

ANAPHYLAXIS A CASE HISTORY APPROACH

DR PAULA FORAN

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Part 1

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CLINICAL SUMMARY
(DEPARTMENT OF FORENSIC MEDICINE MONASH UNIVERSITY 2017¹)




- Mrs CW was 68 years old when she was admitted to a small regional hospital for elective bilateral cataract removal surgery.
- She was in very poor health and in addition to her cataracts she had, raised intraocular pressure (glaucoma), and severe chronic respiratory disease which kept her house-bound.
- The surgery was meant to improve her quality of life at home by allowing her to enjoy craft activities and watch movies.
- Mrs CW had a known allergy to 'sulphas' (also known as 'sulfa drugs').

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CLINICAL SUMMARY
(DEPARTMENT OF FORENSIC MEDICINE MONASH UNIVERSITY 2017¹)

- Her allergy was noted in multiple sections of her medical record and on admission a red identity band was placed on her arm by nursing staff to denote her as a patient with an allergy.
- Her surgeon, Dr. S, was a visiting surgeon to the hospital.
- He had planned to perform a trabeculectomy (surgical procedure used in the treatment of raised intraocular pressure) in addition to the cataract surgery, however, on the day of surgery he decided against it as Mrs CW's general physical condition had deteriorated.



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CLINICAL SUMMARY
(DEPARTMENT OF FORENSIC MEDICINE MONASH UNIVERSITY 2017¹)

- Dr S opted instead to administer medication post-operatively to lower her intraocular pressure.
- The cataract surgery was uneventful.
- Dr S wrote up the post-operative orders, including the order for diamox (acetazolamide, a non-antibiotic sulphonamide), to treat the raised intraocular pressure.


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CLINICAL SUMMARY
(DEPARTMENT OF FORENSIC MEDICINE MONASH UNIVERSITY 2017¹)

- Mrs CW is handed over into your care by the anaesthetist
- You are asked in PACU to give the Diamox to this patient
- Would you be happy to do this???

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CLINICAL SUMMARY
(DEPARTMENT OF FORENSIC MEDICINE
MONASH UNIVERSITY 2017¹)



- Mrs CW was clinically stable at the time.
- The PACU nurse administered the Diamox medication as ordered.
- Approximately 10 minutes later Mrs CW was sweating, short of breath and tachycardic.
- Her anaesthetist, Dr F, was notified and told that Mrs CW had received Diamox – Dr F knew Mrs CW was allergic to 'sulphas' and recognised she was having an allergic reaction.

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CLINICAL SUMMARY
(DEPARTMENT OF FORENSIC MEDICINE MONASH UNIVERSITY 2017¹)

- Dr F stabilised Mrs CW and was organising transfer to a tertiary referral hospital.
- However, she suddenly deteriorated further and died.

Pathology

- Following a postmortem examination, Mrs CW's cause of death was given as anaphylaxis in a woman with atherosclerotic cardiovascular disease and emphysema.
- The precise type of allergy Mrs CW had to sulphonamides was neither known nor documented.

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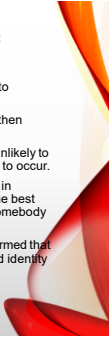
Investigation

- The coroner undertook an inquest into the death of Mrs CW.
- Questions raised during the inquest included how Mrs CW's allergy was recorded in her file and the efficacy of how this was communicated to treating physicians.
- Issues regarding sulphonamide allergies were described, whereby some people are allergic to all sulphonamides, or to antibiotic sulphonamides or non-antibiotic sulphonamides.
- The precise type of allergy Mrs CW had to sulphonamides was neither known nor documented (Department of Forensic Medicine Monash University 2017).

