly

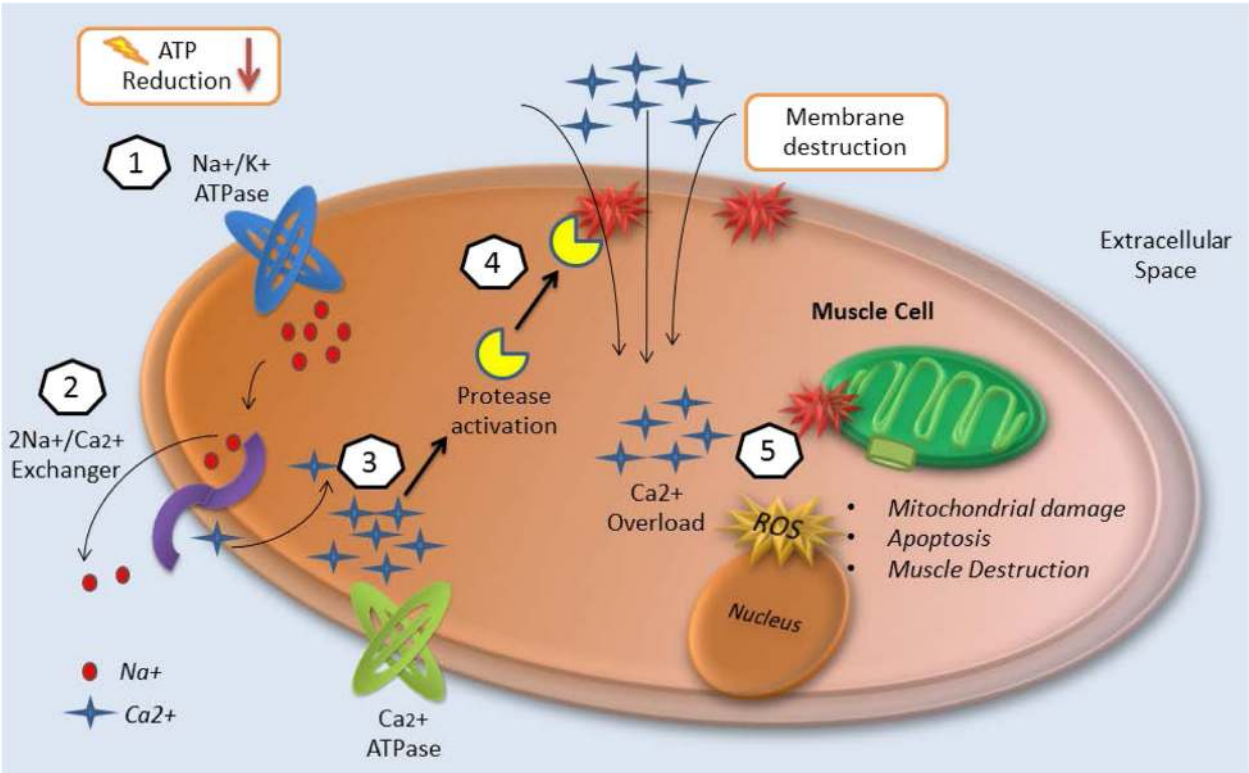

Fig. 2 Injury mechanisms of rhabdomyolysis. (1) Energy (ATP) depletion inhibits Na^+/K^+ ATPase function, thus increasing intracellular sodium. (2) The $2Na^+/Ca^{2+}$ exchanger increases intracellular calcium. (3) Ca^{2+} ATPase is not able to pump out intracellular calcium due to energy depletion. (4) Intracellular calcium activates proteases such as phospholipase 2 (*PLA2*), which destroy structural components of the cell membrane, allowing the entrance of more calcium. (5) Calcium overload disrupts mitochondrial integrity and induces apoptosis leading to muscle cell necrosis

associated with development of AKI in a cohort of 484 patients. However, data regarding the use of myoglobin as an early marker of rhabdomyolysis-associated AKI remains inconclusive since many values of myoglobin overlap [49].

The Risk, Injury, Failure, Loss, and End-stage kidney disease (RIFLE) criteria are used in most studies nowadays to define AKI [50]. However, different criteria have been used to establish the diagnosis of AKI after rhabdomyolysis in clinical studies [34, 51]. Talaie

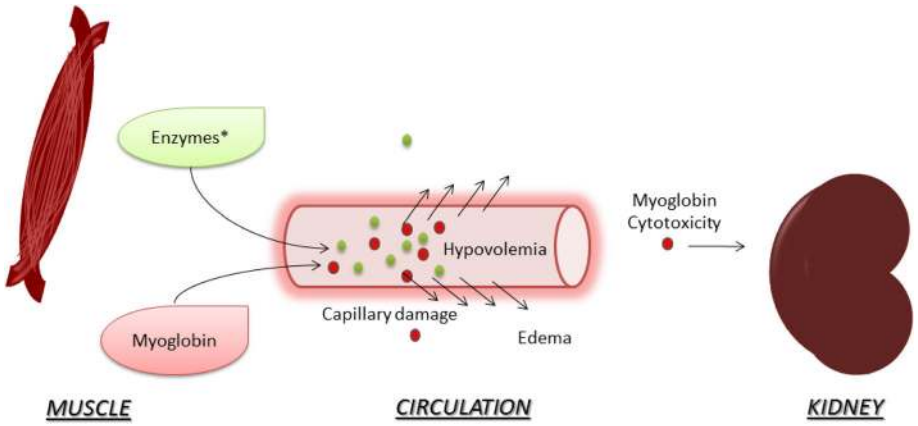

Fig. 3 Acute kidney injury in rhabdomyolysis. *Enzymes**: creatine kinase, aldolase, lactate dehydrogenase. After muscle destruction, myoglobin and enzymes released into the circulation damage capillaries, leading to leakage and edema. Hypovolemia and the decrease in renal bood flow is associated with acute kidney injury. Myoglobin cytotoxicity affects the kidney by lipid peroxidation and production of reactive oxygen species. Tubular obstruction by myoglobin is also associated with AKI

and coworkers [51] diagnosed rhabdomyolysis-induced AKI in patients with a serum creatinine level elevation of more than 30 % in the first days of admission. In another study, Iraj and coworkers [34] established a diagnosis based on two repeated values of creatinine ≥1.6 mg/dL.

The presence of AKI may be accompanied by excessive potassium levels, correlating with the degree of muscle destruction. These levels should be followed closely due to the risk of cardiac dysrhythmias [36]. Serial electrocardiography studies should also be performed to detect abnormalities secondary to electrolyte disturbances [10].

Prolongation of the prothrombin time, thrombocytopenia, and high levels of fibrinogen degradation products may also be detected during rhabdomyolysis [10, 52]. In this setting, serial blood tests are indicated to detect disseminated intravascular coagulopathy as early as possible. Arterial blood gases typically demonstrate metabolic acidosis with an elevated anion gap, reflecting the increase in organic acid levels in the serum due to muscle necrosis [2, 26].

Initial CK and myoglobin levels are inconsistent in predicting mortality or AKI in rhabdomyolysis [49, 53]. McMahon and coworkers [53] have recently validated an instrument for predicting mortality and AKI. This score includes eight variables: age, gender, etiology, and initial levels of creatinine, calcium, phosphate, and serum bicarbonate.

Treatment

Treatment of the underlying source of muscle injury, once identified, is the first component of successful management. This may include cessation of a potentially harmful drug, control of patient temperature, treatment of underlying infection, and more [7, 51].

IV fluid therapy

Fluid replacement is the keystone of rhabdomyolysis treatment. Capillary damage and fluid leakage lead to a "functional" dehydration that requires rapid correction [54]. Early, aggressive fluid therapy increases renal blood flow, thereby increasing secretion of nephrotoxic compounds that may cause AKI [9].

Table 2 shows studies in which IV fluid therapy was described for patients diagnosed with rhabdomyolysis [34, 51, 55–58]. The type of IV fluid varied from the combination of 5 % dextrose and 0.45 normal saline (NS), lactated Ringer's solution, and NS solution with or without bicarbonate [51, 55, 56]. Fluid administration was reported either as an hourly or daily rate. Cho and coworkers [56] prospectively studied 28 patients treated with either NS or lactated Ringer's solution with an IV fluid rate of 400 mL/h and none of the patients developed AKI. Other studies used from 4 to 8 L of IV fluid daily [34, 51, 55].

In 2013, Scharman and coworkers [54] conducted a systematic review of therapies for prevention of rhabdomyolysis-associated AKI; overall, 27 studies were included. The authors concluded that IV fluid therapy should ideally be initiated within 6 h of muscle injury, targeting a urine output of 300 mL/h. No specific recommendations were provided regarding the type of fluid because of the variety of intravenous fluids used in the different studies [54].

In non-traumatic rhabdomyolysis, the use of lactated Ringer's solution was compared with NS in a cohort of 28 patients divided into 13 patients treated with Ringer's solution and 15 patients treated with NS. No significant difference was found either in the rate of reduction of CK levels or in the prevalence of AKI in both groups [56]. Despite the poor literature comparing different fluids, Sever and coworkers suggested in a supplement published in *Nephrology, Dialysis, Transplantation* entitled "Recommendation for the management of crush victims in mass disasters" that isotonic saline should be the initial choice for volume correction in rhabdomyolysis secondary to crush injury [15]. These authors also suggested that initial fluid infusion rates should be 1 L/h for 2 h after injury and 500 mL/h after 120 minutes [15]. However, these recommendations were not based on randomized clinical trials. Patients receiving fluid replacement therapy should be monitored closely to prevent complications such as fluid overload and metabolic acidosis [59].

Treatment of electrolyte abnormalities

Reinstatement of the biochemical equilibrium during rhabdomyolysis should be undertaken with care in order to avoid adverse effects of treatment. Hyperkalemia is the only electrolyte abnormality that requires rapid correction in order to reduce the risk of cardiac dysrhythmias [43, 60]. Administration of calcium chloride/gluconate for hypocalcemia should be avoided since calcium supplementation may increase muscle injury [10]. Correction of hyperphosphatemia requires careful monitoring of both phosphorus and calcium levels since increased levels of phosphorus may promote calcium deposition in necrotic muscle tissue [10].

Bicarbonate for prevention of AKI

The use of bicarbonate for prevention of AKI is based on the concept that an acidic environment promotes myoglobin toxicity; hence, an alkali urine environment may reduce redox-cycling, lipid peroxidation, and myoglobin cast formation [9]. It is thus plausible that increasing urine pH above 6.5 with intravenous sodium bicarbonate could prevent AKI [55]. Besides AKI prevention,

several authors have suggested that sodium bicarbonate should be used to correct metabolic acidosis [38]. However, administration of sodium bicarbonate may also produce paradoxical intracellular acidosis and volume overload, particularly in patients with respiratory or circulatory failure, when the bicarbonate buffering system shifts to increase circulating carbon dioxide ($HCO_3 + H^+ \rightarrow H_2CO_3 \rightarrow H_20 + CO_2$) [61].

Table 2 includes some of the "bicarbonate cocktails" added to IV fluid therapy in some studies. However, none of the studies have actually compared this therapy with intravenous fluid therapy alone [51, 58].

Mannitol

There is no consensus regarding the use of mannitol since its side effects include volume depletion and potentially worsening pre-renal azotemia [9]. However, the theoretical benefits of mannitol administration include improved diuresis, increased renal perfusion, excretion of myoglobin, and a direct antioxidant effect on renal parenchyma [62]. Authors that recommend using mannitol suggest it should only be administered if fluid therapy alone does not lead to urine output exceeding 300 mL/h [15]. Mannitol should be avoided in anuric patients; it is therefore recommended to assess the urinary response starting only with IV fluids prior to deciding whether to proceed with mannitol administration [15].

Continuous renal replacement therapy

Continuous renal replacement therapy (CRRT) clears myoglobin from the bloodstream, thereby potentially decreasing the amount of renal damage [63, 64]. Zeng and coworkers [60] systematically reviewed the potential benefits of CRRT in patients with rhabdomyolysis and AKI. The authors found only three studies for inclusion in their review ($n = 101$ patients). They concluded that, despite the improvement in myoglobin, creatinine, and electrolyte levels in patients treated with CRRT, mortality rates remained unchanged [60]. CRRT should therefore only be considered when life-threatening electrolyte abnormalities emerge as complications of AKI that are non-responsive to initial therapy [43].

Conclusions

Rhabdomyolysis remains a major clinical challenge. Non-specific symptoms, multiple etiologies, and systemic complications obscure the diagnosis and complicate the treatment of this condition. The pathophysiology of myoglobin-induced injury to the renal parenchyma has been elucidated and aggressive fluid therapy remains the keystone of therapy. However, RCTs are sorely lacking regarding the use of both fluids and adjuvant pharmacological therapies (mannitol and bicarbonate) for AKI prevention. CRRT improves myoglobin clearance but does not change mortality. Several important aspects of rhabdomyolysis should be addressed in the future: a homogenous definition should be created for this syndrome, data from past cases should be pooled to derive and validate the best marker for predicting development of AKI, and multicenter RCTs that compare standardized intravenous fluid therapy alone with fluids with sodium bicarbonate and/or mannitol should be planned.

Abbreviations

AKI: acute kidney injury; CK: creatine kinase; CRRT: continuous renal replacement therapy; IV: intravenous; NS: normal saline; RCT: randomized controlled trial; ROS: reactive oxygen species.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

LOC: acquisition of literature, conception and design of manuscript, draft of manuscript. ML: acquisition of literature, analysis of collected literature, helped draft manuscript. SE: revised the manuscript critically and added substantial data. JV: conceived the manuscript, helped in acquisition of important literature, and critically revised the manuscript. All authors read and approved the final manuscript.

