



Guidelines on autopsy practice: Autopsy when drugs or poisoning may be involved

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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 five 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/or other data. These guidelines have 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 these guidelines may therefore be required to report a specimen in a way that maximises benefit to the coroner and the deceased's family.

There is a general requirement from the General Medical Council to have continuous 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 scheme.

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 document was derived from current medical literature and a previous version of the guideline. Much of the content of the document represents custom and practice, and is based on collective substantial clinical experience amongst the consultant authors. All evidence included in these guidelines have been graded using modified SIGN guidance (see Appendix A). The sections of this document 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 Death Investigation Group, Toxicology Special Advisory Committee, Lay Governance Group and Clinical Effectiveness department. This document was placed on the College website for consultation with the membership from 25 April 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

This document was created to address the needs of the non-forensic autopsy pathologist dealing with deaths in which drugs, poisons or toxins may be involved, but which have nonetheless been deemed non-suspicious. Consequently, these deaths do not require a special (forensic) post mortem on behalf of the coroner (and, where appropriate, also by the police and any other relevant investigating authorities).

Drug and poisoning deaths pose unique challenges for the following reasons:

- the initial suspicion for a drug in the first place is largely dependent on the circumstances provided to the pathologist
- the focus of the autopsy is both to exclude a morphological cause of death and investigate pathological consequences of drugs and toxins
- one of the most important purposes of the autopsy is to obtain samples for further investigation
- there may be limited natural disease present, but significant toxin-related disease, particularly in younger people
- the toxicology findings may not be reported for several weeks after the body itself has been interred or cremated
- the laboratory findings may be non-contributory
- the drugs and toxins may have been administered by a third party. In such cases, the post mortem should be performed as a forensic post mortem by a forensic pathologist. It must be noted that information available at the time of post mortem may subsequently change – and then a third party might be implicated, thus the importance of an accurate, detailed internal and external examination is highlighted.

As such, all potential drug deaths should be carried out with high suspicion. The pathologist should be prepared to decline to commence the post mortem and seek further advice when necessary.

Although experience will be gained of common drug deaths, each post-mortem service should be served by a toxicology laboratory that can offer advice and support when it is needed.

1.1 Target users of these guidelines

The target primary users of these guidelines are pathologists performing coronial post mortems. If there is any question of a toxicological involvement in the death the case must be referred to the coroner who will decide whether a coroner's autopsy is required. The recommendations will also be of value to trainees, particularly those approaching the Certificate of Higher Autopsy Training examination. These guidelines are not aimed at and do not claim to cover the investigation of deaths that are deemed suspicious by the relevant investigating parties. Such cases should be conducted as a special (forensic) post mortem by a suitably trained forensic pathologist working to guidelines developed for such suspicious scenarios.

[Level of evidence – Good practice point (GPP).]

2 Role of the autopsy

- To establish whether death is related to a drug or toxin or another process (e.g. positional asphyxia/pneumonia, or a combination of both).
- To establish the pathological consequences of drug or toxin use or misuse.
- To establish if any traumatic injuries were a consequence of previous drug use.
- To establish if there was any natural disease that might have increased susceptibility to the effects of a drug or toxin.
- To consider if the toxicity could have been treated such as to prevent death.
- To obtain appropriate samples for toxicological analysis.

[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.]

3 Information required prior to autopsy

Before undertaking a post-mortem examination, the pathologist should be briefed by the coroner's officer or other parties involved in the investigation. Every examination must be approached with an open mind. However, the initial approach to the examination will rely heavily on any information provided. It is therefore important that the final report contains pertinent details of the history of the case and the source of the information.

The importance of a thorough history cannot be overemphasised. The following information aids any post-mortem examination and, when available, should be provided to the pathologist by the coroner's officer or be sought in the available medical records before the post mortem commences.

3.1 Scene of death

This should include:

- full details of the scene of death (indoors/outdoors, temperature, exposure)
- how the body was discovered
- security of the scene
- place, posture and clothing of the body
- presence/absence of needles, syringes, medicine containers and pills
- provisional description of the body, including injuries (if any)
- identity of person discovering the dead person.

3.2 Circumstances of death

This should include:

- witness statements (coroner's officer, police)
- previous medical history (coroner's officer, ambulance notes, general practitioner [GP], hospital clinical notes)
- medical therapy regimen – current and prior (GP, hospital clinical notes, pharmacist)

- previous surgical operations and other interventions (GP, hospital clinical notes, family members)
- alcohol usage ± illicit drug use (coroner's officer, police, relatives and friends)
- previous imprisonment and date of release from prison (GP, coroner's officer, police)
- if there are multiple deaths (e.g. 'suicide pact') – the circumstances found at the scene should direct the pathologist on which examinations are appropriate, which may differ between the bodies, e.g. one death may be drug related, the other traumatic
- known or suspected blood-borne virus status, e.g. HIV, HBV, HCV (GP, clinical notes)
- family history (relatives, GP)
- electrocardiogram (ECG), enzyme results and other pathological data (GP, clinical notes)
- serum lipid profiles and other biochemical tests (GP, clinical notes, internal laboratory results).

