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Sudden Natural Death: Infectious Diseases

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Abstract

A large number of sudden and unexpected deaths are caused by infections. Bacterial and viral infections remain the most common causes of sudden death from infectious diseases. Sudden deaths resulting from infectious causes involving the cardiovascular system are commonly reported due to myocarditis and infective endocarditis while sudden deaths involving the respiratory system are mostly due to pneumonia and tuberculosis. Detailed medicolegal investigation is warranted in sudden deaths due to infectious diseases involving a thorough autopsy and histopathological evaluation along with the use of microbiology and molecular diagnostic methods.

Introduction

Death occurring from a natural cause within hours of the onset of symptoms in an apparently healthy individual is referred to as sudden. Sudden death thus is an unexpected fatal event that very often is unwitnessed. Many of these deaths occur during sleep or at an unknown time. There is no consensus on the exact duration between the onset of symptoms and death for an unexpected fatal event to be considered sudden in nature. The most acceptable definition of sudden death is given by the World Health Organization, which defines sudden death as any death occurring within 24 h from the onset of symptoms (Saukko and Knight, 2004). Cardiovascular system disorders are reported as the leading causes of sudden deaths. Despite advances in medicine regarding the diagnosis and treatment of infectious diseases, a large number of sudden and unexpected deaths are caused by infections. Sudden deaths resulting from infectious diseases remain a cause of concern, especially in the developing countries (Mittal *et al.*, 2014).

Infectious Diseases and Infectious Agents

“An infectious disease is a disease that is caused by the invasion of a host by agents whose activities harm the host's tissues (i.e., they cause disease) and can be transmitted to other individuals (i.e., they are infectious)” (Understanding Emerging and Reemerging Infectious Diseases, see ‘Relevant Websites’). Infections/infectious diseases are thus caused by the invasion and multiplication of various pathogenic macro- and microorganisms in host tissues. The process usually involves an agent, reservoir, port of exit, mode of transmission, port of entry, and host. These infectious agents include: bacteria, viruses, viroids, and prions, rickettsiae, mycoplasmas, fungi, protozoa, helminths, etc. Various etiological agents and a few common infections caused by them are listed in Table 1. Bacterial and viral

infections remain the most common causes of sudden death from infectious diseases. Infections by prions, rickettsiae, and mycoplasmas are usually not associated with sudden and unexpected deaths.

Organ System Involvement and Cause of Death in Infections

Sudden deaths can result from infectious diseases involving any of the body's systems. The infectious diseases which are commonly associated with increased morbidity and mortality are human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS), pneumonia, tuberculosis, and myocarditis. Death from infectious diseases may occur as a direct consequence of the infection or from complications in an immunosuppressed host. Sudden deaths from infectious diseases are mostly reported in the acute phases of infection, and are due to secondary infections in an immunocompromised host. For example, in adult HIV infections, sudden death may result from infective causes due to opportunistic infections. Untreated/undiagnosed infectious diseases of a chronic nature also form a major portion of reported sudden deaths, especially in developing countries. Sudden death due to infectious

Table 1 Etiological agents and common infectious diseases

Agent	Infectious diseases
Metazoa	Schistosomiasis, ascariasis, and hook worm infestation
Protozoa	Pneumocystis pneumonia, toxoplasmosis, amoebiasis, and malaria
Fungi	Candidiasis, aspergillosis, and histoplasmosis
Bacteria	Tuberculosis, diphtheria, tetanus, and <i>Staphylococcus</i> infection
Rickettsia	Typhus fever and Rocky Mountain spotted fever
Viruses	HIV, influenza, rabies, measles, and rubella
Prions	Creutzfeld–Jacob disease

Table 2 Organ system involvement, common infections causing sudden deaths, and causative infectious agents

Organ system/infection	Infectious agent
Cardiovascular system	
Myocarditis	Coxsackie A and B, Picornaviruses, <i>Neisseria meningitides</i> , <i>Chlamydia pneumoniae</i> , <i>Corynebacterium diphtheriae</i> , <i>Mycobacterium tuberculosis</i>
Infective endocarditis	<i>Staphylococcus aureus</i> , <i>Haemophilus parainfluenzae</i> , <i>Candida albicans</i> , HACEK group of rare bacteria ^a
Respiratory system	
Pneumonia	<i>S. aureus</i> , <i>Haemophilus influenzae</i> , <i>Pseudomonas aeruginosa</i> , <i>Pneumocystis carinii</i> , SARS, RSV, influenza and parainfluenza virus
Tuberculosis	<i>M. tuberculosis</i>
Central nervous system	
Meningitis	<i>H. influenzae</i> , <i>Streptococcus pneumoniae</i> , <i>N. meningitides</i> , <i>Cryptococcus</i>
Encephalitis	HSV-1, <i>Toxoplasma gondii</i> , and <i>Plasmodium falciparum</i>
Gastrointestinal system	
Enterocolitis	<i>Vibrio cholerae</i> , <i>Escherichia coli</i> , <i>Clostridium perfringens</i> , and <i>Entameba histolytica</i>
Peptic ulceration	<i>Helicobacter pylori</i>

^aHACEK: *Haemophilus aphrophilus*, *Actinobacillus actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella corrodens*, *Kingella kingae*.

disease may be categorized based on the organ system involvement. The common infectious causes of sudden death based on organ system involvement are listed in [Table 2](#). Though no organ system is spared by infectious agents, the majority of sudden deaths from infectious causes are due to cardiovascular system and respiratory system involvement. In the pediatric population infections of the respiratory, gastrointestinal, and central nervous system account for the majority of cases of sudden death.