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11

Low Back Pain - Introduction

Derek Moore

TOPIC	QUESTIONS	EVIDENCE	CASES
Review Topic	8	14	1



Introduction

- Low back pain affects 50-80% of population in lifetime
  - $100 billion in annual cost
  - second only to respiratory infection as cause to visit doctors office
- Etiology
  - muscle strain
    - most common cause of low back pain
  - most common degenerative disorders
    - lumbar spinal stenosis
    - lumbar disc herniation
    - discogenic back pain
- Risk factors
  - obesity, smoking, gender
  - lifting, vibration, prolonged sitting
  - job dissatisfaction
- Red flags
  - infection (IV drug user, h/o of fever and chills)
  - tumor (h/o or cancer)
  - trauma (h/o car accident or fall)
  - cauda equina syndrome (bowel/bladder changes)
- Outcomes
  - 90% of low back pain resolves within one year

Presentation

- Symptoms
  - axial pain
    - musculogenic
      - most common cause of back pain
      - associated with activity

- discogenic pain
  - controversial
  - confirmed by discogram
- mechanical pain
  - caused by
    - facet degeneration
    - micro and macro instability
  - worse with activity such as lifting objects and prolonged standing
- sacroiliac symptoms
  - pain originating from sacroiliac joint

- peripheral / neurogenic
  - radicular pain
    - unilateral leg pain
    - usually dermatomal
  - referred pain
    - buttocks
    - posterior thighs
    - inguinal region (think L5-S1)
  - neurogenic claudication
    - pain in buttock and legs that is worse with prolonged standing
    - fairly specific for spinal stenosis
  - myelopathy
    - clumsiness in hands
    - gait instability
    - due to injury of spinal cord (~ L1 or above)
  - conus medullaris syndrome
  - cauda equina syndrome
    - bilateral leg pain
    - LE weakness
    - saddle anesthesia
    - bowel/bladder symptoms
  - spinal cord injury
    - incomplete
    - complete

- Wadell Signs
  - system to evaluate non-organic back pain symptoms,
  - clinically significant if three positive signs are present
    - superficial and non-anatomic tenderness
    - pain with axial compression or simulated rotation of the spine
    - negative straight-leg raise with patient distraction
    - regional disturbances which do not follow dermatomal pattern
    - overreaction to physical examination

Imaging

- Radiographs
  - indications for radiographs
    - pain lasting > one month and not responding to not nonoperative management
    - red flags are present
- MRI

- high rate of abnormal findings on MRI in normal people

Positive MRI Findings in Asymptomatic Patients			
Age	*% HNP*	*% Disc Bulge*	*% Degeneration*
20-39	21	56	34
40-59	22	50	59
60-79	36	79	93

Differential

- Neck and arm pain
  - trauma
  - cervical spondylosis
  - metastatic disease / infection
  - cervical radiculopathy
  - cervical myelopathy
  - ankylosing spondylitis
- Thoracic back and rib pain
  - trauma
  - metastatic disease / infection
  - thoracic disc herniation
  - osteoporotic comression fracture
  - trauma
- Low back pain
  - muscles strain
  - disc herniation / discogenic pain
  - degenerative spondylolithesis
  - spinal stenosis
  - lumbar radiculopathy
  - abdominal aortic aneurism
- Sacroiliac pain
  - SI infection
  - ankylosing spondylitis
- Sacral pain
  - coccydynia
  - sacral insufficiency fracture

Treatment

- Treatment dictated by cause of pain.

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? QUESTIONS (8)

CASES (1)

TOPIC COMMENTS (11)

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Updated: 12/2/2018

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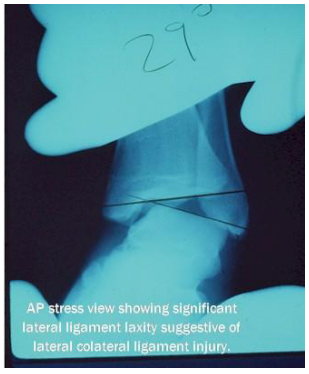
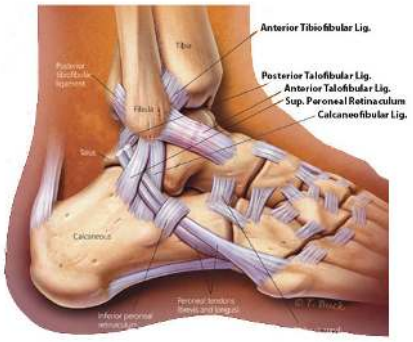
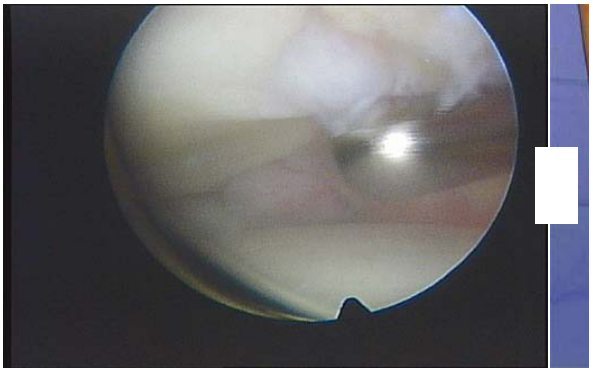
Ankle Sprain

David Macknet | Brian Weatherford

TOPIC	QUESTIONS	EVIDENCE	VIDEOS
Review Topic	15	23	3







Introduction

- Overview
  - ankle sprains involve an injury to the ATFL and CFL and are the most common reason for missed athletic participation
    - treatment usually includes a period of immobilization followed by physical therapy. Only when nonoperative treatment fails is surgical reconstruction indicated.
- Ankle sprains consist of
  - high ankle sprain
    - syndesmosis injury
    - 1-10% of all ankle sprains
  - low ankle sprain (this topic)
    - ATFL and CFL injury
    - >90% of all ankle sprains
- Epidemiology
  - incidence
    - ankle sprains are the most common reason for missed athletic participation
  - demographics
    - most common injury in dancers
  - risk factors
    - patient-related
      - limited dorsiflexion, decreased proprioception, balance deficiency
    - environmental-related
      - indoor-court sports have the highest risk (basketball, volleyball)
- Pathophysiology
  - Mechanism of injury

        - Inversion type ankle injury on a plantarflexed foot
        - Recurrent ankle sprains can lead to functional instability
- Associated injuries/conditions include
    - osteochondral defects
    - peroneal tendon injuries
    - subtle cavovarus foot
    - deltoid ligament injury (isolated deltoid ligament injuries are very rare)
    - complex regional pain syndrome
    - fractures
        - 5th metatarsal base
        - anterior process of calcaneus
        - lateral or posterior process of the talus
- Prognosis
    - natural history
        - pain decreases rapidly during the first 2 weeks after injury
        - 5-33% reports some pain at 1 year
        - increased risk of a sprain to ipsilateral and contralateral ankle

Anatomy

- Ligamentous anatomy of the ankle
- ATFL
    - most commonly involved ligament in low ankle sprains
    - mechanism is plantar flexion and inversion
    - physical exam shows drawer laxity in plantar flexion
- CFL
    - 2nd most common ligament injury in lateral ankle sprains
    - mechanism is dorsiflexion and inversion
    - physical exam shows drawer laxity in dorsiflexion
    - subtalar instability can be difficult to differentiate from posterior ankle instability because the CFL contributes to both
- PTFL
    - less commonly involved

Classification

Classification of Low Ankle Sprains			
	Ligament disruption	*Ecchymosis and swelling*	*Pain with weight bearing*
Grade I	none	minimal	normal
Grade II	stretch without tear	moderate	mild
Grade III	complete tear	severe	severe

Presentation

- Symptoms
    - pain with weight bearing (may or may not be able to bear weight)

- swelling and ecchymosis
- recurrent instability
- catching or popping sensation may occur following recurrent sprains

- Physical exam
  - focal tenderness and swelling over-involved ligament(s)
  - anterior drawer test
    - looks for excessive anterior displacement of talus relative to tibia
    - limited usefulness in acute setting
    - ATFL best tested in plantarflexion, CFL in dorsiflexion
  - Talar tilt test
    - excessive ankle inversion compared to contralateral side indicated injury to ATFL and CFL

Imaging

- Radiographs
  - indications for radiographs with an ankle injury include (Ottawa ankle rules)
    - inability to bear weight
    - medial or lateral malleolus point tenderness
    - 5MT base tenderness
    - navicular tenderness
    - 96-99% sensitive in ruling out ankle fracture
  - radiographic views to obtain
    - standard ankle series (weight bearing)
      - AP
      - lateral
        - ATFL injury suggested with anterior talar translation
      - mortise
    - ER rotation stress view
      - useful to diagnosis syndesmosis injury in high ankle sprain
      - look for asymmetric mortise widening
      - medial clear space widening > 4mm
      - tibiofibular clear space widening of 6 mm
    - varus stress (talar tilt) view
      - used to diagnose injury to CFL
      - measures ankle instability by looking at talar tilt
- MRI
  - indications
    - consider MRI if pain persists for 6-8 weeks following sprain
  - useful to evaluate
    - peroneal tendon pathology
    - osteochondral injury
    - syndesmotic injury

Treatment

- Nonoperative
  - **RICE, elastic wrap to minimize swelling, followed by therapy**
    - indications

        - Grade I, II, and III injuries
    - technique
        - initial immobilization
            - may require short period (approx. 1 week) of weight-bearing immobilization in a walking boot, aircast or walking cast, but early mobilization facilitates a better recovery
            - grade III sprains may benefit from 10 days of casting and nonweightbearing
        - therapy
            - early phase
                - early functional rehabilitation begins with motion exercises and progresses to strengthening, proprioception, and activity-specific exercises
            - strengthening phase
                - once swelling and pain have subsided and patient has full range of motion begin neuromuscular training with a focus on peroneal muscles strength and proprioception training
                - a functional brace that controls inversion and eversion is typically used during the strengthening period and used as prophylactic treatment during high-risk activities thereafte
    - outcomes
        - early functional rehabilitation allows for the quickest return to physical activity
        - supervised physical therapy has shown a benefit in early follow-up but no difference in the long term
- Operative
    - **anatomic reconstruction vs. tendon transfer with tenodesis**
        - indications
            - Grade I-III that continue to have pain and instability despite extensive nonoperative management
            - Grade I-III with a bony avulsion
        - technique (see below)
    - **arthroscopy**
        - indications
            - recurrent ankle sprains and chronic pain caused by impingement lesions
                - anteriorinferior tibiofibular ligament impingement
                - posteromedial impingement lesion of ankle
                - often used prior to reconstruction to evaluate for intra-articular pathology
        - procedure
            - debride impinging tissue

Surgical Techniques

- **Gould modification of Brostrom anatomic reconstruction**

- procedure
  - an anatomic shortening and reinsertion of the ATFL and CFL
  - reinforced with inferior extensor retinaculum and distal fibular periosteum (Gould modification)
- results
  - good to excellent results in 90%
  - consider arthroscopic evaluation prior to reconstruction for intra-articular evaluation

- **Tendon transfer and tenodesis** (Watson-Jones, Chrisman-Snook, Colville, Evans)
  - procedure
    - a nonanatomic reconstruction using a tendon transfer
  - technique
    - any malalignment must be corrected to achieve success during a lateral ligament reconstruction
    - Coleman block testing used to distinguish between fixed and flexible hindfoot varus
  - results
    - subtalar stiffness is a common complication

Rehabilitation

- Return to play
  - depends on, grade of sprain, syndesmosis injury, associated injuries, and compliance with rehab

Classification	*Time to RTP*
Grade I	1-2 weeks
Grade II	1-2 weeks
Grade III	few weeks
High ankle (immobilization)	several weeks
High ankle (screw fixation)	season

- Prevention
  - prevention techniques in athletes with prior sprains includes
    - semirigid orthosis
    - evertor muscle (peroneals) strengthening
    - proprioception exercises
    - season long prevention program

Complications

- Pain and instability
  - Incidence
    - up to 30% continue to experience symptoms following and acute ankle sprain
  - Risk factors
    - most common cause of chronic pain is a missed injury, including

- missed fractures (anterior process of calcaneus, lateral or posterior process of the talus, 5th metatarsal)
- osteochondral lesion
- injuries to the peroneal tendons
- injury to the syndesmosis
- tarsal coalition
- impingement syndromes

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? QUESTIONS (15)

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VIDEOS (3)

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Updated: 9/6/2018

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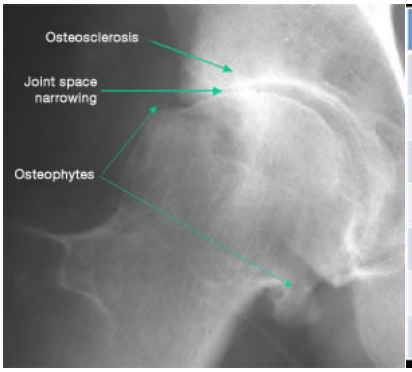
Hip Osteoarthritis

Evan Watts | Mark Karadsheh | Stephen Incavo

TOPIC	QUESTIONS	EVIDENCE	VIDEOS	CASES	TECHNIQUES
Review Topic	2	4	4	7	2



	Aging	Osteoarthritis
Water Content	Decreased	Increased
Collagen	Same	Disorganized
Proteoglycan Content	Decreased	Decreased
Proteoglycan Synthesis	Same	Increased
Chondrocyte Size	Increased	Same
Chondrocyte Number	Decreased	Same
Modulus of Elasticity	Increased	Decreased

