

Peri-operative Anaphylaxis and NAP 6

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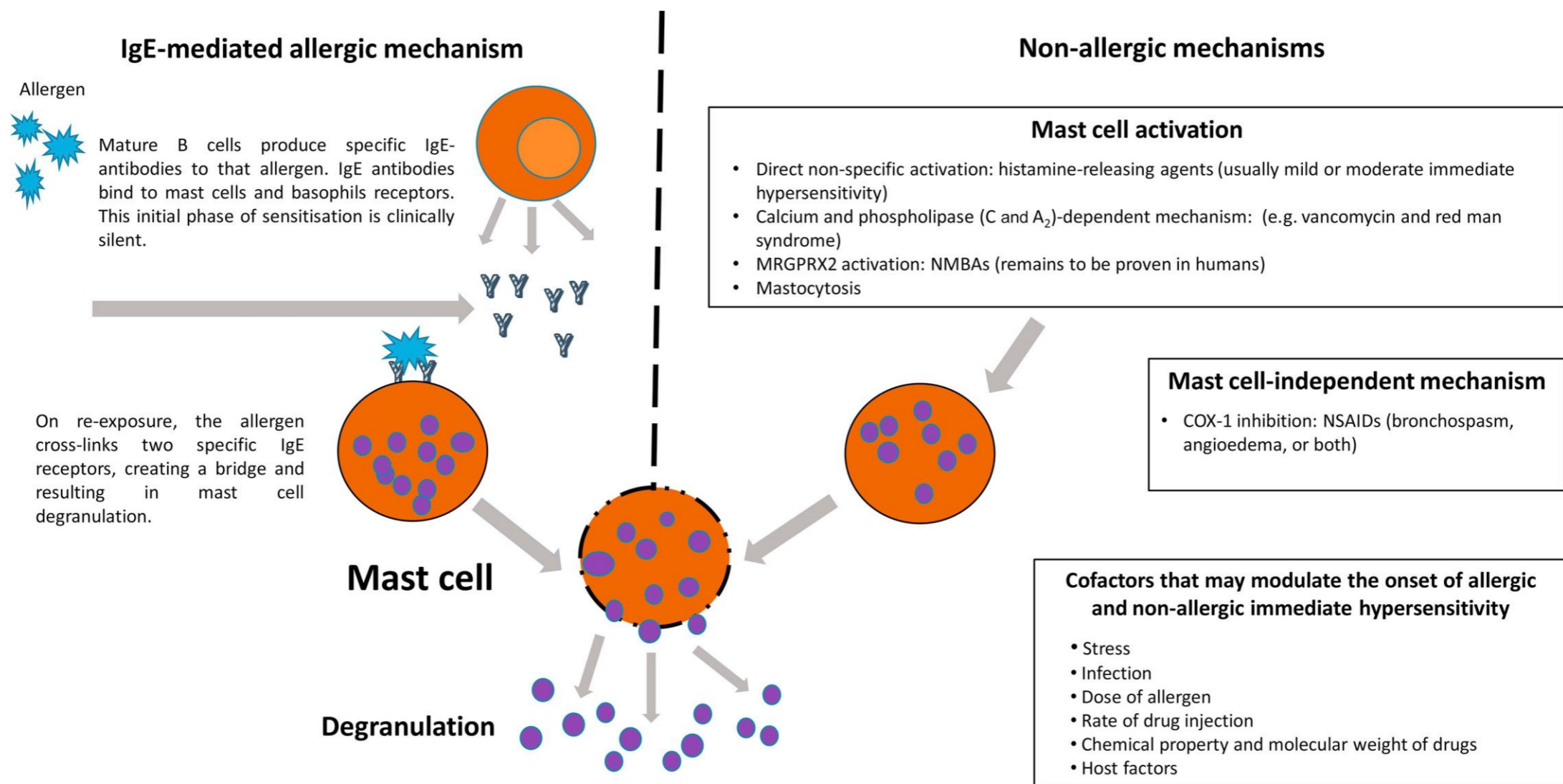
Definition

