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SUMMARY WITH CRITICAL APPRAISAL

Epinephrine Auto-Injectors for Anaphylaxis: A Review of the Clinical Effectiveness, Cost-Effectiveness, and Guidelines

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Abbreviations

AGREE	Appraisal of Guidelines for Research and Evaluation
AMSTAR	A Measurement Tool to Assess systematic Reviews
ANZAAG	Australian and New Zealand Anaesthetic Allergy Group
ANZCA	Australian and New Zealand College of Anaesthetists
CENTRAL	Cochrane Central Register of Controlled Trials
CRD	Centre for Reviews and Dissemination
EAI	Epinephrine auto injector
IM	Intramuscular
IV	Intravenous
JTFPP	Joint Task Force on Practice Parameters
MeSH	Medical Subject Headings
NHMRC	National Health and Medical Research Council
PRISMA	Preferred Reporting Items for Systematics and Meta-Analyses
RCT	Randomized controlled trials

Context and Policy Issues

Anaphylaxis is a potentially life-threatening medical emergency which requires prompt recognition and treatment.[1] The condition is caused by a severe and generalized allergic reaction or hypersensitivity reaction that leads to a sudden release of mast cell and basophil-derived mediators into circulation.[2,3] Onset of a range of clinical symptoms occurs rapidly, and includes severe airway, breathing, and circulation problems.[4] Common causes of anaphylaxis are medication reactions, insect stings, and food allergies.[5]

Epinephrine is the usual treatment for patients experiencing anaphylactic reactions,[2] and the administration of this treatment should be rapidly executed.[6] Epinephrine has several mechanisms of action that reduce and reverse the symptoms of anaphylaxis.[2,7] It works to decrease vasoconstriction and peripheral vascular resistance, decrease upper airway mucosal edema, increase bronchodilation, and decrease mediator release from mast cells and basophils. Delayed administration of epinephrine is associated with poorer outcomes for the patient, emphasizing the importance of prompt treatment.[2] First-line emergency treatment with epinephrine is generally by intramuscular (IM) injection,[5] which can either be administered by an epinephrine auto-injector (EAI) or by manual draw-up and dosing from an epinephrine containing ampoule or vial. Depending on the setting, epinephrine can be administered by the patients experiencing the reaction, by a caretaker, or by various health care professionals.[8,9] There is uncertainty as to which method of IM delivery of epinephrine is preferable in health care settings, and whether EAI or epinephrine vials for manual delivery should be stocked and available for use by health care professionals.

In order to inform policy decisions about the use of either EAI or manual delivery of epinephrine, specific evidence is required. As such, this report aims to review the comparative clinical effectiveness and cost-effectiveness of EAI versus manually administered epinephrine for the management of individuals with anaphylaxis. Additionally, the report aims to review the evidence-based guidelines for the management of anaphylaxis.

Research Questions

1. What is the comparative clinical effectiveness of epinephrine auto-injectors versus manually administered epinephrine for the management of individuals with anaphylaxis?
2. What is the comparative cost-effectiveness of epinephrine auto-injectors versus manually injected epinephrine for the management of individuals with anaphylaxis?
3. What are the evidence-based guidelines regarding management of anaphylaxis?

Key Findings

No evidence regarding the clinical effectiveness of epinephrine auto-injectors compared to manually administered epinephrine for the management of individuals with anaphylaxis was identified.

No evidence regarding the cost-effectiveness of epinephrine auto-injectors compared to manually administered epinephrine for the management of individuals with anaphylaxis was identified.

Two evidence-based guidelines were identified regarding the management of anaphylaxis. One guideline was jointly developed by the Australian and New Zealand College of Anaesthetists and the Australian and New Zealand Anaesthetic Allergy Group. The other guideline was a practice parameter update by the Joint Task Force on Practice Parameters, which represents the American Academy of Allergy, Asthma & Immunology and the American College of Allergy, Asthma & Immunology. Both guidelines recommend epinephrine administration for anaphylaxis, however neither explicitly state a preference for epinephrine auto-injectors versus manually drawn-up epinephrine for the management of individuals with anaphylaxis.

Methods

Literature Search Methods

A limited literature search was conducted by an information specialist on key resources including PubMed, the Cochrane Library, the University of York Centre for Reviews and Dissemination (CRD) databases, the websites of Canadian and major international health technology agencies, as well as a focused internet search. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were epinephrine and anaphylaxis. Filters were applied to limit the retrieval to health technology assessments, systematic reviews and meta-analyses, randomized controlled trials (RCTs), economic studies, non-randomized studies, and guidelines. The search was also limited to English language documents published between January 1, 2015 and March 24, 2020.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection criteria

Population	Individuals (of all ages) experiencing anaphylaxis
Intervention	Q1-Q2: Epinephrine administered by a health care professional using an auto-injector Q3: Interventions for the management of anaphylaxis
Comparator	Q1-Q2: Epinephrine (prepared prior to injection from an ampoule/vial) administered by a health care professional using manual injection Q3: Not applicable
Outcomes	Q1: Clinical effectiveness (e.g., mortality, time to injection, safety [e.g., rates of adverse events]) Q2: Cost-effectiveness (e.g., cost per quality-adjusted life-year gained) Q3: Recommendations regarding best practices (e.g., treatment protocols, guidance around methods of epinephrine injection)
Study Designs	Health technology assessments, systematic reviews, randomized controlled trials, non-randomized studies, economic evaluations, and guidelines

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published prior to 2015. Guidelines with unclear methodology were also excluded.