Introduction

- Definition
  - degenerative disease of synovial joints that causes progressive loss of articular cartilage
- Epidemiology
  - incidence
    - hip OA (symptomatic)
      - 88 per 100,000 per year
    - knee OA (symptomatic)
      - 240 per 100,000 per year
- Risk factors
  - modifiable
    - articular trauma
    - muscle weakness
    - heavy physical stress at work
    - high impact sporting activities
  - non-modifiable
    - gender
      - females >males
    - increased age
    - genetics
    - developmental or acquired deformities
      - hip dysplasia
      - slipped capital femoral epiphysis
      - Legg-Calvé-Perthes disease
- Pathophysiology
  - pathoanatomy

        - articular cartilage
            - increased water content
            - alterations in proteoglycans
                - eventual decrease in amount of proteoglycans
            - collagen abnormalities
                - organization and orientation are lost
                - binding of proteoglycans to hyaluronic acid
        - synovium and capsule
            - early phase of OA
                - mild inflammatory changes in synovium
            - middle phase of OA
                - moderate inflammatory changes of synovium
                - synovium becomes hypervascular
            - late phases of OA
                - synovium becomes increasingly thick and vascular
                - bone
                - subchondral bone attempts to remodel
                - forming lytic lesion with sclerotic edges (different than bone cysts in RA)
                - bone cysts form in late stages
- Cell biology
    - proteolytic enzymes
        - matrix metalloproteases (MMPs)
            - responsible for cartilage matrix digestion
            - examples
                - stromelysin
                - plasmin
                - aggrecanase-1 (ADAMTS-4)
        - tissue inhibitors of MMPS (TIMPs)
            - control MMP activity preventing excessive degradation
            - imbalance between MMPs and TIMPs has been demonstrated in OA tissues
        - inflammatory cytokines
            - secreted by synoviocytes and increase MMP synthesis
                - examples
                    - IL-1
                    - IL-6
                    - TNF-alpha
- Genetics
    - inheritance
        - non-mendilian
    - genes potentially linked to OA
        - vitamin D receptor
        - estrogen receptor 1
        - inflammatory cytokines
            - IL-1
                - leads to catabolic effect
            - IL-4
            - matrilin-3

- BMP-2, BMP-5

Classification

Tonnis Classification		
Grade 0	• normal radiographs	
Grade 1	• sclerosis of femoral head and acetabulum • slight joint space narrowing • slight lipping at joint margins	
Grade 2	• small cysts in femoral head/acetabulum • moderate joint space narrowing • moderate loss of head sphericity	
Grade 3	• large cysts in femoral head/acetabulum • joint space obliteration/severe narrowing • severe femoral head deformity vs. AVN	

Presentation

- History
  - identify age, functional activity, pattern of arthritic involvement, overall health and duration of symptoms
- Symptoms
  - function-limiting hip pain
    - effect on walking distances
  - pain at night or rest
  - hip stiffness
  - mechanical
    - instability, locking, catching sensation
- Physical exam
  - inspection
    - body habitus
    - gait
    - leg length discrepancy
    - skin (e.g. scars)
  - range of motion
    - lack of full extension (>5 degrees flexion contracture)
    - lack of full flexion (flexion < 90-100 degrees)
    - limited internal rotation
- Neurovascular exam
  - straight leg test negative

Imaging

- Radiographs
  - recommended views
    - standing AP pelvis
    - AP + lateral hip

- optional views
  - false profile view (e.g. hip dysplasia)
- findings
  - osteoarthritis
    - joint space narrowing
    - osteophytes
    - subchondral sclerosis
    - subchondral cysts
  - pelvic obliquity
    - may be secondary to spinal deformity
    - may cause leg-length issues
  - acetabular retroversion
    - makes appropriate positioning of acetabular component more difficult intraoperatively

Studies

- Histology
  - loss of superficial chondrocytes
  - replication and breakdown of the tidemark
  - fissuring
  - cartilage destruction with eburnation of subchondral bone

Treatment

- Nonoperative
  - **NSAIDs and/or tramadol**
    - indications
      - first line treatment for all patients with symptomatic arthritis
    - technique
      - NSAID selection should be based on physician preference, patient acceptability and cost
  - **walking stick**
    - decreases the joint reaction force on the affected hip when used in the contralateral upper extremity
  - **weight loss, activity modification and exercise program/physical therapy**
    - indications
      - first line treatment for all patients with symptomatic arthritis
      - BMI > 25
    - technique
      - exercise aimed at increasing flexibility and aerobic capacity
  - **corticosteroid joint injections**
    - indications
      - can be therapeutic and/or diagnostic of symptomatic hip osteoarthritis
  - **controversial treatments**
    - acupuncture
    - viscoelastic joint injections

        - glucosamine and chondroitin
- Operative
    - **arthroscopic debridement**
        - indications
            - controversial
            - degenerative labral tears
    - **periacetabular osteotomy +/- femoral osteotomy**
        - indications
            - symptomatic dysplasia in an adolescent or young adult with concentrically reduced hip and mild-to-moderate arthritis
        - outcomes
            - mixed results
            - literature suggest this can delay need for arthroplasty
    - **femoral head resection**
        - indications
            - pathological hip lesions
            - painful head subluxation
    - **hip resurfacing**
        - indications
            - young active, male, patients with hip osteoarthritis
    - **total hip arthroplasty (THA)**
        - indications
            - end-stage, symptomatic or severe osteoarthritis arthritis
            - preferred treatment for older patients (>50) and those with advanced structural changes

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QUESTIONS (2)

ARTICLES (14)

VIDEOS (4)

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Knee Osteoarthritis

Evan Watts | Mark Karadsheh

TOPIC	QUESTIONS	EVIDENCE	VIDEOS	CASES	TECHNIQUES
Review Topic	15	20	5	5	4



	Aging	Osteoarthritis
Water Content	Decreased	Increased
Collagen	Same	Disorganized
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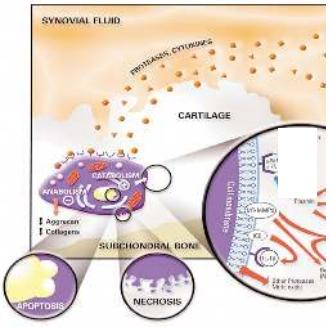
Proteoglycan Synthesis	Same	Increased
Chondrocyte Size	Increased	Same
Chondrocyte Number	Decreased	Same
Modulus of Elasticity	Increased	Decreased



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    - knee OA (symptomatic)
      - 240 per 100,000 per year
- Risk factors
  - modifiable
    - articular trauma
    - occupation, repetitive knee bending
    - muscle weakness
    - large body mass
    - metabolic syndrome
      - central (abdominal) obesity, dyslipidemia (high triglycerides and low-density lipoproteins), high blood pressure, and elevated fasting glucose levels.
  - non-modifiable
    - gender
      - females >males
    - increased age
    - genetics
    - race
      - African American males are the least likely to receive total joint replacement when compared to whites and Hispanics
- Pathophysiology
  - pathoanatomy
    - articular cartilage
      - increased water content
      - alterations in proteoglycans
        - eventual decrease in amount of proteoglycans

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            - organization and orientation are lost
        - binding of proteoglycans to hyaluronic acid
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            - mild inflammatory changes in synovium
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            - moderate inflammatory changes of synovium
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            - synovium becomes increasingly thick and vascular
    - bone
        - subchondral bone attempts to remodel
            - forming lytic lesion with sclerotic edges (different than bone cysts in RA)
        - bone cysts form in late stages
        - osteophytes form through the pathologic activation of endochondral ossification mediated by the Indian hedgehog (Ihh) signaling molecule
- Cell biology
    - proteolytic enzymes
        - matrix metalloproteases (MMPs)
            - responsible for cartilage matrix digestion
                - examples
                    - stromelysin
                    - plasmin
                    - aggrecanase-1 (ADAMTS-4)
        - tissue inhibitors of MMPS (TIMPs)
            - control MMP activity preventing excessive degradation
            - imbalance between MMPs and TIMPs has been demonstrated in OA tissues
        - inflammatory cytokines
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                    - IL-6
                    - TNF-alpha
- Genetics
    - inheritance
        - non-mendilian
    - genes potentially linked to OA
        - vitamin D receptor
        - estrogen receptor 1
        - inflammatory cytokines
            - IL-1
                - leads to catabolic effect
            - IL-4
            - matrilin-3
            - BMP-2, BMP-5

Classification

Kellgren & Lawrence (based on AP weightbearing XRs)	
Grade 0	• no joint space narrowing (JSN) or reactive changes
Grade 1	• possible osteophytic lipping + doubtful JSN
Grade 2	• definite osteophytes + possible JSN

Grade 3	• moderate osteophytes + definite JSN + some sclerosis + possible bone end deformity
Grade 4	• large osteophytes + marked JSN + severe sclerosis + definite bone end deformity

Presentation

- History
  - identify age, functional activity, pattern of arthritic involvement, overall health and duration of symptoms
- Symptoms
  - function-limiting knee pain
    - effect on walking distances
  - pain at night or rest
  - activity induced swelling
  - knee stiffness
  - mechanical
    - instability, locking, catching sensation
- Physical exam
  - inspection
    - body habitus
    - gait
      - often an increased adductor moment to the limb during gait
    - limb alignment
    - effusion
    - skin (e.g. scars)
  - range of motion
    - lack of full extension (>5 degrees flexion contracture)
    - lack of full flexion (flexion <110 degrees)
  - ligament integrity

Imaging

- Radiographs
  - recommended views
    - weight-bearing views of affected joint
  - optional views
    - knee
      - sunrise view
      - PA view in 30 degrees of flexion
  - findings
    - pattern of arthritic involvement
      - medial and/or lateral tibiofemoral, and/or patellofemoral
    - characteristics
      - joint space narrowing
      - osteophytes
      - eburnation of bone
      - subchondral sclerosis
      - subchondral cysts

Studies

- Histology
  - loss of superficial chondrocytes
  - replication and breakdown of the tidemark
  - fissuring

- cartilage destruction with eburnation of subchondral bone

Treatment

- Nonoperative
  - **non-steroidal anti-inflammatory drugs**
    - indications
      - first line treatment for all patients with symptomatic arthritis
    - technique
      - Non-steroidal anti-inflammatory drugs (first choice)
        - selection should be based on physician preference, patient acceptability and cost
        - duration of treatment based on effectiveness, side-effects and past medical history
    - outcomes
      - AAOS guidelines: strong evidence for
  - **tramadol**
    - indications
      - treatment option for patients with symptomatic arthritis
    - technique
      - weak opioid mu receptor agonist
        - good evidence for mid term (8-13 weeks) improvement in pain and stiffness over placebo
    - outcomes
      - AAOS guidelines: strong evidence for
  - **rehabilitation, education and wellness activity**
    - indications
      - first line treatment for all patients with symptomatic arthritis
    - technique
      - self-management and education programs
      - combination of supervised exercises and home program have shown the best results
        - these benefits lost after 6 months if exercises are stopped
    - outcomes
      - AAOS guidelines strong evidence for
  - **weight loss programs**
    - indications
      - patients with symptomatic arthritis and BMI > 25
    - technique
      - diet and low-impact aerobic exercise
    - outcomes
      - AAOS guidelines: moderate evidence for
  - controversial treatments
    - acupuncture
      - AAOS guidelines: strong evidence against
    - viscoelastic joint injections
      - AAOS guidelines: strong evidence against
    - glucosamine and chondroitin
      - AAOS guidelines: strong evidence against
    - needle lavage
      - AAOS guidelines: moderate evidence againnst
    - lateral wedge insoles
      - AAOS guidelines: moderate evidence against
- Operative

- **high-tibial osteotomy**
  - indications
    - younger patients with medial unicompartmental OA
  - technique
    - valgus producing proximal tibial oseotomy
  - outcomes
    - AAOS guidelines: limited evidence for
- **unicompartmental arthroplasty (knee)**
  - indications
    - isolated unicompartmental disease
  - outcomes
    - TKA have lower revision rates than UKA in the setting of unicompartmental OA
- **total knee arthroplasty**
  - indications
    - symptomatic knee osteoarthritis
    - failed non-operative treatments
  - techniques
    - cruciate retaining vs. crucitate sacrificing implants show no difference in outcomes
    - patellar resurfacing
      - no difference in pain or function with or without patella resurfacing
      - lower reoperation rates with resurfacing
    - drains are not recommended

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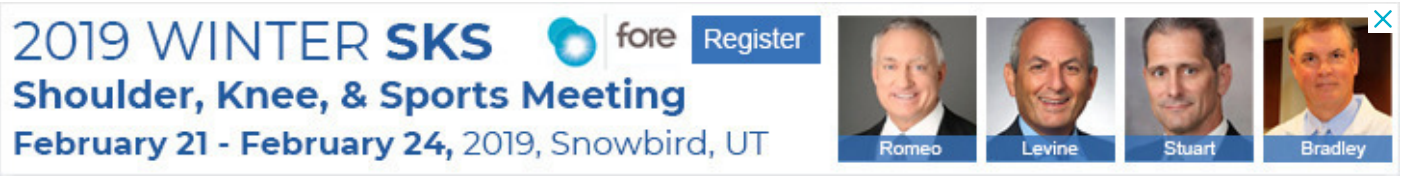

