# ANAPHYLAXIS IN THE PAEDIATRIC INTENSIVE CARE UNIT

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## ABSTRACT

Anaphylaxis is uncommonly seen in the paediatric intensive care unit (PICU). Two circumstances under which anaphylaxis could be encountered in the PICU are when a child is admitted for intensive care after an anaphylactic reaction or when a patient in the PICU develops an anaphylactic reaction to his/her therapy. Refractory airway obstruction or refractory hypotension after anaphylaxis are indications for intensive care. The most common causes of anaphylaxis in the PICU are drugs, with antibiotics, anaesthetic agents and muscle relaxants most commonly involved. Anaphylaxis does occur in infants, even as young as 1 month of age, and may be difficult to recognise. Anaphylaxis has even been postulated as an aetiological factor in sudden infant death syndrome (SIDS). The case of a 6-day-old preterm baby who presented with symptoms and signs suggestive of anaphylaxis, but without an obvious trigger is discussed.

## INTRODUCTION

Anaphylaxis is rarely seen in the paediatric intensive care unit (PICU), and there is not a single entry for 'anaphylaxis' in the index of a recently published paediatric ICU textbook.[1] There are two potential scenarios where anaphylaxis could be encountered in the PICU: (i) a child who is admitted for intensive care after anaphylaxis; or (ii) a patient who develops anaphylaxis to therapy while in the PICU.

## EPIDEMIOLOGY OF ANAPHYLAXIS

The incidence of anaphylaxis in children varies between studies and depends on the setting and country. The incidence of new cases of anaphylaxis is generally considered to be between 8.4 and 21 per 100 000 patient-years, with a lifetime prevalence of 0.05-2%.[2,3] The highest incidence is in children and adolescents.[3] In an Australian study from Queensland the incidence was 1 out of 170 children, which is much more common than in adults.[4] Deaths as a result of anaphylaxis are rare and have been estimated to be approximately 1 per 3 million people per year.[5] In studies based on hospital visits, the mortality rate is 1 per 100-200 cases presenting to emergency units. In children most cases of mortality occur after the age of 10 years. There was only one fatality in a retrospective record review study at the Royal Children's Hospital in Melbourne – in a 7-year-old girl with a background of eczema and asthma and known peanut allergy who developed an anaphylactic reaction to peanut satay sauce.[6] Asthma has frequently been noted as a risk factor for fatal anaphylaxis.

I was unable to find anaphylaxis data for South Africa, but a case report describing an anaphylactic reaction in a 9-month-old boy with severe persistent asthma, eczema and known cow's milk allergy was published in 2005.[7] This child tolerated soy milk but presented to the Red Cross War Memorial Children's Hospital with acute anaphylaxis and respiratory arrest following ingestion of a new brand of soy milk formula. Investigation revealed that the soy milk batch had become contaminated with minute quantities of cow's milk protein, and ingestion of even this small amount of allergen had resulted in a life-threatening event.

## CAUSES OF ANAPHYLAXIS IN CHILDREN

The most common causes of anaphylaxis in children are foods, insect venom and drugs. In the Queensland study food was the most common cause of anaphylaxis, with egg and dairy most often implicated.[4] In the Melbourne study, food was also the most common cause of anaphylaxis in young children, but peanuts and tree nuts (cashew nuts) were the most common causative allergens.[6] In older children drugs were more common than food as an initiating factor, with cephalosporins more commonly involved than penicillin.[6]

## FEATURES OF ANAPHYLAXIS IN CHILDREN

In both Australian studies respiratory symptoms were more common than cardiovascular manifestations of anaphylaxis. In the Melbourne study the dominant features were shortness of breath, stridor and wheezing (30-56% of children) while hypotension was only present in 11% of the patients.[6] Urticaria (72%) and angio-oedema (55%) were also very common manifestations of anaphylaxis.

## ICU MANAGEMENT OF ANAPHYLAXIS

Indications for ICU management of anaphylaxis include persistent airway obstruction or refractory hypotension. The treatment of persistent airway obstruction includes nebulised $\beta_2$-agonists and ipratropium bromide.[8] If bronchospasm does not respond to nebulised treatment, then intravenous salbutamol or aminophylline should be administered as a loading dose followed by a continuous infusion. If life-threatening airway obstruction persists, the patient must be intubated and mechanical ventilation commenced. Nebulised adrenaline is standard treatment for the airway obstruction in croup and it has been postulated that the stridor from an anaphylactic reaction may also respond to this therapy.[9] It is not a substitute for systemic adrenaline in the treatment of anaphylaxis, but an adjunct that may decrease the necessity for airway intervention. If the upper airway is obstructed and cannot be bypassed by an endotracheal tube, a surgical airway may be required (cricothyroidotomy).