[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.]

3.3 Possible sources of this information

Pertinent information (and samples for further analysis) may be available from a variety of sources and this list is not exhaustive. However, common sources of this material are listed below.

3.3.1 Death in community

- Coroner's officer's report.
- Pre-hospital clinician notes (known as PRFs); these come in electronic and two different paper versions.
- GP clinical notes (including past investigations and prescription records).

3.3.2 Death in hospital

- Admission bloods (always preferable to post mortem).
- Urine sample if catheter in situ (may require pre-arrangement with ward).
- Laboratory investigations (arterial blood gas, ECG, imaging, etc).
- Clinical notes (including nursing, prescription charts and paramedic notes).
- Coroner's officer's report.

3.4 Information to be included in the 'History' section of the pathologist's report

Depending on the coroner, the final autopsy may contain varying levels of history and information relating to the circumstances of the death. However, all relevant information should be recorded and available to the pathologist and other interested parties for future reference. It is advisable for the pathologist to include sufficient information to ensure that their own report is adequate as a standalone document. This is so the reader is aware of the context in which the examination was performed and to aid recall at inquest.

4 Health and safety precautions

Mortuaries will have their own local guidelines for dealing with potentially hazardous or infectious cases and the approach taken in suspected drug deaths will vary in line with these. In all cases, the pathologist conducting the post mortem should assess the risks posed by the case and ensure the post mortem is conducted in such a way as to minimise any risk to the pathologist themselves and to all other parties involved. Risk assessment is crucial and use of personal protective equipment is mandatory. Adequate mortuary ventilation is also required and use of downflow mortuary tables is recommended for high-risk cases.

It should be remembered that intravenous drug users (IVDUs) are at an increased risk of hepatitis, HIV and tuberculosis, as well as opportunistic infections if their immune system is compromised.

4.1 Chemicals

Many industrial activities involve the use of toxic chemicals. Companies involved in such work should have full assessments regarding the Control of Substances Hazardous to Health (known as COSHH) for any chemicals they use, but this may not always be the case. In addition, a variety of chemicals can be purchased and used for various purposes including suicide. These agents may be colourless and odourless. A high level of suspicion is needed to detect them before mortuary staff or others are exposed to lethal levels.

In particular, if there is a history of cyanide ingestion, or exposure to hydrogen sulphide, extreme caution is required as the cyanide is converted to the poisonous gas hydrogen cyanide in the stomach, which may be fatal if inhaled. It is worth noting that not everyone can smell cyanide.¹

In cases involving toxic chemicals, the possibility of environmental contamination should also be considered.

It may be that the lead pathologist will be asked to provide safety advice in such cases. This should only be provided if that pathologist is competent to provide such information. Otherwise, resources such as the National Poisons Information Service (NPIS)² or the Centers for Disease Control and Prevention (CDC) website³ may provide useful information.

However, if there is any doubt that the post mortem can be conducted and the body disposed of in a suitable way, the post mortem should not be conducted and the case should be referred to an appropriately equipped mortuary with the correct expertise to deal with such a case.

[Level of evidence – GPP.]

5 Imaging

5.1 Post-mortem imaging

Imaging to determine the possibility of body packing, for the documentation of trauma or for other reasons peculiar to any particular case may be indicated in suspected drug-related deaths. If such imaging studies are felt necessary, access to local service provision should be sought prior to the commencement of the autopsy.

In addition, the role of post-mortem cross-sectional imaging (PMCSI) is expanding as experience and expertise in this field develops. There is clear evidence⁴⁻⁶ to support the use of PMCSI in suspected drug-related deaths. If the history, scene examination, external examination and laboratory results as well as the PMCSI images together support a

diagnosis of drug-related death, then such a cause of death may be provided without the need for an invasive post mortem; however, this is at the discretion of the coroner or other investigating authority. Access to appropriate imaging facilities and expertise to make such a diagnosis does vary around the country, but when available their use should be supported in appropriate circumstances assessed on a case-by-case basis following the criteria used for other prospective PMCSI cases.

5.2 Photography

It is highly desirable to have facilities available to photograph any findings of particular interest.

[Level of evidence – GPP.]

6 External examination

6.1 Clothing

Ideally, clothing should be left in situ. However, this is often not the case in practice, particularly if the deceased has been admitted to hospital prior to death. Any clothing should be documented and a note made of any drug paraphernalia in pockets or on the person. Be careful when checking the pockets as needles may be present.

6.2 External examination

Once items of clothing are removed, a thorough external examination is required looking for signs of recent and chronic misuse of drugs.