Sudden deaths resulting from infectious causes involving the cardiovascular system are commonly due to myocarditis and infective endocarditis. Myocarditis is a major cause of sudden unexpected death in young adults. Infectious causes of myocarditis include bacteria, viruses, and helminths ([Magnani, 2006](#)). Infective endocarditis, however, is mostly of bacterial origin. Sudden deaths involving the respiratory system are mostly due to bacterial infections causing pneumonia and tuberculosis. Sudden death due to viral involvement of the respiratory system may be due to fulminant viral pneumonitis or bacterial pneumonia complicating an initial viral pneumonitis. Similarly the common causes of sudden death from central nervous system involvement are meningitis and encephalitis, which can be bacterial, viral, or fungal in origin.

Bacterial Causes of Sudden Death

Bacteria are unicellular prokaryotic organisms. These are broadly grouped into Gram-positive and Gram-negative groups based on their cell wall structures and Gram stain reaction to it. Common Gram-positive bacteria are *Staphylococcus aureus* (skin, respiratory, and wound infections) and *Clostridium tetani* (tetanus). Some of the Gram-negative organisms are *Salmonella typhi* (typhoid fever), and *Yersinia pestis* (plague).

Table 3 Characteristic granulomatous lesions in infectious diseases of the myocardium

Infection	Characteristic granulomatous lesion
Tuberculosis	Caseating granulomatous inflammation and Langhans' giant cells
Syphilis	Necrosis surrounded by granulation tissue, sparse epithelioid cells
Rheumatic fever	Aschoff bodies
Fungal	Granuloma with/without necrosis, hyphae, and yeasts may be present

Bacterial infections can involve any organ system and cause sudden unexpected deaths in all age groups.

Cardiovascular System

Common bacterial causes of myocarditis include *Corynebacterium diphtheria* (diphtheric myocarditis) and *Neisseria meningitides*. Bartonella-induced silent myocarditis has also been described as a cause of sudden unexpected cardiac death. In infections from *Borrelia burgdorferi*, cardiac involvement occurs in 1–8% of the cases and death is attributed to conduction disturbances. [Wesslen et al. \(2001\)](#) suggested that Bartonella-induced silent subacute myocarditis may eventually lead to electric instability and sudden unexpected cardiac deaths. Granulomatous myocarditis is another rare disease of the heart that is reported in tuberculosis ([Kanchan et al., 2010](#)), syphilis, tularemia, brucellosis, and fungal infections. The mechanism of death includes arrhythmias, cardiac rupture, coronary occlusion, obstruction to pulmonary blood flow leading to fatal hemorrhage, and impaired myocardial contractility. Characteristic granulomatous lesions in infectious diseases of the myocardium are shown in [Table 3](#).

Chlamydial infection has also been associated with endocarditis, myocarditis, and pericarditis (Odeh and Oliven, 1992). *Chlamydia pneumoniae* is considered an unusual cause of myocarditis and sudden unexpected death.

In infective endocarditis, the most common sites of infection are the aortic and mitral valves, except in the intravenous drug abusers, where the right-sided valves are primarily affected. Sudden death in infective endocarditis occurs due to perforation of a free wall myocardial abscess or rupture of a valve leaflet. *Staphylococcus aureus* is responsible for 10–20% of these cases and is the major cause of death in intravenous drug abusers. Other bacterial causes include *Hemophilus*, *Actinobacillus*, *Cardiobacterium*, *Eikenella*, and *Kingella* (HACEK group). Tertiary syphilis causing aortitis may cause sudden death from rupture of aortic aneurysms with aortic dissection. The mechanism of death is either blood loss with hypovolemic shock or a fatal cardiac tamponade from intrapericardial rupture.

Respiratory System

Lobar pneumonia (Figure 1) and confluent bronchopneumonia are the most frequent causes of sudden death from acute pulmonary disease. Approximately 90–95% of lobar pneumonia is due to *Streptococcus pneumoniae* (type 3). Bronchopneumonia is caused by *Staphylococci*, *Streptococci*, *Haemophilus influenzae*, *Pseudomonas aeruginosa*, and coliform bacteria. Legionnaire's disease, caused by *Legionella pneumophila*, a facultative intracellular organism, is associated with outbreaks of sudden death. It causes severe pneumonia in the elderly, smokers, and in immunocompromised patients.

Pulmonary tuberculosis (Figure 2) is another frequent cause of sudden death, especially in developing countries (Kanchan *et al.*, 2012). Tuberculosis is caused by *Mycobacterium tuberculosis*, and it may cause hemoptysis, resulting in hypovolemic shock and sudden death. Though tuberculosis is restricted to the lungs in the



Figure 2 Pulmonary tuberculosis: Cut section of the lung showing tuberculous caseation (courtesy of Dr. Ramadas Naik, Professor of Pathology, Yenepoya Medical College, Mangalore, India).