- **Anaphylaxis** – ‘A severe, life-threatening generalised or systemic hypersensitivity reaction’
- **Peri-operative**
 - general anaesthesia
 - regional anaesthesia
 - sedation
 - managed anaesthesia care (anaesthetist monitoring only)
 - under the care of an anaesthetist
 - between the period of first administration of a drug (including premed) and the post-procedure transfer to the ward, or critical care
- **Allergic anaphylaxis** - IgE mediated reactions
- **Non-Allergic anaphylaxis** - non IgE mediated reactions

Incidence and common culprits NAP6

- * Overall 1 in 10,000 anaesthetics.
- * Antibiotic-induced anaphylaxis 4.0 per 100,000 exposures (47%).
 - teicoplanin (16.4 per 100,000),
 - co-amoxiclav (8.7 per 100,000).
- * NMBA-induced anaphylaxis 5.3 per 100,000 exposures (33%).
 - suxamethonium (11.1 per 100,000),
 - rocuronium (5.88 per 100,000),
 - atracurium (4.15 per 100,000),
 - mivacurium (3.25 per 100,000).
- * Chlorhexidine 0.78 per 100,000 exposures (9%).
- * Patent Blue was 14.6 per 100,000 exposures (4.5%).

Pathophysiology



Release of preformed (e.g. histamine, tryptase) followed by newly formed mediators (e.g. prostaglandin D₂, leukotrienes, thromboxane A₂) results in clinical manifestations of IgE-mediated anaphylaxis.

Clinical presentation severity grading

Grade	Features	NAP6
1 <i>Not life-threatening</i>	Rash, erythema and/or swelling	Excluded
2 <i>Not life-threatening</i>	Unexpected hypotension – not severe, eg, not requiring treatment and/or bronchospasm – not severe, eg, not requiring treatment +/- Grade 1 features	Excluded
3 <i>Life-threatening</i>	Unexpected severe hypotension and/or severe bronchospasm and/or swelling with actual or potential airway compromise +/- Grade 1 features	Included if perioperative anaphylaxis suspected
4 <i>Life-threatening</i>	Fulfilling indications for CPR	Included if perioperative anaphylaxis suspected
5 <i>Fatal</i>	Fatal	Included if perioperative anaphylaxis suspected



Clinical presentations of peri-operative immediate hypersensitivity based on Ring and Messmer IV step grading scale.