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CLINICAL SUMMARY (DEPARTMENT OF FORENSIC MEDICINE MONASH UNIVERSITY 2017¹)

- The Western Australian therapeutics advisory group's position on allergic reactions to sulphonamides was referred to during the inquest.
- If Mrs CW had an allergy to both antibiotic as well as non-antibiotic sulphonamides then prescribing Diamox would have been contraindicated.
- If her allergy was to only antibiotic sulphonamides then administering Diamox was unlikely to have caused an allergic reaction, however idiosyncratic reactions have been known to occur.
- Dr S believed Mrs CW had suffered an idiosyncratic response however, a professor in ophthalmology provided an expert opinion to the court in which he suggested that the best course of action would be to follow the product advice and avoid using Diamox in somebody with a known sulpha allergy.
- Regarding the communication of Mrs CW's allergy to all her care-givers it was confirmed that her allergy had been recorded in her medical record and she was also wearing a red identity band.
- Though he admitted seeing it in theatre, Dr S apparently was 'unaware' of the significance of the band.



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CLINICAL SUMMARY (DEPARTMENT OF FORENSIC MEDICINE MONASH UNIVERSITY 2017¹)

- Dr S admitted that he had Mrs CW's documentation with him when he wrote his post-operative orders but was unaware she had an allergy to 'sulphas'.

Coroner's findings

- The coroner heard that the hospital had improved its 'team timeout process' immediately prior to surgery so that it was mandatory for all team members to acknowledge a patient's allergy.
- The coroner commented that this step would increase the awareness of allergies but there was a need for, 'precision' when describing a patient's allergy.
- The term sulphas is not sufficiently precise to provide a nurse doctor or surgeon with sufficient information as to the nature of the allergy.



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CLINICAL SUMMARY (DEPARTMENT OF FORENSIC MEDICINE MONASH UNIVERSITY 2017¹)

- Two recommendations were made by the coroner.
- Firstly, that all nurses, doctors and surgeons working at the hospital were to be reminded about the necessity of recording the precise nature of patients' allergies and this precise nature was to be known by the prescriber of medication.
 - The second recommendation was that a protocol be developed to mandate the minimum acceptable standards of practice which doctors and surgeons, not employed by the department of health, agree to adopt before being allowed to practice in the hospital.
 - The protocol should cover the existence of any protective procedures or systems such as the wearing of a red allergy alert band.

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Authors comments

- Mrs CW's case illustrates the importance of standardised, accurate recording of allergies and the effective communication of this information for health professionals.
- It also highlights the confusion that can arise from inconsistent reporting of the details of allergies.
- Examples include the frequency with which patients disclose their allergies, the nature of their allergy (ranging from mild intolerance to anaphylaxis), and the specificity of the substance which causes an adverse reaction (one medication or a whole class of medications).
- Research has demonstrated that drug allergy alerts had a high chance of being judged as inappropriate thus overridden by clinicians.



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Part 2

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ANAPHYLAXIS

- Although infrequent, potentially catastrophic anaphylactic reactions may occur anytime during the perioperative period thus anaphylaxis continues to be a major concern for all perioperative staff²
- The effective anticipation, prevention, and treatment of these reactions represent real challenges for all medical and nursing staff who must work in a close cooperation during these events²



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ANAPHYLAXIS

• Anaphylaxis may be defined as a potentially life-threatening emergency requiring early recognition of signs and symptoms, early administration of adrenaline (epinephrine) in adequate dosage, and aggressive fluid volume replacement³

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ANAPHYLAXIS

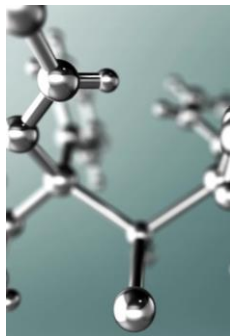
- The immune system serves to protect us from harmful substances
- Inappropriate activation of this system has deleterious effects
- Allergic response or hypersensitivity reaction
- A magnified or inappropriate response by the host to an antigen



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ANAPHYLAXIS

- Reactions are Unpredictable in any patient
- Incidence is increased in patients with;
 - a history of atomy
 - many exposures to a substance, for example latex