Critical Appraisal of Individual Studies

The included publications were critically appraised by one reviewer using the Appraisal of Guidelines for Research and Evaluation (AGREE) II instrument [10] as a guide. Summary scores were not calculated for the included studies; rather, the strengths and limitations of each included study were described narratively.

Summary of Evidence

Quantity of Research Available

A total of 392 citations were identified in the literature search. Following screening of titles and abstracts, 363 citations were excluded and 29 potentially relevant reports from the electronic search were retrieved for full-text review. Sixteen potentially relevant publications were retrieved from the grey literature search for full-text review. Of these potentially relevant articles, 43 publications were excluded for various reasons, and two publications met the inclusion criteria and were included in this report. These were two evidence-based guidelines. Appendix 1 presents the PRISMA[11] flowchart of the study selection. Additional references of potential interest are provided in Appendix 5.

Summary of Study Characteristics

Two evidence-based guidelines[1,12] were identified for inclusion in this review. No relevant health technology assessments, systematic reviews, RCTs, non-randomized studies, or economic evaluations were identified. Additional details regarding the characteristics of included publications are provided in Appendix 2, Table 2.

Study Design

Two evidence-based guidelines were included in this report. One guideline[1] was jointly developed by the Australian and New Zealand College of Anaesthetists (ANZCA) and Australian and New Zealand Anaesthetic Allergy Group (ANZAAG). The guidelines were published in 2016 as a revision to guidelines originally developed in 2013 by ANZAAG. A systematic literature search was performed, however no relevant RCTs were identified, and therefore the guidelines are consensus statements. The level of evidence and the grades of the recommendation were assessed using a modified version of the National Health and Medical Research Council (NHMRC) levels of evidence (from ”Level I” [highest] to “Level V” [lowest]) and the NHMRC grades of recommendation (from “A” [highest] to ”D” [lowest]). These assessments of the level of evidence and grade of recommendation were taken from published reviews and other guidelines for the management of anaphylaxis (they were not assessed directly by the ANZCA/ANZAAG guideline authors).

The other guideline[12] was developed by the Joint Task Force on Practice Parameters (JTFPP), which represents the American Academy of Allergy, Asthma & Immunology and the American College of Allergy, Asthma & Immunology. These practice parameters were a 2015 update from the previously published 2010 parameters. The practice parameters update was formulated using a systematic literature review, in combination with consensus expert opinion and supplementary documents identified by the workgroup. The strength of the recommendations (”Strong Recommendation” to “No Recommendation”) and the quality of evidence (from “A” [highest] to “D” [weakest]) were assessed using unreferenced classification guides.

Country of Origin

The guidelines were developed in the United States[12] and Australia and New Zealand.[1]

Patient Population

The intended users of the ANZCA/ANZAAG guidelines[1] were anaesthetists, and the target populations were patients experiencing perioperative anaphylaxis. The intended users of the JTFPP guidelines[12] were practicing physicians. The target populations of guidelines were not explicitly stated, but they appear to be intended for patients experiencing anaphylaxis.

Interventions and Comparators

One guideline examined the management (including diagnosis, immediate emergency treatment, and post-emergency treatments) of perioperative anaphylaxis.[1] The other guideline provided evidence-based recommendations for the diagnosis and management of anaphylaxis in various settings (e.g., in-office), when exposed to various allergens (e.g., foods or insect stings), and with various medical histories (e.g., patients with mastocytosis).[12]

Outcomes

The ANZCA/ANZAAG guidelines[1] were based on a literature review which identified guidelines for management of anesthetic anaphylaxis as well as on general guidelines for the management of anaphylaxis. The guideline documents included limited details surrounding the inclusion criteria for the literature review; the specific outcomes considered by the guideline development group were not explicitly reported. As no RCTs were identified in the literature search, the ANZCA/ANZAAG guidelines were developed as

consensus statements with the objective of optimizing the management of perioperative anaphylaxis for anesthetists. Relevant to this review, the guidelines provided recommendations for: 1) immediate crisis in adults, 2) immediate crisis in pediatrics, 3) refractory management in adults, and 4) refractory management in pediatrics. Recommendations for differential diagnosis and post-crisis management were also included, however they were not relevant to this report.

The JTFPP guidelines[12] were based on a systematic literature review which aimed to identify new references to update practice parameters previously published in 2010. The guidelines aimed to improve the care of patients by providing evidence-based recommendations for physicians for the diagnosis and management of anaphylaxis. As with the other guideline in this report, the JTFPP guideline documents included limited details surrounding the inclusion criteria (including the outcomes considered) for the literature review. The guidelines presented recommendations for the general evaluation and management of anaphylaxis for: 1) evaluation and management of patients with a history of anaphylaxis, 2) office management of anaphylaxis, 3) anaphylaxis to foods, 4) anaphylaxis to drugs and biological agents, 5) insect sting anaphylaxis, 6) perioperative anaphylaxis: anaphylaxis before, during, or immediately after anesthesia, 7) seminal fluid anaphylaxis, 8) exercise-induced anaphylaxis, 9) anaphylaxis to subcutaneous allergen immunotherapy extract (vaccine), 10) anaphylaxis in mastocytosis, monoclonal mast cell activating syndrome, and mast cell activating syndrome, and 11) unusual presentations of anaphylaxis.