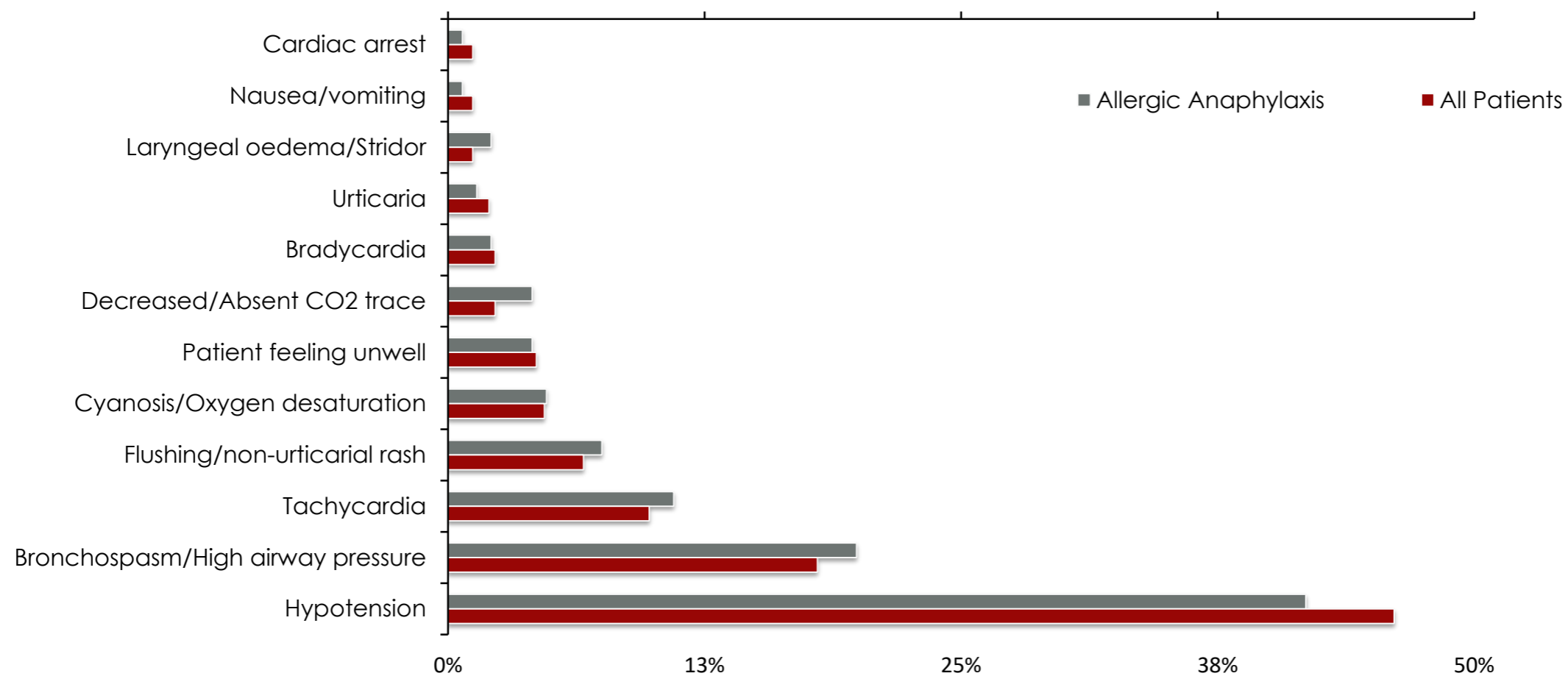
Grade	Clinical signs
I	Mucocutaneous signs: generalised erythema, extensive urticaria with or without angioedema
II	Moderate multivisceral signs: mucocutaneous signs, moderate hypotension, tachycardia, or both with or without moderate bronchospasm or gastrointestinal symptoms
III	Life-threatening mono- or multivisceral signs: life-threatening hypotension, tachycardia or bradycardia with or without cardiac arrhythmia, mucocutaneous signs, severe bronchospasm or gastrointestinal symptoms The cutaneous features may be absent before the restoration of haemodynamic stability
IV	Cardiac arrest

Time from exposure to presenting feature (NAP6)

Time from exposure to presenting feature (mins)	Number (Percentage) of patients
0 – 5	176 (66.2%)
6 – 10	44 (16.5%)
11 – 15	13 (4.9%)
16 – 30	19 (7.1%)
31 – 60	7 (2.6%)
61 – 120	3 (1.1%)
> 120	2 (0.75%)
Blank	2

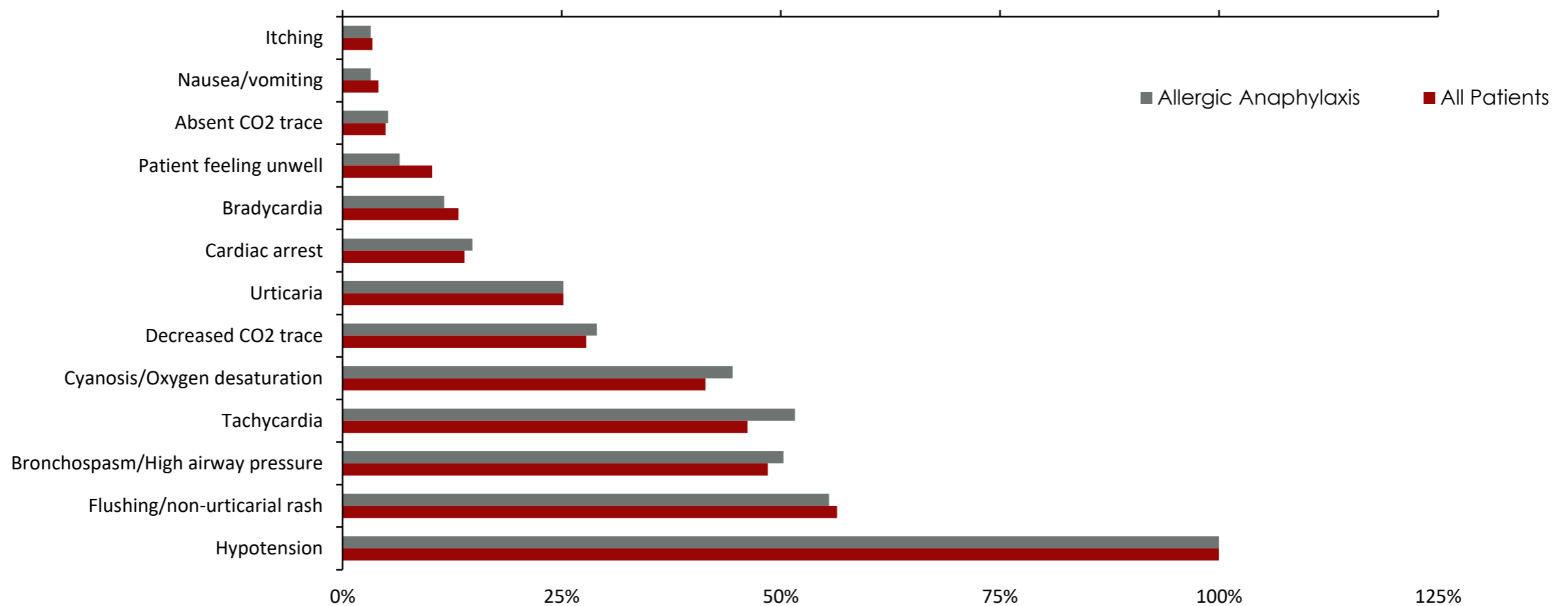
- Rapid onset for most culprit agents
 - Exceptions: chlorhexidine, Patent Blue dye, oral drugs