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ANAPHYLAXIS

- Reactions are more likely to follow intra-venous than intra-muscular injection
- A history of exposure does not exclude the possibility of allergic reaction
- Thus, we must always be prepared for the possibility of anaphylactic reactions



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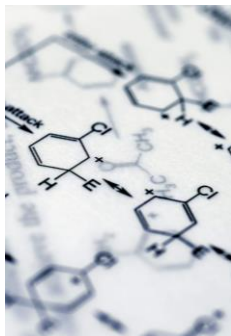
THERE ARE 2 TYPES OF ANAPHYLAXIS

- Immunoglobulin E - IgE- triggered (formally anaphylaxis)
- Non-immunoglobulin E - non-IgE- triggered (formally anaphylactoid)⁴

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**IgE ANAPHYLAXIS
FORMALLY ANAPHYLAXIS**

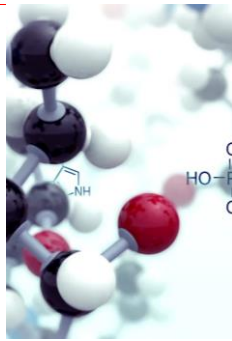
- In order for this to occur there must be;
 - previous exposure to an agent
 - production of antibodies
- The first exposure stimulates the patient's B-lymphocytes to produce IgE antibodies specific for that agent



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ANAPHYLAXIS

- As most drugs have a low molecular weight, they only produce an antibody reaction combined to a protein as a hapten
- The IgE attaches to receptor sites on mast cells packed with histamine granules and basophils



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ANAPHYLAXIS

- At the second exposure the drug binds to the cell bound IgE and causes the cell to degranulate and release vasoactive amines;
 - Chemical mediators
 - Histamine
 - Leukotrienes
 - Prostaglandin
 - Serotonin

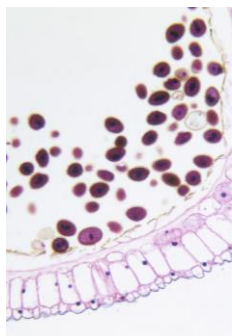


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ANAPHYLAXIS

Histamine release causes;

- Dilation of terminal arterioles and increased capillary permeability
- Contraction of bronchial smooth muscle
- A-V conduction block and ventricular arrhythmia's



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ANAPHYLAXIS

This is explosive in nature causing;

- circulatory shock
- upper airway obstruction
- respiratory failure



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NON IgE – ANAPHYLAXIS

No previous exposure is required

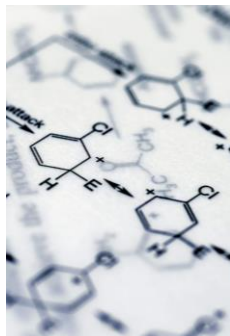
- Does not require antibody production
- Non IgE – Anaphylaxis can be triggered by compliment or bradykinin activation or can be mediated by an IgG antigen
- Proteins C3a & C5a can degranulate or lyse mast cells ⁴

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* ANAPHYLAXIS

Note

- true IgE anaphylaxis can occur on first exposure when sensitized to one of its components
- Some cosmetics contain quaternary ammonium ion (QAI) which is a component of muscle relaxants
 - PHO
 - Blue dyes



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ANAPHYLAXIS

'Clinically the reactions are indistinguishable'

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PATHOPHYSIOLOGY OF SYMPTOMS

- Inflammatory mediators released from mast cells and basophils such as histamine, proteases (among which is tryptase), leukotrienes, and prostaglandins elicit immediate symptoms of an allergic reaction such as pruritis
- Wheezing, or hypotension, can induce cardiovascular collapse
- Cardiac mast cells can release chymase and carboxypeptidase, which activate the renin-angiotensin system

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PATHOPHYSIOLOGY OF SYMPTOMS

- Inflammatory mediators released from cardiac mast cells decrease myocardial perfusion & contractility
- Platelet-activating factor can constrict coronary arteries & ↓ coronary perfusion & ↓ contractility
- This can contribute to coronary plaque rupture