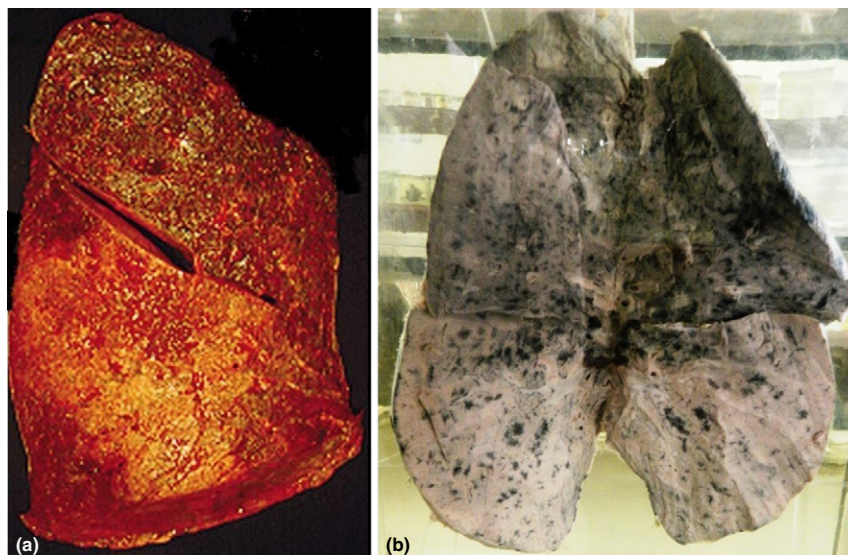


Figure 1 Lobar pneumonia: (a) Left lung showing consolidation of the lower lobe (courtesy of Dada, M.A., Lazarus, N.G., 2005. Sudden natural death: Infectious diseases. In: Payne-James, J. (Ed.), Encyclopedia of Forensic and Legal Medicine, first ed., vol. 4. Oxford: Elsevier Ltd., pp. 229–236. (b) Cut section showing gray hepatization of the lower lobe of the lung (courtesy of Dr. Ramadas Naik, Professor of Pathology, Yenepoya Medical College, Mangalore, India).

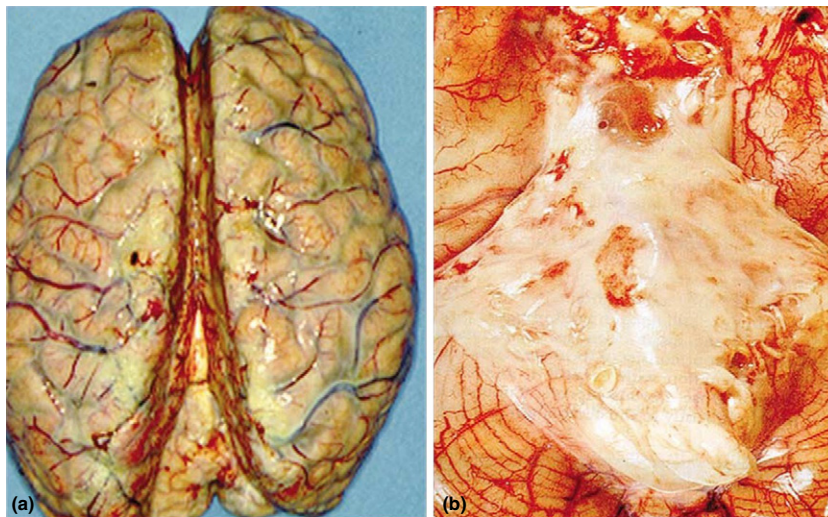


Figure 3 Bacterial meningitis: presence of exudate over convexities and base of the brain (courtesy of Dada, M.A., Lazarus, N.G., 2005. Sudden natural death: Infectious diseases. In: Payne-James, J. (Ed.), *Encyclopedia of Forensic and Legal Medicine*, first ed., vol. 4. Oxford: Elsevier Ltd., pp. 229–236).

majority of the cases, spread and multisystem involvement in miliary tuberculosis has been documented as a cause of sudden death (Rastogi *et al.*, 2011). The most common target organs in miliary tuberculosis are the liver, spleen, and kidneys.

Corynebacterium diphtheriae produces a gray pseudomembrane in the pharynx and larynx, which may lead to respiratory obstruction and sudden death. Sudden death from acute epiglottitis occurs from respiratory obstruction caused by swelling of the epiglottic folds, uvula, and vocal cords. The most common cause of acute epiglottitis in developing countries is *H. influenzae* (Type B). In countries with established immunization programs, the incidence of *H. influenzae* epiglottitis has decreased and other bacteria, such as streptococcus, staphylococcus, and pneumococcus, have been implicated as possible causes.

Central Nervous System

Pyogenic meningitis is a common cause of sudden death involving the central nervous system. Bacterial spread commonly occurs through the blood stream. Other routes of spread include local extension of infection, for example, paranasal sinusitis, osteomyelitis, direct implantation, and via the peripheral nervous system. Diffuse bacterial meningitis may follow the rupture of a brain abscess, which may lead to sudden death. Meningitis affects all ages and the causative organism of bacterial meningitis may differ according to the age of the individual – newborns: *Group B Streptococcus*, *Escherichia coli*, *Listeria monocytogenes*; infants and children: *S. pneumoniae*, *H. influenzae* type B, *Neisseria meningitidis*; young adults: *N. meningitidis*, *S. pneumoniae*; and older adults: *S. pneumoniae*, *N.*

meningitidis, *L. monocytogenes* (Centers for Disease Control and Prevention, Bacterial meningitis, see Relevant Websites). The location of the exudates also depends on the organism causing meningitis. In *H. influenzae* the exudates are located basally, while in pneumococcal meningitis they are found over the convexities of the brain in the parasagittal region (Figure 3).

Gastrointestinal System

Bacterial infections of the gastrointestinal tract include severe bacterial enterocolitis that may lead to sudden death, especially in the young. The pathogenesis of diarrhea varies among the different pathogens. *Vibrio cholerae* and *Clostridium perfringens* cause diarrhea by ingestion of a preformed toxin present in contaminated foods. Enteroinvasive organisms, such as *Salmonella*, *Shigella*, and enteroinvasive *E. coli*, invade and destroy mucosal epithelial cells. Death occurs as a result of dehydration and electrolyte imbalance. Bleeding peptic ulcers that are caused by *Helicobacter pylori* account for 25% of ulcer-related deaths, many of which are sudden and unexpected. Fulminant bacterial peritonitis secondary to acute appendicitis, acute salpingitis, ruptured peptic ulcer, diverticulitis, intestinal obstruction, and cholecystitis are other causes of sudden death. Sudden deaths can result from splenic rupture in typhoid. Primary peritonitis may occur post-splenectomy, and in patients with splenic hypoplasia. Patients with sickle-cell disease may have anatomical or functional asplenia. The former is due to repeated bouts of infarction leading to autosplenectomy while the latter is due to a defect in opsonization of encapsulated bacteria.