First presenting feature



Peri-operative anaphylaxis can present as isolated organ system involvement.

All clinical features



Hypotension universal during peri-operative anaphylaxis. Consider anaphylaxis as differential diagnosis during unexplained peri-operative hypotension.

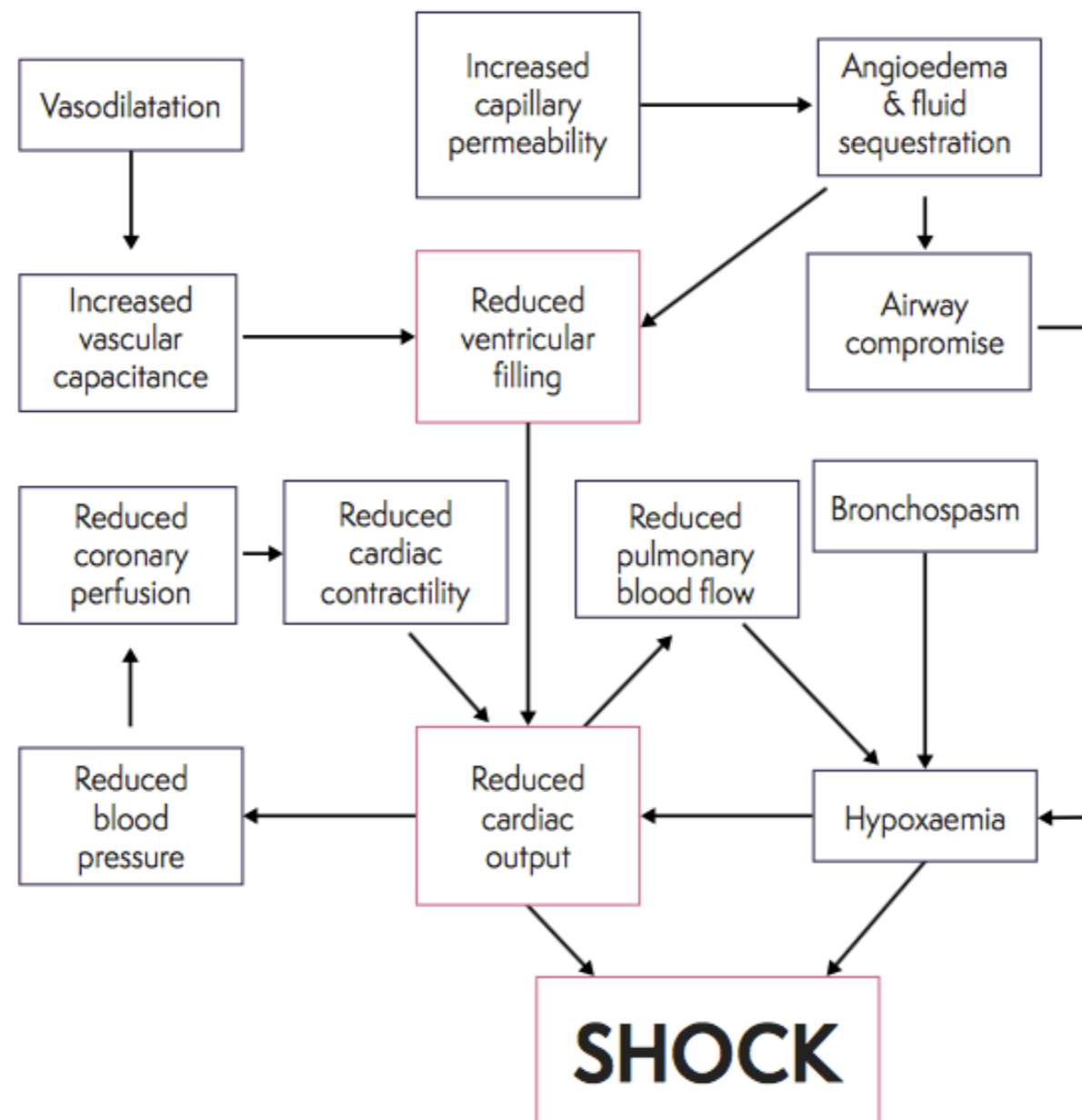
Time to suspect and treat (NAP6)

