

**Guidelines on autopsy practice:
Autopsy for suspected acute anaphylaxis (includes anaphylactic shock
and anaphylactic asthma)**

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NICE has accredited the process used by The Royal College of Pathologists to produce its autopsy guidelines. Accreditation is valid for 5 years from 25 July 2017. More information on accreditation can be viewed at www.nice.org.uk/accreditation.

For full details on our accreditation visit: www.nice.org.uk/accreditation.

Foreword

The autopsy guidelines published by The Royal College of Pathologists (RCPATH) are guidelines which enable pathologists to deal with non-forensic consent and coroner's post mortems in a consistent manner and to a high standard. The guidelines are systematically developed statements to assist the decisions of practitioners and are based on the best available evidence at the time the document was prepared. Given that much autopsy work is single observer and one-time only in reality, it has to be recognised that there is no reviewable standard that is mandated beyond that of the FRCPath part 2 exam. Nevertheless, much of this can be reviewed against ante-mortem imaging and other data. This guideline has been developed to cover most common circumstances. However, we recognise that guidelines cannot anticipate every pathological specimen type and clinical scenario. Occasional variation from the practice recommended in this guideline may therefore be required to report a specimen in a way that maximises benefit to pathologists, the coroner and the deceased's family.

There is a general requirement from the General Medical Council to have continuing professional development in all practice areas and this will naturally encompass autopsy practice. Those wishing to develop expertise/specialise in pathology are encouraged to seek appropriate educational opportunities and participate in the relevant external quality assessment.

The guidelines themselves constitute the tools for implementation and dissemination of good practice.

The stakeholders consulted for this document were the Human Tissue Authority and its Histopathology Working Group, which includes representatives from the Association of Anatomical Pathology Technology, Institute of Biomedical Science, The Coroners' Society of England and Wales, the Home Office Forensic Science Regulation Unit and Forensic Pathology Unit and the British Medical Association.

The information used to develop this guideline was collected from electronic searches of the medical literature, previous recommendations of the RCPATH, and local guidelines in the United Kingdom and has been graded using modified SIGN guidance (see Appendix A). The sections of these autopsy guidelines that indicate compliance with each of the AGREE II standards are indicated in Appendix B.

No major organisational changes or cost implications have been identified that would hinder the implementation of these guidelines.

A formal revision cycle for all guidelines takes place on a five-year cycle. The College will ask the authors of the guideline, to consider whether or not the guideline needs to be revised. A full consultation process will be undertaken if major revisions are required. If minor revisions or changes are required, a short note of the proposed changes will be placed on the College website for two weeks for members' attention. If members do not object to the changes, the short notice of change will be incorporated into the guideline and the full revised version (incorporating the changes) will replace the existing version on the College website.

These guidelines have been reviewed by the Clinical Effectiveness Department, Death Investigation Group, Immunology Specialty Advisory Committee and Lay Governance Group. This document was placed on the College website for consultation with the membership from 25 April 2018 to 23 May 2018. All comments received from the membership were addressed by the author to the satisfaction of the Clinical Director of Clinical Effectiveness.

These guidelines were developed without external funding to the writing group. The College requires the authors of guidelines to provide a list of potential conflicts of interest; these are monitored by the Clinical Effectiveness Department and are available on request. The authors of this document have declared that there are no conflicts of interest.

1 Introduction

Anaphylaxis kills by either shock or asphyxia. These typically occur with no other signs of an allergic reaction. Consequently, anaphylactic shock is likely to be misdiagnosed as myocardial infarction. Shock in hospital is usually rapid (median: five minutes) and associated with arrhythmia and pre-existing cardiac disease. Outside hospital, it is typically slower (median: 15 minutes), often with pulseless electrical activity and a healthy heart. Myocardial ischaemia is very probable (almost inevitable) in shock deaths, which may therefore be mistaken for primary myocardial infarction. Furthermore, food and aspirin anaphylaxis are likely to be misdiagnosed as fatal asthma. Asphyxia may be due to asthma (most common for food allergy or non-steroidal anti-inflammatory drug [NSAID]/aspirin sensitivity) or laryngeal oedema (most common for stings). Death may be delayed for up to three hours, for example after ingestion of NSAIDs.

1.1 Target users of these guidelines

The target primary users of these guidelines are consultant pathologists performing coronial post-mortem examinations. The recommendations will also be of value to trainee pathologists, especially those considering the Certificate of Higher Autopsy Training (CHAT).

