ANZCOR Guideline 11.5 – Medications in Adult Cardiac Arrest

Summary

Who does this guideline apply to?

This guideline applies to adults who require advanced life support (ALS).

Who is the audience for this guideline?

This guideline is for health professionals and those who provide healthcare in environments where equipment and drugs are available.

Recommendations

The Australian and New Zealand Committee on Resuscitation (ANZCOR) make the following recommendations:

1. Intravenous (IV) administration is the preferred means of administering medications to patients during or after cardiac arrest, followed by intraosseous (IO) access.

2. Given the observed benefit on short-term outcomes, standard dose adrenaline (epinephrine) is administered to adult patients in cardiac arrest.

3. Vasopressin is not be added to standard dose adrenaline (epinephrine) during cardiac arrest.

4. Given the observed benefit on short-term outcomes, amiodarone is used in adult patients with refractory VF/pVT.

5. Other drugs, including calcium, lidocaine (lignocaine), magnesium (magnesium sulfate heptahydrate), potassium, sodium bicarbonate (and other buffers) may be considered to help manage particular conditions that are associated with patients who have arrested.

6. Fibrinolytics should not be used routinely in cardiac arrest, but may be used when pulmonary embolus is the suspected cause of cardiac arrest.
Guideline

While the listed drugs have theoretical benefits in selected situations, no medication has been shown to improve long-term survival in humans after cardiac arrest. Priorities are defibrillation, oxygenation and ventilation together with external cardiac compression.

1 Administration

1.1 Intravenous (IV) route

Intravenous (IV) drug administration is preferable and IV access is quickly and most easily achieved via a peripheral cannula inserted into a large peripheral vein. If there are no visible peripheral veins, the external jugular vein should be considered. Lower limb veins should be avoided due to impairment of venous return below the diaphragm during cardiac arrest. Intravenous drug administration must be followed by a fluid flush of at least 20-30 mL and external cardiac compression. If a central line is present it should be used. Central access provides more rapid drug delivery but insertion of a new line may be difficult, takes time to establish and has major risks [Class A; Expert consensus opinion].

1.2 Intraosseous (IO) route

Intraosseous is the preferred route if intravenous access is not available. Two prospective trials in adults and children and 6 other studies documented that IO access is safe and effective for fluid resuscitation, drug delivery, and laboratory evaluation, and is attainable in all age groups. If IV access cannot be established, intraosseous (IO) delivery of resuscitation drugs will achieve adequate plasma concentrations. A number of devices are now available for use in adults [Class A; Expert consensus opinion].

1.3 Endotracheal route

If IV/IO access cannot be attained and an endotracheal tube is present, endotracheal administration of some medications is possible, although the absorption is variable and plasma concentrations are substantially lower than those achieved when the same drug is given by the intravenous route (increase in dose 3-10 times may be required). There are no benefits from endobronchial injection compared with injection of the drug directly into the tracheal tube. Dilution with water instead of 0.9% saline may achieve better drug absorption. Adrenaline (epinephrine), lidocaine (lignocaine) and atropine (atropine sulfate monohydrate) may be given via endotracheal tube, but other cardiac arrest drugs should NOT be given endotracheally as they may cause mucosal and alveolar damage. This route cannot be used if a laryngeal mask airway is present [Class A; Expert consensus opinion].

1.4 Intracardiac injection

Intracardiac injection is not recommended because of the limited benefit and the high risk of complications.
2 Classes of Drugs and Order of Drug Administration