Severe intractable hypotension is probably the most ominous manifestation of anaphylaxis. The hypotension is as a result of fluid shifts from the intravascular to the extravascular space. The first step is to restore the intravascular volume. This is achieved by the

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administration of large volumes of intravenous fluid. It would appear that rapid administration of fluid is more important than the choice of fluid. If the patient remains hypotensive, ICU admission is indicated for intensive monitoring and vasopressors. If intravenous adrenaline does not reverse the hypotension, dopamine should be administered. Patients who are taking β-blockers may be very resistant to standard vasopressors, and in such cases intravenous glucagon is indicated. Glucagon is a polypeptide hormone and is produced by the pancreas. It is a phosphodiesterase inhibitor and its action is thus independent of catecholamines.[8]

A recent article addresses bee stings in children and when endotracheal intubation should be performed in these patients.[10] The authors point out that insect stings seldom cause life-threatening anaphylaxis in children and systemic reactions are found in less than 1% of children who have been stung. Stings to the mouth and pharynx are uncommon but could cause life-threatening airway obstruction. Three cases are described in which children suffered bee stings to the tongue and one on the lower eyelid, with resultant severe facial oedema and airway compromise in all. All the children were intubated; three had relatively uncomplicated courses and could be extubated between 24 and 48 hours later. The fourth child had a severe reaction with intrathoracic airway obstruction that proved refractory to treatment; he required mechanical ventilation for 10 days. Three of the children had symptoms due to direct toxic effects of the bee venom, while the fourth had an anaphylactic reaction. None of these children was investigated for bee-venom anaphylaxis, but the child who had a prolonged hospital stay was referred to the allergy clinic for further investigation and immunotherapy.

### *Anaphylaxis occurring in PICU patients*

The most common causes of anaphylaxis in the PICU are drugs, with antibiotics, anaesthetic agents and muscle relaxants most commonly involved. Theoretically latex allergy may also be a problem, but even in patients at high risk, e.g. children with spina bifida, the prevalence in South Africa has been found to be low.

The most commonly described antibiotic allergy is to beta-lactams. Drug allergy and anaphylaxis are uncommon in children. In the Melbourne study only 6% of the anaphylactic reactions were caused by drugs, and these presented in older children (median age 13 years, range 6-15 years).[6]

Fischer[11] recently reviewed anaphylaxis in the ICU setting. She pointed out that muscle relaxants are responsible for 60% of anaphylactic reactions in the critical care and peri-anaesthetic setting. A recent case report discussed a 6-year-old child with severe life-threatening airway obstruction following induction with thiopentone and cisatracurium.[12] He had mild pre-existing asthma but no other risk factors for drug anaphylaxis. He developed severe acute bronchospasm 60 seconds after the administration of cisatracurium, an intermediate-acting bis-benzylisoquinolinium neuromuscular blocker. The bronchospasm was unresponsive to halothane, theophylline, salbutamol and steroids; the child developed severe respiratory failure and proved extremely difficult to ventilate. He only responded after the administration of two intravenous boluses of adrenaline followed by a continuous adrenaline infusion.

An extensive work-up was done during this patient's PICU admission. Special investigations revealed slightly raised tryptase and histamine and markedly raised eosinophil cationic protein levels in a blood sample taken 45 minutes after induction of anaesthesia. Specific IgE levels for quaternary ammonium, thiopentone and cisatracurium were also weakly positive.

Muscle relaxants cause anaphylaxis either by means of histamine release by mast cells or IgE-mediated reactions. All muscle relaxants have a common ammonium group that can be bound by IgE, thus causing cross-reactions across all neuromuscular blocking agent groups. The mechanism in this patient appears to be an IgE-mediated reaction to the cisatracurium.

Other agents used in the PICU that may cause anaphylaxis in susceptible children are hypnotics such as barbiturates and propofol, plasma volume expanders such as dextran and hydroxyethyl starch, and local anaesthetic agents. Allergy to egg and soya may predispose children to reactions to propofol, which contains egg lecithin and soybean oil.[13]

## CASE REPORT

A 7-week-old baby girl was referred to me for assessment after she had apparently suffered an anaphylactic reaction at the age of 6 days. She had been born at 30 weeks' gestation, weighing 1 350 g, after her mother had suffered an antepartum haemorrhage. She was admitted to the neonatal ICU (NICU) within 24 hours with severe hyaline membrane disease. She was given two doses of surfactant (Curosurf®, Poractant alfa, porcine lung surfactant) and ventilated by means of high-frequency oscillatory ventilation. She responded well to the treatment and was discharged from the ICU at the age of 5 days. She had received penicillin G and gentamicin until the day of discharge from the NICU.