2 Role of the autopsy

To determine whether on the balance of probability there is:

- morbid anatomical evidence to support the suspected anaphylaxis and its timing
- evidence of other pathological conditions that could account for death or contributed to death
- biochemical evidence suggestive of anaphylaxis
- serological evidence of the agent (i.e. any medication or food taken immediately and up to one hour prior to collapse, or any sites of stinging or biting invertebrates [e.g. wasp or bees stings]) responsible for initiating anaphylaxis, if possible.

[Level of evidence – GPP.]

3 Pathology of anaphylaxis encountered at the autopsy¹⁻⁵

- Often there is little or nothing specific to see, grossly or histopathologically.
- There may be laryngeal (or pharyngeal, or other upper airway) oedema.
- Pulmonary oedema, if present, may indicate epinephrine (adrenaline) overdose.
- Mucus plugging and hyper-expansion of the lungs may indicate an asthmatic crisis or anaphylactic fatal asthma.
- If the patient was resuscitated, survived but then died in intensive care, much additional pathology may supervene.

[Level of evidence D – the evidence has been taken from reviews of various texts/case reports and other presented cases in medical and legal settings.]

4 Specific health and safety aspects

None.

5 Clinical information relevant to the autopsy

- The complete medical notes, with statements from witnesses as to the final events at collapse, if witnessed.
- Evidence to suggest poorly controlled asthma, e.g. due to under-treatment or recent exacerbation.
- Previous history of food, drug or insect sting allergy or asthma aggravated by NSAIDs (these patients usually have nasal polyps).
- Any medication or food taken immediately prior to collapse, or any wasp or bee sting.
- The complete drug schedule, with times, doses and routes of administration.
- Circumstances of body and surroundings if death not witnessed.
- Time of death with respect to any suspected reaction.
- Whether the patient had cardiopulmonary resuscitation/cardiac defibrillation or details of resuscitation, if relevant.

[Level of evidence – GPP.]

6 The autopsy procedure²

- Careful external examination, which includes searching for sites of stinging or biting invertebrates (e.g. wasp or bee stings) if there is reason for suspicion.
- Perform complete autopsy examination with blood, vitreous and urine collection.
- Examine stomach contents, particularly if anaphylaxis related to food is suspected.
- Examine the site of emergency epinephrine (adrenaline) injection, if known, and determine skin-to-muscle depth for comparison with length of injector needle.

[Level of evidence – GPP.]

7 Specific significant organ systems to be considered^{1,3-6}

- Lung, larynx and airways examination for significant oedema (often difficult to identify after death, even if recognised during attempted resuscitation).
- Lung for evidence of acute asthma (airway plugging and eosinophilia) and/or chronic asthma (airway remodelling, basement membrane thickening, mucinous metaplasia, bronchial wall inflammatory cell infiltrate).
- Nasal sinuses for evidence of extensive nasal polyps, which would support a likely diagnosis of NSAID-intolerant asthma in the presence of a suitable history (Samter's triad).
- Coronary arteries and heart for contributory ischaemic heart disease (myocardial ischaemia is an inevitable consequence of anaphylactic shock, even with normal coronary arteries).
- During coronary artery stenting, some patients may suffer allergic reaction to anti-clotting drugs or materials incorporated into the stent; this may also lead to local thrombosis from hypotension.

[Level of evidence D – the evidence has been taken from reviews of various texts/case reports and other presented cases in medical and legal settings.]

8 Organ retention

None specifically required.

9 Histological examination¹⁻⁷

This should include:

- heart – note contraction band necrosis that may reflect inotropic resuscitation measures. Use trichrome and phosphotungstic acid haematoxylin stains to assess fibrosis and ischaemic damage.
- coronary artery (decalcified sections ideally)
- lung with airways
- vocal cord mucosa (longitudinal sections through larynx).

[Level of evidence D – the evidence has been taken from reviews of various texts/case reports and other presented cases in medical and legal settings.]

10 Toxicology

Serum drug levels should be reported, e.g. for aspirin, opiates, paracetamol, alcohol.

11 Other samples required^{8,9}

Note: Extreme caution is required in interpreting post-mortem tryptase levels. The advice of an experienced allergist or immunologist is required to avoid false-positive or false-negative interpretations. Anaphylaxis can occur without detectable tryptase in blood.