- Speed of response by anaesthetist varies.
- Response <10 mins when presenting feature was cardiac arrest, bradycardia, reduced/absent CO2 trace, laryngeal oedema.
- Longer delays when presenting feature was hypotension, bronchospasm/high airway pressure, cyanosis, non-specific flushing.

Key points

- Presenting features of peri-operative anaphylaxis may have many other causes.
- Early recognition key to successful treatment.
- Anaphylaxis should be considered in unexpected peri-operative hypotension.
- Likewise in bronchospasm (asthmatic patients).
- Peri-operative anaphylaxis can present as isolated organ system involvement.
- Cutaneous signs uncommon presenting features.
- Majority of reactions present rapidly.
- Education and training in recognition/treatment of anaphylaxis recommended.

Figure 1. Physiological mechanisms responsible for anaphylactic shock



Treatment

- ① Call for **help**. Note the time. Stop or do not start non-essential surgery.
- ② Call for cardiac arrest trolley, anaphylaxis treatment pack and investigation pack.
- ③ **Remove** all potential **causative agents** and maintain anaesthesia.
 - Important culprits: antibiotics, neuromuscular blocking agents, patent blue.
 - Consider chlorhexidine as cause (impregnated catheters, lubricants, cleansing agents).
 - Consider i.v. colloids as a possible cause.
 - Change to inhalational anaesthetic agent (if not already).
- ④ Give **100% oxygen** and ensure adequate ventilation:
 - Maintain the airway and, if necessary, secure it with tracheal tube.
- ⑤ Elevate patient's legs if there is hypotension.
- ⑥ If systolic blood pressure < 50 mmHg or cardiac arrest, start CPR immediately.
- ⑦ Give drugs to treat hypotension (Box A):
 - Hypotension may be resistant and may require prolonged treatment.**
 - Give adrenaline** bolus and repeat as necessary.
 - Consider starting an adrenaline infusion after three boluses.
 - If hypotension resistant, give alternate vasopressor (e.g. metaraminol, noradrenaline infusion +/- vasopressin)
 - Give glucagon in β -blocked patient unresponsive to adrenaline.
- ⑧ Give rapid **i.v. crystalloid: 20 ml.kg⁻¹** initial bolus, repeated until hypotension resolved.
- ⑨ Give **hydrocortisone** as part of resuscitation (Box B).
- ⑩ If bronchospasm is persistent, consider → 3-4
- ⑪ Take 5-10 ml clotted blood sample for **serum tryptase** as soon as patient is stable.
 - Plan for repeat sample at 1-2 hours and >24 hours.
- ⑫ Give chlorphenamine when feasible (Box B).
- ⑬ Plan transfer of the patient to an appropriate **critical care** area. Note tasks in Box D.
- ⑭ Prevent re-administration of possible trigger agents (allergy band, annotate notes/drug chart)