Summary of Critical Appraisal

Additional details regarding the strengths and limitations of included publications are provided in Appendix 3, Table 3

Guidelines

In both guidelines,[1,12] the objectives and health questions were clearly described, the development groups included individuals from all relevant professional groups, and the target users were clearly defined. Additionally, systematic methods were used to identify evidence, strengths and limitations of the evidence were listed, and clear links between the evidence and the recommendations were provided. Overall, the JTFPP guidelines[12] provided clear presentation of recommendations. In one guideline,[1] the intended population to whom the guideline applies was clearly defined, but not in the other guideline.[1] One of the guidelines[1] provided tools, in the form of a ”toolbox of cards” for putting the recommendations into practice.

Limitations to the guidelines were identified. Neither of the guidelines[1,12] stated whether the views and preferences of the target populations were sought. There was a lack of clarity in both guidelines surrounding the methods for formulating the recommendations (including the literature search), the external review process, and the criteria for selecting evidence. The AANZCA/ANZAAG guidelines[1] did not clearly provide their recommendations. Furthermore, neither of the guidelines[1,12] provided a description of the barriers and facilitators to following the guidelines or the resource implications of the guidelines. The potential influence of the funding bodies and the competing interests were not described in one of the guidelines, and therefore the potential for bias cannot be ruled out.

Summary of Findings

A table of the main study findings and authors' conclusions are presented in Appendix 4, Table 4.

Clinical Effectiveness of Epinephrine Auto-injectors versus Manually Administered Epinephrine

No relevant evidence regarding the clinical effectiveness of EAI versus manually administered epinephrine for the management of individuals with anaphylaxis was identified; therefore, no summary can be provided.

Cost-Effectiveness of Epinephrine Auto-injectors versus Manually Administered Epinephrine

No relevant evidence regarding the cost-effectiveness of EAI versus manually administered epinephrine for the management of individuals with anaphylaxis was identified; therefore, no summary can be provided.

Guidelines

Relevant to this report, the ANZCA/ANZAAG guidelines[1] did not make any explicit distinction or recommendation for EAI versus manually administered epinephrine for the management of anaphylaxis. The guideline recommends the administration of epinephrine for immediate management of adults experiencing anaphylaxis (Level IV evidence, Grade C recommendation). The guidelines state that diagnosis must be rapid, with epinephrine administered early and at the appropriate dose in order to optimize outcomes (Level V evidence, Grade D recommendation). Potential allergens which may be the trigger to the anaphylaxis should be ceased as soon as possible (Level V evidence, Grade D recommendation). This is especially important in the case of refractory anaphylaxis (Level V evidence, Grade D recommendation). The guidelines state that patients should be returned to the supine positions as soon as possible, and a leg elevation should be considered when hypotension is prominent (Level IV evidence, Grade D recommendation). Aggressive fluid resuscitation is recommended (Level IV evidence, Grade D recommendation).The benefits of IM epinephrine for the management of anaphylaxis were found to outweigh the risks (Level I evidence), and the guidelines recommend IM administration in the initial management of perioperative anaphylaxis when IV access has not yet been established or is lost, where hemodynamic monitoring is not in place at the start of the reaction, or while waiting for an epinephrine infusion (Level 1 evidence, Grade B recommendation). Dose intervals of five minutes is recommended (Level V evidence, Grade D recommendation). The guidelines further recommend initial use of an IV bolus of epinephrine (Grade D recommendation). The guidelines recommend the use of an epinephrine infusion after three boluses of either IV or IM epinephrine have been administered (Level III evidence, Grade D recommendation). The guidelines state that there is little evidence to inform the immediate management of anaphylaxis in pediatric patients, and the scientific rationale for management in these patients is essentially the same as for adults.

For management of refractory anaphylaxis in adults, the ANZCA/ANZAAG guidelines[1] recommend obtaining an arterial line where possible (Grade D recommendation), and the use of ultrasound to diagnose pneumothorax (Grade D recommendation). Cardiac bypass or extracorporeal membrane oxygenation can be considered to re-establish adequate perfusion (Grade D recommendation). The guidelines state that alternative vasopressors should only be considered following appropriate administration of epinephrine and IV fluids

(Level V evidence, Grade D recommendation), and glucagon can be included in the management of resistant hypotension (Level V evidence, Grade D recommendation). In cases of resistant bronchospasm, salbutamol can be administered (Level V evidence, Grade D recommendation). Alternatively, IV magnesium or inhalation anesthetics and ketamine can be administered (Level V evidence, Grade D recommendation). For pregnant patients, manual left uterine displacement positioning is recommended in situations where the uterus is above the umbilicus (Level V evidence, Grade D recommendation). The guidelines further recommend that in the case of cardiac arrest, peri-mortem caesarean delivery should be performed (Level V evidence, Grade D recommendation).

For management of refractory anaphylaxis in pediatrics, the ANZCA/ANZAAG guidelines[1] recommend first requesting advice and/or more assistance (Grade D recommendation). IV aminophylline and hydrocortisone are recommended along with inhaled salbutamol and IV magnesium recommendations (Grade D recommendation).