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GRADES OF ANAPHYLAXIS³

Grade 1 Mild

- Generalised mucocutaneous signs: Erythema, Urticaria+/- Angioedema

Grade 2 Moderate

- Moderate – Multi-organ manifestation may include:
- Hypotension, tachycardia
- Evidence of bronchospasm, cough, difficult ventilation
- Mucocutaneous signs

Grade 3 Life threatening

- Life threatening and requiring immediate and specific treatment:
- Bradycardia or tachycardia, arrhythmias
- Severe bronchospasm, and/or airway oedema
- Cutaneous signs may be absent, or present only after correction of hypotension

Grade 4 Arrest

- Cardiopulmonary Arrest

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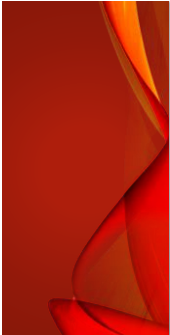
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RESEARCH

KEY FINDINGS FROM NAP 6 2018⁵

- NAP 6 reviewed 266 case reports of Grade 3–5 anaphylaxis over a 12-month period from all National Health Service hospitals (ANZCA grade 3–4)
- The estimated incidence of perioperative anaphylaxis was 1:10,000 anaesthetics (some case exclusion due to incomplete data meant that a true incidence may be 70% higher)
- The 199 identified culprits were antibiotics 47%, neuromuscular blocking agents (NMBA) 33%, chlorhexidine 9%, and Patent Blue dye 4.3%
- Teicoplanin comprised 12% of antibiotic exposures, however, was responsible for 38% of antibiotic-induced anaphylaxis
 - Used in serious staphylococcal or streptococcal infections which cannot be treated using less toxic antibiotics
 - osteomyelitis, septic arthritis, septicæmia

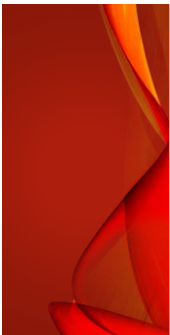
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**RESEARCH
KEY FINDINGS FROM NAP 6 2018 ⁵**

- Anaphylaxis from Suxamethonium mainly presenting with bronchospasm
- There were no reports of anaphylaxis to latex
- Commonest presenting features were hypotension (46%), bronchospasm (particularly in patients with morbid obesity and asthma) (18%), tachycardia (9.8%), oxygen desaturation (4.7%), bradycardia (3%), and reduced/absent capnography trace (2.3%)
- All patients displayed hypotension
- Stroke Volume x Heart Rate = Cardiac Output
 - SV↓ HR↑
- Onset was rapid for NMBAs and antibiotics however was delayed with chlorhexidine and Patent Blue dye

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**RESEARCH
KEY FINDINGS FROM NAP 6 2018 ⁵**

The exact mechanism of the sensitisation to Patent Blue is uncertain, but it is known that this is highly water-soluble, found in numerous everyday foods, and is used to colour medication and to dye clothing

One likely hypothesis is that sensitisation may occur through contact with or consumption of everyday products containing E131, but this is uncertain

E131 is banned as a food dye in Australia, however cases of suspected allergy are still described in Australian breast cancer patients⁶

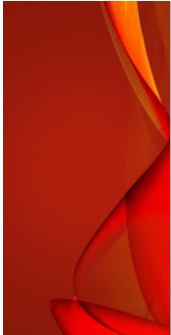
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**CAUSATIVE
AGENTS
FROM THE
USA**

The most common causes of perioperative hypersensitive reactions in the USA have been reported as neuromuscular blocking drugs, latex, and antibiotics, although there are other more emerging causative agents (such as patent blue)⁶

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**RESEARCH
KEY FINDINGS FROM NAP 6 2018 ⁵**