Treatment

Box A: DRUGS TO TREAT HYPOTENSION

- Adult adrenaline: i.v. 50 μg (= 0.5 ml of 1:**10 000**)
i.m. 0.5 mg (= 0.5 ml of 1:**1000**) *if i.v. not possible*
- Paediatric adrenaline: i.v. 1.0 $\mu\text{g.kg}^{-1}$ (0.1 ml.kg⁻¹ of 1:**100 000**)
[1:**100 000** solution made by diluting 1 ml of 1:**10 000** up to 10 ml]
- If no i.v. access, intraosseous adrenaline dose same as i.v.
- Suggested adrenaline infusion regimes (adult):
5 mg in 500 mL dextrose = 1:**100 000**, titrate to effect
3 mg in 50 mL saline. Start at 3 ml.h⁻¹ (= 3 $\mu\text{g.min}^{-1}$), titrate to maximum 40 ml.h⁻¹ (= 40 $\mu\text{g.min}^{-1}$)
- Glucagon (adult): 1 mg, repeat as necessary
- Vasopressin (adult): 2 units, repeat necessary (consider infusion)

Treatment

Box B: OTHER DRUGS

- Hydrocortisone i.v. doses:
- Adult: 200 mg
 - Child 6-12 years: 100 mg
 - Child 6 months-6 years: 50 mg
 - Child <6 months: 25 mg

- Chlorphenamine i.v. doses:
- Adult: 10 mg
 - Child 6-12 years: 5 mg
 - Child 6 months-6 years: 2.5 mg
 - Child <6 months: 250 $\mu\text{g}\cdot\text{kg}^{-1}$

Follow up

Box D: DON'T FORGET

- Repeat testing for serum tryptase at 1-2 hours and >24 hours.
- Liaise with hospital laboratory about analysis of samples.
- Liaise with department anaphylaxis lead regarding referral to a specialist allergy or immunology centre to identify the causative agent (see www.bsaci.org for details).
- Inform the patient, surgeon and general practitioner.
- Report to MHRA (www.mhra.gov.uk/yellowcard).
- NAP6 online resource: <http://www.nationalauditprojects.org.uk/NAP6-Resources#pt>

3-1 Anaphylaxis v.3

- Unexplained hypotension
- Unexplained bronchospasm (*wheeze may be absent if severe*)
- Unexplained tachycardia or bradycardia

- Angioedema (*often absent in severe cases*)
- Unexpected cardiac arrest where other causes are excluded
- Cutaneous flushing in association with one of more of the signs above (*often absent in severe cases*)

- 1 Call for help. Note the time. Stop or do not start non-essential surgery.
- 2 Call for cardiac arrest trolley, anaphylaxis treatment pack and investigation pack.
- 3 Remove all potential causative agents and maintain anaesthesia.
 - Important culprits: antibiotics, neuromuscular blocking agents, patent blue.
 - Consider chlorhexidine as cause (impregnated catheters, lubricants, cleansing agents).
 - Consider i.v. colloids as a possible cause.
 - Change to inhalational anaesthetic agent (if not already).
- 4 Give 100% oxygen and ensure adequate ventilation:
 - Maintain the airway and, if necessary, secure it with tracheal tube.
- 5 Elevate patient's legs if there is hypotension.
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- 11 Take 5-10 ml clotted blood sample for **serum tryptase** as soon as patient is stable.
 - Plan for repeat sample at 1-2 hours and >24 hours.
- 12 Give chlorphenamine when feasible (Box B).
- 13 Plan transfer of the patient to an appropriate critical care area. Note tasks in Box D.
- 14 Prevent re-administration of possible trigger agents (allergy band, annotate notes/drug chart)

Box A: DRUGS TO TREAT HYPOTENSION IF CARDIAC ARREST → 2-1

- Adult adrenaline: i.v. 50 µg (= 0.5 ml of 1:10 000)
i.m. 0.5 mg (= 0.5 ml of 1:1000) *if i.v. not possible*
- Paediatric adrenaline: i.v. 1.0 µg.kg⁻¹ (0.1 ml.kg⁻¹ of 1:100 000)
[1:100 000 solution made by diluting 1 ml of 1:10 000 up to 10 ml]
- If no i.v. access, intraosseous adrenaline dose same as i.v.
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Box B: OTHER DRUGS