Relevant to this report, the JTFPP guidelines[12] did not make any explicit distinction or recommendation for EAI versus manually administered epinephrine for the management of anaphylaxis. The guidelines provide 79 summary statement recommendations covering the 11 overall topics. These recommendations cover both diagnosis and management of anaphylaxis in different situations. Most recommendations focus on recognizing triggers and supplying the patients with education for the condition (various levels of recommendation and evidence). For in-office management of anaphylaxis, the guidelines recommend: 1) administering epinephrine IM (administration method not specified), 2) removing the allergen, assessing airway, breathing, circulation, and mentation and summoning appropriate assistance from staff members, and 4) starting, if needed, cardiopulmonary resuscitation and summoning emergency medical services. These were strong Recommendations based on level D Evidence.

Limitations

Several limitations must be considered when reviewing this report. The guidelines were released in the Unites States,[12] and in Australia and New Zealand,[1] and therefore their relevance to the Canadian context is unclear. Furthermore, neither guideline made recommendations as to whether an EAI or manual draw-up of epinephrine would be more favourable for health care practitioners in face of anaphylaxis. The guideline methodology was unclear, and the completeness of the evidence-search cannot be thoroughly analyzed.

Conclusions and Implications for Decision or Policy Making

No evidence was identified regarding the clinical effectiveness or cost-effectiveness of epinephrine auto-injectors compared to manually administered epinephrine for the management of individuals with anaphylaxis. Although no studies were identified that directly compared EAI versus manually administered epinephrine, two simulation studies[6,13] in which radiology healthcare professionals participated in simulated anaphylaxis scenarios demonstrated that EAI administration was quicker and had less administration errors than manual epinephrine delivery. Whether these findings extend to real-life anaphylaxis situations is unknown.

Two evidence-based guidelines[1,12] were identified that provide recommendations regarding the management of anaphylaxis. The guidelines present recommendations for various anaphylaxis situations, and they generally recommend and support the use of epinephrine for anaphylaxis. Neither guideline explicitly recommends any particular modality of

epinephrine administration (i.e., EAI versus manual draw-up of epinephrine) by health care professionals. Both guidelines included systematic literature searches to inform the recommendations, however it was noted that limited evidence existed, and therefore most of the recommendations were formulated by expert-consensus. While one of the guidelines[12] provided clear summary statements for the recommendations, the other guideline[1] did not clearly present the included recommendations. Neither guideline[1,12] was developed specifically for the Canadian context.

Overall, limited evidence was identified to address the research questions of this report. No clinical effectiveness studies or cost-effectiveness studies were identified; therefore, no conclusions can be drawn. Due to the life-threatening severity of anaphylaxis, RCTs directly investigating the clinical effectiveness of EAI versus manual delivery are likely unethical. As for the evidence-based guidelines, no recommendations were identified recommending one method of epinephrine administration over the other. Therefore, it may be too early to draw conclusions to support the use of EAI compared to manual delivery of epinephrine.

References

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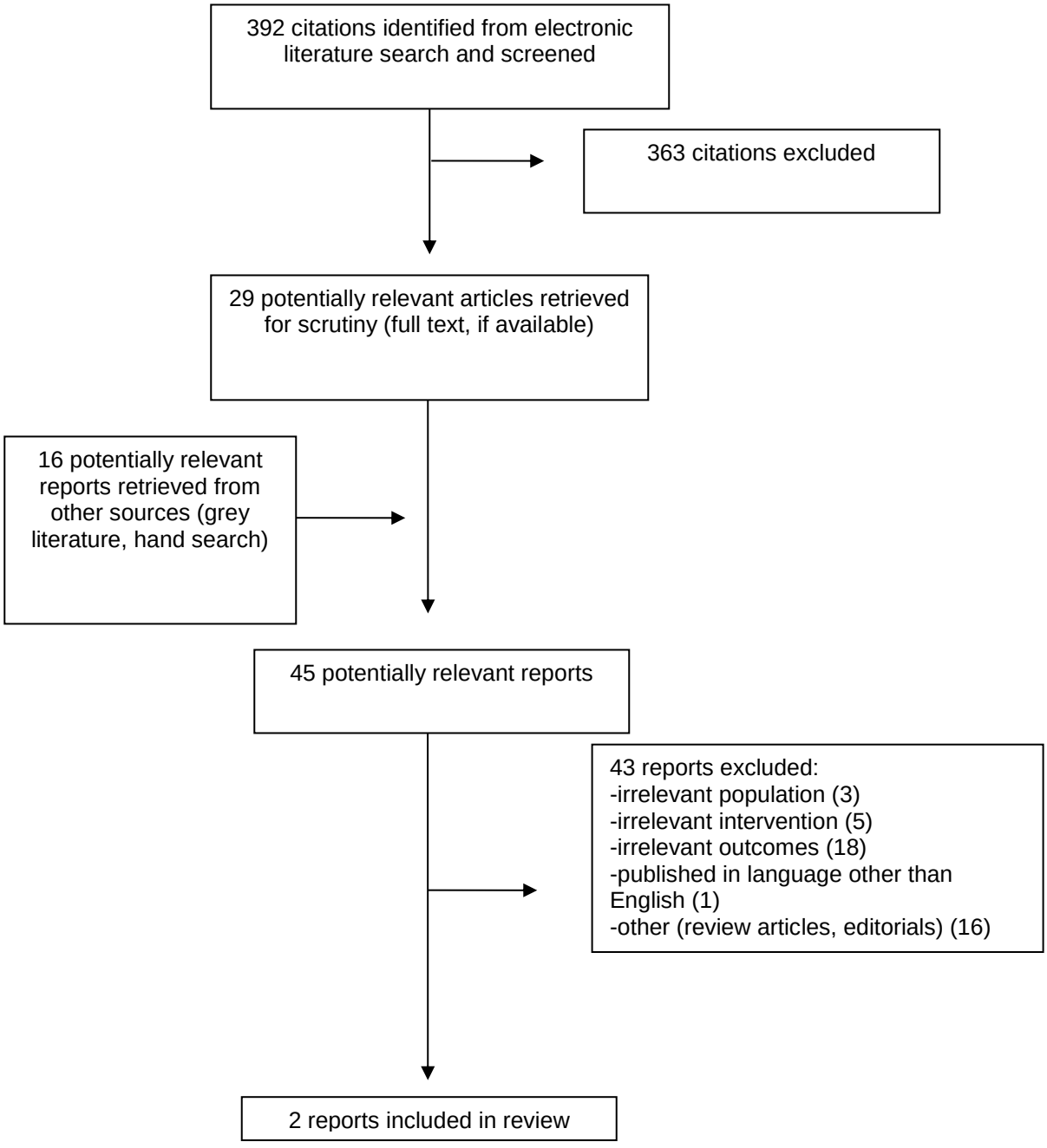
Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 2: Characteristics of Included Guidelines