It is recognised that the vast majority of studies assessing the effects of drugs on survival have not been able to control for the quality of cardiopulmonary resuscitation. Furthermore, most drug evaluations to date have been conducted before recent advances in post-cardiac arrest care including Targeted Temperature Management. Since most drug trials have, at most, demonstrated only short-term outcome advantage it may be important to evaluate long-term outcome when these drugs are combined with optimized post-cardiac arrest care. One study compared the use of all drugs (adrenaline (epinephrine), amiodarone, atropine (atropine sulfate monohydrate), vasopressin), without isolating the effect of each individual drug alone, with placebo in adult out-of-hospital cardiopulmonary resuscitation and demonstrated improvement in return of spontaneous circulation and survival to hospital and intensive care unit admission, but no difference in survival to discharge or neurologic outcomes at discharge and at 1-year follow-up; however, this study was not powered to detect clinically meaningful differences in long-term outcome.3

There are no studies that addressed the order of drug administration.4 There is inadequate evidence to define the optimal timing or order for drug administration. An incomplete review of animal studies suggests that timing of vasopressor administration may affect circulation and further investigations are important to help guide the timing of drug administration.4

There is some evidence from 8 observational studies (of cardiac arrest both in and out-of-hospital), to suggest that for cardiac arrest with an initial non-shockable rhythm, if adrenaline (epinephrine) is to be administered, it is given as soon as feasible after the onset of the arrest (CoSTR 2015 weak recommendation, low quality evidence).5

For cardiac arrest with an initial shockable rhythm, there is insufficient evidence to make a treatment suggestion regarding the timing of administration of adrenaline (epinephrine), particularly in relation to defibrillation, and the optimal timing may vary for different groups of patients and different circumstances.

2.1 Vasopressors

Despite the continued widespread use of adrenaline (epinephrine) and increased 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.4 Although there is evidence that vasopressors (adrenaline (epinephrine) or vasopressin) may improve return of spontaneous circulation and short-term survival, there is insufficient evidence to suggest that vasopressors improve survival to discharge and neurologic outcome. There is insufficient evidence to suggest the optimal dosage of any vasopressor in the treatment of adult cardiac arrest. Given the observed benefit in short-term outcomes, ANZCOR suggest that standard dose adrenaline (epinephrine) is administered to adult patients in cardiac arrest (CoSTR 2015, weak recommendation, very low quality evidence).5
2.2 Other drugs

There is no convincing evidence that the routine use of other drugs (atropine (atropine sulfate monohydrate), amiodarone, lidocaine (lignocaine), procainamide, bretylium, magnesium (magnesium sulfate heptahydrate), buffers, calcium, hormones or fibrinolytics) during human CPR increases survival to hospital discharge.4

3 Specific Resuscitation Drugs

3.1 Adrenaline (Epinephrine)

This is a naturally occurring catecholamine with alpha and beta effects. It is administered in cardiac arrest to cause peripheral vasoconstriction via its alpha-adrenergic action (directing available cardiac output to myocardium and brain). It may facilitate defibrillation by improving myocardial blood flow during CPR.

One study retrospectively compared adrenaline (epinephrine) with no adrenaline (epinephrine) for sustained VF and PEA/asystole and found improved ROSC with adrenaline (epinephrine) for both rhythms but no difference in survival. In a large retrospective registry-based study from Sweden adrenaline (epinephrine) was an independent predictor of poor outcome.

Three randomised studies and a meta-analysis demonstrated no difference in outcomes (ROSC, survival to discharge, or neurologic outcome) with vasopressin when compared with adrenaline (epinephrine) as a first line vasopressor in cardiac arrest.

Two randomised studies demonstrated no difference in outcomes (ROSC, survival to discharge, or neurologic) comparing adrenaline (epinephrine) in combination with vasopressin with adrenaline (epinephrine) alone in cardiac arrest.