That night while in the ward she appeared to have an anaphylactic reaction. She developed swelling of the cheeks and neck; this spread rapidly to the head and tongue and subsequently to the abdomen and legs. She developed a bradycardia and became hypoxic. She was intubated, given intravenous adrenaline, promethazine and hydrocortisone, and transferred to the NICU. The oedema and cardiovascular effects resolved rapidly and she could be extubated the following day. At the time of her admission she was on meropenem and vancomycin, aminophylline, vitamin D, caffeine, multivitamin drops, a phosphate mixture and TPN (total parenteral nutrition, intravenous amino acid and lipid mixture). Her condition responded rapidly to therapy; she was extubated the following day and discharged from the NICU. Unfortunately no investigations such as serum tryptase were done, so it is impossible to be sure that this was an anaphylactic reaction.

The other interesting feature from the history is that her maternal grandmother was allergic to bee venom. The family history was negative for hereditary angio-oedema.

At the age of 7 weeks she was clinically well and thriving. Although it was thought extremely unlikely that this was an anaphylactic reaction because of her age, she was investigated for penicillin and latex allergy and C1 esterase inhibitor deficiency. All investigations were normal. Follow-up 6 weeks later revealed a thriving child with no recurrence of her symptoms.

## ANAPHYLAXIS IN INFANTS

According to Simons[14] the incidence of anaphylaxis in infants younger than 2 years is unknown, but it has been described in infants as young as 1 month of age. She describes a case of anaphylaxis to cow's milk in a 9-month-old boy. Foods, particularly cow's milk or egg, most commonly trigger anaphylaxis in young infants.

Less commonly anaphylaxis is caused by beta-lactam antibiotics, neuromuscular blockers, latex, insect venoms and vaccinations. Idiopathic anaphylaxis has also been described in this group of children.

Allergen-induced anaphylaxis has been proposed as one of the possible causes of the sudden infant death syndrome (SIDS).[15] SIDS encompasses sudden and unexpected death in infants who have been completely healthy. It is a diagnosis by exclusion with no obvious cause found at autopsy. Certain environmental factors have been implicated in its causation, such as prone sleeping, maternal smoking, and poor socioeconomic status. Allergens may play a role, either alone or in combination with other factors. One theory holds that sensitised infants may suffer an anaphylactic reaction after vomiting and then inhaling cow's milk while sleeping. A postmortem study showed significantly higher serum tryptase levels in infants who died from SIDS compared with other causes of death, thus supporting fatal anaphylaxis as a possible cause of death in these infants.[15]

Infants can obviously not describe subjective anaphylaxis symptoms and so one should have a high index of suspicion in these children. Most of the anaphylactic episodes in infants are IgE-mediated, and the choice of allergens for testing should be determined by the history. Prevention of repeat anaphylaxis is difficult as the adrenaline auto-injectors are designed for bigger children, but a 1 ml syringe and a vial of adrenaline together with detailed instructions can be given to the caregiver.

## DISCUSSION OF THE CASE

Did the little girl referred to me have an anaphylactic reaction and, if so, to what? If it was an anaphylactic reaction, this case would probably be the youngest child described. In addition, she was preterm and so her immune system should not have been sufficiently developed to react to an allergen. Unfortunately no tests were done when she manifested the episode and so, unless she has a repeat episode, we will never know whether this was in fact an anaphylactic reaction or not. Any of the antibiotics or other treatments she received could have been implicated in the causation of an anaphylactic reaction.

## AVOIDING RISK AFTER ANAPHYLAXIS IN CHILDREN

What advice should one give families after a child has had an anaphylactic reaction to food? Kemp and Hu[16] point out that, since food is essential, it is impossible to completely avoid the risk of exposure. Food allergy and anaphylaxis are 'high-stakes and highly uncertain issues, where the outcome may be the sudden and unpredictable death of a child.' It is difficult to quantify the risk, since we know that labelling of foods is not always accurate and cross-contamination does occur. This leads to uncertainty on the part of the carer – uncertainty about the magnitude of the risk, how to avoid exposure, and when to administer injectable adrenaline. This uncertainty causes stress. Kemp and Hu believe that patients and their parents should not have to deal with unnecessary uncertainty, and that the medical profession as well as policy makers should address concerns about food allergy.