Intended users, target population	Intervention and practice considered	Major outcomes considered	Evidence collection, selection, and synthesis	Evidence quality assessment	Recommendations development and evaluation	Guideline validation
AANZCA-ANZAAG, 2016[1]						
Intended users: anaesthetists Target population: patients experiencing perioperative anaphylaxis	Management of anesthetic anaphylaxis and general management of anaphylaxis	Evidence to inform the following recommendations (Relevant to this report): 1) immediate crisis in adults, 2) immediate crisis in pediatrics, 3) refractory management in adults, and 4) refractory management in pediatrics The specific outcomes considered by the guideline development group were not explicitly reported	Published in 2016 as a revision to guidelines originally developed in 2013 by ANZAAG. Systematic literature search was performed	Modified version of the NHMRC levels of evidence: Level 1 (highest) to Level V (lowest) [a]	Recommendations developed by consensus (as no relevant RCTs were identified) Recommendations evaluated with NHMRC grades of recommendation: ”A” (strongest) to “D” (weakest) [a] The recommendation evaluations were taken from published reviews and other guidelines for the management of anaphylaxis.	None reported
JTFPP, 2015[12]						
Intended users: practicing physicians **Target population:** patients experiencing anaphylaxis (not explicitly stated)	Diagnosis and management of anaphylaxis	Evidence-to inform the following: 1) Evaluation and Management of Patients with a History of Anaphylaxis, 2) Office Management of Anaphylaxis, 3) Anaphylaxis to Foods, 4) Anaphylaxis to Drugs and Biological Agents, 5) Insect Sting Anaphylaxis, 6) Perioperative	Published in 2015 as an update from the previously published 2010 parameters. Systematic literature search was performed in PubMed, CENTRAL, Google Scholar, and Science Direct.	Unreferenced classification guide: “A” (strongest) to ”D” (weakest) [b]	Evidence from the systematic literature search results, in combination with consensus expert opinion and workgroup-identified supplementary documents identified by the workgroup Recommendations evaluated with an unreferenced classification guide: “Strong recommendation” to ”No recommendation” [b]	None reported

Intended users, target population	Intervention and practice considered	Major outcomes considered	Evidence collection, selection, and synthesis	Evidence quality assessment	Recommendations development and evaluation	Guideline validation
		Anaphylaxis: Anaphylaxis before, during, or Immediately after Anesthesia, 7) Seminal Fluid Anaphylaxis, 8) Exercise-induced Anaphylaxis, 9) Anaphylaxis to Subcutaneous AIT Extract (vaccine), 10) Anaphylaxis in Mastocytosis, MMAS, and MCAS, and 11) Unusual Presentations of Anaphylaxis. The specific outcomes considered by the guideline development group were not explicitly reported				

AIT = Allergen immunotherapy; ANZAAG = Australian and New Zealand Anesthetic Allergy Group; ANZCA = Australian and New Zealand College of Anaesthetists; CENTRAL = Cochrane Central Register of Controlled Trials; JTFPP = Joint Task Force on Practice Parameters; MCAS = Mast cell activating syndrome; MMAS = Monoclonal mast cell activating syndrome; NHMRC = National Health and Medical Research Council; RCT = randomized controlled trials.

[a] Detailed description of Levels of Evidence (based on NHMRC levels) and NHMRC grades of recommendation in Appendix 4, Table 4.

[b] Detailed description of the unreferenced recommendation guide in Appendix 4, Table 4.