- Urgently seek any ante-mortem blood specimens (in pathology laboratories) before they are discarded. Serum tryptase is stable in blood so, in a deceased patient from whom further sample collection is impossible, serum, heparinised or ethylenediaminetetraacetic acid-treated plasma may be analysed.
- Cadaveric blood, preferably taken from a femoral artery, should be centrifuged and sent for mast cell tryptase (MCT) measurement. Tryptase is a stable analyte; samples should always be taken, even if the autopsy is done days, or even weeks, post mortem. Tryptase concentrations can be increased by cell autolysis or liquefaction, thus careful interpretation of the results is essential.
- The site of sampling for tryptase measurements post mortem is important because, in individual patients, there may be marked differences between the tryptase results in samples from the aorta, subclavian artery and femoral artery. It is preferable, therefore, that post-mortem samples for tryptase are taken from femoral blood vessels; in any case, the site of sampling should be specified on the request form.
- Note that MCT is not always raised in anaphylaxis, and may be moderately raised for other reasons, such as major trauma or following prolonged cardiopulmonary resuscitation. Serum tryptase concentration can also be raised in systemic mastocytosis, some myelodysplastic syndromes, mast cell leukaemia and end-stage renal failure.
- Serum tryptase concentrations of greater than 100 µg/L in a post-mortem sample¹⁰ would be consistent with anaphylaxis contributing to, or being the cause of, death provided there are relevant clinical or post-mortem findings.

- Serum tryptase concentrations of greater than 50 µg/L, in a sample taken within an hour of the onset of symptoms, would be consistent with anaphylaxis (provided other causes e.g. systemic mastocytosis have been excluded). However, a normal serum tryptase concentration cannot completely eliminate the possibility of an anaphylactic reaction.
- Blood taken post mortem may be useful for the measurement of specific IgE antibodies to the allergen(s) implicated in the suspected reaction. These may include some drugs (e.g. penicillin), foods (e.g. peanut, fish, etc.) or venoms (e.g. bee or wasp venom). The allergens must be carefully selected according to the pre-test probability, led by the history and, if necessary, expert consultation before testing from an allergist or immunologist with relevant experience. It is inappropriate to request a wide selection in the hope of identifying the causative allergen. The results of any specific IgE testing must be interpreted with caution; specific IgE even to the causative allergen may be low or undetectable after a severe reaction and positive results cannot prove causation. However, results can add to the 'balance of probability' if interpreted in the context of the clinical history.
- Analysis of gastric contents may allow identification of drugs and foods recently ingested. Immediate visual inspection is essential.
- Your local immunology department should be able to advise you on sample collection, suitability and result interpretation. Many immunology departments provide tryptase and other measurements. Specialist advice on samples and interpretation is available at the Supraregional Protein Reference Unit at St George's Hospital London and Northern General Hospital Sheffield. Local centres with expertise in drug or other allergies can be found at the British Society for Allergy and Clinical Immunology website using their clinic database.

[Level of evidence D – the evidence has been taken from reviews of various texts/case reports and other presented cases in medical and legal settings.]

12 Imaging

The utility of post-mortem cross-sectional imaging (PMCSI) is expanding as experience and expertise in this field develops. There is some published evidence to support the use of PMCSI as an adjunctive modality in suspected cases of anaphylaxis (e.g. to identify acute airway oedema prior to evisceration)¹¹ and in the investigation of known or suspected specific pathology (e.g. sudden cardiac death).¹²

Access to appropriate imaging facilities and expertise does vary around the country but where they are available, the use of PMCSI as an adjunct to standard autopsy should be supported.

13 Modes of death in anaphylaxis⁴

- Cardiac arrest secondary to peripheral vasodilation and myocardial ischaemia.
- Asphyxia and respiratory arrest due to upper airway oedema, lower airway mucus plugging or aspiration of vomit.
- Delayed deaths: coma due to hypoxic encephalopathy, respiratory failure due to pneumonia.
- Subsequent cardiac pathology as a consequence of the anaphylaxis.

[Level of evidence D – the evidence has been taken from reviews of various texts/case reports and other presented cases in medical and legal settings.]

14 Clinicopathological summary

The following should be documented:

- the gross and histological findings
- blood MCT
- other serological investigations, if carried out
- the clinical sequence of events, to identify any possible culprits.

On the balance of probabilities (civil standard) it should be decided whether:

- the death was reasonably attributable to anaphylaxis and, if possible, which agent or drug was responsible
- raised blood MCT indicates anaphylaxis (especially if there is a dynamic increase from a baseline sample), in which case discuss with an allergist or clinical immunologist to determine if the death was caused by other natural or unnatural conditions
- normal blood MCT excludes fatal anaphylaxis (especially asthmatic and food-related), in which case discuss with an allergist or clinical immunologist where the history is suspicious for anaphylaxis
- the cause of death cannot be ascertained.