No study has demonstrated a long term survival benefit with high-dose versus standard-dose adrenaline (epinephrine) in cardiac arrest. Pooled data from 4 RCTs comparing standard dose adrenaline (epinephrine) (SD) with High Dose adrenaline (epinephrine) (HD) shows a survival to hospital admission advantage with HD (CoSTR 2015, weak recommendation, low quality evidence). 5

Six randomised studies reported improvement in ROSC using high-dose adrenaline (epinephrine). One meta-analysis of pooled data from 5 studies supported improvement in ROSC with high-dose adrenaline (epinephrine) but no change in survival outcomes.4

Indications

There is insufficient evidence to suggest the optimal dosage of any vasopressor in the treatment of adult cardiac arrest. ANZCOR suggest that, given the observed benefit in short-term outcomes, standard does adrenaline (epinephrine) is administered to adult patients in cardiac arrest (CoSTR 2015 weak recommendation, very low quality evidence). 5

Give for:

• Ventricular Fibrillation/pulseless Ventricular Tachycardia after initial counter shocks have failed (after 2nd shock then after every second loop)
• Asystole and electromechanical dissociation (pulseless electrical activity) in initial loop (then every second loop).

[Class A; Expert consensus opinion]

ANZCOR suggests that vasopressin should not be used instead of adrenaline (epinephrine) in cardiac arrest (CoSTR 2015 weak recommendation, low quality evidence). However, if there are settings where vasopressin is already being used instead of adrenaline (epinephrine), this use may be continued (CoSTR 2015 weak recommendation, low quality evidence).

ANZCOR suggest against adding vasopressin to standard dose adrenaline (epinephrine) during cardiac arrest (CoSTR 2015 weak recommendation, moderate quality evidence).

Values and Preferences

There is no evidence to indicate that settings that use adrenaline (epinephrine) should switch to using vasopressin, but it is acknowledged that vasopressin is already used in some settings, and the available data do not indicate any reason to change this. There is no evidence to suggest that adding vasopressin to the use of adrenaline (epinephrine) results in patient benefit.

Adverse effects:

• Tachyarrhythmias
• Severe hypertension after resuscitation
• Tissue necrosis if extravasation occurs.

Dosage:

The initial adult dose is 1mg (1 mL of 1:1,000 or 10 mL of 1:10,000) and this should be repeated at regular intervals (every 2nd loop) during CPR. Higher doses of adrenaline (epinephrine) have not been shown to improve long-term outcome. Adrenaline (epinephrine) may be required in repeated small doses or by infusion to produce an adequate blood pressure after return of a patient generated pulse. In this situation adrenaline (epinephrine) by infusion (1-20 mcg/min) should be delivered by a dedicated central line as soon as possible.

3.2 Amiodarone

Amiodarone is an antiarrhythmic drug with complex pharmacokinetics and pharmacodynamics. It has effects on sodium, potassium and calcium channels as well as alpha and beta-adrenergic blocking properties.

One RCT has shown a higher rate of ROSC for amiodarone (after adrenaline (epinephrine)) compared with no drug.

Two randomized trials demonstrated the benefit of amiodarone over standard of care, which included lidocaine (lignocaine) in 80% of cases, or routine use of lidocaine (lignocaine) for
shock refractory or recurrent VT/VF for the endpoint of survival to hospital admission, but not to survival to hospital discharge.\textsuperscript{4}

An additional nine studies document consistent improvement in defibrillation response when amiodarone is given to humans or animals with VF or hemodynamically unstable VT. There was little evidence to suggest a survival-to-discharge advantage with any antiarrhythmic drug used during resuscitation from out-of-hospital or in-hospital cardiac arrest.\textsuperscript{4}

ANZCOR suggest the use of amiodarone in adult patients with refractory VF/pVT to improve rates of ROSC (CoSTR 2015, weak recommendation, moderate quality evidence).\textsuperscript{5}

\textbf{Give for:} VF/pulseless VT (between the third and fourth shock, when refractory to defibrillator shocks and a vasopressor) [Class A; Expert consensus opinion].

\textbf{Consider administration for:}

- Prophylaxis of recurrent VF/VT.

\textbf{Adverse effects:}

- Hypotension
- Bradycardia
- Heart block.

\textbf{Dosage:}

Initial bolus dose is 300 mg. An additional dose of 150 mg could be considered. This may be followed by an infusion (i.e. 15 mg/kg over 24 hours).