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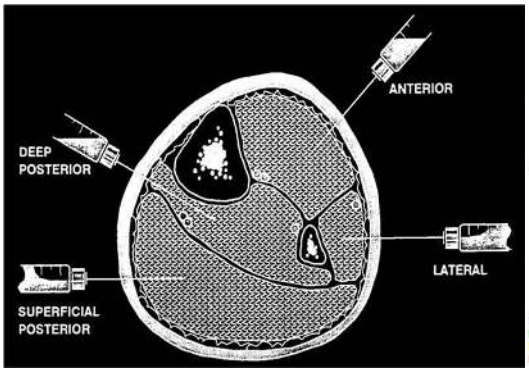
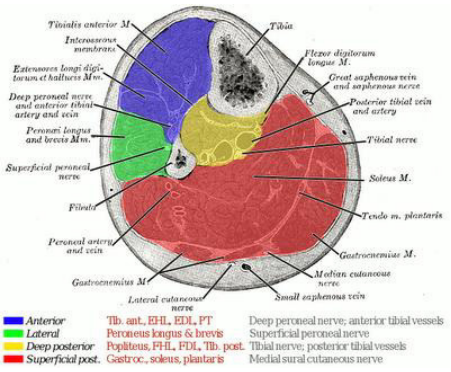
Leg Compartment Syndrome

Mark Karadsheh

TOPIC	QUESTIONS	EVIDENCE	VIDEOS	TECHNIQUES
Review Topic	23	15	6	2





Introduction

- Devastating condition where an osseofascial compartment pressure rises to a level that decreases perfusion
  - may lead to irreversible muscle and nerve damage
- Epidemiology
  - location
    - compartment syndrome may occur anywhere that skeletal muscle is surrounded by fascia, but most commonly
      - leg (details below)
      - forearm
      - hand
      - foot
      - thigh
      - buttock
      - shoulder
      - paraspinous muscles
- Pathophysiology
  - etiology
    - trauma
      - fractures (69% of cases)
      - crush injuries
      - contusions
      - gunshot wounds
    - tight casts, dressings, or external wrappings
    - extravasation of IV infusion
    - burns
    - postischemic swelling

        - bleeding disorders
        - arterial injury
    - pathoanatomy
        - cascade of events includes
            - local trauma and soft tissue destruction**>**
            - bleeding and edema **>**
            - increased interstitial pressure **>**
            - vascular occlusion **>**
            - myoneural ischemia

Anatomy

- 4 compartments of the leg
    - anterior compartment
        - function
            - dorsiflexion of foot and ankle
        - muscles
            - tibialis anterior
            - extensor hallucis longus
            - extensor digitorum longus
            - peroneus tertius
    - lateral compartment
        - function
            - plantarflexion and eversion of foot
        - muscles
            - peroneus longus
            - peroneus brevis
        - isolated lateral compartment syndrome would only affect superficial peroneal nerve
    - deep posterior compartment
        - function
            - plantarflexion and inversion of foot
        - muscles
            - tibialis posterior
            - flexor digitorum longus
            - flexor hallucis longus
    - superficial posterior compartment
        - function
            - mainly plantarflexion of foot and ankle
        - muscles
            - gastrocnemius
            - soleus
            - plantaris

Presentation

- Symptoms
    - pain out of proportion to clinical situation is usually first symptom
        - may be absent in cases of nerve damage

        - pain is difficult to assess in a polytrauma patient and impossible to assess in a sedated patient
        - difficult to assess in children (unable to verbalize)
- Physical exam
    - pain w/ passive stretch
        - is most sensitive finding prior to onset of ischemia
    - paresthesia and hypoesthesia
        - indicative of nerve ischemia in affected compartment
    - paralysis
        - late finding
        - full recovery is rare in this case
    - palpable swelling
    - peripheral pulses absent
        - late finding
        - amputation usually inevitable in this case

Imaging

- Radiographs
    - obtain to rule-out fracture

Studies

- Compartment pressure measurements
    - indications
        - polytrauma patients
        - patient not alert/unreliable
        - inconclusive physical exam findings
    - relative contraindication
        - unequivocally positive clinical findings should prompt emergent operative intervention without need for compartment measurements
    - technique
        - should be performed within 5cm of fracture site
        - anterior compartment
            - entry point
                - 1cm lateral to anterior border of tibia within 5cm of fracture site if possible
            - needle should be perpendicular to skin
        - deep posterior compartment
            - entry point
                - just posterior to the medial border of tibia
            - advance needle perpendicular to skin towards fibula
        - lateral compartment
            - entry point
                - just anterior to the posterior border of fibula
        - superficial posterior
            - entry point
                - middle of calf within 5 cm of fracture site if possible
- Diagnosis

- based primarily on physical exam in patient with intact mental status

Treatment

- Nonoperative
  - **observation**
    - indications
      - diastolic differential pressure (delta p) is > 30
      - presentation not consistent with compartment syndrome
  - **bi-valving the cast and loosening circumferential dressings**
    - indications
      - initial treatment for swelling or pain that is NOT compartment syndrome
    - splinting the ankle between neutral and resting plantar flexion (37 deg) can also decrease intracompartmental pressures
  - **hyperbaric oxygen therapy**
    - works by increasing the oxygen diffusion gradient
- Operative
  - **emergent fasciotomy of all four compartments**
    - indications
      - clinical presentation consistent with compartment syndrome
      - compartment pressures within 30 mm Hg of diastolic blood pressure (delta p)
        - intraoperatively, diastolic blood pressure may be decreased from anesthesia
          - must compare intra-operative measurement to pre-operative diastolic pressure
          - attempt to restore systemic blood pressure prior to measurement
    - contraindications
      - missed compartment syndrome
- Special considerations
  - pediatrics
    - children are unable to verbalize feelings
      - if suspicion, then perform compartment pressure measurement under sedation
  - hemophiliacs
    - give Factor VIII replacement before measuring compartment pressures

Techniques

- **Emergent fasciotomy of all four compartments**
  - dual medial-lateral incision
    - approach
      - two 15-18cm vertical incisions separated by 8cm skin bridge
        - anterolateral incision
        - posteromedial incision
    - technique

- anterolateral incision
  - identify and protect the superficial peroneal nerve
  - fasciotomy of anterior compartment performed 1cm in front of intermuscular septum
  - fasciotomy of lateral compartment performed 1cm behind intermuscular septum
- posteromedial incision
  - protect saphenous vein and nerve
  - incise superficial posterior compartment
  - detach soleal bridge from back of tibia to adequately decompress deep posterior compartment
- post-operative
  - dressing changes followed by delayed primary closure or skin grafting at 3-7 days post decompression
- pros
  - easy to perform
  - excellent exposure
- cons
  - requires two incisions

- single lateral incision
  - approach
    - single lateral incision from head of fibula to ankle along line of fibula
  - technique
    - identify superficial peroneal nerve
    - perform anterior compartment fasciotomy 1cm anterior to the intermuscular septum
    - perform lateral compartment fasciotomy 1cm posterior to the intermuscular septum
    - identify and perform fasciotomy on superficial posterior compartment
    - enter interval between superficial posterior and lateral compartment
    - reach deep posterior compartment by following interosseous membrane from the posterior aspect of fibula and releasing compartment from this membrane
      - common peroneal nerve at risk with proximal dissection
  - pros
    - single incision
  - cons
    - decreased exposure

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Hand & Forearm Compartment Syndrome

Mark Karadsheh

TOPIC	QUESTIONS	EVIDENCE	VIDEOS	TECHNIQUES
Review Topic	2	5	3	3








Introduction

- Increased osseofascial compartment pressure leads to decreased perfusion
- May lead to irreversible muscle and nerve damage
- May occur anywhere that skeletal muscle is surrounded by fascia, but most commonly
  - leg
  - forearm (details below)
  - hand (details below)
  - foot
  - thigh
  - buttock
  - shoulder
  - paraspinous muscles
- Pathophysiology
  - local trauma and soft tissue destruction> bleeding and edema > increased interstitial pressure > vascular occlusion > myoneural ischemia
- Causes
  - trauma
    - fractures (most common)
      - distal radius fractures in adults
      - supracondylar humerus fracture in children
    - crush injuries
    - contusions
    - gunshot wounds
  - tight casts, dressings, or external wrappings
  - extravasation of IV infusion
  - burns
  - postischemic swelling

    - bleeding disorders
    - arterial injury
- Outcomes
    - may lead to
        - loss of function
        - Volkmann ischemic contracture
        - neurologic deficit
        - infection
        - amputation

Anatomy

- Forearm compartments
    - 3 in total
        - volar
            - most commonly affected
        - dorsal
        - mobile wad (lateral)
            - rarely involved
            - muscles
                - brachioradialis
                - extensor carpi radialis longus
                - extensor carpi radialis brevis
- Hand compartments
    - 10 in total
        - hypothenar
        - thenar
        - adductor pollicis
        - dorsal interosseous (x4)
        - volar (palmar) interosseous (x3)

Presentation

- Symptoms
    - pain out of proportion to clinical situation is usually first symptom
        - may be absent in cases of nerve damage
        - difficult to assess in
            - polytrauma
            - sedated patients
            - children
- Physical exam
    - pain w/ passive stretch of fingers
        - most sensitive finding
    - paraesthesia and hypoesthesia
        - indicative of nerve ischemia in affected compartment
    - paralysis
        - late finding
        - full recovery is rare in this case
    - palpable swelling

        - tense hand in intrinsic minus position
            - most consistent clinical finding
    - peripheral pulses absent
        - late finding
        - amputation usually inevitable in this case

Evaluation

- Radiographs
    - obtain to rule-out fracture
- Compartment pressure measurements
    - indications
        - polytrauma patients
        - patient not alert/unreliable
        - inconclusive physical exam findings
    - relative contraindication
        - unequivocally positive clinical findings should prompt emergent operative intervention without need for compartment measurements
    - threshold for decompression
        - controversial, but generally considered to be
            - absolute value of 30-45 mm Hg
            - within 30 mm Hg of diastolic blood pressure (delta p)
                - intraoperatively, diastolic blood pressure may be decreased from anesthesia
                    - if delta p is less than 30 mmHg intraoperatively, check preoperative diastolic pressure and follow postoperatively as intraoperative pressures may be low and misleading

Treatment

- Nonoperative
    - indications
        - exam not consistent with compartment syndrome
        - delta p > 30
- Operative
    - **emergent forearm fasciotomies**
        - indications
            - clinical presentation consistent with compartment syndrome
            - compartment measurements with absolute value of 30-45 mm Hg
            - compartment measurements within 30 mm Hg of diastolic blood pressure (delta p)
                - intraoperatively, diastolic blood pressure may be decreased from anesthesia
                    - must compare intra-operative measurement to pre-operative diastolic pressure
    - **emergent hand fasciotomies**
        - indications
            - clinical presentation consistent with compartment syndrome

- compartment measurements with absolute value of 30-45 mm Hg
- compartment measurements within 30 mm Hg of diastolic blood pressure (delta p)
  - intraoperatively, diastolic blood pressure may be decreased from anesthesia
    - must compare intra-operative measurement to pre-operative diastolic pressure

Surgical Techniques

- Forearm
  - **emergent fasciotomies of all involved compartments**
    - approach
      - volar incision
        - decompresses volar compartment, dorsal compartment, carpal tunnel
          - incision starts just radial to FCU at wrist and extends proximally to medial epicondyle
          - may extend distally to release carpal tunnel
      - dorsal incision
        - decompresses mobile wad
          - dorsal longitudinal incision 2cm distal to lateral epicondyle toward midline of wrist
    - technique
      - volar incision
        - open lacertus fibrosus and fascia over FCU
        - retract FCU ulnarly, retract FDS radially
        - open fascia over deep muscles of forearm
      - dorsal incision
        - dissect interval between EDC and ECRB
        - decompress mobile wad and dorsal compartment
    - post-operative
      - leave wounds open
        - wound VAC
        - sterile wet-to-dry dressings
      - repeat irrigation and debridement 48-72 hours later
        - debride all dead muscle
        - possible delayed primary wound closure
        - VAC dressing when closure cannot be obtained
          - follow with split-thickness skin grafting at a later time
- Hand
  - **emergent fasciotomies of all involved compartments**
    - approach
      - two longitudinal incisions over 2nd and 4th metacarpals
        - decompresses volar/dorsal interossei and adductor compartment
      - longitudinal incision radial side of 1st metacarpal
        - decompresses thenar compartment

        - longitudinal incision over ulnar side of 5th metacarpal
            - decompresses hypothenar compartment
    - technique
        - first volar interosseous and adductor pollicis muscles are decompressed through blunt dissection along ulnar side of 2nd metacarpal
    - post-operative
        - wounds left open until primary closure is possible
            - if primary closure not possible, split-thickness skin grafting is used

Complications

- Volkman's ischemic contracture
    - irreversible muscle contractures in the forearm, wrist and hand that result from muscle necrosis
    - contracture positioning
        - elbow flexion
        - forearm pronation
        - wrist flexion
        - thumb adduction
        - MCP joints in extension
        - IP joints in flexion
    - classification
        - Tsuge Classification (see table below)

Stages & Treatment of Volkman's Ischemic Contracture of Hand		
Stage	*Affected muscle*	*Treatment*
Mild	Finger flexors	Dynamic splinting, tendon lengthening
Moderate	Wrist and finger flexors	Excision of necrotic tissue, median and ulnar neurolysis, BR to FPL and ECRL to FDP tendon transfers, distal slide of viable flexors
Severe	Wrist/finger flexors and extensors	Same as above (moderate) with possible free muscle transfer