There were 40 cardiac arrests and 10 deaths
The review panel judged that cardiac compressions should be started in adults with systolic blood pressure <50 mmHg
Pulseless electrical activity (or electromechanical dissociation) was the usual type of cardiac arrest, often with bradycardia
Poorer outcomes were seen with increased age, ASA grade, obesity, beta-blocker, and/or ACE inhibitor medication
(Royal College of Anaesthetists 2018)

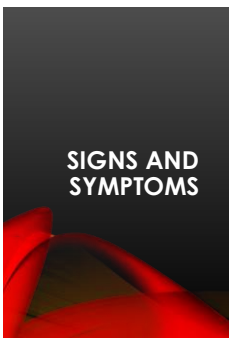
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**SIGNS AND
SYMPTOMS**

- There is great inter patient variability
- Acute reactions develop quickly, maximum intensity < 30 minutes
- Severity is affected by;
 - amount of drug administered
 - reactivity of mast cells
 - responsiveness of vascular and bronchial muscle and autonomic activity

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SIGNS AND SYMPTOMS

Transient bronchospasm or difficulty in lung inflation may be an early sign

Skin changes;

- erythema
- wheals
- oedema - often of eyelids and rarely of the larynx

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SIGNS AND SYMPTOMS

- Hypotension and tachycardia leading to cardio-vascular collapse
- Bradycardia may also be seen
- Bronchospasm and hypoxia
- Asthmatic patients usually get bronchospasm
- Hyperperistalsis

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SIGNS AND SYMPTOMS

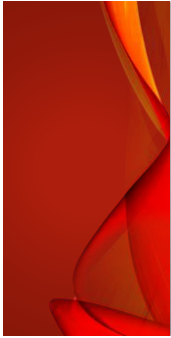
Ventricular ectopic beats

A-V conduction block

Clotting defects

Leukopaenia

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ANZAAG 2022³

- Anaphylaxis should be considered if skin signs co-exist with bronchospasm or hypotension, or hypotension or tachycardia alone
- This is especially the case where the patient is unresponsive to vasopressors or where the symptoms were unanticipated, raising suspicions
- Bradycardia may also be a presenting sign of anaphylaxis
- Bronchospasm or difficulty with ventilation may be a feature of anaphylaxis or the sole presenting feature in some cases
- It is also worth remembering that the absence of skin signs does not rule out the diagnosis, as skin signs may not appear until circulation is restored

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TREATMENT

- Management of anaphylaxis consists of prompt diagnosis, immediate treatment, refractory management, and post crisis management
- Discontinue drug administration
- Treatment varies according to symptoms and severity
- Resuscitation 100% oxygen
intravascular volume expansion (N.B. 40% of the intravascular volume can be lost to the interstitial space)
- correct metabolic acidosis
- ventilatory support

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TREATMENT

- Adrenaline/epinephrine is vital in the management and, in the recommended doses, causes vasoconstriction, bronchodilation, increased cardiac output, reduced mucosal oedema, and reduced mediator release ³
- The mainstay of moderate to life-threatening anaphylaxis during anaesthesia is carefully titrated intravenous (I.V.) adrenaline/epinephrine with close monitoring of cardiovascular responses ³
- Because adrenaline/epinephrine has a narrow therapeutic window clinicians need to be aware of the potential for toxicity including accidental overdose, particularly during crisis management ³
- IV solution **1mg adrenaline/epinephrine in 9mls normal saline**



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TREATMENT

- Life threatening symptoms, severe hypotension, bronchospasm, (Grade 3) 50-100 mcg 0.5-1 mL of a 1:10,000 dilution solution. If no response give 200mcg 2mls reverse bronchospasm
 - act as an inotrope
 - to cause vasoconstriction³
- **If the patient is pulseless then administer 1 mg Adrenaline/epinephrine IV every 1-2 minutes** and institute rapid volume replacement³
- Intramuscular (IM) adrenaline/epinephrine into the lateral thigh should be considered in the initial management of perioperative anaphylaxis where IV access is not yet established or is lost, where haemodynamic monitoring is not in-situ at the start of the reaction, or while awaiting preparation of an adrenaline/epinephrine infusion³