Recent signs include needle puncture marks, powder and frothy blood-tinged fluid from the mouth or nose, faecal or urinary soiling, petechia (ears, mouth, chin and forehead), vomitus, recent bruising and injury. Make sure there is no foreign body within the mouth and no injury to the back.

Chronic signs of drug use include perforated nasal septum, thrombophlebitis, self-harm marks, recent bruising or injury.

The features listed in sections 6.2.1–6.2.5, while non-specific, are associated with drug and chronic alcohol abuse, and these should be specifically checked for.

6.2.1 General

- Identification – especially important to note in cases of decomposition/trauma how identification was made, as well as the chain of identification to the point of autopsy.
- Malnourished, unkempt.
- Recent injury.
- Needle puncture marks.
- Chronic injection sinuses.
- Evidence of previous/current self-harm.
- Examination of mouth, anus, vagina and under foreskin for evidence of body packing.
- Signs of resuscitation (cannulas, LUCAS mark, ECG stickers) – may explain presence of needle puncture marks.
- Skin abscess ('skin popping').

- Track hyperpigmentation.
- Scars/'homemade' tattoos.
- Bright red hypostasis – associated with carbon monoxide poisoning or hypothermia – as well as any other tissue/skin discolouration that may suggest evidence of poisoning.
- An abnormal pattern of hypostasis (particularly head or torso dependent) should prompt contemplation of so-called postural/positional asphyxiation while intoxicated and/or incapacitated, as the physical signs are not specific and this potential mode of dying is easily overlooked without an index of suspicion.
- Always check the back for any of the above.

6.2.2 Chest/abdomen

- Spider naevi (superior vena cava distribution).
- Gynaecomastia.
- Abdominal distension (ascites).
- Bruising/caput medusae.
- Haemorrhoids.
- Testicular atrophy.

6.2.3 Face

- Jaundice (sclera and skin).
- Nasal septum perforation (cocaine).
- Necrosis of nasal tip (endocarditis).
- Blood-tinged froth around mouth/nose (pulmonary oedema).
- Abnormal coating on tongue.
- Foreign body in mouth or nose.
- Unlike in life, pupil size is rarely of value after death owing to rigor mortis of intrinsic eye muscles.

6.2.4 Limbs

- Peripheral oedema.
- Erythema over joints (hypothermia).

6.2.5 Hands

- Clubbing, nicotine staining, splinter haemorrhages (infected endocarditis).
- Dupuytren's contracture
- Palmar erythema.

[Level of evidence – GPP.]

7 Internal examination

Complete evisceration and examination of the organ systems should be conducted as standard.

The internal findings listed in sections 7.1–7.6 are non-specific but can be associated with drug use.

7.1 Cardiovascular system

- Dilated cardiomyopathy (ethanol).
- Infective endocarditis (uncommon; more likely right sided).

7.2 Gastrointestinal system

Invert the oesophagus to look for pills or signs of lacerations from violent retching (Mallory-Weiss tears). Varices are difficult to demonstrate post mortem owing to collapse of venous circulation. Chronic haemorrhagic gastritis is a well-known consequence of ethanol abuse.

It is unlikely that the ingestion of medications will cause marked gastric changes as these drugs are often designed to minimise such effects. By contrast, ingestion of chemicals such as paraquat will often result in marked necrosis and inflammation of mucosa.

The pancreas may show signs of acute haemorrhagic pancreatitis (a potential cause of death) or chronic pancreatitis, often owing to chronic ethanol abuse. In practice this is often difficult to assess owing to haemorrhagic autolytic changes and histology is recommended if there is doubt.

The liver may be obviously steatotic or cirrhotic in cases of chronic hepatitis or alcoholic liver disease. It is not possible to rule out more uncommon causes of liver disease macroscopically and histology should be taken where possible to rule out more unusual diseases such as hereditary haemochromatosis, particularly in at-risk populations.

The intestines should be fully opened whenever 'drug packing' might reasonably be suspected (custodial deaths, death in a nightclub or recent travel from another country). Assess for any evidence of mucosal discolouration.

When removing the intestines, check for segments of infarcted bowel (due to hypotension or emboli).

Other potential findings include:

- cirrhosis/fatty liver (ethanol)
- upper gastrointestinal haemorrhage from gastritis, gastric erosions, Mallory-Weiss tears
- intestinal ischaemia
- pancreatitis.

Consequences of cirrhosis (and subsequent portal hypertension) include:

- splenomegaly
- oesophageal varices
- spontaneous bacterial peritonitis
- increased cancer risk associated with chronic alcohol abuse (hepatocellular, oesophageal, oral, pharyngeal).

7.3 Central nervous system

The head should be opened and examined in all cases to exclude trauma or occult bleeding and to demonstrate hypoxic change. This includes examination of the sinuses and dural stripping.

The brain may show cerebral oedema demonstrated by increased weight, flattening of gyri and filling of sulci. If oedema is extreme, herniation may occur.

