Is there a need for autopsies in the management of fungal disease?

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Summary   The autopsy rates in Germany became low like in other European, American and Asian countries. Main reasons for this development are the lack of acceptance of autopsy in the society as well as in the medical profession, the introduction of a requirement for consent, unclear legal position, the public health system, pressure of costs and a change in the field of activity in pathology with much more diagnostics of surgical and biopsy material. The autopsy is missing with respect to the reliability of causes of death and morbidity statistics and other epidemiological studies. Published data indicate that up to 20–30% of patients who die in hospitals have important diseases/lesions that remain undetected before death but that are found at autopsy. For infectious diseases, the data are similar. Therefore, a higher incidence of invasive fungal infections was found. Some rare fungal disorders are diagnosed by autopsy. Only exact death statistics makes specific health care possible and is cost saving in a public health system in the long term. Autopsy remains an important tool for quality control in medical diagnostic and therapeutic activity. It is also essential for fundamental medical education and further training.

Key words: fungal diseases, autopsy, morbidity.

Frequencies and validity of autopsy in general

Clinic-pathological autopsy rates in an international comparison

The autopsy rates in Germany became low like in other European, American and Asian countries.[1,2] Between 1980 and 1999 in Germany, the frequency of clinic-pathological autopsies decreased from 10% to 3.1% of all deaths.[2,3] The spectrum of autopsy frequency extended from 10.1% to 47.4% for university institutes and 2.6–52.8% for community institutes.[4] The median value of 23.3% and 13.3% respectively for each group is clearly below the recommended value of at least 30%,[2,5] based on statistical considerations, or 25–40%.[4]

Svendsen and Hill [6] collected data concerning autopsy laws, regulations, rates, and practice from 29 industrialized countries. In many countries, laws have been revised in recent years and rules that are more restrictive have been introduced. The introduction of a requirement for consent was followed by a decline in the autopsy rate.

In 1983, 34% of all persons who died in the Republic of Austria were autopsied.[7] The annual autopsy rate between 1983 and 1987 was on average 51–53%. The reason for this high autopsy rate is that the Austrian law permits the autopsies without the consent of next of kin, if it appears indicated for medical, scientific or educational reasons. The diagnoses were inaccurate or incomplete in 15% of all cases.

In Sweden, there has been a continuous decrease in the autopsy rate during the last 25–30 years.[8] The autopsy rate in the city of Malmø has declined from 81% in 1984 to 34% in 1993. However, patients submitted for autopsy represented, with regard to age, sex, cause and place of death, a selected group of all deceased. Veress *et al.* [9] found in the area of Stockholm comparing the years 1977/1978 and 1987/1988 that the autopsy rate decreased from 80% to 39%, which might explain the increased discrepancy rate from 22% to 27% regarding the diagnoses of major, principal diseases.

Since 1990, a new Danish legislation has provoked a dramatic fall in the autopsy rate, which had already declined from 45% in 1970 to 35% in 1980.[10] In the first half of 1990, the rate was 24%; in the second half of the same year, it had fallen to 16% in whole Denmark.

The autopsy rate in the United Birmingham Hospital has fallen from 74.4% in 1958 to 46% in 1972.[11] In the Birmingham region as a whole over the 4 years, 1968–1972, it showed a downward trend from 34.5% in 1968 to 27.3% in 1972.

In the United States, the autopsy rate dramatically dropped off in the past 50 years.[12] In Houston, the rate declined significantly over three periods (1989–1993, 1994–1998 and 1999–2003) from 67%, 34% and 26% respectively ($P < 0.0001$).[13]

Further details on the clinic-pathological autopsy rates in an international comparison are given in Table 1.