\section{3.3 Calcium}

Calcium is essential for normal muscle and nerve activity. It transiently increases myocardial excitability and contractility and peripheral resistance.

Three randomized control trials and three cohort studies and one case series demonstrated no effect on survival when calcium was given to in-hospital or out-of-hospital cardiac arrest patients. Two adult studies suggest that calcium administration during cardiac arrest was associated with decreased survival to hospital discharge.\textsuperscript{4} In VF, calcium did not restore a spontaneous circulation.

In one study of PEA arrests, calcium demonstrated improved ROSC, without reporting long-term survival, but only in a subgroup of patients with wide QRS. Another study showed improved ROSC and survival to hospital arrival; however, there was no significant effect on survival. Another study showed decreased rate of ROSC in the calcium group. In two studies of asystole calcium administration failed to show any improvement in ROSC or survival to hospital discharge. One study showed reduced ROSC in the calcium group.\textsuperscript{4}

Routine administration of calcium for treatment of in-hospital and out of hospital cardiac arrest is not recommended [Class A; Expert consensus opinion].
Consider administration for:

- Hyperkalaemia
- Hypocalcaemia
- Overdose of calcium-channel blocking drugs.

Adverse effects:

- Possible increase in myocardial and cerebral injury by mediating cell death
- Tissue necrosis with extravasation.

Dosage:

The usual adult bolus dose in these settings is 5-10 mL of 10% calcium chloride (calcium chloride dihydrate) (10 mL 10% calcium chloride dihydrate = 6.8 mmol Ca ions = 360 mg elemental calcium). An alternative formulation is calcium gluconate (calcium gluconate monohydrate) (10 mL of 10% calcium gluconate (calcium gluconate monohydrate = 2.2 mmol Ca ions).

3.4 Lidocaine (lignocaine)

Lidocaine (lignocaine) acts as a sodium channel blocker.

Two randomized trials demonstrated the benefit of amiodarone over standard of care, which included lidocaine (lignocaine) in 80% of cases, or routine use of lidocaine (lignocaine) for shock refractory or recurrent VT/VF for the endpoint of survival to hospital admission, but not to survival to hospital discharge. A retrospective review demonstrated improved survival to admission with lidocaine (lignocaine) (compared with standard treatment) for patients in VF out of hospital. There is inadequate evidence to support or refute the use of lidocaine (lignocaine) in VT/VF not terminated by defibrillation, or VT/VF recurrence in out-of-hospital cardiac arrest or in-hospital cardiac arrest.

ANZCOR suggest that lidocaine (lignocaine) may be used as an alternative to amiodarone in patients with refractory VF/pVT (CoSTR 2015, weak recommendation, very low quality evidence).

Consider administration for:

- VF/pulseless VT as an alternative to amiodarone
- Prophylaxis in the setting of recurrent VF or VT.

Adverse effects:

- Slurred speech, altered consciousness, muscle twitching, and seizures
- Hypotension, bradycardia, heart block and asystole.
Dosage:

Lidocaine (lignocaine) is given initially as a 1mg/kg bolus. During resuscitation an additional bolus of 0.5 mg/kg may be considered. It is not recommended to commence a lidocaine (lignocaine) infusion until return of spontaneous circulation.

3.5 Magnesium (magnesium sulfate heptahydrate)

Magnesium is an electrolyte essential for membrane stability. Hypomagnesaemia causes myocardial hyperexcitability particularly in the presence of hypokalaemia and digoxin. Four randomized controlled trials did not show any increase in ROSC or survival when magnesium was compared with placebo for patients in VF in the prehospital, intensive care unit and emergency department settings.¹

ANZCOR suggest that magnesium (magnesium sulfate heptahydrate) should not be routinely used in adult cardiac arrest (CoSTR 2015 strong recommendation, low quality evidence).² Magnesium (magnesium sulfate heptahydrate) should be given for hypomagnesemia and torsades de pointes.