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Quadriceps Tendonitis

Evan Watts

TOPIC
Review Topic



Introduction

- Inflammation of the suprapatellar tendon of the quadriceps muscle
- Epidemiology
  - demographics
    - 8:1 male-to-female ratio
    - more common in adult athletes
  - risk factors
    - jumping sports
      - basketball
      - volleyball
      - athletics (e.g., long jump, high jump, etc)
- Pathophysiology
  - mechanism of injury
    - occurs as the result of repetitive eccentric contractions of the extensor mechanism
  - pathoanatomy
    - microtears of the tendon most commonly at the bone-tendon interface
- Associated conditions
  - Jumper's knee
    - patellar tendonitis
      - more commonly affects the insertion of the patella tendon at the patella.
      - less commonly the insertion at the tibial tubercle
  - Quadriceps tendinosis
    - chronic quad tendon degeneration with no inflammation

Anatomy

- Knee extensor mechanism
  - quadriceps muscles
    - rectus femoris, vastus medialis, vastus lateralis, vastus intermedius
  - quadriceps tendon
    - common trilaminar tendon of quadriceps muscles
      - anterior layer = rectus femoris

        - middle layer = vastus medialis and vastus lateralis
        - deep layer = vastus intermedius
- Vascular supply
    - medial, lateral and peripatellar arcades
- Innervation
    - innervated by muscular branches of the femoral nerve (L2, L3, L4)

Presentation

- History
    - overuse injury in a jumping athlete
    - recent increase in athletic demands or activity
    - often a recurring injury
- Symptoms
    - pain localized to the superior border of patella
    - worse with activity
    - associated swelling
- Physical examination
    - inspection
        - knee alignment
        - swelling
    - palpation
        - tenderness to deep palpation at quadriceps tendon insertion at the patella
        - palpable gap would suggest a quads tendon tear
        - patellar subluxation
    - motion
        - pain with resisted open chain knee extension
        - able to actively extend the knee against gravity

Imaging

- Radiographs
    - recommended views
        - AP and lateral of knee
    - optional views
        - Sunrise or Merchant views for patella instability
    - findings
        - usually normal
        - may see tendon calcinosis in chronic degeneration
    - measurement
        - evaluate knee alignment for varus/valgus angle
        - evaluate for patellar height (patella alta vs baja) for suspected quadriceps tendon rupture
            - Blumentsaat's line should extend to inferior pole of the patella at 30 degrees of knee flexion
            - Insall-Salvati method
                - normal between 0.8 and 1.2
- Ultrasound
    - indications
        - suspected acute or chronic
    - findings
        - effective at detecting and localizing disruption in tendon
        - operator and user-dependent
- MRI

- indications
  - most sensitive imaging modality
- findings
  - intrasubstance signal and thickening of tendon

Treatment

- Nonoperative
  - **activity modification, NSAIDS, and physical therapy**
    - indications
      - mainstay of treatment
    - technique
      - rest until pain is improved
      - physical therapy starting with range of motion and progressing to eccentric exercises
      - cortisone injections contraindicated due to risk of quadriceps tendon rupture
- Operative
  - **quadriceps tendon debridement**
    - indications
      - very rarely required

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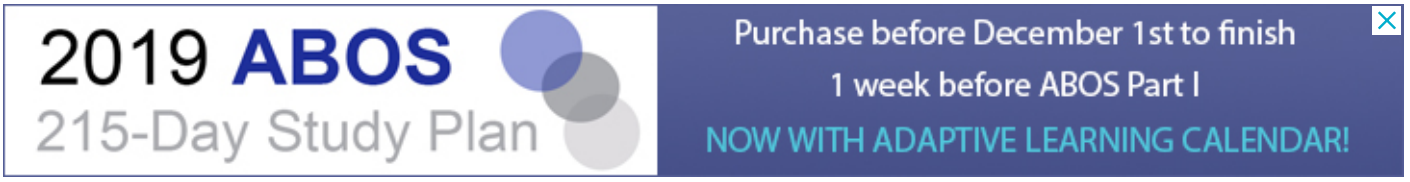

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Quadriceps Contusion

Michael Hughes MD

TOPIC	QUESTIONS	EVIDENCE	CASES
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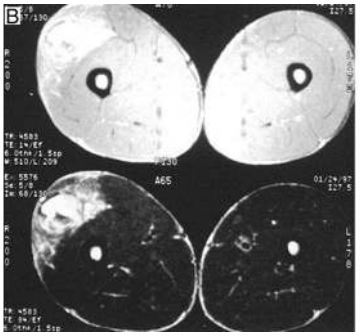



Introduction

- An injury commonly seen in athletes
  - occurs as a result of direct trauma
  - common in contact sports

Presentation

- Symptoms
  - pain at anterior thigh
- Physical exam
  - tenderness at anterior thigh
  - limited active knee flexion due to pain
  - possible knee effusion
  - peform straight leg raise to ensure extensor mechanism is intact
  - test sensory branches of femoral nerve (lateral, intermediate, and medial cutaneous nerves) during evaluation for compartment syndrome

Imaging

- Radiographs
  - imaging not necessary if mild contusion and extensor mechanism intact
  - plain radiograph to evaluate for myositis ossificans in chronic injuries
- MRI
  - has the highest sensitivity and specificity for disorders of the quadriceps
  - MRI helpful in moderate to severe contusions or if quadriceps tendon competency in doubt

Treatment

- Nonoperative
  - **immobilize in 120 degrees of knee flexion for 24 hours followed by therapy**
    - indications
      - acute injuries
    - technique

        - acute phase
            - cold therapy
            - ACE bandage or hinged knee brace
        - subacute phase
            - begin active pain-free quadriceps stretching several times a day thereafter
            - weight bearing as tolerated with use of crutches often needed initially
            - close monitoring for compartment syndrome
    - **Angiotensin II receptor blockade (e.g. Losartan)**
        - indications
            - increase muscle regeneration after contusion
            - decrease fibrosis
        - mecahnism
            - blockade of insulin-like growth factor
            - reduces apoptotic cascade of muscle
- Operative
    - **thigh fasciotomies**
        - indications
            - compartment syndrome present

Complications

- Compartment syndrome
    - usually rupture of deep perforating branches of the vastus intermedius
- Myositits ossificans
    - incidence of 5-9% rate with quadriceps contusion

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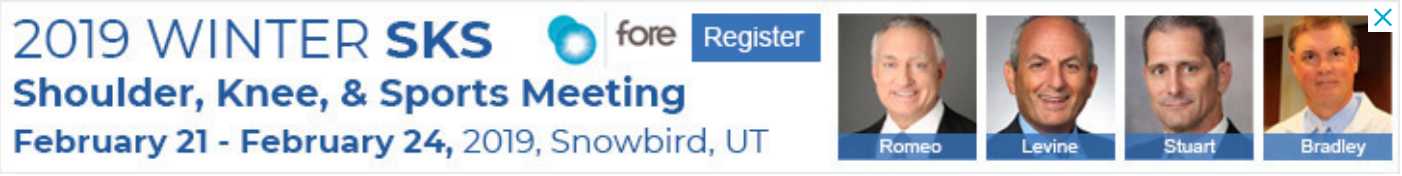

QUESTIONS (4)

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Complex Regional Pain Syndrome (CRPS)

Daniel Hatch

TOPIC	QUESTIONS	EVIDENCE
Review Topic	11	15




Introduction

- Sustained sympathetic activity in a perpetuated reflex arc characterized by pain out of proportion to physical exam findings
  - also known as complex regional pain syndrome (CRPS)
  - known as causalgia when associated with defined nerve
- Pathophysiology
  - trauma from an exagerrated response to injury
    - most common reason for a poor outcome following a crush injury to the foot
  - surgery
  - prolonged immobilization
  - possible malingering
- Prevention
  - vitamin C 500 mg daily x 50 days in distal radius fractures treated conservatively
    - 200mg daily x 50 days if impaired renal function
  - vitamin C also has been shown to decrease the incidence of CRPS (type I) following foot and ankle surgery
  - avoid tight dressings and prolonged immobilization
- Prognosis
  - responds poorly to conservative and surgical treatments

Classification

Lankford and Evans Stages of RSD			
Stage	*Onset*	*Exam*	*Imaging*
Acute	0-3 months	Pain, swelling, warmth, redness, decreased ROM, hyperhidrosis	Normal x-rays, positive three-phase bone scan
Subacute	3 to 12 mos	Worse pain, cyanosis, dry skin, stiffness, skin atrophy	Osteopenia on x-ray
Chronic	> 12 months	Dimished pain, fibrosis, glossy skin, joint contractures	Extreme osteopenia on x-ray

- International Association for the Study of Pain Classification
  - type I
    - CRPS without demonstrable nerve lesions
    - most common
    - from trauma, cast or tight bandage
  - type II
    - CRPS with evidence of identifiable nerve damage
    - minimal positive response with sympathetic blocks

Presentation

- Cardinal signs
  - exaggerated pain
  - swelling
  - stiffness
  - skin discoloration
- Physical exam
  - vasomotor disturbance
  - trophic skin changes
  - hyperhidrosis
  - "flamingo gait" if the knee is involved

Imaging

- Radiographs
  - patella osteopenia if the knee is involved
- Three-phase bone scan
  - indications
    - to rule out CRPS type I (has high negative predictive value)
  - findings
    - RSD shows positive phase III that does not correlate with positive phase I and phase II
    - phase background
      - phase I (2 minutes)
        - shows an extremity arteriogram
      - phase II (5-10 minutes)
        - shows cellulitis and synovial inflammation
      - phase III (2-3 hours)
        - shows bone images
      - phase IV (24 hours)
        - can differentiate osteomyelitis from adjacent cellulitis
- Thermography
  - questionable utility
- EMG/NCV
  - may show slowing in known nerve distribution e.g. slowing of median nerve conduction for CRPS type II in forearm

Studies

- Diagnosis
  - diagnosis is clinical, but can be confirmed by pain relief with sympathetic block
  - early diagnosis is critical for a successful outcome

Treatment

- Nonoperative
  - **physical therapy and pharmacologic treatment**
    - indications
      - indicated as first line of treatment
    - modalities
      - gentle physiotherapy
      - tactile discrimination training
      - graded motor imagery
      - medications
        - NSAIDs
        - alpha blocking agents (phenoxybenzamine)
        - antidepressants
        - anticonvulsants
        - calcium channel blockers
        - GABA agonists
  - **nerve stimulation**
    - indications
      - symptoms present mainly in the distribution of one major peripheral nerve
    - programmable stimulators placed on affected nerves
  - **chemical sympathectomy**
    - indications
      - acts as another option when physical therapy and less aggressive nonoperative management fails
- Operative
  - **surgical sympathectomy**
    - indications
      - failed nonoperative management, including chemical block
  - **surgical decompression**
    - indications
      - CRPS type II with known nerve involvement e.g. carpal tunnel release if median nerve involved

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QUESTIONS (11)

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Open Fractures Management

Ryan Berger | Benjamin C. Taylor

TOPIC	QUESTIONS	EVIDENCE	CASES
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Introduction

- Open fracture definition
  - a fracture with direct communication to the external environment
  - historically described as a "compound" fracture
  - a soft tissue wound in proximity to a fracture should be treated as an open fracture until proven otherwise
- Often associated with additional injuries
- Orthopaedic urgency
  - in the absence of life-threatening injuries, there is no clinical advantage to performing surgery within 6 hours of injury versus 6-24 hours

Classification

- Gustilo Classification
- Tscherne Classification

Antibiotic Management

- Gustilo Type I and II
  - 1st generation cephalosporin
  - clindamycin or vancomycin can also be used if allergies exist
- Gustilo Type III
  - 1st generation cephalosporin + aminoglycoside
- Farm injuries, heavy contamination, or possible bowel contamination
  - add high dose penicillin for anaerobic coverage (clostridium)
- Special considerations
  - fresh water wounds

        - fluoroquinolones or 3rd or 4th generation cephalosporin
    - saltwater wounds
        - doxycycline + ceftazidime or a fluoroquinolone
- Duration
    - initiate as soon as possible
        - studies show increased infection rate when antibiotics are delayed for more than 3 hours from time of injury
    - continue for 24 hours after initial injury if wound is able to be closed primarily
    - continue for 24 hours after final closure if wound is not closed during initial surgical debridement (72 hours for Type III wounds)

Tetanus

- Initiate in emergency room or trauma bay
- Two forms of prophylaxis
    - toxoid dose 0.5 mL, regardless of age
    - immune globulin dosing
        - <5-years-old receive 75 U
        - 5-10-years-old receive 125 U
        - >10-years-old receive 250 U
    - toxoid and immunoglobulin should be given intramuscularly with two different syringes in two different locations
- Guidelines for tetanus prophylaxis depend on 3 factors
    - complete or incomplete vaccination history (3 doses)
    - date of most recent vaccination
    - severity of wound

Emergency Room Management

- Fracture management begins after initial trauma survey and resuscitation is complete: airway, breathing, circulation, disability, and exposure (ABCDE)
- Antibiotics
    - initiate early IV antibiotics and update tetanus prophylaxis as indicated
    - low-energy gunshot wounds should be treated with a single dose of a 1st generation cephalosporin in the ED
- Control bleeding
    - direct pressure will control active bleeding
    - do not blindly clamp or place tourniquets on damaged extremities
- Assessment
    - soft-tissue damage
    - neurovascular exam
        - if concern for vascular insult, ankle brachial index (ABI) should be obtained
            - normal ratio is >0.9
            - vascular surgery consult and angiogram is warranted if ABI <0.9
    - consider saline load test if concern for traumatic arthrotomy
- Dressing
    - remove gross debris from wound, do not remove any bone fragments
    - place sterile saline-soaked dressing on wound
    - little evidence to support aggressive irrigation or irrigation with antiseptic

solution in the ED, as this can push debris further into wound
- Stabilize
  - splint, brace, or traction for temporary stabilization
    - decreases pain, minimizes soft tissue trauma, and prevents disruption of clots