Other System Involvement

Among bacterial urogenital tract infections, fulminant acute bacterial pyelonephritis may lead to septicemia and sudden death.

Viral Causes of Sudden Death

Viruses are ubiquitous and cause a wide spectrum of diseases in humans ranging from asymptomatic infection, severe debilitating illness, and sudden death. Viruses are broadly classified as ribonucleic acid (RNA) and deoxyribonucleic acid (DNA) based on the genome. Some DNA viruses are adenoviruses, parvoviruses, and herpes viruses. Significant RNA viruses are picornaviruses, myxoviruses, and paramyxoviruses. Viral infections causing sudden death usually involve the cardiac, respiratory, or the central nervous system. Although viral infections are a common cause of sudden deaths across all age groups, viral hemorrhagic fevers such as Marburg, Lassa, and Ebola virus may cause sudden death in children in particular.

Cardiovascular System

Cardiac involvement in viral infections usually takes the form of myocarditis. Viruses are the most common infectious causes of myocarditis. Viruses that cause myocarditis include adenovirus, cytomegalovirus, Epstein–Barr virus, herpes simplex virus type 1 and 2, HIV-1, influenza A and influenza B, parvovirus, picornavirus, RSV, rotavirus, etc. Adenoviruses and enteroviruses such as the coxsackie viruses are the most common cause of myocarditis (Yajima and Kowlton, 2009). Indirect damage to the myocardium may occur as an allergic response to a viral infection and eosinophilia, for example, eosinophilic myocarditis. This is a rare cause of sudden death in apparently healthy children due to the cardiac toxicity of eosinophils. Enteroviral infection may also play an important role in coronary plaque instability and may precipitate coronary thrombosis, leading to ventricular tachyarrhythmias and sudden death.

Respiratory System

Viral pneumonitis is an important viral cause of sudden death. Viruses implicated in viral pneumonitis include respiratory syncytial virus (RSV), human herpes virus, and parainfluenza virus in children, and adenovirus and influenza A and B viruses in adults. Fulminant Coxsackie virus infection may also cause leptomeningitis and florid interstitial pneumonitis. Emergent diseases such as severe acute respiratory syndrome (SARS) have a high mortality and may cause death within hours. SARS refers to an acute respiratory illness caused by infection with a novel coronavirus referred to as the SARS virus.

Central Nervous System

Sudden death may occur due to direct infection of the nervous system or a complication of a viral infection such as toxoplasmosis in HIV/AIDS. Encephalitis is an acute inflammation of the brain which along with meningitis is known as meningoencephalitis. Viral meningoencephalitis can be a cause of sudden death. Herpes simplex virus 1, a cause of encephalitis, usually occurs due to reactivation of latent infection. Commonly affected sites include the temporal lobe(s) (medial before lateral), the inferior frontal lobe(s), and the sylvian cortex(es).

Other System Involvement

Rotaviruses, adenoviruses, calciviruses, and astroviruses can cause fatal gastroenteritis. Rotavirus is considered as the most common cause of gastroenteritis among infants and young children while calcivirus (norovirus) is most commonly implicated in viral gastroenteritis among adults. Fulminant coxsackie virus infection may cause pancreatitis and focal hepatic necrosis. Other viral infections causing sudden deaths are influenza, measles, and mumps by myxoviruses and paramyxoviruses, and HIV-AIDS caused by the retroviruses. Infectious mononucleosis may sometimes lead to splenic rupture and sudden death.

Fungal Causes of Sudden Death

Sudden death due to fungal infection may occur in an immunocompromised host such as in HIV/AIDS. Fungi commonly implicated are *Cryptococcus neoformans* (meningitis or disseminated disease) and *Pneumocystis carinii* (pneumonia). The possibility of opportunistic infections such as pulmonary aspergillosis as the cause of sudden unexpected deaths exists in countries where tuberculosis is endemic (Bhagavath *et al.*, 2009). Intravenous drug abusers are susceptible to endocarditis due to fungi such as candida. These patients are prone to fungal thromboembolism, leading to sudden death. Sudden death may also be due to a complication of fungal diseases such as fatal subarachnoid hemorrhage complicating actinomycotic meningitis or fatal hemoptysis complicating pulmonary mucormycosis.

Protozoal Causes of Sudden Death

Sudden deaths are occasionally attributed to protozoan infections, such as malaria and amebiasis. Malaria has been reported as a cause of sudden unexplained death in malaria endemic regions (Rastogi *et al.*, 2010; Menezes *et al.*, 2010). Malaria is caused by a protozoal parasite belonging to the genus *Plasmodium* and is transmitted by the female anopheles mosquitoes. Malaria is broadly classified as falciparum and non-falciparum. Death is rare

with non-falciparum malaria; however, the mortality approaches 10–20% in patients with complicated falciparum malaria. It may be the cause of sudden death in nonimmune and susceptible individuals such as immigrants, tourists, business travelers, and sailors. Malaria is also a cause of disease and death among children under 5 years and pregnant women. Cerebral malaria (Alunni-Perret *et al.*, 2010), acute renal insufficiency, acute pulmonary edema, and acute respiratory distress syndrome are possible mechanisms of sudden death due to malaria (Menezes *et al.*, 2012). Sudden death in malaria may also be due to rupture of an enlarged spleen, which is fragile in malaria and more vulnerable to rupture.

Amebiasis is another cause of death from parasitic infections, which is caused by the protozoan *Entamoeba histolytica*. *Entamoeba histolytica* infection primarily causes amebic dysentery or amebic liver abscess. Sudden death may follow the rupture of an amebic liver abscess. Untreated liver abscesses can extend into the neighboring organs including lung (Figure 4) and heart. Fatal cardiac tamponade may occur with intrapericardial rupture of an amebic liver abscess.

