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Editorial

Anaphylaxis management — Why are guidelines inconsistent?

A rapid review of advanced life support guidelines for cardiac arrest associated with anaphylaxis

Anaphylaxis is a serious systemic hypersensitivity reaction that is usually rapid in onset and may cause death.[1] Anaphylaxis is not uncommon, with an estimated incidence in Europe of 1.5–7.9 per 100,000 person-years and a lifetime prevalence of 1 in 300.[2] Although hospital admissions due to anaphylaxis are increasing globally, the overall prognosis for anaphylaxis is good with a case fatality rate of under 1% in those presenting to a medical facility.[3] In the United Kingdom (population 66 million), there are around 20–30 deaths per year due to anaphylaxis.[4]

International guidelines recommend intramuscular (IM) adrenaline (epinephrine) as the first line treatment for anaphylaxis.[5] Some guidelines also include intravenous adrenaline as an option to treat peri-operative anaphylaxis by experienced anaesthetists,[6,7] but this is not otherwise recommended due to the risk of tachyarrhythmias, severe hypertension, myocardial infarction and stroke. The use of IM adrenaline is supported by observational data and animal models[8]; there are no data from randomised controlled trials due to the ethical challenges of conducting such a study. However, beyond the use of adrenaline, there is now significant divergence between guidelines.

In the linked paper, McLure et al. describe a rapid review which was undertaken to assess if a systematic review with respect to the management of intra-arrest anaphylaxis is warranted.[9] The authors also reviewed differences between guidelines in the management of acute anaphylaxis. They identified 8 international guidelines and 5 national Australian guidelines and report significant variation in treatment recommendations. With respect to intra-arrest management, half the guidelines emphasised the need to follow standard cardiac arrest protocols, including the use of intravenous bolus adrenaline (in preference to IM adrenaline) in the absence of cardiac output. However, in some guidelines, there was a blurring between management of acute anaphylaxis and anaphylaxis in the arrest situation, with recommendations including the administration of antihistamines and corticosteroids. McLure et al. emphasise the lack of evidence underpinning the management of peri-arrest anaphylaxis,[9] but this is unsurprising given the circumstances.

The lack of high-level evidence underpinning interventions for acute anaphylaxis is often compared to the evidence base for parachutes in reducing deaths from free fall injuries. However, the two scenarios are not equivalent. There are no randomised controlled trials underpinning the use of parachutes, however it is a reasonable to assume that failure to activate a parachute during free fall is very likely to result in significant morbidity if not death.[10] In contrast, data from large case series (including the European Anaphylaxis Registry) indicate that a significant proportion (around 80%) of anaphylaxis reactions resolve without or despite no treatment with adrenaline.[11,12] It is clearly inappropriate to intentionally *not* to treat anaphylaxis with adrenaline. However, there is also potential that the use of interventions other than adrenaline, on the basis of historical precedent rather than evidence, could cause harm. McLure et al. highlight the variation in recommendations with respect to antihistamines and corticosteroids.[9] This may be due to the recent evolution in management, with more recent guidelines downgrading or even recommending against the use of antihistamines and corticosteroids for the acute management of anaphylaxis due to an absence of evidence that these interventions lead to clinical improvement.[1,8,13] Their use may delay administration of further adrenaline,[14,15] and in the case of parenteral H1-antihistamines, precipitate hypotension.[1] For corticosteroids, there are now legitimate concerns that their use may increase the need for intensive care admission.[16]

Evidence suggests that cardiovascular compromise in anaphylaxis occurs as a consequence of a profound reduction in venous tone and fluid extravasation.[17,18] Allergic mediators can also impair cardiac function.[17] This results in a mix of hypovolemic, distributive and possibly cardiogenic shock, which combine to reduced venous return (Fig. 1).[17–19] Adrenaline reverses peripheral vasodilation and reduces tissue oedema. Its beta-receptor activity dilates the bronchial airways, increases the force of myocardial contraction, and suppresses histamine and leukotriene release from mast cells.[1] Early administration of adrenaline may therefore limit the severity of IgE-mediated allergic reactions. This is consistent with data suggesting delayed adrenaline may be associated with poor outcomes in anaphylaxis, including death.[1]

In severe anaphylaxis, up to one third of the circulating volume can leak out of the circulation within minutes.[20] Evidence from case series[21,22] and animal models[23] suggests that severe reactions most commonly result from a combination of delayed or insufficient

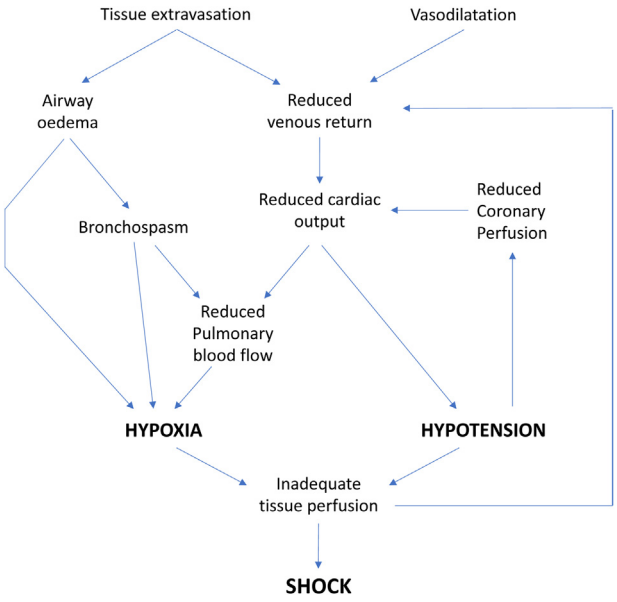

Fig. 1 – Physiological mechanisms responsible for anaphylactic shock. Adapted from Harper et al.[18]

adrenaline administration (due to circulatory hypovolaemia) and progression of the reaction due to the ongoing release of inflammatory mediators. It is therefore important to optimize delivery of adrenaline in severe anaphylaxis, through the use of intravenous (or interosseous) adrenaline infusion and rapid fluid resuscitation: large volumes of crystalloid (3–5 litres) may be required to restore adequate circulation.[1] In the cardiac arrest scenario, intravenous bolus administration is required, but this must be supported with intravenous fluid bolus treatment and adequate CPR. Only once these 3 strategies have been optimised should consideration be given to other pharmacological treatments.

Anaphylaxis is anaphylaxis, irrespective of where it occurs: it does not vary in presentation or response to treatment depending on country or region. It is therefore odd that significant differences in anaphylaxis guidelines continue to persist. This may, in part, be due to the poor underlying evidence base. However, rather than guidelines continuing to recommend "further research", it would be more appropriate to achieve an international consensus on what we do know, and transparency over those areas for which (at best) there is limited evidence and at worst, emerging data that such interventions may do harm. The wide variation in guidelines identified by McLure et al. indicate that there is still some way to go.

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