Operating Room Management

- Aggressive debridement and irrigation
  - thorough debridement is critical to prevention of deep infection; remove foreign bodies
  - expose fracture by recreating mechanism of injury, extend wound proximally and distally in line with extremity
  - low pressure irrigation is preferred over high pressure pulse lavage
  - saline shown to be most effective irrigating agent
    - on average, 3L of saline are used for each successive Gustilo type
      - Type I: 3L
      - Type II: 6L
      - Type III: 9L
  - bony fragments without soft tissue attachments should be removed
- Fracture stabilization
  - internal fixation, external fixation, or intramedullary nail as indicated
    - avoid placement of pins in proximity to planned definitive incisions
- Staged debridement and irrigation
  - perform every 24 to 48 hours as needed
- Early soft tissue coverage or wound closure is ideal
  - timing of flap coverage for open tibial fractures remains controversial, <5 days is desired
  - increased risk of infection beyond 7 days
  - can proceed with bone grafting after wound is clean and closed
  - negative-pressure wound therapy may be utilized during debridement until definitive coverage can be achieved
- Can place antibiotic bead-pouch in open dirty wounds
  - beads made by mixing methylmethacrylate with heat-stable antibiotic powder
- Reconstruction options for bone loss
  - Masquelet technique
  - distraction osteogenesis
  - vascularized bone flap/transfer

Complications

- Infection
- Neurovascular injury
- Compartment syndrome
  - can still occur in the setting of open fractures

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Programa Nacional para a Tuberculose

MANUAL DE TUBERCULOSE E MICOBACTÉRIAS NÃO TUBERCULOSAS

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Glossário

ADA	Adenosina deaminase
ALT	Alanina aminotransferase
Anti-TNF-α	Anti-factor de necrose tumoral alfa
ARV	Anti-retrovíricos
AST	Aspartato aminotransferase
BCG	Bacillus Calmette-Guérin
DHL	Desidrogenase lática
E	Etambutol
H	Isoniazida
HTA	Hipertensão arterial
IGRA	Testes de interferon gama
MDR	*Multidrug-resistant*
MNT	Micobactéria não tuberculosa
MT	*Mycobacterium tuberculosis*
R	Rifampicina
RM	Ressonância magnética
S	Estreptomicina
SNC	Sistema nervoso central
TAAN	Teste de amplificação de ácidos nucleicos
TAC	Tomografia axial computadorizada
TARV	Terapêutica anti-retrovírica
TB	Tuberculose
TBIL	Tuberculose infecção latente
TNF-α	Factor de necrose tumoral alfa
TOD	Toma observada diretamente
TSA	Teste de susceptibilidade a antibacilares
TST	Teste tuberculínico
VIH	Vírus de imunodeficiência humana
Z	Pirazinamida

1. Diagnóstico

A abordagem diagnóstica de um indivíduo com suspeita de doença inclui uma avaliação clínica detalhada e recurso a exames e técnicas que têm sofrido importantes avanços nas últimas décadas. [1-3]

O diagnóstico de tuberculose (TB) é confirmado se houver identificação do *Mycobacterium tuberculosis* (MT) em exame cultural, ou se o exame direto e o teste de amplificação de ácidos nucleicos (TAAN) forem positivos. [1]

Contudo, a decisão de iniciar tratamento é baseada, na maior parte das vezes, num diagnóstico provável, ou seja, num doente com suspeita de tuberculose em que se verifica uma das seguintes condições: exame direto do estudo micobacteriológico positivo, TAAN positivo ou exame histológico sugestivo de tuberculose, nomeadamente perante a demonstração de granulomas e/ou necrose caseosa.

Perante suspeita de tuberculose deve-se procurar alcançar o diagnóstico o mais precocemente possível, sobretudo nos casos em que há atingimento das vias aéreas, nomeadamente TB pulmonar e/ou laríngea devido ao risco de contágio. Face à suspeita de tuberculose pulmonar, é uma boa prática a colheita de 2 amostras de expetoração no mesmo dia, com envio imediato ao laboratório. Esta prática, permite um diagnóstico célere da doença. Perante um resultado negativo, deve-se insistir na colheita de mais amostras ou mesmo avançar para técnicas de diagnóstico invasivas, como broncofibroscopia.

Os testes de amplificação de ácidos nucleicos apresentam uma elevada sensibilidade (95%) e especificidade (97-98%) perante amostras positivas em exame direto. Nas amostras com exame direto negativo a sensibilidade é reduzida e variável com os estudos (57 a 76 %), não permitindo excluir o diagnóstico de TB.[4]

Assim, é importante fazer o TAAN das amostras se:

- Houver risco de se tratar de micobactéria não tuberculosa (doentes infectados por vírus de imunodeficiência humana (VIH), doentes com alterações pulmonares estruturais

como por exemplo, doentes com doença pulmonar obstrutiva crónica ou bronquiectasias)

- Não houver suspeita de tuberculose (amostra positiva em exame direto, em doente sem clínica e/ou alterações imagiologias sugestivas de tuberculose).
- Sempre, antes de se avançar para rastreios alargados (o TAAN negativo em amostra positiva em exame direto permite evitar rastreios desnecessários).

Em indivíduos com suspeita de tuberculose e exame direto negativo, a realização de Xpert pode permitir fazer o diagnóstico de tuberculose (sensibilidade 67% e especificidade 99%) e identificar a mutação responsável pela resistência à rifampicina, permitindo iniciar precocemente um esquema de tratamento adequado.[5]

O diagnóstico célere de resistência, particularmente de multirresistência é muito importante. Deve ser sempre efetuado teste molecular de resistência nos indivíduos com fatores de risco de tuberculose multirresistente, nomeadamente na presença de pelo menos uma das seguintes situações:

- história prévia de tuberculose submetida a tratamento
- contacto com doente com tuberculose multirresistente
- toxicodependentes
- doentes infectados por VIH
- reclusos
- profissionais de saúde
- Imigrantes de países de elevada prevalência de tuberculose multirresistente

As manifestações clínicas da TB são frequentemente sistémicas e inespecíficas, pelo que, o diagnóstico precoce pode ser difícil, particularmente nos doentes imunodeprimidos e em grupos etários extremos (crianças e idosos). Adicionalmente, a TB extrapulmonar, pela diversidade de apresentação, constitui um desafio clínico considerável, não só porque os órgãos envolvidos condicionam múltiplos quadros clínicos mas também porque é frequentemente necessário o recurso a exames complementares de diagnóstico invasivos (Quadro 1).

Os testes imunológicos (teste tuberculínico e testes de interferon gama) atualmente disponíveis, não permitem distinção entre tuberculose ativa, latente ou passada.[6]

Quadro 1 - Apresentação clínica e exames complementares no diagnóstico de tuberculose extrapulmonar

Localização	Sintomas e Sinais	Exames de diagnóstico
Pleural	Tosse seca, toracalgia com características pleuríticas, dispneia, hipersudorese, perda de peso e febre. Derrame pleural de pequeno/médio volume. Envolvimento pulmonar frequente (70%).	Rx tórax, colheita de expetoração (para diagnóstico de TB pulmonar), toracocentese (contagem diferencial de células, DHL, proteínas, ADA, pH, glicose, exame micobacteriológico, TAAN) e biópsia pleural (histologia, exame micobacteriológico, TAAN)
Ganglionar	Apresentação extrapulmonar mais frequente, 41% com envolvimento pulmonar. Adenomegalias sólidas, crescimento gradual, duras, inicialmente indolores e sem sinais inflamatórios cutâneos. Envolvimento cervical mais frequente. Sintomatologia constitucional rara nos casos limitados.	Ecografia, biópsia ganglionar (aspirativa/excisional – histologia, exame micobacteriológico, TAAN).
Osteoarticular	Mais frequente envolvimento da coluna vertebral e grandes articulações. Dor articular, limitação funcional e outas manifestações neurológicas, sinais inflamatórios.	TAC/RM, Exame micobacteriológico direto e cultural, TAAN de amostras – aspirado de abcesso, líquido sinovial, outros).
TB disseminada	Febre, astenia, anorexia, perda de peso e outros sintomas dependendo dos órgãos envolvidos. Envolvimento pulmonar concomitante – padrão radiológico miliar (85%).	Rx tórax, TAC torácico, broncoscopia com LBA e biópsia Transbrônquica. Outros exames complementares dependendo dos órgãos envolvidos. (exemplo: biópsia hepática, biópsia de medula óssea.
SNC	Apresentação dependente do tamanho e localização do tuberculoma	Punção lombar (citologia, proteínas, glicose, exame micobacteriológico, TAAN, ADA), TAC/RMN.
Abdominal	Mais frequente peritonite e região ileocecal. Distensão e dor abdominal, ascite, febre, anorexia, perda de peso	Paracentese (exame micobacteriológico direto e cultural, TAAN, ADA); ecografia abdominal, biópsia de lesões, laparoscopia.
Pericárdica	Dispneia, taquicardia, distensão venosa jugular, hepatomegalia, pulso paradoxal, atrito pericárdio, febre. Derrame pericárdico.	Pericardiocentese (contagem diferencial de células, DHL, proteínas, ADA, exame micobacteriológico direto e cultural, TAAN) e biópsia pericárdica (com histologia, exame micobacteriológico direto e cultural e TAAN). Ecocardiograma para avaliação do derrame e do espessamento pericárdico.
Genito-urinária	Disúria, polaquiúria, hematúria, urgência urinária, edema testicular e dor lombar. Infeções bacterianas de repetição	Exame micobacteriológico direto e cultural de urina, TAAN, ecografia/TC pélvica, biópsia de lesões suspeitas

Nota: em qualquer caso de Tuberculose deve ser realizado o rastreio de infeçao pelo VIH.

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2. Tratamento da tuberculose pulmonar

Princípios:

- Terapêutica combinada;
- Duração mínima de 6 meses (182 tomas);
- Toma única diária em regime de toma observada diretamente (TOD).

Esquemas terapêuticos:

Quadro 2 - Esquemas terapêuticos recomendados

	Fase inicial	Fase continuação [1]
Primeiro tratamento	• Sem resistências ou ainda sem TSA nem teste molecular de resistências - 2HRZE • Teste molecular ou TSA com resistências – Quadro 3	• TSA comprovando suscetibilidade a todos os fármacos de 1ª linha - 4,7,10 HR [2] • TSA com resistências – Quadro 3
Retratamento sem resultados moleculares de resistência [3,4]	• 2HRZE+ injetável[4] , ajustado assim que se obtiver testes moleculares ou TSA (ter sempre em atenção o TSA do tratamento anterior)	• Ajustar de acordo com resultado de TSA

[1] Fase continuação: quando cultura negativa, TSA disponível e 56 tomas observadas;

[2] 7 meses se cultura positiva aos 2 meses de tratamento, forma cavitada ou fase inicial sem Z; 10 meses se envolvimento SNC e ósseo;

[3] Considera-se retratamento sempre que exista tratamento anterior superior a 1 mês e se verifica reaparecimento de exames diretos/culturais positivos, independentemente do tempo decorrido entre o primeiro tratamento e o atual.

[4] Realizar teste molecular de resistência à H e/ou R antes de iniciar novo esquema e de acordo com o resultado utilizar esquema ajustado a/as resistências encontradas.

Quadro 3 - Esquemas terapêuticos recomendados em caso de mono ou polirresistência

Padrão de Resistência	Esquema recomendado	Duração mínima tratamento (meses)	Comentários
H (±S)	R+Z+E	6 a 9	Fluoroquinolona se doença extensa e introduzida na fase inicial do esquema. Nunca associar como fármaco isolado num esquema em falência.
H e Z	R+E+ Fluoroquinolona	9 a 12	Tratamento mais longo se doença extensa.
R	H+E+ Fluoroquinolona+ (Z durante os 2 -3 primeiros meses)	12 a 18	Agente injetável se doença extensa e introduzida na fase inicial do esquema. Nunca associar como fármaco isolado num esquema em falência.
R + E (±S)	H+Z+fluoroquinolona+(injetável durante 2-3 primeiros meses)	18	Período superior (6 meses) do fármaco injetável se doença extensa
R+Z (±S)	H+E+fluoroquinolona+(injetável durante 2-3 primeiros meses)	18	Período superior (6 meses) do fármaco injetável se doença extensa

H= isoniaziada; R= rifampicina; Z= pirazinamida; E=etambutol; S=estreptomicina

Quadro 4 - Monitorização do tratamento

Monitorização do tratamento									
Mês de tratamento	0	0,5	1	1,5	2	3	4	5	6
Clínica (incluir peso/efeitos adversos/ adesão)	×	×	×	×	×	×	×	×	×
AST/ALT/Bilirrubina total	×	×	×	×	×	×	×	×	×
Exame micobacteriológico (direto e cultural)	×	#			×				×
Teste de suscetibilidade	×				+				
Radiografia de tórax	×				×		×		×

De 15 em 15 dias até 2 amostras de exame direto consecutivas negativas.

+ Se exame cultural ainda positivo.