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TREATMENT

- **After three boluses** of adrenaline/epinephrine via either the IV or IM route an adrenaline/epinephrine infusion should be prepared and commenced as early as possible in the clinically appropriate dosage³
- Adequate fluid resuscitation is a critical step in the management of hypotension. This requires aggressive management, and repeated fluid boluses of 20mL/kg may be required³
- Large bore IV access should be secured as soon as possible³
- **If the patient is pulseless** then administer 1 mg Adrenaline/epinephrine IV every 1-2 minutes and institute rapid volume replacement³



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Anaphylaxis during Anaesthesia Immediate Management



TREATMENT

CD/DAC ALERTS Severe Allergic Activity (SAA)	• Immediately stop CD/DAC • Stop all CD/DAC agents • Stop all CD/DAC agents • Stop all CD/DAC agents
DR Drugs	• Stop all CD/DAC agents • Stop all CD/DAC agents • Stop all CD/DAC agents
S Send for help and prepare team	• Call for help and prepare team • Call for help and prepare team • Call for help and prepare team
AB Check Airway, Breathing Circulation 100% oxygen	• Check airway - 100% oxygen • Check airway - 100% oxygen • Check airway - 100% oxygen
C Place fluid bolus Time for rapid volume replacement	• Place fluid bolus • Place fluid bolus • Place fluid bolus
D Administer Bolus Repeat or initiate Infusion if required Prepare to intubate	• Initial IV Adrenaline Bolus (Adult) 1 mg IV 10-15 sec 1:10,000 solution • Repeat every 1-2 minutes if required • If not responding 1 mg IV 10-15 sec 1:10,000 solution
100 Adrenaline (Adult) 100 mcg 10-15 sec 1:10,000 solution • 100 mcg 10-15 sec 1:10,000 solution • 100 mcg 10-15 sec 1:10,000 solution	• 100 mcg 10-15 sec 1:10,000 solution • 100 mcg 10-15 sec 1:10,000 solution • 100 mcg 10-15 sec 1:10,000 solution
Adrenaline infusion (Adult) 200 mcg 10-15 sec 1:10,000 solution • 200 mcg 10-15 sec 1:10,000 solution • 200 mcg 10-15 sec 1:10,000 solution	• 200 mcg 10-15 sec 1:10,000 solution • 200 mcg 10-15 sec 1:10,000 solution • 200 mcg 10-15 sec 1:10,000 solution
• NOT RESPONDING see Adult airway management	



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TO CONTINUE THE CASE OR NOT???

- Australian research looked at 223 cases retrospectively of proven acute hypersensitivity reactions from 2005 to 2014 in Western Australia where anaphylaxis was recognised by the treating clinician before or during surgery
- The aim was to determine whether recovery outcomes were adversely affected by proceeding with the planned procedure
- Surgery proceeded in 104 patients (47%) and was abandoned in 119 (53%)
- Results suggest that, once initial resuscitation has been achieved and if resuscitative efforts can be re-instituted if required, continuing with planned surgery in grade 1, 2 and 3 immediate hypersensitivity was not associated with poorer outcomes
- After grade 3 reactions, there was a significant incidence of complications attributable to acute hypersensitivity regardless of whether surgery proceeded or was abandoned
- Incidence of acute Anaphylaxis in the study was 1 in 11,000 anaesthetics delivered in WA*

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DOCUMENTATION

- Documentation is vital ;
 - to enable further investigation of the collapse
 - medico-legal requirements
- Take blood for Mast cell Tryptase
- Take Tryptase levels immediately, 1 hr, 4hrs, in Serum or plain tube³

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HOW DO YOU DO THIS IN YOUR HOSPITAL

- You may like to check with your pathology department as to the appropriate sample required & protocol for testing
- Patients need a detailed letter
- Must wear an alert bracelet or medallion
- Record all events and possible precipitating drugs

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GUIDELINES

- ANZAAG 2022 guidelines on Anaphylaxis Management
- Please access and read these comprehensive documents
- They are freely available on the ANZAAG