The usefulness of the autopsy

Data regarding the usefulness of the autopsy indicate that 20–30% of patients who die in hospitals have important diseases/lesions that remained undetected before death but that are found at autopsy. This is true for both adult and paediatric patients.[22] Therefore, 63 paediatric oncologic patients died during the period 1982–1991, 28 of whom underwent postmortem examination.[23] Class I findings (those who would have altered management if they had been known during life:[24,25] Table 2) were found in seven cases (25%). Major pathological findings that would not have altered management (class II) were discovered in 14.3% of cases. This study confirms that postmortem examination can provide valuable new information even for patients who had been widely investigated in life and in whom the cause of death may appear obvious.

In all years (1959, 1969, 1979 and 1989) analysed in a study from Germany, about 10% of the autopsies

Table 2 Modified Goldman's criteria (after Goldman L *et al.* [24]; Dimopoulos G *et al.* [25])

Major discrepancies	
Class I	Undiagnosed major unexpected findings before death that probably would have changed the therapy or improved survival
Class II	Undiagnosed major unexpected findings before death, which would not have changed the treatment or the patient's survival because a. of ineffective therapy b. the patient received the indicated treatment even though the diagnosis was unknown c. The patient refused evaluation or therapy
Minor discrepancies	
Class III	Unexpected findings that were not immediate or primary causes of death but could have influenced the prognosis, or the processes leading to death in a terminally ill patient
Class IV	Unexpected findings (non-diagnosable) of possible epidemiological or genetic importance.

Table 1 Clinic-pathological autopsy rates in an international comparison

National studies		
Germany	1980: 10%; 1991: 8%; 1994: 4.2%; 1999: 3.1%	Ref. 2, 3
East Germany	1979: 30%; 1987: 18%	Ref. 4, 14
Austria (university)	1983–1987: 51–53% (total); 1999: 30–35%	Ref. 4, 7
Switzerland	1950: 55%;1991: 25%; 2002: 20%	Ref. 16
Sweden	1969: 46%; 1992: 16%; 1994: 25%	Ref. 10, 15
Denmark	1970: 45%; 1980: 35%; 1990: 24%, 16%; 1992: 13.6%	Ref. 10, 17
Norway	1987: 1.2%; 1992: 2.1%	Ref. 18
Great Britain	1999: 17.3%	Ref. 2
England	1950–1960: 30–40%; 1994: 5%; 1999: 2.1%*	Ref. 28
Wales	1966: 8.9%; 1991: 1.7%	Ref. 2, 73
USA	1964: 41%; 1974: 18%; 1988: 12%; 1999: 5–0%	Ref. 12
Regional studies		
Hamburg (Germany)	1990: 60%; 1999: 21% (7 largest pathol. departments)	Ref. 19
Kiel (Germany; univ.)	1959: 88%; 1979: 58%; 1989: 36%	Ref. 20
Bad Saarow (Germany)	1973–1991: 80%; 1992–2001: 28%	Ref. 44
Stockholm Karolinska (Sweden)	1977: 80%; 1987: 39%	Ref. 9
Malmø (Sweden)	1984: 81%; 1993: 34%	Ref. 8
Birmingham (England)	1954: 74.4%; 1972: 46% (in a hospital) and 27.3% in the region	Ref. 11
Belfast (Ireland)	1990: 21.6%, 1999: 7.9%	Ref. 21
Houston Cancer Centre (USA)	1989–1993: 67%; 1994–1998: 34%; 1999–2003: 26%	Ref. 13

* Differences between death in hospital, nursing home or at home.

revealed a misdiagnosis; another 25% disclosed a false negative diagnosis, which did not influence the patient's prognosis and about 10% disclosed a false-positive diagnosis, which again did not influence the patient's prognosis.[26] Roosen *et al.* [27] compared the clinical diagnoses and postmortem major diagnoses of 100 patients and found in 16% the disclosure of a major diagnosis that, if known before death, might have led to a change in therapy and prolonged survival.