Quadro 5 – Classificação dos fármacos e doses recomendadas

Classificação	Nome	mg/Kg	Dose média [máxima] [mg]
Grupo 1			
Orais de 1ª linha	Isoniazida (H)	5	300 [300]
	Isoniazida Crianças	10-15	300
	Rifampicina (R)	10	600 [600]
	Rifampicina Crianças	10-20	600
	Pirazinamida (Z)	25 (20-30)	1500 [2000]
	Pirazinamida Crianças	15-30	2000
	Etambutol (E)	20 (15-25)	1200 [2000]
	Etambutol Crianças*	15-20	1000
	Rifabutina (RIF)	5	300 [300]
Grupo 2			
Injetáveis	Estreptomicina (S)	15(10-15)	1000[1000]
	Canamicina (Km)	15-20	750-1000 [1000]
	Amicacina (Am)	15-20	750-1000 [1000]
	Capreomicina (Cm)**	15-20	750-1000 [1000]
Grupo 3			
Fluoroquinolonas	Ofloxacina (Ofx)	7,5-15	600-1000
	Levofloxacina (Lfx)	-	500-1000
	Moxifloxacina (Mfx)	-	400

Nas crianças a partir dos 40 Kg as doses são semelhantes às dos adultos (ou até atingir a dose máxima);

*Não utilizar em crianças abaixo dos 5 anos por não ser possível avaliar a acuidade visual.

** Não disponível em Portugal.

Preparações disponíveis em dose fixa:

- *Rifater:* Isoniazida 50mg, Rifampicina 120mg, Pirazinamida 300mg
- *Rifinah:* Isoniazida 150mg, Rifampicina 300mg

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3. Tratamento da tuberculose extrapulmonar

A TB pode afetar qualquer órgão ou tecido, sendo as formas não pulmonares mais frequentes nas crianças e nos imunodeprimidos[2].

Os princípios básicos do tratamento são comuns à TB pulmonar[2]. No entanto, o envolvimento de certos órgãos determina especificidades terapêuticas, nomeadamente quanto à sua duração ou à necessidade de corticoterapia .

Quadro 6 – Tratamento da tuberculose extrapulmonar: esquema e duração [1,2]

Forma	Fase Inicial	Fase de Continuação	Duração Total (meses)#
SNC (incluindo meninges)	HRZE (2 meses/56 tomas)	HR (10 meses)	12
Ganglionar		HR (4 meses)	6-9*
Pericárdica		HR (4 meses)	6
Disseminada		HR (10 meses)	12
Osteoarticular (incluindo coluna vertebral)		HR (10 meses)	12
Outras formas		HR (4 meses)	6

*O tratamento deve ser prolongado se a resposta for lenta.

Quadro 7 – Corticoterapia na TB extrapulmonar: indicação, doses e duração do tratamento [1,2,3].

Indicação	Dose	Duração
TB pericárdica	*Prednisolona* Adultos: 60 mg/dia Crianças: 1mg/Kg/dia (máx: 40 mg)	Adultos e crianças Desmame progressivo: 60 mg/dia - 4 semanas 30 mg/dia - 4 semanas 15 mg/dia - 2 semanas 5mg/dia na semana nº 11
TB meníngea	*Prednisolona* Adultos: Esquema com R: 20-40 mg/dia Esquema sem R: 10-20 mg/dia Crianças: 1-2 mg/kg/dia (máx 40mg) *Dexametasona* Adultos e Crianças > 25Kg: 12mg/dia Crianças <25Kg: 8 mg/dia	Iniciar o desmame após a 3ª semana de tratamento e prolongá-lo durante 3 semanas

Tuberculose Ganglionar

Durante um tratamento bem-sucedido e na ausência de recidiva, podem persistir ou surgir novos gânglios ou ocorrer fistulização com drenagem. Pensa-se que estes fenómenos são induzidos imunologicamente, pelo que não obrigam ao prolongamento do tratamento, a não ser que se verifique resposta lenta.

A excisão ganglionar terapêutica está indicada em situações excecionais[2]. No entanto, a exérese ganglionar não dispensa o tratamento com antibacilares , pela possibilidade de focos residuais persistentes[1].

Tuberculose Osteoarticular

No caso de TB da coluna vertebral, deve ser realizada TAC/RM.

A abordagem cirúrgica está indicada em casos de falência terapêutica, instabilidade ou compressão da medula espinhal[1].

Tuberculose Pericárdica

Pode cursar com tamponamento cardíaco e pericardite constritiva, associando-se a elevada morbimortalidade[1]. Pode ser necessário realizar pericardiocentese, pericardectomia ou janela pericárdica [1].

Tuberculose Pleural

O empiema pleural, que resulta da drenagem de uma cavidade para o espaço pleural, necessita frequentemente de abordagem cirúrgica[2].

Tuberculose Miliar

A duração do tratamento depende da presença de envolvimento do SNC, documentada por TC, RM e/ou punção lombar [1].

Tuberculose Genitourinária

As obstruções do trato urinário devem ser resolvidas. A nefrectomia pode ser necessária no rim não funcionante, com dor persistente ou HTA associada[2]. Os abcessos tubo-ováricos residuais podem ter de ser removidos cirurgicamente[2].

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4. Tratamento em situações particulares

Na Grávida

Na grávida, o diagnóstico e tratamento devem ser iniciados de forma precoce, independentemente do trimestre da gravidez, pelo risco que a doença constitui para a mãe e para o feto. Os antibacilares de primeira linha são considerados seguros na grávida, sendo que o risco de toxicidade é ultrapassado pela vantagem do tratamento da doença.

O esquema e duração do tratamento é semelhante ao dos doentes em geral, excepto a utilização de estreptomicina por ser ototóxica para o feto. Recomenda-se a administração de piridoxina (25 mg/dia) a todas as mulheres medicadas com isoniazida que estejam grávidas ou em período de amamentação.

Na Criança

As formas mais frequentes neste grupo etário têm, em geral, pouca carga bacilífera, com pouco risco de desenvolvimento de resistências, pelo que o esquema inicial não inclui, em geral, o etambutol.

Se a forma de tuberculose é de tipo adulto, com aumento da carga bacilífera, a fase intensiva pode incluir o etambutol. Desaconselha-se, no entanto, que este fármaco seja utilizado em crianças muito pequenas.

A duração do tratamento é semelhante ao preconizado no adulto.

Monitorização do tratamento

- Idêntico aos dos restantes grupos;
- Radiografias torácicas de seguimento podem ser menos frequentes visto que a resposta imagiológica é mais lenta;
- Os efeitos adversos da medicação na criança são raros, pelo que na ausência de sintomas não se preconiza a realização rotineira de análises clinicas para detecção de toxicidade hepática.

No doente com coinfecção pelo vírus de imunodeficiência humana (VIH)

O princípio do tratamento é o mesmo que nos doentes VIH negativos.

Todos os doentes VIH positivos com diagnósticos de TB devem iniciar tratamento antibacilar de imediato.

Num doente com infeção pelo VIH e sob ARV, estes não devem ser interrompidos. As interacções entre os fármacos antibacilares e os antiretroviricos (ARV) devem ser revistas e tidas em consideração (quadro 8 e 9) e se necessário devem ser alterados os esquemas terapêuticos de forma a minimizar o risco de interação e toxicidade.

Tratando-se de um doente com infeção pelo VIH, sem terapêutica antiretrovírica no momento do diagnóstico de tuberculose, o início dos anti bacilares é prioritário. Posteriormente, e tendo em consideração o estado de imunosupresssão, a tolerância aos antibacilares, as implicações decorrentes do aumento do risco de toxicidade (como por exemplo, a necessidade de interrupção de todos os fármacos em caso de toxicidade hepática grave) e a adesão do doente, deve programar-se o início da terapêutica antiretrovírica. Regra geral, quanto maior for o estado de imunosupressão maior é o benefício decorrente do início precoce dos ARV. Alguns estudos, realizados maioritariamente na Africa Subsahariana e Ásia, mostraram que em doentes com contagem de linfócitos T CD4+ <50/mm3 o início de ARV deve ocorrer nas primeiras 4 semanas após o início de anti bacilares, podendo ser protelado para após as 8 semanas no doente com CD4+ >200/mm3. Este momento coincide com a redução significativa do número de comprimidos, com a diminuiçao da probabilidade de ocorrência de efeitos adversos e com uma fase em que o estado global do doente regra geral é significativamente melhor, factores que podem contribuir para uma melhor tolerância e garantir maior adesão à terapêutica.

Quadro 8 – Esquemas terapêuticos TB/VIH

ARV	Anti-TB	Comentários
EFV + TDF/FTC ou ABC/3TC	HRZE	Os fármacos antirretrovirais e anti-tuberculosos não necessitam de ajuste posológico

EFV- Efavrirenz; TDF – Tenofovir; FTC – Entricitabina; ABC – Abacavir; 3TC – Lamivudina

Quadro 9 – Regimes Alternativos de ARV em doentes sob tratamento da tuberculose

ARV	Anti-TB	Comentários
IP/r + ABC/3TC ou TDF/FTC	H+Rifabutina+Z+E	- Ajustar a posologia da Rifabutina: a) Rifabutina+(ATV/r ou DRV/r ou SQV/r ou FPV/r): 150 mg/dia b) Rifabutina + LPV/r: 150 mg/dia ou 300 mg 3x semana
RAL + ABC/3TC ou TDF/FTC	HRZE Ou H+Rifabutina +Z+E	- A associação de RAL e rifampicina só deve ser utilizada se não houver alternativa terapêutica. Nesse caso, a posologia de RAL deve ser aumentada para 800 mg/2xdia - No caso da utilização da rifabutina, deve-se prescrever a posologia padrão dos dois fármacos (RAL: 400 mg/2xdia; rifabutina 300 mg/dia)

3TC – Lamivudina; ABC – Abacavir; ATV – Atazanavir; DRV – Darunavir; FPV – Fosamprenavir; FTC – Entricitabina; IP - Inibidores da protéase; LPV – Lopinavir; TDF – Tenofovir; RAL – Raltegravir; r – Ritonavir; SQV – Saquinavir.

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5. Efeitos adversos dos antibacilares

Todos os antibacilares têm efeitos adversos, que devemos conhecer de forma a identificar e agir prontamente. A maioria dos efeitos adversos ocorre nos primeiros 2 meses de tratamento e incluem: neuropatia periférica, intolerância gastrointestinal, toxicidade hepática e alterações neurológicas. No quadro 10 estão descritos os principais efeitos secundários dos fármacos de 1ª linha.

Quadro 10 – Efeitos adversos associados aos fármacos de primeira linha

	Efeitos adversos principais	**Efeitos adversos raros**
Isoniazida	Neuropatia periférica	Convulsões
	Rash cutâneo	Psicose
	Hepatite	Artralgia
	Sonolência e letargia	Anemia
Rifampicina	Gastrointestinais (dor abdominal, náusea, vómitos)	Osteomalacia
	Hepatite	Colite pseudomembranosa
	Reação cutânea generalizada	Insuficiência renal aguda
	Púrpura trombocitopénica	Anemia hemolítica
Pirazinamida	Artralgias	Reações cutâneas
	Hepatite	Anemia sideroblástica
	Gastrointestinais	
Etambutol	Nevrite retrobulbar	Reação cutânea generalizada
		Artralgia
		Neuropatia periférica
Estreptomicina	Lesão vestibular ou do nervo auditivo	Dor
	Lesão renal	*Rash*
	Reação de hipersensibilidade	Indução no local de injeção

Perante a ocorrência de efeitos adversos deve-se: confirmar a dose dos fármacos, excluir outras causas para os sinais e sintomas do doente, avaliar a gravidade dos efeitos adversos, suspender o(s) fármaco(s) responsáveis, reintroduzir os fármacos de forma gradual após a resolução do quadro[2].

De notar as potenciais interacçoes da rifampicina com outros fármacos e a necessidade de ajuste de dosagens, nomeadamente: antretroviricos, metadona, anti-coagulantes, entre outros.

Perturbações Gastrointestinais

Os efeitos adversos mais frequentes nas primeiras semanas de tratamento são os gastrointestinais, nomeadamente náuseas e vómitos.

Pode-se alterar a hora de administração, tomar um alimento antes da medicação, evitar a administração de anti-inflamatórios não esteroides e de álcool e excluir gravidez. Se perante estas atitudes o doente mantiver as queixas, considerar medicação sintomática, como um inibidor da bomba de protões ou anti-eméticos[2,3].

Hepatotoxicidade

É comum e potencialmente grave, definindo-se como[4]:

- Elevação das transaminases superior a 3x o limite superior do normal, na presença de sintomas;
- Elevação das transaminases superior a 5x o limite superior do normal, na ausência de sintomas.

É mais frequente nos indivíduos com elevada ingestão alcoólica, nos co-infetados pelo vírus de hepatite C ou B e nos indivíduos mais idosos.

Perante um quadro de hepatotoxicidade recomenda-se suspensão de todos os fármacos potencialmente hepatotóxicos (H, R, Z) e a identificação de outras causas possíveis (ex: vírica, álcool).

Caso a resolução do quadro seja lenta, prevê-se a introdução temporária de um esquema terapêutico com fármacos com menor potencial hepatotóxico (ex: etambutol + estreptomicina/amicacina + fluoroquinolona).

Quando o valor das transaminases, após a suspensão da medicação, for inferior a 2x o limite superior do normal, recomenda-se a reintrodução progressiva dos fármacos (Quadro 11).

Quadro 11 - Esquema de reintrodução dos fármacos[2]

Dia	Isoniazida	Rifampicina	Pirazinamida
1	50	-	-
2	100	-	-
3	150	-	-
4	300	75	-
5	300	150	-
6	300	300	-
7	300	450 (<50Kg)/600 (>50Kg)	-
8	300	450 (<50Kg)/600 (>50Kg)	250
9	300	450 (<50Kg)/600 (>50Kg)	500
10	300	450 (<50Kg)/600 (>50Kg)	1000
11	300	450 (<50Kg)/600 (>50Kg)	1500 (<50Kg)/2000 (>50Kg)
12	300	450 (<50Kg)/600 (>50Kg)	1500 (<50Kg)/2000 (>50Kg)
13	300	450 (<50Kg)/600 (>50Kg)	1500 (<50Kg)/2000 (>50Kg)

Quando se identifica o fármaco responsável pela hepatotoxicidade devem-se elaborar esquemas alternativos e eficazes (Quadro 12).