Other potential findings include:

- abscess, meningitis, mycotic aneurysms, empyema (subdural or epidural)
- cerebellar atrophy
- bilateral symmetric necrosis of the globus pallidus (associated with heroin)
- subdural haemorrhage (trauma)
- subarachnoid haemorrhage (if pre-existing berry aneurysm/weakness)
- Wernicke-Korsakoff syndrome (thiamine deficiency in alcoholics; mammillary body atrophy and haemorrhage)
- central pontine demyelination (associated with rapid rehydration and hyponatraemia).

7.4 Musculoskeletal system

Intoxicated individuals are more prone to trauma and are at higher risk of assault. Possible findings include:

- fractures
- osteoporosis
- infectious spondylitis and sacroiliitis (IVDU)
- thrombophlebitis (IVDU)
- myositis ossificans in the brachialis muscle (IVDU).

7.5 Respiratory system

Removal of the tongue along with the other neck structures is important; look for signs of tongue biting (seizure activity), airway obstruction and gross congestion of the pharynx (anaphylaxis).

The lungs may show massive pulmonary oedema, characterised by increased weight (weigh pre-dissection). There is an increased tuberculosis risk in homeless populations (see section 4: Health and safety precautions) and pneumonia is associated with chronic alcohol abuse.

7.6 Genitourinary system

The bladder should be removed and examined in all cases; urinary retention is associated with psychoactive substances, such as MDMA or amphetamine, and incontinence associated with seizure activity.

Other potential findings include:

- bladder distension (MDMA)
- urinary incontinence (seizure activity)

- urinary retention (anti-cholinergic drugs)
- haemorrhagic cystitis (ketamine).

[Level of evidence – GPP.]

8 Sampling: toxicology

8.1 When to take toxicology specimens

Toxicology samples are best taken before any significant disruption of the body has occurred from the autopsy, even if it is later decided that toxicology testing is not required. In non-forensic settings, post-mortem toxicology is generally taken:

- where death is very likely to be due to a drug
- where no cause of death is found at autopsy
- death by suicide/misadventure with the possibility of impaired reasoning
- where it is necessary to exclude toxicology as a likely cause of death
- any case where there is deprivation of liberty
- where poor compliance may have contributed to death (e.g. antiepileptic medication).

8.1.1 What samples should be taken?⁷

All samples collected should be submitted to the toxicology laboratory. Close collaboration between the pathologist and toxicologist is necessary to ensure the right samples are taken, and that these are correctly preserved and submitted. Practices may differ slightly between toxicology laboratories; thus, liaison should occur before an autopsy is undertaken, e.g. if starting work in a new mortuary/hospital.

The name of the individual who collected the samples must be recorded.

The site from which each sample is taken must be recorded.

Sampling has barely changed since the seminal guidelines of the 1990s⁸ but most toxicology laboratories will accept the samples listed below.

Currently, although point of care testing capacity may be available in some clinical settings, such analysis is not considered to have been sufficiently validated, in the autopsy setting, to be recommended.

Blood

The ideal samples are ante-mortem blood samples. The coroner has the power to seize any such samples in England and Wales. Caution may be required with ante-mortem samples as the gels used in many serum gel tubes may absorb drugs and thus affect the blood concentration.

In most post-mortem cases, blood remains the single most important specimen to analyse. In the UK, cardiac samples tend not to be taken but are useful for screening if there is minimal peripheral blood. Interpretation of the quantification of drugs in cardiac blood is more prone to the effects of post-mortem redistribution than peripheral blood. In addition, the published data used to aid quantitative interpretation is generally based upon analysis of peripheral blood, rather than cardiac.

Toxicology laboratories are moving towards more sensitive analysers and so the volume of blood required is reducing, but at present, at least 10 ml peripheral blood (femoral or iliac

access) is suggested. The evidence for clamping prior to sampling is variable. Often such volume (10 ml) may not be available and so as much as practical has to be accepted. Sodium fluoride/potassium oxalate (preferably 2% w/v) should be used as a preservative unless there is suspicion of poisoning with fluoride or a fluoride-producing compound exists.

All samples must be collected in separate containers. For most specimens, disposable hard plastic or glass tubes are recommended.

Samples should be stored at a maximum temperature of 4°C when analysed promptly after autopsy. Otherwise they should be stored at -20°C. When liquid specimens are to be frozen, it is recommended to leave a small (10–20%) headspace in the specimen tubes.

Urine

If practical, at least 20 ml urine should be collected in post-mortem cases. If catheter urine is sent, this is acceptable but it should be recorded as such. The use of fluoride as a preservative is encouraged.

Analysis of the drug concentration in urine (or its presence or absence) may give some idea of timescale between drug ingestion and the time of death.

Urine should be collected into a clean universal container by creating a nick in the upper anterior fundus, or by aspiration with a 20 ml needle and syringe.