Among 2984 ICU admissions in Brussels, there were 489 deaths; 222 autopsies were conducted (45.4% autopsy rate).[25] Postmortem examination revealed unexpected findings in 50 patients (22.5%), which were class I in 12 (5.4%) patients, class II in seven (3.1%) and class III in 31 (14%) patients (Table 2). In an ICU in Finland, an autopsy was performed in 346 (89%) of the deceased patients.[28] A class I discrepancy was found in eight patients (2.3%) and a class II discrepancy in 11 patients (3.2%). Five of the eight (62%) class I discrepancies were infections inclusive of a case of systemic candidosis, which occurred in patients already treated for another infections. Perkins *et al.* [29] from Birmingham ICU found that out of total 636 deaths, only 49 (7.7%) underwent postmortem examinations. Of these, 38 (78%) cases were available for review. They found that postmortem findings were in complete agreement with predeath diagnoses in fewer than half of the cases ($n = 17$; 45%). Major missed diagnoses were present in 15 cases (39%).

In 1096 cases of death (autopsy rate 63.8%), the accuracy of clinical diagnoses was investigated by comparing clinical diagnoses with recorded autopsy findings.[30] In 81.3% of the cases, the primary disease had been determined correctly. In more than half of these cases, the immediate cause of death or an additional disease contributing to death had not been correctly identified. In 16% of the cases, the diagnosis proved to be inadequate and in 2.6% the primary disease, cause of death and accompanying illnesses were misdiagnosed. Bauer *et al.* [31] compared the findings in 780 autopsies, performed between 1977 and 1990, with the clinical diagnoses. Autopsy confirmed the clinical diagnosis in 74.9% of all cases; a clinically not diagnosed basic disease was demonstrated in 13.6%, and a not recognized final complication in 11.5%. In 9.7% of autopsies previously unrecognized but clinically important additional diseases were found.

Shojania *et al.* [32] also found in a systematic literature search for English-language articles available on MEDLINE from 1966 to 2002 that substantial discrepancies exist between clinical diagnoses and findings at autopsy. Of 53 autopsy series with prospectively defined criteria identified, 42 reported major errors and 37 class I errors.

Reasons and consequences for the development of the autopsy rates

There are various reasons for the development of the autopsy rates and negative consequences. One underlying reason is the lack of acceptance of the autopsy in the society as well as in the medical profession based on emotional aspects, legal-philosophical ideas and ignorance of the practical details.[4] Introduction of a requirement for consent was followed by a decline in the autopsy rate.[6] Reasons are also lying in the public health system and in the area of responsibility of there working persons. There are wrong assessments by treating physician (case is 'clear') and fear of clearing the own mistakes in diagnostics and therapy. Amount of work and time, missing awareness about understanding of autopsy and missing experience in enlightenment of relatives are other reasons. Pressure of costs and obligation to make savings, insufficient refund, a change in the field of activity in pathology with much more diagnostics of surgical and biopsy material and unclear legal position are additional causes.[1,2]

Without enough autopsies, the statistics about causes of death and the event of illness are not right. This will also have a negative effect on the education of students, the special training of physicians and on the identification of an alteration in well-known clinical symptoms and the appearance of new disorders. For autopsy performing to be safe – for infectious diseases in particular – it requires adequate training of pathologists.

By autopsy detected or confirmed mycoses

For infectious diseases, the data are similar to those described above: a substantial number of infections remain undetected before death but are detected by postmortem examination.[33]

Mycoses in patients with malignancies and from ICUs

Jandrlic *et al.* [34] stated in a group of 40 patients with haematological malignancies whose autopsy diagnosed a higher proportion of fungal infections than during the patient's life ($P < 0.01$). A higher incidence of invasive fungal infections (IFI) was found in patients with haematological malignancies as compared to the control group ($P < 0.01$).

In an attempt to estimate the frequency of fungal infections among cancer patients, Bodey *et al.* [35] conducted a survey of 4096 autopsy examinations in 12 hospitals in Western Europe, Canada and Japan. The majority (68%) was performed on subjects with solid tumours. In 91 cases (2%) fungal infection was the primary cause of death. A total of 455 fungal infections were identified most often in leukaemia patients and transplant recipients (25% each). 58% of fungal infections were caused by *Candida* spp. and 30% by *Aspergillus* spp. In 11% of the cases, the infecting fungus was not identified. Cryptococcosis ranged from 0% to 4% of all fungal infections. In candidosis, the most frequently involved organ was the lung, followed by the oesophagus, stomach and kidney. In aspergilloses, in nearly 80%, the lung was involved and other organ involvement occurred infrequently. A few patients had evidence of widely disseminated cryptococcoses. Brain or meninges were not involved routinely.