Appendix 3: Critical Appraisal of Included Publications

Table 3: Strengths and Limitations of Guidelines Using AGREE II[10]

Item	Guideline	
	AANZCA-ANZAAG, 2016[1]	JTFPP, 2015[12]
Domain 1: Scope and Purpose		
1. The overall objective(s) of the guideline is (are) specifically described.	Yes	Yes
2. The health question(s) covered by the guideline is (are) specifically described.	Yes	Yes
3. The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.	Yes	No (but implied)
Domain 2: Stakeholder Involvement		
4. The guideline development group includes individuals from all relevant professional groups.	Yes	Yes
5. The views and preferences of the target population (patients, public, etc.) have been sought.	NR	Yes (Limited)
6. The target users of the guideline are clearly defined.	Yes	Yes
Domain 3: Rigour of Development		
7. Systematic methods were used to search for evidence.	Yes	Yes
8. The criteria for selecting the evidence are clearly described.	No	No
9. The strengths and limitations of the body of evidence are clearly described.	Yes	Yes
10. The methods for formulating the recommendations are clearly described.	No	No
11. The health benefits, side effects, and risks have been considered in formulating the recommendations.	NR	NR
12. There is an explicit link between the recommendations and the supporting evidence.	Yes	Yes
13. The guideline has been externally reviewed by experts prior to its publication.	NR	NR
14. A procedure for updating the guideline is provided.	Yes	NR
Domain 4: Clarity of Presentation		
15. The recommendations are specific and unambiguous.	No	Yes
16. The different options for management of the condition or health issue are clearly presented.	Yes	Yes
17. Key recommendations are easily identifiable.	Yes	Yes
Domain 5: Applicability		

Item	Guideline	
	AANZCA-ANZAAG, 2016[1]	JTFPP, 2015[12]
18. The guideline describes facilitators and barriers to its application.	NR	NR
19. The guideline provides advice and/or tools on how the recommendations can be put into practice.	Yes	NR
20. The potential resource implications of applying the recommendations have been considered.	NR	NR
21. The guideline presents monitoring and/or auditing criteria.	NR	Yes
Domain 6: Editorial Independence		
22. The views of the funding body have not influenced the content of the guideline.	NR	Yes
23. Competing interests of guideline development group members have been recorded and addressed.	NR	Yes

ANZAAG = Australian and New Zealand Anesthetic Allergy Group; ANZCA = Australian and New Zealand College of Anaesthetists; JTFPP = Joint Task Force on Practice Parameters; NR = not reported.

Note: “Not reported” indicates there was insufficient detail provided to be able to firmly conclude the AGREE II criteria was or was not met.

Appendix 4: Main Study Findings and Authors' Conclusions

Table 4: Summary of Recommendations in Included Guidelines

Recommendations, Quality of Evidence and Strength of Recommendations	Quality of Evidence and Strength of Recommendations Grading Systems
AANZCA-ANZAAG, 2016[1]	
Key recommendations relevant to this report are included below. Please refer to the full text for additional recommendations available in the guideline. **Adult Immediate Management:** The guidelines recommend stopping administration of potential anaphylaxis triggers, placing the patient in a supine position (or leg elevation when hypotension is prominent), repeating fluid boluses, and administering epinephrine rapidly. "the recommendation in these guidelines is to use 1 mg of adrenaline every 1 to 2 minutes if required initially with rapid administration of adequate volume resuscitation and the early addition of alternative vasopressors when initial therapy is inadequate [(The adrenaline dosing is consistent with the recommendations in the French guidelines (Level IV evidence, Grade D recommendation)] (p. 5)."[1] "Adrenaline is pivotal in the management of anaphylaxis because of its unique pharmacology. [Level IV evidence, Grade C recommendation]" (p. 6)"[1] "Diagnosis must therefore be rapid, and adrenaline administered early and in adequate doses to optimise outcome [Level V evidence, Grade D recommendation] (p. 7)."[1] "I.M. adrenaline should be considered in the initial management of perioperative anaphylaxis where I.V. 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 [Level I evidence, Grade B recommendation] (p. 7)."[1] "The dose interval of five minutely [for IM epinephrine] has been adopted from the European Academy of Allergy and Clinical Immunology recommendations [Level V evidence, Grade D recommendation] (p. 7)."[1] "The guidelines recommend the initial use of I.V. bolus adrenaline in keeping with other international perioperative anaphylaxis management guidelines. [Grade D recommendation]" (p. 7)."[1] "After three boluses via either the I.V. or I.M. route an adrenaline infusion should be prepared and commenced as early as possible in the clinically appropriate dosage [Level III evidence, Grade D recommendation]" (p. 8)."[1] **Pediatric Immediate Management:** The guidelines note that there is no specific evidence for the management of pediatric perioperative anaphylaxis, and therefore the recommendations are the same as for an adult population. **Adult Refractory Management:** The guidelines recommend an arterial line for cardiovascular monitoring, an ultrasound to assess for pneumothorax, cardiac bypass/ECMO to establish adequate perfusion, and administration of alternative following initial administration of epinephrine. "Levels of evidence for their use [alternative vasopressors] are weaker than for adrenaline and they should only be used following adequate administration of adrenaline and I.V. fluids [Level V evidence, Grade D recommendation] (p. 10)."[1] **Pediatric Refractory Management:**	Levels of Evidence (based on NHMRC levels) [1] **Level I:** Systematic reviews, meta-analysis, randomised controlled trials **Level II:** A randomised controlled trial. **Level III-1:** A pseudorandomised controlled trial. **Level III-2**: A comparative study with concurrent controls (Case-control study) **Level III-3:** A comparative study without concurrent controls Level IV Descriptive studies that include analysis of outcomes (single subject design, case series) **Level V:** Case reports and expert opinion that include narrative literature, review, and consensus statements NHMRC Grades of Recommendation[1] **A:** Body of evidence can be trusted to guide practice **B:** Body of evidence can be trusted to guide practice in most situations **C:** Body of evidence provides some support for recommendation(s) but care should be taken in its application **D:** Body of evidence is weak and recommendation must be applied with caution