Vitreous humour

Samples should be collected routinely in appropriate cases. At present, vitreous humour is used primarily to quantitate ethanol, urea, electrolytes and beta hydroxybutyrate. As toxicology analysers become more sensitive, there is a growing database for vitreous drug concentrations, but these are not yet routine tests.

Glucose analysis may be useful to exclude hypoglycaemia, and hence insulin excess, but the glucose will fall rapidly post mortem, so caution is required with interpretation.

All vitreous humour from both eyes should be collected; however, it can be collected into a single container. Following removal, the shape of the eyes can be restored by injecting water. If this has occurred, it should be recorded in case of a second autopsy requiring repeat sampling.

Gastric contents

Oral ingestion remains a common route of exposure to drugs and poisons. However, the most important investigation is the observation of undigested pills and tablets. If these are present, they should be separated and placed into plastic pillboxes for analysis.

There are only a few toxicology laboratories in the UK that will now routinely screen or quantify drugs in gastric content, the reasoning being that the drugs do not have a pharmacological effect if they are in the stomach.

Stomach content is heterogeneous. If only an aliquot of stomach content is collected, the total volume/weight should be recorded. Quantitative measurement and a knowledge of the volume enables the total amount of the drug of interest in the stomach to be calculated, but this may overestimate drug concentration if the aliquot contains drug debris.

One caveat is that if cardiac/central blood is being quantified, there is the possibility that drugs may redistribute from the gastric content into blood after death.

Other samples

- Bile – can be a useful for screening (but not quantitation) if no other samples are available.
- Liver (deep within right lobe) – can be useful for screening but quantitations are hampered by poor databases of reference values.
- Muscle – can be useful for screening but quantitations are hampered by poor databases of reference values. There is much debate around which muscle should be sampled, but the psoas muscle is normally used. The source of the sample should be recorded.
- Injection site (skin) – may be useful in determining the type of substance that has been injected, such as insulin or heroin. Again, it is rarely required but needs to be considered. Always send a control site sample for comparison.
 - To sample the injection site, excise a wide skin ellipse, down to subcutaneous tissue. Place the specimens in clean, labelled universal containers.
 - If the specimen is for histology, add neutral buffered formalin. When fixed, examine and serially slice; if a tract is not identified, submit the entire specimen for histological examination. Otherwise, do not fix the specimen; instead, send the specimen immediately to the laboratory.
- Lung tissue – approximately 2 cm cubed, sealed either in a glass airtight container or universal wrapped in parafilm, may be useful.
- Bone marrow – may be analysed qualitatively where only skeletonised remains are recovered, however, few laboratories offer this analysis.
- Hair analysis – has no direct link to the cause of death. Hair grows at about 1 cm per month (on the posterior vertex), thus hair samples may be of limited value in determining whether drugs have been taken in the few days prior to death. It is rarely taken or required for most coroner's investigations. However, examination of hair can be useful in the following situations:
 - to assess claim of a drug-facilitated sexual offence prior to death
 - to provide long-term information on drug compliance or abstinence
 - to assess previous use in drug users with abstinence, loss of tolerance and relapse
 - chronic heavy metal poisoning.

Hair samples – should be collected before the body is opened to avoid contamination of the hair with body fluids. The sample should be cut from the posterior vertex region of the head, as close as possible to the scalp, since this is the region of least variation in growth rate. If not, the source of the sampling should be described.⁹

Specify which end of the hair bundle is the cut end by tying a piece of cotton or string around the hair at that end, then wrap in an inert covering such as aluminium foil.

8.1.2 Scenarios for toxicology analysis

Ideal sampling for most therapeutic and illicit drugs includes:

- ante-mortem samples (blood and urine)
- post-mortem femoral/iliac venous blood
- post-mortem urine
- vitreous (preferably fluoride oxalate preserved).

Carbon monoxide cases require:

- ante-mortem samples (blood)

- post-mortem femoral/iliac venous blood.

Volatile compounds are poorly detected in blood, so ideally the following should be sampled:

- lung tissue (approximately 2 cm cubed), sealed either in a glass airtight container or universal wrapped in parafilm
- brain tissue (approximately 2 cm cubed), sealed either in a glass airtight container or universal wrapped in parafilm.

Heavy metals cases require:

- ante-mortem samples (blood and urine)
- post-mortem femoral/iliac venous blood.

Note that hair is often required to investigate chronicity.

Insulin overdose cases should consider the following:

- insulin and glucose degrade rapidly post mortem, which can cause issues in accurately measuring concentrations. The assay for insulin in the UK is only an immunoassay and post-mortem work on insulin analysis is still minimal. If required, samples can be sent abroad.
- ideally, a fluoride oxalate vitreous sample will be obtained for glucose analysis
- blood should be sampled from a peripheral vein as soon as possible, ideally before any dissection, and separated by centrifugation with the serum component frozen immediately prior to analysis (haemolytic enzymes will destroy insulin rapidly). There is some work on vitreous insulin and C-peptide, but this is not yet routinely available.