## CONCLUSION

Anaphylaxis in the PICU is uncommon, but can pose both diagnostic and management challenges. It is important to have a high index of suspicion in infants as anaphylaxis may be difficult to diagnose in this group of children. The initial management consists of the ABCs of emergency treatment, together with the administration of adrenaline and other therapy as indicated, and is detailed in the algorithm from the Resuscitation Council of Southern Africa (Fig. 1). This is followed by investigations to confirm the diagnosis and establish the cause of the reaction. After this, planning to reduce the risk of future anaphylactic episodes is essential.

### Declaration of conflict of interest

The author declares no conflict of interest with regard to the subject matter of this article.

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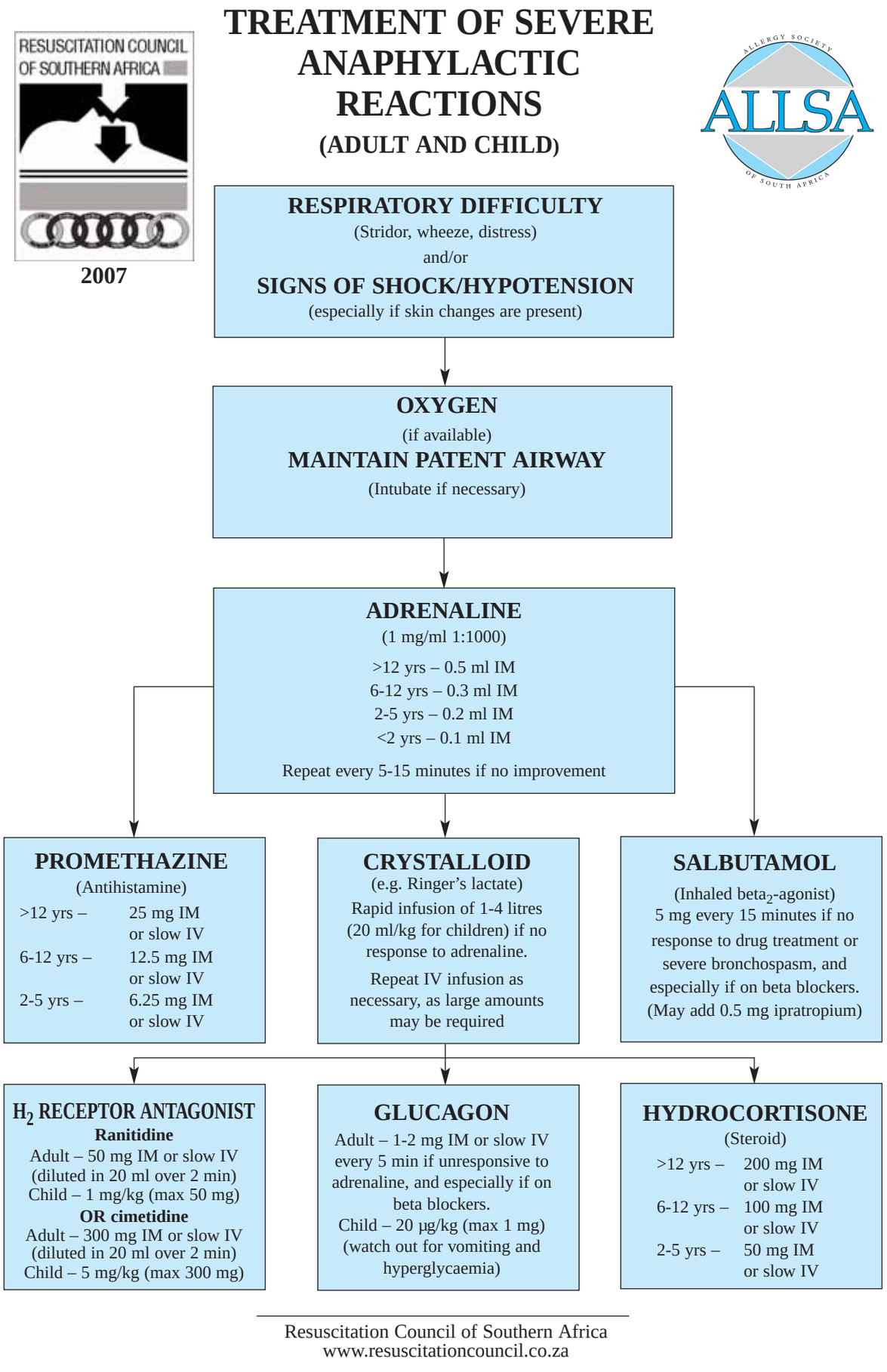


*Fig. 1. Algorithm of treatment of severe anaphylactic reactions.*