Recommendations, Quality of Evidence and Strength of Recommendations	Quality of Evidence and Strength of Recommendations Grading Systems
The guidelines recommend requesting advice from pediatric anaesthetists/intensivists, and the administration of additional treatments from what would be used in adult care.	
JTFPP, 2015[12]	
Recommendation summary statements relevant to this report are included below, along with a high-level summary of other key statements. Please refer to the full text for additional recommendations available in the guideline. **I. Evaluation and Management of Patients with a History of Anaphylaxis** The guidelines recommend evaluating the patient to determine the cause of anaphylaxis, referring the patient to an allergist or immunologist, and supplying the patient with an EAI. "Summary Statement 2: Supply any patient who has experienced an episode of anaphylaxis for which the allergen cannot be easily and completely avoided with an AIE and instructions as to when and how to administer this injector and emphasize that they should carry 2 AIEs with them at all times [Strong Recommendation; C Evidence] (p. 350)."[12] **II. Office Management of Anaphylaxis** The guidelines recommend ensuring staff are appropriately trained and are aware of how to rapidly respond to anaphylaxis. "Summary Statement 11: At the onset of anaphylaxis, (1) administer epinephrine intramuscularly in the mid-outer thigh; (2) remove the inciting allergen, if possible (eg, stop an infusion); (3) quickly assess airway, breathing, circulation, and mentation and summon appropriate assistance from staff members; and (4) start, if needed, cardiopulmonary resuscitation and summon EMS [Strong Recommendation; D Evidence] (p. 358)."[12] **III. Anaphylaxis to Foods** The guidelines recommend providing instruction and information to patients and providing patients with two EAIs. "Summary Statement 27: Recognize that some patients are at high risk for fatal, food-induced anaphylaxis, such as (1) adolescents, (2) patients with a history of reaction, (3) patients allergic to peanut or tree nuts, (4) patients with a history of asthma, (5) those presenting with the absence of cutaneous symptoms, or (6) those with delayed administration of epinephrine [Recommendation; C Evidence] (p. 366)."[12] "Summary Statement 32: Prescribe 2 epinephrine auto-injectors for all patients at risk for food-induced anaphylaxis [Recommendation; B Evidence] (p. 366)."[12] **IV. Anaphylaxis to Drugs and Biological Agents** The guidelines recommend recognizing the presentation of anaphylaxis to various drugs, and to advise patients to carry an EAI. "Summary Statement 40: Because of the risk of anaphylaxis, prescribe an AIE for all patients receiving omalizumab and instruct patients in its use. Advised them to carry it before and 24 hours after their omalizumab injection [Strong Recommendation; D Evidence] (p. 367)."[12] **V. Insect Sting Anaphylaxis** The guidelines recommend ruling out mastocytosis, recognising that diagnosis can not be based on skin and serum testing alone, and recommending VIT for patients with systemic sensitivity to stinging insects. **VI. Perioperative Anaphylaxis: Anaphylaxis before, during, or Immediately after Anesthesia**	Category of Evidence[12] **Ia** Evidence from meta-analysis of randomized controlled trials **Ib** Evidence from at least 1 well-designed randomized controlled trial **Ic** Evidence from at least 1 randomized controlled trial that was not very well designed **IIa** Evidence from at least 1 controlled study without randomization **IIb** Evidence from at least 1 other type of quasi-experimental study **IIc** Evidence from one of the above that was not very well designed **IIIa** Evidence from well-designed nonexperimental descriptive studies, such as comparative studies **IIIb** Evidence from nonexperimental descriptive studies, such as comparative studies, that were not very well designed **IVa** Evidence from expert committee reports and/or opinions or clinical experience of respected authorities Recommendation Rating Scale[12] **Strong recommendation:** A strong recommendation means the benefits of the recommended approach clearly exceed the harms (or that the harms clearly exceed the benefits in the case of a strong negative recommendation) and that the quality of the supporting evidence is excellent (grade A or B)*. In some clearly identified circumstances, strong recommendations might be made based on lesser evidence when high-quality evidence is