Consider administration for:

- Torsade de pointes
- Cardiac arrest associated with digoxin toxicity
- VF/pulseless VT (usually administered when refractory to defibrillator shocks and a vasopressor)
- Documented hypokalaemia
- Documented hypomagnesium.

[Class A; Expert consensus opinion]

Adverse effects:

- Excessive use may lead to muscle weakness and respiratory failure.

Dosage:

A bolus of 5 mmol of magnesium (magnesium sulfate heptahydrate), which may be repeated once and followed by an infusion of 20 mmol over four hours.

3.6 Potassium

Potassium is an electrolyte essential for membrane stability. Low serum potassium, especially in conjunction with digoxin therapy and hypomagnesaemia, may lead to life threatening ventricular arrhythmias.

Consider administration for:

- Persistent VF due to documented or suspected hypokalaemia.

[Class A; Expert consensus opinion]
Adverse effects:

- Inappropriate or excessive use will produce hyperkalaemia with bradycardia, hypotension and possible asystole
- Extravasation may lead to tissue necrosis.

Dosage:

A bolus of 5 mmol of potassium chloride is given intravenously.

3.7 Sodium Bicarbonate (and other buffers)

Sodium bicarbonate is an alkalising solution, which combines with hydrogen ions to form a weak carbonic acid. This breaks down to produce CO₂ and H₂O. In most cardiac arrests early efficient CPR and adequate ventilation negate the need for any NaHCO₃.

Two studies evaluated buffering agents during cardiopulmonary resuscitation. Both had limitations but showed no improvement in outcome. Two retrospective cohort studies also showed no benefit in the use of buffering agents during cardiopulmonary resuscitation. Two studies demonstrated increased return of spontaneous circulation, hospital admission and survival at hospital discharge with bicarbonate use. Four cohort studies reported that bicarbonate use was associated with poor short- and long-term outcome.⁴

Routine administration of sodium bicarbonate for treatment of in-hospital and out-of hospital cardiac arrest is not recommended. [Class A; Expert consensus opinion]

Consider administration for:

- Hyperkalaemia
- Treatment of documented metabolic acidosis
- Overdose with tricyclic antidepressants
- Protracted arrest (greater than 15 mins).

[Class A; Expert consensus opinion]

Adverse effects:

- Metabolic alkalosis, hypokalaemia, hypernatraemia and hyperosmolality
- Intra cellular acidosis may develop or worsen when the CO₂ liberated from NaHCO₃ freely enters the cells
- Sodium bicarbonate and adrenaline (epinephrine) or calcium when mixed together may inactivate each other, precipitate and block the IV line

Dosage:

1mmol/kg, is initially given over 2-3 minutes, then as guided by arterial blood gases.
3.8 Vasopressin

Vasopressin is commonly referred to as antidiuretic hormone. In high doses vasopressin acts as a nonadrenergic peripheral vasoconstrictor and therefore is an effective vasopressor.

Three randomized studies and a meta-analysis demonstrated no difference in outcomes (ROSC, survival to discharge, or neurologic outcome) with vasopressin when compared with adrenaline (epinephrine) as a first line vasopressor in cardiac arrest.4

Six RCTs have shown no improvement in outcomes (ROSC, survival to discharge, or neurologic) with the addition of vasopressin to adrenaline (epinephrine).5

There is insufficient evidence to suggest the optimal dosage of any vasopressor in the treatment of adult cardiac arrest.