Naegleria fowleri is associated with fatal amebic meningoencephalitis which is characterized by meningeal hemorrhage with fibrinoid necrosis of blood vessels. The causative organism enters the arachnoid space through the cribriform plate. Sudden death due to cardiac involvement in Chagas disease (*Trypanosoma*

cruzi) is reported in 5–10% of acute cases. The damage to the myocardium causes fatal ventricular tachycardia.

Helminthic Causes of Sudden Death

Clinically occult helminthic diseases such as hydatid disease (*Echinococcus granulosus*) and neurocysticercosis (*Taenia solium*) may cause sudden death. In neurocysticercosis death may occur due to epilepsy or raised intracranial pressure. Isolated cardiac hydatid cyst is an uncommon manifestation and accounts for fewer than 3% of all hydatid disease. Sudden death may be an initial manifestation of the disease. Death may be due to involvement of the left ventricular myocardium or to massive pulmonary embolism.

Emergence and Reemergence of Infectious Diseases

Infectious diseases remain the leading cause of death worldwide (Understanding Emerging and Reemerging Infectious Diseases, see Relevant Websites). New diseases such as AIDS, Legionnaire disease, Ebola hemorrhagic fever, and hantavirus pulmonary syndrome that have been identified in the last few decades are referred to as emerging infectious diseases. Reemerging Infectious Diseases refer to the resurgence of traditional diseases such as malaria and tuberculosis that appeared to be ‘on their way out’ (Understanding Emerging and Reemerging Infectious Diseases, see Relevant Websites). Thus, emerging infectious diseases are newer infections whose incidence has increased in recent years and/or threaten to increase in the near future, while reemergence refers to the reappearance of a known infection after a period of disappearance or decline.

The emergence of severe acute respiratory syndrome coronavirus (SARS-CoV) in 2002 that originated in China's Guangdong Province affected more than 8000 patients in 26 countries and resulted in 774 deaths worldwide (Global Alert and Response: Summary of probable SARS cases with onset of illness from 1 November 2002 to 31 July 2003, see ‘Relevant Websites’). In 2012 the emergence of a highly pathogenic novel coronavirus – Middle East respiratory syndrome coronavirus (MERS-CoV) – caused 178 laboratory-confirmed cases and 76 deaths (Milne-Price *et al.*, 2014).

Medicolegal Investigations into Infectious Deaths

Forensic investigations are carried out into cases of sudden and unexpected deaths according to existing local legislation. Most medicolegal systems approve of the forensic investigation of these deaths. For example in India, police investigations are followed by medicolegal autopsies in all cases of sudden deaths (Kumar *et al.*, 2006).



Figure 4 Amebic liver abscess and its extension into the lower lobe of the right lung (courtesy of Dr. Ramadas Naik, Professor of Pathology, Yenepoya Medical College, Mangalore, India).

Detailed forensic investigations are mostly associated with nonnatural causes. The investigating authorities should not treat the investigation of alleged sudden natural death and crime investigation differently unless proven otherwise. It is emphasized that the forensic investigations hold the key to identify and exclude the small percentage of deaths occurring from nonnatural causes (Mittal *et al.*, 2014). Preliminary investigations are followed by autopsy and ancillary investigations to ascertain the exact cause of death.

Autopsy in Cases of Sudden Death Due to Infectious Causes

Forensic pathologists/forensic medicine experts frequently encounter a wide range of deaths from natural causes. The primary aim of a medicolegal autopsy in sudden unexplained deaths is to ascertain the exact cause of death and at the same time rule out the possibility of any nonnatural cause of death (Kanchan *et al.*, 2013). All autopsies must adhere to the principles of universal precautions. In sudden deaths complete autopsy examination is recommended with appropriate tissue and body fluid sampling for special investigations. If there is any suspicion of a viral hemorrhagic fever, special care must be taken to avoid unwarranted exposure to health workers. The local public health officials must be informed and consideration given to a limited autopsy examination in consultation with a virologist (e.g., postmortem blood sampling and liver biopsy).

Gross/Macroscopic Observations

The cause and manner of death are determined mostly during gross/macroscopic examination at autopsy. Macroscopic findings at autopsy may be generalized or localized to a particular organ depending on the causative organism, the site, and the host response to the organism. Specific macroscopic features observed in target organs during autopsies may include a flabby mottled appearance of the heart in viral myocarditis, valvular involvement in the form of a perforation or rupture of a valve leaflet in infective endocarditis, consolidation and pneumonic changes such as gray hepatization in pneumonia (Figure 1), tubercles and cavitary lesions in tuberculosis (Figure 2), exudates over the convexities and base of the brain in bacterial meningitis (Figure 3), widespread and asymmetrical necrosis, prominent hemorrhage and swelling with raised intracranial pressure and brain herniation in fulminant viral encephalitis, abscesses/ruptured abscesses in parasitic infections (Figure 4), hemorrhagic ulcers in the gastric mucosa, brain swelling with a 'slate gray' discoloration due to the brown-black malarial pigment called hemozoin in cerebral malaria, a markedly enlarged spleen in malaria, and thick exudates in other organs. In



Figure 5 Hydrocephalus with basal oblitative, granulomatous cysticercus meningitis (courtesy of Professor RH Hewlett, University of Stellenbosch). Reproduced from Dada, M.A., Lazarus, N.G., 2005. Sudden natural death: Infectious diseases. In: Payne-James, J. (Ed.), *Encyclopedia of Forensic and Legal Medicine*, first ed., vol. 4. Oxford: Elsevier Ltd., pp. 229–236.

neurocysticercosis, parasitic cysts containing scolices are present, especially in the subarachnoid space, cortical sulci, and cortical gray matter. Large multilocular cysts (racemose cysts) may be present in the basilar cisterns near the cerebellopontine angle (Figure 5).