Recommendations, Quality of Evidence and Strength of Recommendations	Quality of Evidence and Strength of Recommendations Grading Systems
The guidelines recommend recognizing that perioperative anaphylaxis has greater morbidity and mortality than other forms of anaphylaxis and that is difficult to diagnose. **VII. Seminal Fluid Anaphylaxis** The guidelines recommend diagnosis with skin testing with fresh whole human seminal plasma or its fractions obtained from the male partner, and to instruct patients to have an EAI readily available. "Summary Statement 57: Instruct women with systemic seminal plasma hypersensitivity to have AIE readily available in the event of possible barrier failure with condoms occurs [Strong Recommendation; C Evidence] (p. 376)." [12] **VIII. Exercise-induced Anaphylaxis** The guidelines recommend recognizing that some patients experience exercised-induced anaphylaxis only when cofactors are present, avoiding exercise directly after eating, and that the patient carry two EAIs and exercise with a partner. "Summary Statement 66: Advise all patients to carry 2 epinephrine auto-injectors and exercise with a partner who can recognize symptoms and administer epinephrine [Strong Recommendation; D Evidence] (p. 378)."[12] **IX. Anaphylaxis to Subcutaneous AIT Extract (vaccine)** The guidelines recommend advising patients about the risk of immediate and late-onset reactions, and recognizing pre-existing risk factors for anaphylaxis. **X. Anaphylaxis in Mastocytosis, MMAS, and MCAS** The guidelines recommend recognizing that patients with SM or MMAS are at an increased risk of anaphylaxis, to treat patients in the same way as for a patient with anaphylaxis to a known trigger, and to provide patients with an EAI. "Summary Statement 78: Provide patients with SM, MMAS, and MCAS with AIE to use in the event of anaphylaxis [Strong Recommendation; D Evidence] (p. 381)."[12] **XI. Unusual Presentations of Anaphylaxis** "Summary Statement 79: Be aware that anaphylaxis can present with unusual clinical manifestations such as chest pain and that these patients might require treatment with epinephrine [Recommend; C Evidence] (p. 384)."[12]	impossible to obtain and the anticipated benefits strongly outweigh the harms. **Recommendation:** A recommendation means the benefits exceed the harms (or that the harms clearly exceed the benefits in the case of a negative recommendation), but the quality of evidence is not as strong (grade B or C)*. In some clearly identified circumstances, recommendations might be made based on lesser evidence when high-quality evidence is impossible to obtain and the anticipated benefits outweigh the harms. **Weak:** An option means that the quality of evidence that exists is suspect (grade D)* or that well-done studies (grade A, B, or C)* show little clear advantage to one approach vs another. **No recommendation:** No recommendation means there is a lack of pertinent evidence (grade D)* and an unclear balance between benefits and harms. *Strength of Evidence **A** Directly based on category I evidence that is well designed **B** Directly based on category II evidence or recommendation from category I evidence that is not well designed **C** Directly based on category III evidence or recommendation from category II evidence that is not well designed **D** Directly based on category IV or recommendation from category III evidence that is not well designed **LB** Laboratory based **NR** Not rated

AIE = Auto-injectable epinephrine; AIT = Allergen immunotherapy; ANZAAG = Australian and New Zealand Anesthetic Allergy Group; ANZCA = Australian and New Zealand College of Anaesthetists; ECMO = extracorporeal membrane oxygenation; EIA = Exercise-induced anaphylaxis; EMS = Emergency medical services; IM = intramuscular; IV = intravenous; JTFPP = Joint Task Force on Practice Parameters; MCAS = Mast cell activating syndrome; MMAS = Monoclonal mast cell activating syndrome; NHMRC = National Health and Medical Research Council; NSAID = Nonsteroidal anti-inflammatory drug; RSM = Radiocontrast material; SM = Systemic mastocytosis; SR = Systemic reaction; VIT = Venom immunotherapy.

Note: "Adrenaline" is synonymous with "epinephrine".

Appendix 5: Additional References of Potential Interest

Guidelines with Unclear Methodology

1. ASCIA guidelines: acute management of anaphylaxis. Australasian Society of Clinical Immunology and Allergy; 2019: https://www.allergy.org.au/images/stories/pospapers/ASCIA_Guidelines_Acute_Management_Anaphylaxis_2019.pdf Accessed 2020 Apr 20.

2. BC Centre for Disease Control. Communicable disease control Manual: chapter 2: immunization. Part 3 - management of anaphylaxis in a non-hospital setting; 2019 Feb: http://www.bccdc.ca/resource-gallery/Documents/Guidelines%20and%20Forms/Guidelines%20and%20Manuals/Epid/CD%20Manual/Chapter%202%20-%20Imms/Part_3_Anaphylaxis.pdf Accessed 2020 Apr 20.

Related CADTH Reports

1. Epinephrine auto-injector availability in public settings: clinical effectiveness and guidelines (*Rapid response report: summary of abstracts*). Ottawa (ON): CADTH; 2015 Mar: https://www.cadth.ca/sites/default/files/pdf/htis/mar-2015/RB0803%20Public%20Epinephrine%20Auto-injector%20Final.pdf Accessed 2020 Apr 20.

2. Higher than recommended doses of epinephrine for patients with an allergic reaction: clinical evidence and safety (*Rapid response report: summary of abstracts*). Ottawa (ON): CADTH; 2011 May: https://www.cadth.ca/sites/default/files/pdf/htis/may-2011/RB0354_EpinephrineDosing_Final.pdf Accessed 2020 Apr 20.

3. Different routes of epinephrine for anaphylaxis: clinical efficacy. Ottawa (ON): CADTH; 2008 Jan: https://www.cadth.ca/sites/default/files/pdf/htis/Different%20Routes%20of%20Epinephrine%20for%20Anaphylaxis%20Clinical%20Efficacy.pdf Accessed 2020 Apr 20.