- | | |
|--|---|
| <input type="checkbox"/> Hydrocortisone i.v. doses: <ul style="list-style-type: none">• Adult: 200 mg• Child 6-12 years: 100 mg• Child 6 months-6 years: 50 mg• Child <6 months: 25 mg | <input type="checkbox"/> Chlorphenamine i.v. doses: <ul style="list-style-type: none">• Adult: 10 mg• Child 6-12 years: 5 mg• Child 6 months-6 years: 2.5 mg• Child <6 months: 250 µg.kg⁻¹ |
|--|---|

Box C: CRITICAL CHANGES

CARDIAC ARREST → 2-1

Box D: DON'T FORGET

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- Liaise with hospital laboratory about analysis of samples.
- Liaise with department anaphylaxis lead regarding referral to a specialist allergy or immunology centre to identify the causative agent (see www.bsaci.org for details).
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Clinical pearls

- When cuteness sings initially lacking, appearance of erythema or urticaria indicates restored cutaneous perfusion - need for adrenalin should be r/v
- When cardiovascular collapse with paradoxical bradycardia - avoid atropine

Key Findings – Outcomes

- Of the 266 cases reviewed, 40 patients experienced cardiac arrest and 10 patients died
- More than half of patients required admission to critical care (70% for Level 3 care)
- Poor outcomes were associated with increased age, ASA grade, obesity, beta-blocker, and/or ACE inhibitor medication
- Adverse sequelae (104) included anxiety, mood and memory changes, alteration in coordination, mobility or PTSD-like symptoms
- A small number of patients experienced a myocardial infarction, acute kidney injury or new shortness of breath
- Fewer than a quarter of cases were reported to MHRA

Key Findings – Clinical Features and Management

- Anaphylaxis presented within 10 minutes of exposure to the culprit agent in 83% of cases.
- Anaphylaxis caused by chlorhexidine and Patent Blue dye had a slower onset
- Skin signs were uncommon in the more severe cases of anaphylaxis, sometimes only occurring after resuscitation
- All patients were resuscitated by an anaesthetist of appropriate grade, and recognition of a critical event was prompt
- When cardiac compressions were indicated there was delay starting them in more than half of cases.
- IV fluid administration was frequently insufficient and was inappropriate in 19% of cases.

Recommendations for antibiotics

Institutional

- Patients with reported allergy to a beta-lactam antibiotic and at least one other class of antibiotics should be referred for allergy investigation, before elective surgery, in line with *NICE CG183: Drug allergy: diagnosis and management*.
- If antibiotic allergy is suspected despite negative skin tests, challenge testing should be considered
- Broad beta lactam avoidance advice should be discouraged and patients should be further investigated to clarify the drug(s) to avoid and to identify safe alternatives.

Individual

- Ninety per cent of anaphylaxis due to antibiotics presents within ten minutes of administration. **When perioperative antibiotics are indicated they should be administered as early as possible, where practical at least 5-10 minutes before induction of anaesthesia, providing this does not interfere with their efficacy.**
- The anaesthetist should consider co-amoxiclav or teicoplanin amongst the likely culprits when anaphylaxis occurs after their administration.
- Avoid test doses of antibiotic

Key recommendations for Chlorhexidine

- **National:**
 - Prominent labelling (MHRA & manufacturers)
- **Institutional:**
 - Alternatives should be available
 - All cases should be tested for chlorhexidine with at least 2 modalities of test; and all potential culprits should be tested
- **Individual:**
 - Improved awareness of chlorhexidine and allergy history taking
 - Chlorhexidine coated CVCs should be removed when anaphylaxis occurs following insertion

Paediatrics

- Rare 2.7:100,000
- No deaths
- Well managed
- Atracurium single biggest trigger agent
- Clinic and follow up can be improved

Obstetrics

- Incidence of severe obstetric peri-operative anaphylaxis of 3.4 per 100,000 (95% CI 1.48-6.74 per 100,000)



Questions?