<https://anzaag.com/anaphylaxis-management/management-resources/>

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The Pholcodine Hypothesis

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THE PHOLCODINE HYPOTHESIS

- Studies by Florvaag and Johansson (2011 & 2012) indicated that there was a large difference in rates of anaphylaxis to Neuro-Muscular Blocking Agents (NMBA) in Norway where it was high, compared to Sweden where anaphylaxis to NMBA was low^{8,9}
- They searched the homes of residents in both countries to try and identify sources tertiary or quaternary ammonium ion (QAI)^{8,9}
- The predominant difference was the availability and use of the over-the-counter cough suppressant pholcodine (PHO)
- PHO was not available in Sweden and was widely used in Norway⁸
- It was postulated that the substituted ammonium ion structure of PHO was resulting in sensitisation and an increased reaction rate to NMBAs observed in Norway relative to Sweden⁸
- The subsequent 'pholcodine hypothesis' led to the voluntary withdrawal of the single PHO product on the market in Norway^{8,9}

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THE PHOLCODINE HYPOTHESIS

- Six years after removing PHO from the market in 2007, the Norwegian population has gradually become significantly less IgE-sensitized ¹⁰
- In Australia, the argument has been hindered by a lack of mandatory reporting of such serious reactions¹¹
- The TGA cited a lack of reported cases of anaphylaxis in Australia to show that there is not a significant problem with NMBA anaphylaxis in this country ¹¹
- McAleer et al. (2017) suggest that it is timely to again raise the issue of possible harm related to the free availability of PHO with the drug regulation agencies in Australia and New Zealand

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REFERENCES

1. Department of Forensic Medicine Monash University, Victorian Institute of Forensic Medicine. Clinical Communiqué [electronic resource]. [Internet]. 2017; 4(3). Available from: www.vifm.communiqués.org
2. Mertes P, Florvaag E. Anaphylaxis in the operating theatre. Presse Medicale. 2014;45(9):750-2.
3. Australian and New Zealand Anaesthetic Allergy Group (ANZAAG). Guidelines Anaphylaxis Australian & New Zealand College of Anaesthetists Anaphylaxis Guidelines. 2022
4. Narred C. Anesthetic-induced Anaphylaxis. American Association Nurse Anesthetists Journal 2012;80(2):129-50.
5. Royal College of Anaesthetists. Anaesthesia, Surgery and Life-Threatening Allergic Reactions. Royal College of Anaesthetists, 4th National Audit Project: Perioperative Anaphylaxis. London: NAA Health Services Research Centre Royal College of Anaesthetists 2018.
6. Wong A, Spillane A. Patent Blue V dye anaphylaxis: experience of Australian and New Zealand surgeons. Breast Surgeons of Australia and New Zealand incorporated. ANZ Journal Of Surgery. 2016;84(11-12):37-41.
7. Sadleir P, Clarke R, Bozic B, Platt P. Consequences of proceeding with surgery after resuscitation from intra-operative anaphylaxis. Anaesthesia 2018;73:32-9.
8. Florvaag E, Johansson S, Irgens A, de Pater G. IgE sensitization to the cough suppressant pholcodine and the effects of its withdrawal from the Norwegian market. Allergy. 2011;66:955-60.
9. Florvaag E, Johansson S. The pholcodine case. Cough medicines, IgE sensitisation, and anaphylaxis: a devious connection. World Allergy Organ. 2012;5:73-8.
10. de Pater G, Florvaag E, Johansson S, Irgens A, Petersen M, Guttormsen A. Six years without pholcodine: Norwegians are significantly less IgE-sensitized and clinically more tolerant to neuromuscular blocking agents. Allergy. 2017;72(3):3-9.
11. McAleer P, McNicol L, Rose M. Perioperative anaphylaxis: progress, prevention and pholcodine policy. Anaesthesia & Intensive Care 2017;45(2):147-50.

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Discussion

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