15 Examples of cause of death opinions/statements

- Anaphylactic shock.
- Allergy to penicillin.

16 Criteria for audit

The following standards are suggested criteria that might be used in periodic reviews to ensure a post-mortem report for coronial autopsies conducted at an institution complies with the national recommendations provided by the 2006 National Confidential Enquiry into Patient Outcome and Death (known as NCEPOD) study:¹³

- supporting documentation:
 - standards: 95% of supporting documentation was available at the time of the autopsy
 - standards: 95% of autopsy reports documented are satisfactory, good or excellent
- reporting internal examination:
 - standards: 100% of autopsy reports must explain the description of internal appearances
 - standards: 100% of autopsy reports documented are satisfactory, good or excellent
- reporting external examination:
 - standards: 100% of autopsy reports must explain the description of external appearances
 - standards: 100% of autopsy reports documented are satisfactory, good or excellent.

A template for coronial autopsy audit can be found on the Royal College of Pathologists website (www.rcpath.org/clinical-effectiveness/clinical-audit/clinical-audit-templates/cellular-pathology-audit-templates.html).

17 References

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Appendix A **Summary table – Explanation of grades of evidence**
(modified from Palmer K *et al. BMJ* 2008;337:1832)

Grade (level) of evidence	Nature of evidence
Grade A	<p>At least one high-quality meta-analysis, systematic review of randomised controlled trials or a randomised controlled trial with a very low risk of bias and directly attributable to the target population</p> <p>or</p> <p>A body of evidence demonstrating consistency of results and comprising mainly well-conducted meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a low risk of bias, directly applicable to the target population.</p>
Grade B	<p>A body of evidence demonstrating consistency of results and comprising mainly high-quality systematic reviews of case-control or cohort studies and high-quality case-control or cohort studies with a very low risk of confounding or bias and a high probability that the relation is causal and which are directly applicable to the target population</p> <p>or</p> <p>Extrapolation evidence from studies described in A.</p>
Grade C	<p>A body of evidence demonstrating consistency of results and including well-conducted case-control or cohort studies and high-quality case-control or cohort studies with a low risk of confounding or bias and a moderate probability that the relation is causal and which are directly applicable to the target population</p> <p>or</p> <p>Extrapolation evidence from studies described in B.</p>
Grade D	<p>Non-analytic studies such as case reports, case series or expert opinion</p> <p>or</p> <p>Extrapolation evidence from studies described in C.</p>
Good practice point (GPP)	<p>Recommended best practice based on the clinical experience of the authors of the writing group.</p>

Appendix B AGREE II compliance monitoring sheet

The guidelines of The Royal College of Pathologists comply with the AGREE II standards for good quality clinical guidelines. The sections of these autopsy guidelines that indicate compliance with each of the AGREE II standards are indicated in the table below.

AGREE II standard	Section of guideline
Scope and purpose	
1 The overall objective(s) of the guideline is (are) specifically described	Foreword
2 The health question(s) covered by the guideline is (are) specifically described	Foreword, 1
3 The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described	Foreword, 1
Stakeholder involvement	
4 The guideline development group includes individuals from all the relevant professional groups	Foreword
5 The views and preferences of the target population (patients, public, etc.) have been sought	Foreword
6 The target users of the guideline are clearly defined	1
Rigour of development	
7 Systematic methods were used to search for evidence	Foreword
8 The criteria for selecting the evidence are clearly described	Foreword
9 The strengths and limitations of the body of evidence are clearly described	Foreword
10 The methods for formulating the recommendations are clearly described	Foreword
11 The health benefits, side effects and risks have been considered in formulating the recommendations	n/a
12 There is an explicit link between the recommendations and the supporting evidence	2–15
13 The guideline has been externally reviewed by experts prior to its publication	Foreword
14 A procedure for updating the guideline is provided	Foreword
Clarity of presentation	
15 The recommendations are specific and unambiguous	2–15
16 The different options for management of the condition or health issue are clearly presented	2–15
17 Key recommendations are easily identifiable	2–15
Applicability	
18 The guideline describes facilitators and barriers to its application	Foreword
19 The guideline provides advice and/or tools on how the recommendations can be put into practice	Foreword
20 The potential resource implications of applying the recommendations have been considered	Foreword
21 The guideline presents monitoring and/or auditing criteria	16
Editorial independence	
22 The views of the funding body have not influenced the content of the guideline	Foreword
23 Competing interest of guideline development group members have been recorded and addressed	Foreword