In sudden unexpected deaths resulting from infectious diseases, the macroscopic findings at autopsy may be inconclusive, obscure, or nonspecific, and hence, there is a need for further microscopic evaluation. In this regard the histopathological evaluation may play a defining role in ascertaining the cause of death (Kanchan and Krishan, 2013). The National Association of Medical Examiners recommends histopathological examination in all cases with no gross anatomic or toxicological cause of death (Christiansen and Collins, 2007).

Histology, Microbiology, and Molecular Diagnosis of Sudden Infectious Deaths

Histological examination and specific observations in different organs among various causes of sudden death from infectious diseases are described below.

Pulmonary tuberculosis is characterized by the presence of caseating granulomas. Similar granulomas may be observed in different organs involved in miliary tuberculosis (Figure 6). Histological examination of the myocardium in cardiac tuberculosis may show a nodular, miliary, or diffuse infiltrative pattern. There may be narrowing of coronary arteries with/without complete occlusion from intimal or diffuse tuberculous arteritis. Alveoli are filled with inflammatory exudate in pneumonia (Figure 7). Diffuse alveolar damage is generally indicative of infective causes such as influenza, parainfluenza, respiratory syncytial, and adenoviruses, chlamydia, mycoplasma, pneumococcus, legionella, and

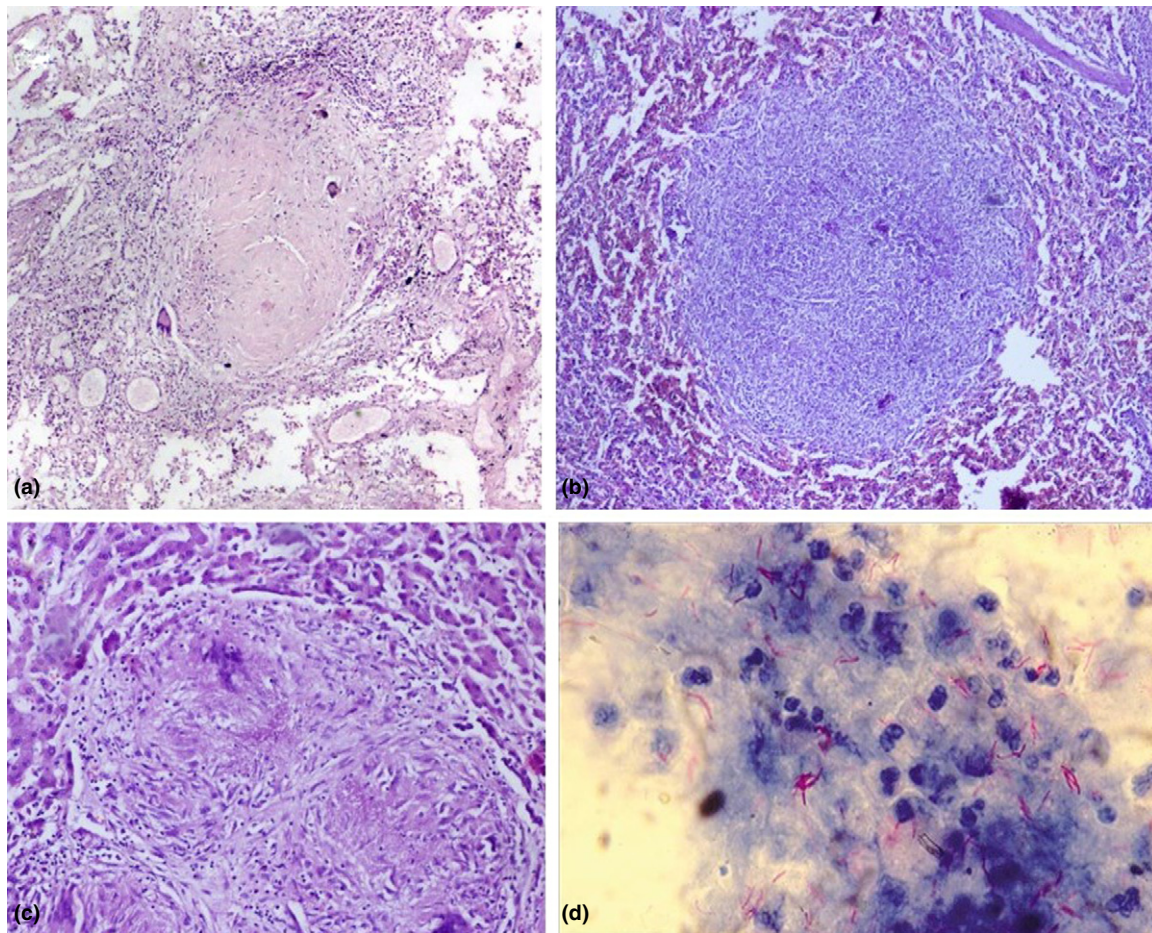


Figure 6 Miliary tuberculosis. (a) Pulmonary tuberculosis showing caseating granulomas and Langhans' giant cells. (b) Granuloma with caseous necrosis in the spleen. (c) Caseating granuloma in the liver tissue (courtesy of Dr. Ramadas Naik, Professor of Pathology, Yenepoya Medical College, Mangalore, India). (d) Acid-fast bacilli demonstrated using a Ziehl-Neelsen stain (courtesy of Dada, M.A., Lazarus, N.G., 2005. Sudden natural death: Infectious diseases. In: Payne-James, J. (Ed.), Encyclopedia of Forensic and Legal Medicine, first ed., vol. 4. Oxford: Elsevier Ltd., pp. 229–236).

