# Investigating infectious diseases at autopsy

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## Abstract

Autopsy has a central role in diagnosing severe infectious diseases of all types: virus, prions, bacteria, mycobacteria, fungi, protozoa and helminths. The majority can be identified using histopathology – with special stains and immunohistochemistry - which is an essential part of the autopsy. In addition, cytology, microbiology culture and molecular diagnostics, serology and urine antigen testing are important adjuncts. This review encompasses a general overview of infectious autopsies, recommends working practices, and highlights the scenarios of HIV, post-transplantation and post-vaccine deaths, and rabies.

**Keywords** Autopsy; Cytology; Histopathology; HIV; Infections; Sepsis; Transplantation; Vaccination

## Introduction

Autopsy work – whether medico-legal or consented/hospital autopsies – frequently involves examination of cadavers with infectious diseases. Most of those infections encountered pose no significant risk to mortuary staff, but some are potentially serious, and a few are so virulent and dangerous that routine autopsy is effectively banned.

The categorisation of infectious hazards across all areas of Medicine is regulated by the Health and Safety Executive's (HSE) Advisory Committee on Dangerous Pathogens (ACDP).[1] The schedule is regularly reviewed and updated in the light of global epidemiological trends. All agents across the globe are considered, not just those prevalent in the UK. Since international travel is the norm, people with a potentially lethal infection can now travel from any one country to any other within 24 h, and present ill or moribund to a heathcare centre; and some people die shortly after receiving travel-related vaccination.

There are four Hazard Groups of infectious biological agents, categorised along three considerations:

- the likelihood that it will cause disease by infection or toxicity in humans
- how likely it is that the infection would spread to the community
- the availability of any prophylaxis or treatment.

Table 1 presents the definitions and examples of such infections.

Applying sensible universal precautions, the risk of infection with most of the HG2 & 3 agents is small during autopsy work; for further information on safe working practice in the mortuary, consult the forthcoming RCPath guideline.[2] It includes information on appropriate vaccination schedules for APTs and pathologists.

This review does not include the well-known protocols for dealing with possible infection in SUDI/SIDS deaths or with the transmissible encephalopathies. Infections encountered in the UK mortuaries in all other scenarios, and how to approach their investigation are the main topic.

## Before the autopsy: when to suspect an infectious disease

The information presented to pathologists includes – ideally - the recent and past clinical history, laboratory test data, indications of immunocompromise states, and travel history.

Whilst we tend to parcel patients into the binary groups of 'normal' and 'immunocompromised', in reality there is a broad spectrum. Damaged immune systems means malfunctioning innate, antibody-mediated, and cell-mediated immunities, often in combination. Table 2 lists the causes of these states, which enhance infection intensities, and alter their gross and histomorphology.

Another clinical history clue to infection is a foreign travel history. *'Under venis?'* [where have you come from?] is the question, since many severe infections cannot be acquired in north-west Europe (including leishmania and histoplasmosis). There is much available diagnostic serology for parasitic and fungal infections, which will often have been performed before death. Gathering all the available microbiology data is critical for evaluating possible infectious deaths. However, it does not generally have to be done before commencing the autopsy; the standard practice in such autopsies is to sample all relevant organs (and blood as necessary), so the pre-mortem test data can be acquired afterwards. This is important since post-mortem autolysis is the enemy of good histo-morphology, the bedrock of infection diagnostics at autopsy: do not delay the autopsy unnecessarily.

The list is not exclusive, but other scenarios of death raise the probability of significant infection: intravenous drug injection habit, chronic fibrosing and industrial lung disease, people from Africa and Asia (higher risk of tuberculosis), the homeless and the emaciated. Deaths during pregnancy and around delivery are commonly related to sepsis (*E. coli* during the second trimester, and *Strep. pyogenes* in the third) and require detailed examination.[3]

'Severe sepsis' syndromes: systemic sepsis is common, but over-diagnosed clinically. In addition to clinical suspicion, laboratory tests such as raised CRP and low platelets are evidence for sepsis. About one third of genuine sepsis cases have negative microbiology (due to prior antibiotic administration). Pathologically, systemic sepsis manifests a systemic inflammatory response syndrome (SIRS), with characteristic haemophagocytosis (in marrow and liver Kupffer cells), lymphoid atrophy, enhanced expression of intercellular adhesion molecule-1 (ICAM-1) in endothelial cells on histology, and sometimes disseminated intravascular coagulation (DIC).[4] But so do the non-infection-related autoinflammatory syndromes which are now more widely recognised.[5,6] One of the commoner, causing rapid multi-organ failure from SIRS, and mimicking sepsis, is adult onset Still's disease (AOSD). A major role for the autopsy in modern medicine is the discrimination of the common systemic

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## Hazard group (HG) definitions