To determine the prevalence of fungal liver infection at autopsy in marrow transplant recipients, Rossetti *et al.* [36] reviewed autopsy results of the Seattle Cancer Research Centre for the period 1980–1989. Fungal liver infection was found in 67 (9%) of 731 patients. Liver imaging studies performed during the last 15 days of life had a sensitivity of only 18% for detecting fungal liver lesions.

Roosen *et al.* [27] compared in an ICU the clinical diagnoses and postmortem major diagnoses of 100 patients who died in 1996 (autopsy rate of 93%). In 16%, autopsy findings revealed a major diagnosis. The most frequent class I missed major diagnoses (Table 2) were fungal infection, cardiac tamponade, abdominal haemorrhage and myocardial infarction.

Postmortem examination in ICU by Dimopoulos *et al.* [25] revealed unexpected findings in 50 patients (22.5%). Major (class I/II) findings (Table 2) included fungal infections in nine of 222 autopsies (4%). Minor findings included *Candida* oesophagitis. Koszyca *et al.* [23] found that their most common class I findings were fungal infections with *Aspergillus* or *Candida* species. Seven of the 91 autopsied patients of another medical ICU had organ transplantation.[37] Three of these patients had discordant diagnoses between clinical cause of death and autopsy diagnoses, including two patients with disseminated fungal infection that was not diagnosed clinically. Silfvast *et al.* [28] saw that five of the eight (62%) class I discrepancies were infections inclusive mycoses, which occurred in patients already treated for another infections.

Autopsies from 289 patients who died in a Brussels ICU during a 2-year period were studied.[38] Postmortem examination revealed unexpected findings in 61 patients (21%) including malignancy, pulmonary embolism, aspergillosis, myocardial or mesenteric infarction and unsuspected bacterial, viral or fungal infection. Between 1980 and 1989 in Birmingham, 32 cases of invasive aspergillosis were identified out of 2315 consecutive autopsies, an incidence of 1.4%.[39] *Aspergillus* was isolated during life in only eight cases.

Autopsy-proven mycoses of CNS

Most described cases of cerebral mycosis were only detected by autopsy.

In a study from Berlin, about 80% of the fatal mycoses of the central nervous system (CNS; *n* = 28) remained undetected while the patients were alive.[40] The authors found 39% candidosis, 36% aspergillosis, 5% cryptococcosis, one case of zygomycosis, one trichosporosis and one coccidiomycosis.

Abe *et al.* [41] histopathologically verified cerebral mycoses in seven cases, although brain tissue was examined in only 46% of 528 autopsy cases. Among these cerebral mycoses, one had double fungal infections with *Aspergillus* and *Candida*, while others were as follows: aspergillosis (two cases), mucormycosis (two cases), candidosis (one case) and cryptococcosis (one case). Six cases were not diagnosed ante-mortem with exception of a case of cryptococcosis.

De Madeiros *et al.* [42] retrospectively assessed the autopsy findings of CNS infections in marrow transplant recipients. From 1987 to 1998, 845 patients were submitted to bone marrow transplantation. The CNS of 180 patients was studied by autopsy. Twenty-seven patients (15%) presented brain parenchyma infection. Fungi were isolated in approximately 60% of the cases. *Aspergillus* spp. was the most prevalent fungus (30%), followed by *Candida* spp. (18%). There was one case of *Fusarium* spp. infection and two cases of unidentified fungi. All patients with fungal infections had documented involvement at widespread sites.