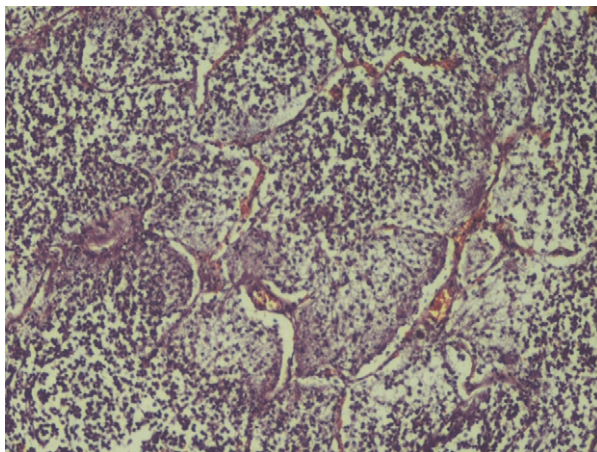


Figure 7 Pneumonia: alveoli filled with inflammatory exudate (courtesy of Dr. Ramadas Naik, Professor of Pathology, Yenepoya Medical College, Mangalore, India).

pneumocystis. Infective endocarditis on histology is characterized by the presence of vegetations showing fibrinous material along with acute inflammatory cells (Figure 8).

Morphological findings in viral infections may include intranuclear and/or intracytoplasmic inclusions, multinucleate giant cells, and tissue necrosis (cytopathic effect). Histology in viral myocarditis usually reveals focal infiltrates of inflammatory cells (neutrophils and/or lymphocytes, plasma cells, and macrophages). Focal aggregates of lymphocytes not associated with necrosis may, however, be seen in elderly patients and are not diagnostic of myocarditis. The Dallas criteria of histopathological categorization were proposed for the diagnosis of myocarditis. As per this criteria, an inflammatory infiltrate and associated myocyte necrosis or damage not characteristic of an ischemic event is diagnostic of myocarditis. However, its diagnostic utility

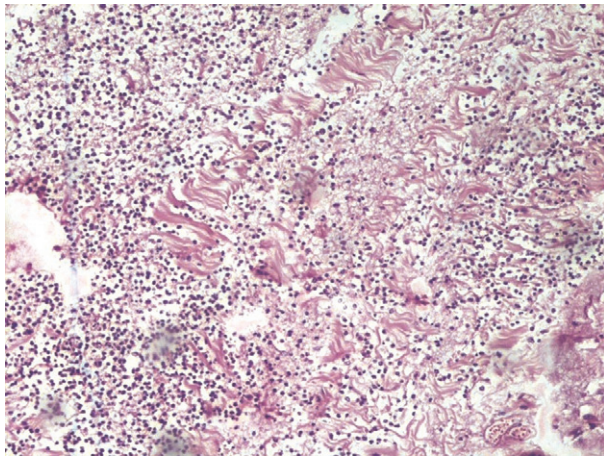


Figure 8 Infective bacterial endocarditis: vegetations showing fibrinous material along with acute inflammatory cells (courtesy of Dr. Ramadas Naik, Professor of Pathology, Yenepoya Medical College, Mangalore, India).

is questioned due to sampling errors, and variation in expert interpretation, etc. (Baughman, 2006). Myocardial involvement may be patchy. It is recommended that at least 5–10 sections be taken from various areas of the myocardium for adequate histological sampling in the diagnosis of mild forms of myocarditis (Kitulwatte *et al.*, 2010).

Microscopic findings in viral pneumonitis are usually nonspecific and include edema and widening of the intra-alveolar septa with a mononuclear cell infiltrate. In some cases, diagnostic viral inclusions may be demonstrated. In SARS, postmortem histopathological evaluations of lung tissue show diffuse alveolar damage consistent with the pathological manifestations of acute respiratory distress syndrome. There is usually mild interstitial inflammation with scattered alveolar pneumocytes showing cytomegaly, and enlarged nuclei with prominent nucleoli.

In viral central nervous system infections the brain may appear macroscopically normal; specimens thus should be taken for histology and microbiology. Serum and cerebrospinal fluid (CSF) should be sent for antibody studies. Tissue for histological examination should be taken from normal, obviously abnormal, and transition areas. Routine sections should be taken from the cerebral cortex (all four lobes), thalamus, basal ganglia, hippocampus, brain stem, and cerebellum. Microscopic examination in viral meningitis reveals neutrophils filling the subarachnoid space with extension of the inflammation into the leptomeningeal veins in fulminant cases. Histological findings in viral encephalitis include perivascular cuffing by mononuclear cells (Figure 9). In a small number of cases, intranuclear inclusions may be seen in astrocytes and neurons. Acute anterior poliomyelitis has been reported as a cause of sudden and unexpected death in a male infant. It is therefore

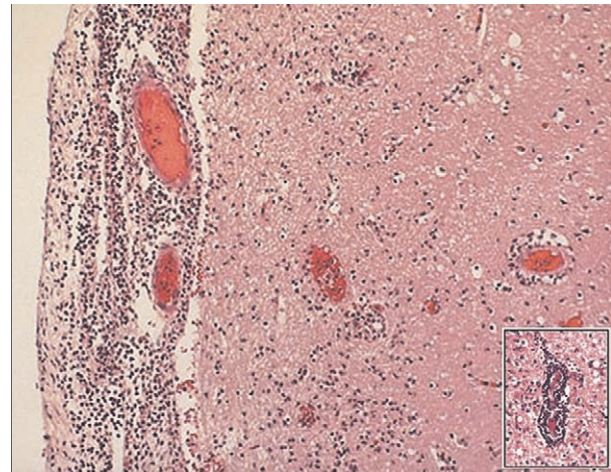


Figure 9 Viral meningoencephalitis showing lymphocytic infiltration of brain parenchyma. Insert: perivascular cuffing by lymphocytes (courtesy of Dada, M.A., Lazarus, N.G., 2005. Sudden natural death: Infectious diseases. In: Payne-James, J. (Ed.), Encyclopedia of Forensic and Legal Medicine, first ed., vol. 4. Oxford: Elsevier Ltd., pp. 229–236).

suggested that autopsy protocols in sudden infant death should include histological examination of brain stem and spinal cord (Dunne *et al.*, 1984).