ANZCOR suggest against using vasopressin instead of adrenaline (epinephrine) for cardiac arrest (CoSTR 2015, weak recommendation, moderate quality evidence). 5

ANZCOR suggest against adding vasopressin to standard dose adrenaline (epinephrine) during cardiac arrest (CoSTR 2015 weak recommendation, low quality evidence). 5

4 Other Drugs and Fluids

4.1 Aminophylline

One case series and 3 small randomized trials indicate that aminophylline does not increase ROSC when given for brady-asystolic cardiac arrest. No studies have shown an effect of aminophylline on rates of survival to hospital discharge. There is no evidence of harm from giving aminophylline in brady-asystolic cardiac arrest.1

4.2 Fluids

No published human study directly compared outcome of routine intravenous fluid administration with no fluid administration during CPR. Two animal studies report that normothermic fluid infusion during CPR cause a decrease in coronary perfusion pressure and another animal study shows that the coronary perfusion pressure rise with adrenaline (epinephrine) during CPR is not improved with the addition of a fluid infusion. Most animal studies of fluid infusion during CPR do not have a control group that receives no fluids to enable an assessment of benefit or harm from fluid therapy.4 Hypertonic fluid: One small RCT in adults found no significant return of spontaneous circulation or survival benefit with hypertonic intravenous fluid infusion when compared to isotonic intravenous fluid infusion during CPR. One animal study shows that hypertonic saline improves cerebral blood flow during CPR. Two animal studies found neither benefit nor harm with infusion of hypertonic saline.4

Chilled Fluid vs. Room Temperature fluid: Two adult studies and two animal studies showed no improvement in return of spontaneous circulation when cold intravenous fluids (compared with room temperature intravenous fluids) are infused during CPR. One of the reported animal studies showed that the infusion of cold fluids during CPR caused a decrease in coronary perfusion pressure when compared to no fluids.4
There is insufficient evidence to recommend for or against the routine infusion of intravenous fluids during cardiac arrest resuscitation.\(^4\)

**Fluids should be infused if hypovolemia is suspected (hypovolemic shock would normally require the administration of at least 20 mL/kg)** [Class A; Expert consensus opinion].

### 4.3 Steroids

For OHCA, one RCT and one non-RCT did not show benefit in survival with the addition of steroids during cardiac arrest. Additionally, the RCT did not show improvement in ROSC, but the non-RCT did.

For IHCA, two RCTs (from the same investigators) showed improved outcome (ROSC) with methylprednisolone, vasopressin, and adrenaline (epinephrine) during cardiac arrest, and improved outcomes (survival and neurology) with the addition of hydrocortisone to those with post-ROSC shock compared with only adrenaline (epinephrine) and placebo.

ANZCOR suggests against the routine use of steroids during CPR for OHCA (CoSTR 2015 weak recommendation, very low quality evidence).\(^5\)

ANZCOR makes no recommendation either for or against the use of steroids for in-hospital cardiac arrest.

**Values and Preferences**

For IHCA, it is acknowledged that there are no studies assessing the effect of the addition of steroids alone to standard treatment for IHCA. Also, although the triple-agent drug regimen used (methylprednisolone, vasopressin and adrenaline (epinephrine)) appears to suggest an association with improved outcome, the population studied had very rapid advanced life support, a high incidence of asystolic cardiac arrest, and low baseline survival compared to other IHCA studies, so some of the observed effects might be peculiar to the population studied.

### 4.4 Thrombolytics

Two randomised studies failed to show any improvement in short or long term outcomes with the use of fibrinolytics. One study showed an increased risk of intracranial bleeding associated with the routine use of fibrinolytics during cardiac arrest. Seven studies showed benefit from fibrinolytic therapy in the treatment of victims of cardiopulmonary arrest unresponsive to standard therapy; however, these studies had significant limitations.\(^4\) Routine administration of fibrinolytics for the treatment of in-hospital and out-of hospital cardiac arrest is not recommended [Class A; Expert consensus opinion].

Fibrinolysis should be considered in adult patients with cardiac arrest with proven or suspected pulmonary embolism (CoSTR 2015, weak recommendation, very low quality evidence).\(^5\) If a fibrinolytic drug is given in these circumstances, consider performing CPR for at least 60–90 min before termination of resuscitation attempts [Class A; Expert consensus opinion].
References


Further Reading

Amiodarone


**Lidocaine (lignocaine)**


**Steroids**