Group 1 — Unlikely to cause human disease.
Group 2 — Can cause human disease and may be a hazard to employees; it is unlikely to spread to the community and there is usually effective prophylaxis or treatment available.
*HG 1 & 2 are the common infections in human medicine (virus, bacteria, fungus, protozoan, helminth), as well as the more esoteric:* e.g. *legionellosis, nocardiosis, amoebiasis, non-tuberculosis mycobacteria.*
Group 3 — Can cause severe human disease and may be a serious hazard to employees; it may spread to the community, but there is usually effective prophylaxis or treatment available. *The most commonly encountered are the non-A viral hepatitides, HIVs, tuberculosis and other mycobacteria, imported fungal infections such as histoplasmosis, and transmissible encephalopathies.*
Group 4 — Causes severe human disease and is a serious hazard to employees; it is likely to spread to the community and there is usually no effective prophylaxis or treatment available. *The imported viral infections in HG 4 — such as Ebola and Lassa fevers — are only autopsied under exceptional circumstances, and are not considered further here.*

**Table 1**

sepsis deaths from the rarer autoinflammatory syndromes; it is important to feed back these diagnoses to the treating doctors, for their audit and practice improvement. This requires close attention to the histopathology of SIRS, particularly the presence of haemophagocytosis (Figure 1).

A final note on cadaveric imaging: in the realm of infectious diseases: primary diagnostic cadaveric imaging has no role to play. Pre-death imaging provides clues to undiagnosed significant infections, but there is no infection scenario where a cadaveric CT or MRI scan can diagnose or exclude a particular infection.

## The aetiologies of immunocompromised states

1. HIV-related impairment of cell-mediated immunity (CMI)
2. Congenital immune disorders:
   a Chronic granulomatous disease
   b Hyper-IgE syndrome
   c Severe combined immunodeficiency
   d X-linked hyper-IgM syndrome
   e Wiskott-Aldrich syndrome
   f Di George syndrome
   g Common variable immunodeficiency
   h Defects in the interferon-γ-interleukin -12 axis
   i Myeloperoxidase deficiency
3. Burns
4. Diabetes mellitus
5. Sickle cell disease (HbSS and HbSC genotypes)
6. Cystic fibrosis
7. Chronic renal failure and dialysis
8. Liver cirrhosis of any cause
9. Malignancies per se, e.g. leukaemia and lymphoma
10. Iatrogenic damage to the immune system:
    a Cancer chemotherapy treatments
    b Transplantation and anti-rejection regimes
       i Solid organ
       ii Bone marrow allograft
    c Specific immunosuppressive therapy (e.g. anti-TNF)
    d Steroid therapy
    e Intensive care organ support systems, including vascular catheter lines and ECMO
11. Old age, with resultant impaired CMI

**Table 2**

## Pathology encountered at autopsy

This review is cannot depict in detail the pathology of all the infections encountered at autopsy. It highlights some of the gross and histo-morphological features of infections that cause diagnostic problems in the UK.

### External findings suggesting an infection

Skin and subcutis: a generalised erythematous rash (common in bacteraemias) or petechial haemorrhages (vasculitis or

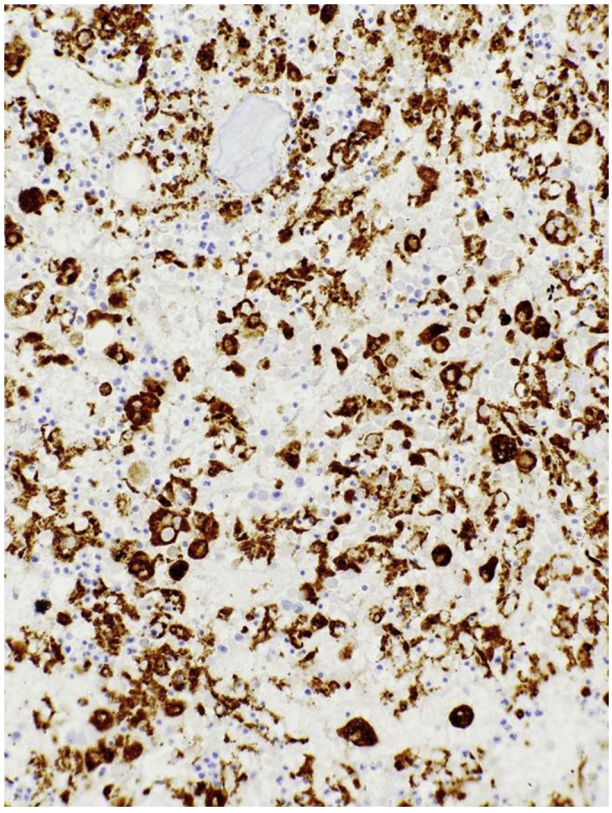

**Figure 1** Haemophagocytosis in bone marrow highlighted by CD68 macrophage stain — this is a constant feature of SIRS.




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