Quadro 12 – Esquemas terapêuticos perante impossibilidade, por hipersensibilidade, de utilizar isoniazida, rifampicina ou pirazinamida

Fármaco responsável pela hepatotoxicidade	Esquema recomendado (Fase inicial/Fase manutenção)	Duração mínima tratamento
H	RZE / RE (ou RZ)	6 a 9 meses
R	HZE / HE (ou HZ)	12 a 18 meses
Z	HRE / HR	9 meses

Nefrotoxicidade

Todos os aminoglicosídeos podem causar nefrotoxicidade, pelo que é importante a monitorização renal e uma hidratação adequada.

No caso de creatinina menor do que 30 ml/min é necessário ajustar as doses de pirazinamida, etambutol e estreptomicina (Quadro 13).

Nos doentes a fazer hemodiálise, a administração da medicação deve ser efetuada após a diálise, de modo a evitar a remoção prematura de alguns fármacos[2,4] ou, em alternativa, 4-6 horas antes da diálise, reduzindo a toxicidade dos fármacos[5].

Quadro 13 – Doses recomendadas dos antibacilares de primeira linha perante insuficiência renal[2,4]

Fármaco	Alteração na dose fármaco?	Dose recomendada se *clearance* creatinina <30mL/min ou hemodiálise
Isoniazida	Não	300 mg/dia
Rifampicina	Não	600 mg/dia
Pirazinamida	Sim	25 a 35 mg/Kg por dose (administrado 3 vezes por semana)
Etambutol	Sim	15 a 25 mg/Kg por dose (administrado 3 vezes por semana)
Estreptomicina	Sim	12 a 15 mg/Kg por dose (administrado 3 vezes por semana)

Lesões cutâneas

Podem ser provocadas por qualquer um dos antibacilares e podem variar desde um discreto prurido cutâneo até lesões eritematosas extensas. A abordagem depende da gravidade da situação. Se a extensão das lesões for ligeira é suficiente a associação de um anti-histamínico. Nas reações graves deverá ser suspensa toda a medicação até remissão do quadro e reintrodução gradual dos fármacos de 1ª linha[2,3].

Reação de Hipersensibilidade

Foi descrita com diversos antibacilares. Esta síndrome é uma reação idiossincrática, caraterizada pelo desenvolvimento de febre, *rash* e envolvimento de um ou mais órgãos, que pode surgir 1-2 meses após início dos antibacilares[3].

A apresentação clínica é variável, desde vários tipos de *rash*, a lesão das mucosas, linfadenopatia (>75%), hepatite (>50%), eosinofilia[3].

No caso de suspeita de reação de hipersensibilidade deverá ser suspensa toda a terapêutica até desaparecimento da reação e medicar com corticóide e anti-histamínico.

O doente deverá ser encaminhado para uma consulta de imunoalergologia para realização de estudo alergológico. Entretanto deverá iniciar tratamento com esquema alternativo, com fármacos não utilizados no esquema inicial.

Neuropatia periférica

Os fármacos que mais frequentemente causam neuropatia são a isoniazida, etionamida, cicloserina e linezolide[3]. A neuropatia ocorre com maior frequência em doentes com diabetes, alcoolismo, infeção pelo VIH, hipotiroidismo, gravidez, amamentação, lactentes, doença hepática, neuropatia pré-existente e desnutrição.

A piridoxina reduz os efeitos centrais e periféricos da isoniazida sobre o SNC, estando nestes casos recomendada a associação de piridoxina (25mg/dia), podendo a dose ser aumentada até 100 a 150 mg/dia[3].

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6. Abandono/descontinuação da terapêutica

A atitude face ao abandono ou descontinuação da terapêutica depende de:

- Resultados de exames micobacteriológicos
- Fase de tratamento em que esta ocorreu e duração da interrupção
- Proporção de doses completadas em relação ao esquema previsto

Independentemente da fase em que ocorreu a descontinuação, se na data da reintrodução dos antibacilares o doente apresentar exame direto ou cultural positivo, deverá ser sempre reiniciado o esquema terapêutico e pedido um TSA.

Se o abandono da terapêutica se der na fase inicial e a interrupção for:

- **Inferior a 14 dias** – o doente deverá prosseguir o esquema terapêutico (e completar as 56 tomas previstas na fase inicial)
- **Superior a 14 dias** – deverá ser reiniciado o tratamento.

Quando a suspensão da terapêutica se dá na fase da manutenção:

- Se o doente tiver cumprido **mais de 80% das tomas previstas**, considerar termo de tratamento se as baciloscopias forem negativas;
- Se o doente tiver cumprido **menos de 80% das tomas previstas** e a interrupção for **inferior a 3 meses** – prosseguir o esquema terapêutico e completar o tratamento;
- Se o doente tiver cumprido **menos de 80% das tomas previstas** e a interrupção for **superior a 3 meses** – Reiniciar tratamento.

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7. O que fazer quando não se confirma o diagnóstico

A suspeita de TB pode ser baseada na clínica e em alterações radiológicas, mas o diagnóstico definitivo requer o isolamento do *Mycobacterium tuberculosis* em exame cultural [1,3,5], dado ser o único que confirma a viabilidade das micobactérias [2,3].

Nos casos em que não é possível estabelecer um diagnóstico laboratorial definitivo e o tratamento presuntivo é iniciado (com base em sinais e sintomas, alterações radiológicas, TST positivo ou exposição a caso infeccioso), o tratamento deve ser continuado se as culturas iniciais se revelarem positivas ou se se verificar resposta à prova terapêutica [4,5].

Se não houver confirmação da doença e se não se verificar qualquer resposta ao tratamento, este deve ser interrompido e repetido todo o estudo.

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8. Abordagem do doente com tuberculose pulmonar em ambiente hospitalar

Idealmente, a tuberculose pulmonar deve ser tratada em regime de ambulatório. No entanto, existem algumas situações em que o internamento destes doentes é necessário (quadro 14).

Quando o doente é internado e existe a suspeita de tuberculose pulmonar ou há a confirmação de que se trata de um doente contagioso (exame micobacteriológico direto **ou** cultural positivo **ou** pesquisa de ácidos nucleicos do M. tuberculosis positiva em amostras respiratórias), este deve ser internado em quarto individual, sob medidas de isolamento respiratório (figura 1).[1] O objetivo destas medidas é reduzir o risco de transmissão hospitalar a outros doentes e aos profissionais de saúde envolvidos. As medidas de isolamento devem ser do conhecimento de todos os profissionais de saúde e devem ser prontamente explicadas ao doente e às suas visitas (quadro 14). O risco de transmissão da tuberculose é mínimo, se forem cumpridas todas as medidas preventivas. O isolamento respiratório pode ser suspenso caso não se confirme o diagnóstico de tuberculose. Nos doentes com tuberculose confirmada, o isolamento respiratório pode terminar assim que se verificarem **todas** as seguintes condições: melhoria clínica, 15 dias de tratamento antibacilar e exame direto negativo (figura 1). Os doentes com diagnóstico prévio de tuberculose que apresentem exame direto negativo mas cultural positivo à admissão no hospital devem permanecer em isolamento, apesar de apresentarem um risco de contágio inferior ao dos doentes bacilíferos e deve ser aguardado o teste de susceptibilidades aos antibacilares. No caso de se confirmar o diagnóstico de tuberculose multirresistente, o doente deve permanecer em isolamento durante um período mínimo de 8 semanas de tratamento (esquema para MDR) e a existência de 3 microscopias negativas consecutivas, com um intervalo mínimo de 8 horas entre cada colheita, apesar de ainda não existir forte evidência científica que o fundamente.[2]

O período de internamento deve ser limitado ao tempo suficiente para estabilizar o doente e optimizar o seu tratamento. Assim, o doente deve ter alta hospitalar quando houver melhoria da situação clínica que motivou o seu internamento, ainda que mantenha baciloscopias positivas, desde que não haja suspeita de tuberculose multirresistente e sua situação familiar/social permita o cumprimento do plano terapêutico em regime de ambulatório.

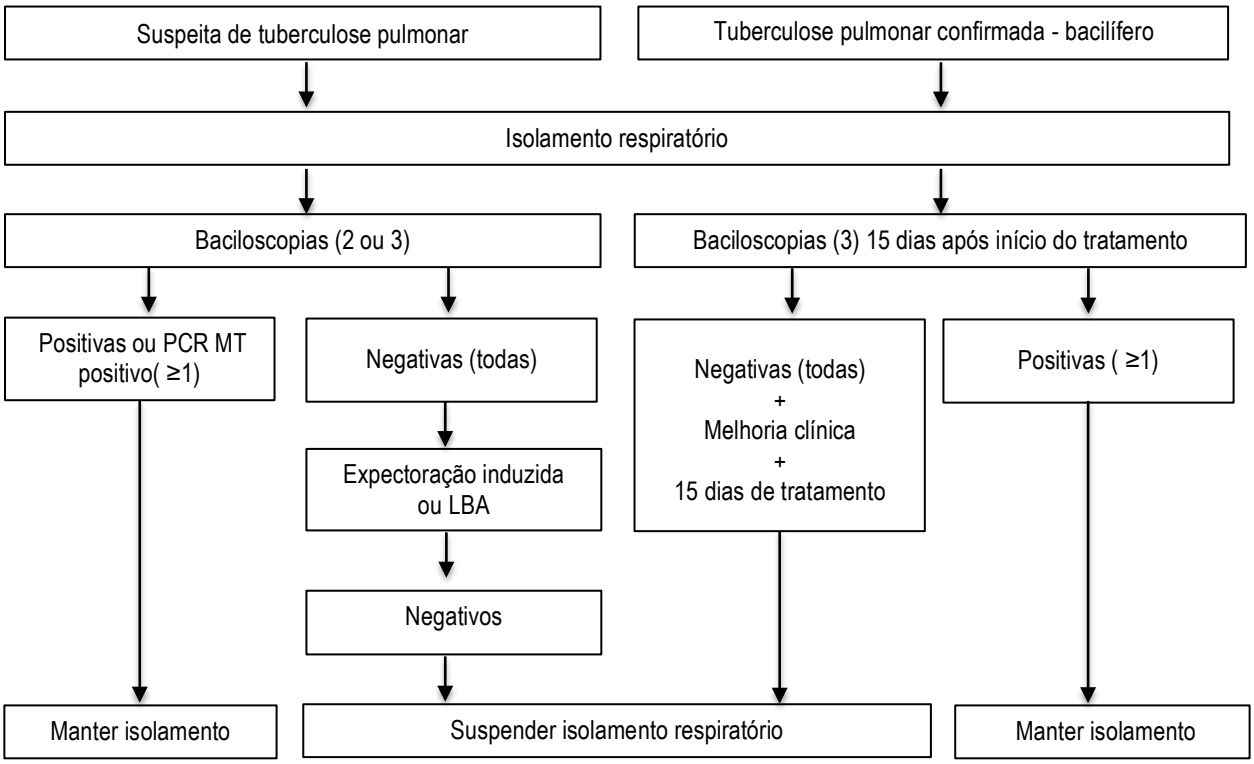

Figura 1 - Algoritmo de decisão para iniciar e suspender o isolamento respiratório

Quadro 14 – Doente com tuberculose pulmonar: critérios de internamento, medidas de isolamento e critérios de alta hospitalar

Critérios de internamento do doente com tuberculose (pelo menos 1)
✓ Tuberculose multirresistente bacilífera
✓ Instabilidade clínica associada à doença e/ou a comorbilidades (p.ex.: hemoptises grande volume)
✓ Vómitos ou diarreia persistente
✓ Insuficiência hepática grave
✓ Falta de apoio familiar /social (principalmente em doentes com fatores de risco para não adesão ao tratamento)
Medidas de isolamento respiratório
✓ Quarto individual de isolamento, com sistema de ventilação com pressão negativa
✓ Evitar a utilização de aerossóis
✓ Os profissionais de saúde e as visitas do doente que entrarem no quarto de isolamento devem utilizar uma máscara N95 ou superior
✓ Sempre que houver necessidade de sair do quarto (exames, tratamentos), o doente deve utilizar uma máscara cirúrgica e os profissionais de saúde uma máscara N95 ou superior
✓ As mãos devem ser sempre higienizadas com solução alcoólica à saída do quarto de isolamento
Critérios necessários para a alta hospitalar do doente (todos)
✓ Melhoria clínica
✓ Medicação antibacilar bem tolerada, sem efeitos adversos graves
✓ Apoio familiar
✓ Toma observada direta garantida em ambulatório e plano de *follow-up*

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1. Rastreio de contactos

A transmissão do *Mycobacterium tuberculosis* ocorre geralmente por inalação de partículas infectadas, após exposição a um caso infeccioso.

O risco de transmissão do MT depende dos seguintes fatores:
- Características do caso fonte;
- Proximidade, frequência e duração do contacto;
- Características do local onde ocorreu o contacto;
- Características do contacto.

De uma forma geral, só as pessoas com atingimento das vias aéreas (tuberculose pulmonar ou laríngea) podem transmitir a infeção. Em termos de investigação de contactos, assume-se que na tuberculose pleural há envolvimento pulmonar (enquanto não se obtiverem os resultados micobacteriológicos de expetoração – direto e cultural), uma vez que é frequente o aparecimento de culturas positivas mesmo que não seja evidente envolvimento pulmonar na radiografia do tórax.
Todo o doente com tuberculose extrapulmonar deve fazer exclusão de doença pulmonar.