Rare poisoning cases should consider the following:

- if there is an unusual poisoning suspected it is worth contacting either your local toxicology laboratory or NPIS for further advice. Indeed, it is worth contacting your local laboratory with any queries.

8.1.3 Summary

If requesting toxicology, always test for a panel. Again, it is vital to liaise with the local toxicologist to determine what compounds are analysed as standard, and which require specific additional requests, or will need to be sent away for analysis. It is advised that before requesting analyses, which may need to be sent away, the coroner is informed so they are aware of the cost implications.

A 'fatal' level of a drug may not be the causative agent (particularly in long-standing addicts) and may mask overdose from another unsuspected drug, particularly novel psychoactive substances.

If you encounter a suspected death involving drugs, illicit or otherwise, the following steps should be taken:

- take, as standard, blood, vitreous fluid and urine
- request drugs of abuse panel and ethanol levels – be familiar with the local panel
- be prepared if investigation comes back negative; is there other supporting evidence?
- be prepared if an unsuspected drug is found; does this correlate with clinical history and post-mortem findings? If not, consider referring to the findings in the report but without ascribing particular significance to it.

- there is limited value in carrying out post-mortem toxicology if a patient has been in hospital more than 24 hours (barring drug error cases), but ante-mortem samples are valuable in this scenario.

[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.]

8.2 Extent of toxicology screens

8.2.1 The role of the toxicologist and referral laboratory

Pathologists should be aware of:

- what specific drugs or metabolites are tested for in standard drugs of abuse panels
- whether the laboratory is ISO accredited (15189 + ILAC 19/9 or 17025 + ILAC 19/9)
- what happens when a requested drug is not on the panel
- cost of off-site referral
- specific samples required.

8.2.2 What information to provide the toxicology laboratory

The investigation of a death involving suspected drugs, illicit or otherwise, is very much a cooperative effort between the pathologist and toxicologist. The information made available to the pathologist by the coroner's office (G5/Sudden Death Report/coroner's referral document) should also be made available to the toxicologist.

Toxicology involves not just the identification and quantification of drugs in the body, but interpretation of the results. The most qualified person to do this is usually the toxicologist.

However, while the toxicologist can comment on whether levels of a drug are those required to cause significant harm or death, they can only assist the pathologist in the formulation of the cause of death (which is usually, however, only 'preliminary' in coroner's cases as at inquest the coroner will finalise the cause of death).

The pathologist has the obligation to provide the best possible samples in the best conditions and with good information regarding the circumstances of the case.

For qualitative documentation of a particular substance at the time of death, at a minimum, the post-mortem interval and site sampled should be given.

However, if the candidate drug is suspected to have directly caused or contributed to death, then quantitation is more likely to be required and the more information provided, the more helpful the analysis is likely to be. With sufficient background information, it may be possible to arrive at an explanation as to why death occurred at a specific concentration of drug, even if levels are below the reference lethal range.

Information of relevance to interpretation of toxicological data:

- sex, age, body habitus, state of decomposition
- occupational history, if relevant (industrial, agricultural)
- medical history (particularly drugs of abuse and medications)
- symptoms, if any (length, onset)
- estimated interval since drug taken (if suspected overdose)
- circumstantial evidence (empty bottles, packets, powder, note)

- main pathological findings at autopsy and impression
- post-mortem interval before samples were obtained and date and time of sampling
- high-risk group (IVDU) or known notifiable disease
- name, address and telephone number of pathologist.

If there has been a delay in submitting or transporting the samples, it is useful to note the condition in which they have been stored (refrigeration, deep freeze).

8.2.3 Interpretation of results

The autopsy pathologist and toxicologist must view the results in light of the clinical, scene and post-mortem findings. This goes beyond the remit of this autopsy practice guideline. The toxicologist's opinion on the likely contribution to death should be provided in their report. However, it is the pathologist's responsibility to provide a medical cause of death when autopsy has been carried out.

Most post-mortem toxicology data relies on small case studies and individual reports in the literature. These are well summarised in the standard toxicology textbooks^{10,11} and larger databases based on, for example, femoral blood samples.¹²

There are minimal pharmacokinetic data on illicit drugs, and individuals often do not know the doses they are taking. Although there is some pharmacokinetic analysis carried out before therapeutic drugs are allowed to be prescribed, there is a lot of variation that may be caused by:

- sex, age, body habitus
- genotype/genetic polymorphisms
- fast/slow metabolisers
- whether taken on a full or empty stomach
- natural disease
- other concurrent substance (may accentuate or inhibit effects)
- tolerance
- dose of drug
- purity of drug.