In cases of sudden death due to malaria, the microscopic examination of organs (brain, spleen, liver, lungs, heart, and kidneys) in malaria reveals intravascular parasitized red blood cells with malarial pigment in the blood capillaries. Small perivascular inflammatory foci called malarial or Durck's granulomas may be present. Histological examination in Chagas disease (*T. cruzi*) shows myofiber necrosis with an acute inflammatory reaction. Clusters of organisms may be found within dilated myofibers, resulting in intracellular pseudocysts. Fungal infections are confirmed by the histological demonstration of the organisms in the affected tissues (Mathai *et al.*, 2009).

Autopsy sampling for microbiological investigations is indicated in sudden unexpected deaths in children and adults, deaths in immunocompromised patients, deaths in patients with clinically suspected infections, and deaths with organ changes suggestive of infection. Postmortem blood cultures may help in ascertaining the exact cause of sudden deaths in bacterial infections. In bacterial meningitis, the organisms may be demonstrated by microbiological culture of the CSF and examination of Gram stains of the CSF and brain tissue. Spleen and heart blood are the most promising media for postmortem bacteriological cultures (Tsokos and Püschel, 2001). A pure growth of a pathogen in blood or CSF should be considered as a possible contributing factor to, or cause of, death (Morris *et al.*, 2006).

Special staining techniques and molecular tests are used in order to improve the diagnostic yield in infectious

Table 4 Special techniques used to demonstrate infectious agents

Agent	Technique
Bacteria	Gram stain, silver stain, acid-fast stain, culture, DNA probes, PCR and ligase chain reaction for <i>Mycobacteria</i> Giemsa, culture in <i>Chlamydia</i>
Virus	Hematoxylin and eosin stain, culture, antibody probes, DNA probes
Fungi	Periodic acid–Schiff stain, silver stain, and Giemsa stain. Mucicarmine for capsules of <i>Cryptococcus</i>
Protozoa	Giemsa stain, periodic acid–Schiff stain, DNA probes
Helminths	Modified acid-fast stain

diseases (Table 4). The acid-fast bacilli in tuberculosis may be demonstrated using the Ziehl–Neelsen stain (Figure 6(b)) or molecular tests such as the ligase chain reaction (LCR) and polymerase chain reaction (PCR) may be used to demonstrate the presence of *Mycobacterium tuberculosis* DNA complex. *Legionella pneumophila* which causes legionnaire’ disease may be demonstrated by a modified silver stain (Dieterle stain) or by immunofluorescence and culture. Microscopy of cadaveric blood smears in malaria may reveal remnants of intraerythrocytic parasites. This postmortem finding of parasitemia in sudden death due to malaria, however, varies between 25% and 80% (Muehlethaler *et al.*, 2005; Wichmann *et al.*, 2003). The diagnosis of viral infections in many cases can only be made on special investigations, for example, culture, electron microscopy, serology, or molecular testing. Diagnostic modalities in fungal infections include culture of the organism and histological demonstration of the organisms in tissue, which may be facilitated by special stains such as the periodic acid–Schiff (PAS) or Grocott’s methenamine silver stain.

Microbiological demonstration of an organism does not necessarily mean that an individual was suffering from an infectious disease, as a host may be colonized by bacteria or the patient may have had an asymptomatic viral infection. Highly sensitive molecular tests such as PCR may exacerbate the problem of accurate diagnosis of infectious disease and the causative agent if the results are not correlated with the pathological findings at autopsy.

The problems encountered with autopsy microbiological testing are due to contamination during procurement of the sample because of poor technique or the postmortem spread of commensals. To prevent false-positive postmortem blood cultures the following procedures should be observed. The body should be refrigerated as soon as possible and movement of the body should be limited to decrease the possibility of postmortem bacterial spread. An aseptic technique should be used to collect the sample, which should be stored and transported in the correct medium and at the right temperature. Close liaison with the microbiology

and virology laboratories is important to guide the collection, preservation, transport, and evaluation of specimens. This is particularly important in cases where there are positive cultures with negative histological findings. Sampling at multiple sites and determining the antibiotic sensitivities may also be helpful in determining the significance of positive cultures. The finding of a ‘pure’ as opposed to ‘mixed’ culture helps to determine the significance of findings. The type of organism in relation to the site where it was cultured also may help to differentiate contaminants from significant positive cultures.

Conclusion

Infectious agents are not an uncommon cause of sudden death. A thorough medicolegal investigation is warranted in these deaths, which should include a complete and detailed autopsy examination. In cases with non-specific morphological changes, investigation of appropriate autopsy samples by recently developed laboratory techniques may prove invaluable and shed light on the cause of death. Although the role of histology in cases of sudden death has been highlighted, histological evaluation is not very commonly done in many areas, especially in developing countries; its significance, therefore, needs to be emphasized along with the use of microbiology and molecular diagnostic methods. Genetic engineering has led to the development of highly infectious and virulent strains of microorganisms. Forensic pathologists should be aware of the importance of infectious causes of sudden death in the present era of bioterrorism and emergent and reemerging diseases.

See also: Children: Sudden Natural Infant and Childhood Death. Sudden Natural Death: Central Nervous System and Miscellaneous Causes

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