If the toxicological findings raise the index of suspicion that a death is due to an adverse reaction to a prescription medicine, whether in normal clinical use or in cases of deliberate or inadvertent overdose, this should be reported via the recognised Yellow Card Scheme (<https://yellowcard.mhra.gov.uk/>).

8.2.4 Summary

- The results of toxicology should be interpreted in light of the clinical history and circumstances.
- There is often considerable variation between reference tables.
- The biological effect of a particular concentration of a drug varies between individuals, and is dependent on other factors such as tolerance. The LD50 is a research device used by pharmacologists and toxicologists to compare toxicity between drugs in animal models. It is inappropriate to use it in a clinical context where there are too many variables between individuals and unknowns.
- Attempts to back-calculate dosage from levels at post mortem should not be made.

- The pathologist's role is to obtain samples and, with the help of the clinical toxicologist and coroner's officer, evaluate all non-toxicological data to see if they can modify circumstances enough to allow an explanation of death.

[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.]

9 Sampling: histology

Histology is of value in confirming, evaluating and sometimes revising the course of natural disease processes. It is important that any natural disease in the deceased is well documented so any possible role it played in the cause of death is known.

The Coroners (Amendment) Rules 2005 require the pathologist to retain material which, in their opinion, has a bearing on the cause and circumstances of the death.¹³

Any sampling must be within the limits of consent in the case of a consented autopsy or within the limits of the relevant medico-legal legislation and guidelines, if the case is of a medico-legal nature.

Examples of histology and possible findings in a drug death are listed in sections 9.1–9.6.

9.1 Lung (at least one piece per lobe)

- Confirmation of pneumonia versus pulmonary oedema (macroscopic inspection is unreliable).
- Aspiration pneumonia, inhalation of vomit, presence and effect of injected material.
- Emphysematous changes (smoking).
- Marked anthracosis (cannabis).
- Septic pulmonary abscesses.
- Tuberculosis (IVDU).
- Perivascular pulmonary talc granulomas (IVDU).
- Foreign body emboli (IVDU).
- Pulmonary necrotising angitis (IVDU).
- Atelectasis, fibrosis (smoking, cannabis).¹⁴

9.2 Kidney (one piece per kidney)

- Glomerulosclerosis, amyloid (IVDU).
- 'Cocaine' nephropathy (cocaine).

9.3 Cerebrum and cerebellum (particularly hippocampus, cerebral cortex and dentate nucleus)

- Evaluation of hypoxic/ischaemic neuronal damage.

9.4 Heart (as per cardiac death guidelines)

- Evidence of 'cocaine' cardiomyopathy (cocaine).
- Left ventricle – fibrosis, contraction bands, ischaemic heart disease (cocaine).
- Right ventricle – hypertrophy secondary to cor pulmonale (IVDU).
- If conduction anomaly suspected, refer to cardiac death guidelines and consider referral of heart to cardiac pathologist.

9.5 Liver (one piece, away from capsule)

- Assessment of fatty liver/cirrhosis and investigation of aetiology (especially in those of a younger age).
- Investigation of hepatitis (viral, alcohol, other).
- Talc granulomas (IVDU).

9.6 Additional histology samples according to case

- Skin injection sites, if determining presence and their age is critical (IVDU).
- Quadriceps and psoas muscle, if rhabdomyolysis suspected (ecstasy/opiates).

In all cases, the histological sampling required must be guided by the clinical judgement of the pathologist conducting the case and guided by the specific requirements of that case. In cases with medico-legal implications, tissue should ideally be retained until the coroner completes their investigations.

[Level of evidence – GPP.]

10 Sampling: organ retention

While there is no specific role for organ retention in a death from suspected illicit drugs, these deaths tend to occur in a younger population than the average post mortem and may demonstrate limited natural pathology at autopsy. By the time a negative toxicology report has been received, the opportunity to identify subtler causes of death may be lost.

The pathologist should keep an open mind when reading the clinical history for conditions such as cardiac abnormalities or epilepsy, which may require referral for expert opinion.

Where appropriate, these organs should be sampled as per their respective guidelines if no other pathology is identified at post mortem.

[Level of evidence – GPP.]

11 Clinicopathological correlation

It is advisable for the pathologist to include sufficient information to ensure that their own report is adequate as a standalone document.

Non-forensic pathologists commonly encounter potential drug deaths in the following situations:

- where death is very likely to be due to a known drug ('overdose')
- where death is by suicide/misadventure with possibility of impaired reasoning by drugs
- in 'negative' autopsies
- where death is due to natural disease that has arisen as a result of drug use.

In potential overdose situations, it is important to consider whether the reported symptoms prior to death match the putative drug. Just because a drug or its metabolites have been identified does not mean the level is necessary fatal or exclude the effects of another unsuspected drug.

In cases of suicide or misadventure, the cause of death may be obvious (e.g. hanging or drowning). However, intoxication may have played a role prior to death and, in these situations, may be listed under part two in the cause of death.

Natural diseases that arise from drug abuse are myriad and it is beyond the scope of this document to list them all. The effects may be the result of cumulative injury (alcohol cirrhosis) or a consequence of a transient effect of the drug (aortic dissection due to transient hypertension from cocaine).

It may not be possible to prove such findings resulted directly from drug use; however, it is acceptable to use past medical history and information available at the time of autopsy to make an informed interpretation provided the source of information is noted.

There may be a lag from the use of a drug to the eventual cause of death and this raises the question of whether drug use should be listed as the cause of death if death resulted from, for example, the consequences of HIV contracted from needle sharing many years ago. There are social consequences to listing this in the death certificate. In many cases, the source may not be known. For this reason, it is advisable to list a drug as the cause of death only if it has a direct proven causality. It is acceptable to list prior drug use in part two of the certification. In all cases, care should be taken to minimise distress.

In situations where drug use has resulted directly in impaired consciousness with subsequent complications e.g. aspiration pneumonia, the drug may still be considered a direct cause of death and should be included in part one of the death certificate. Toxicology may not be informative in these cases but the history will be indicative.

[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.]

11.1 Examples of causes of death

Direct toxic effects leading to death are difficult to demonstrate, require circumstantial information and toxicology, and do not require long-standing use. These include:

- transient hypertension (cocaine)
 - intracerebral haemorrhage
 - aortic dissection
 - acute cardiac necrosis
- arrhythmia
- cardiorespiratory depression (opiates, ethanol, antidepressants)

- biochemical imbalance (including ‘water overdose’ in ecstasy).

Subacute direct toxic effects of a drug may be fatal. The inciting drug itself may not be detectable. These effects include:

- pulmonary oedema
- hypoxic encephalopathy
- aspiration of gastric contents and inhalational pneumonia.

Chronic indirect effects due to previous or current long-standing drug use include:

- natural disease arising due to drug use
 - cirrhosis (alcohol)
 - cardiac fibrosis (amphetamine and cocaine abuse)
- infective endocarditis and mycotic aneurysm
- HCV, HBV and HIV infection
- pulmonary hypertension
- injection abscess
- secondary amyloidosis.

[Level of evidence – GPP.]

12 The negative autopsy

“The absence of injuries, evidence of poisoning, lethal infection or well-recognised natural disease is in itself significant negative evidence.”

- Saukko P, Knight B. *Knight’s Forensic Pathology (4th edition)*. Boca Raton, USA: CRC Press, 2015, page 15.¹⁵

Many deaths caused by suspected illicit drugs do not show significant pathology at the time of autopsy. This may be partially due to the younger age of these patients; the elderly are more likely to have existing natural disease that is significant to count as a cause of death ‘on the balance of probabilities’.

As there is always the risk that toxicology may come back negative, it is advisable to take full histology and toxicology samples in cases where a likely cause of death is not identified at autopsy.

Negative autopsies are not a sign of failure on the part of the pathologist but rather confidence that any reasonable natural death has been routinely excluded. The documentation of absence of significant other findings is in itself an important negative finding. Of all deaths, 5% are unascertained.

Death may be due to apnoea/central nervous system depression or biochemical imbalances. Alcohol may be associated with alcoholic cardiomyopathy/sudden death in association with alcohol misuse and other cardiac functional abnormalities. These are difficult to demonstrate on histology and if toxicology is negative or not permitted, the pathologist may be left with a conundrum.

The pathologist has the duty of candour; if significant natural disease is not identified, or is unlikely to be sufficient to cause death, it is best to be clear about this in the report rather than giving the impression of more certainty than is warranted. Attempts to ascribe more significance to minor findings simply because the toxicology has come back negative should be avoided.

It should be noted that under guidance by the General Medical Council there is a duty of candour to release information about a person who has died in order for the death certificate to be completed 'honestly and fully', thus the presence of matters such as the role of drugs in the death must be fully disclosed if felt relevant. There is also a duty to assist the coroner in doing the same at inquest.

[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.]

13 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 comply with the national recommendations provided by the 2006 National Confidential Enquiry into Patient Outcome and Death (known as NCEPOD) study:¹⁶

- clear rationale for taking toxicology:
 - standards: 95% of supporting documentation was available at the time of the autopsy
 - standards: 95% of autopsy reports documented are satisfactory, good or excellent.
- 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 appearance
 - 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 appearance
 - 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/profession/quality-improvement/conducting-a-clinical-audit/clinical-audit-templates.html).

14 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 cancer type</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 this autopsy guideline 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 | 1–12 |
| 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 | 1–12 |
| 16 The different options for management of the condition or health issue are clearly presented | 1–12 |
| 17 Key recommendations are easily identifiable | 1–12 |
| 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 | 1–12 |
| 20 The potential resource implications of applying the recommendations have been considered | Foreword |
| 21 The guideline presents monitoring and/or auditing criteria | 13 |
| 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 |