Cerebral aspergilloses may lead to a cerebral vascular accident such as intracranial haemorrhage or cerebral infarction. Matsumura *et al.* [43] presented two patients with cerebral aspergillosis accompanied by intracranial haemorrhage. The autopsies of a 9-year-old girl and a 15-year-old boy revealed that an *Aspergillus* arteritis was the cause of repeated haemorrhage.

Epidemic studies of fungal infections in autopsies

Autopsies are essential for solid epidemiologic findings. Koch *et al.* [44] published a study on systemic mycoses

in the autopsy material of an institute of pathology from Eastern Germany. During the period from 1973 to 2001, they found in case of rapidly fallen autopsy frequency, an increase in the incidence of mycoses and a shift in favour of aspergillosis. Forty-seven systemic mycoses were diagnosed in 4813 autopsies of deceased adults, corresponding to 0.98%. They were diagnosed during life of the patients in only three cases. The autopsy frequency fell from about 80% (1973–1991) to about 28% (1992–2001).

Schwesinger *et al.* [45] analysed data from 2027 autopsies performed at the midsize University Hospital of Greifswald in Eastern Germany during the period from 1994 to 2003. The autopsy rate also dropped in the years before and after opening of the Wall in 1989. They found 164 cases of invasive candidosis and aspergillosis (8.1%). On five occasions, a simultaneous infection by *Candida* and *Aspergillus* existed. Other mycoses played a negligible part. In these 10 years, mycoses and in particular candidosis increased in spite of slightly decreased numbers of autopsies. The differences comparing the 5-year periods (1994–98 and 1999–2003) were highly significant for both mycoses and candidosis. They were not significant for aspergillosis. There was no case of AIDS.

Groll *et al.* [46] evaluated data from 8124 autopsies performed between 1978 and 1992 on patients who died at the University Hospital of Frankfurt/Main. The overall autopsy rate was 74.6%, dropping from 77.6% to 71.9%. During that period, 278 IFI were found. The prevalence rose from 2.2% (1978–1982) and 3.2% (1983–1987) to 5.1% in the years 1988–1992 ($P < 0.001$). There was a significant increase in *Aspergillus* infections ($P < 0.001$). The prevalence of *Candida* infections showed a declining trend within the last period. After exclusion of 60 AIDS cases from the analysis, their results remained significant.

From 1970 to 1993, 93 endomycoses confirmed by postmortem examination were diagnosed in the autopsy material of the Berlin Charité.[40] These comprised 51 candidoses (54.8%), 24 aspergilloses (36.6%), five cryptococcoses (5.4%), one zygomycosis, one trichosporosis and one coccidioidomycosis. This corresponded to 0.7% of the 13 375 diseased persons autopsied during this period. The frequency of autopsy was 85.3%.

In Houston, Chamilos *et al.* [13] determined autopsy-proven IFI in patients with haematic malignancies over three periods (1989–1993, 1994–1998 and 1999–2003). IFI were identified in 314 (31%) of 1017 autopsies. Most IFI (75%) were not diagnosed ante mortem. The prevalence of invasive mold infections increased significantly (19% to 24% to 25%; $P = 0.05$) in parallel with the emergence of *Zygomycetes* (0.9% to 4% to 3%; $P = 0.03$). The prevalence of all other IFI remained relatively constant. In Peking, there were 85 cases of IFI among 3447 cases at autopsy from 1953 to 1993.[47] The prevalence steadily increased, especially during the recent 20 years. Only five patients were diagnosed clinically (5.9%). The primary diseases were mainly leukaemia, cancer, and sepsis.

Garcia-Fontgivell *et al.* [48] carried out a retrospective study in Spain (1994–2004). They found 0.24% of the studied cases (78 310 biopsies and 753 autopsies) were diagnosed as fungal infections (0.21% of the total studied biopsy and 4.25% of the whole autopsies). 61% of studied cases were caused by *Candida* spp., followed by *Aspergillus* spp. (10%) and *Zygomycetes* (5%). Subira *et al.* [49] from Barcelona caused some alarm having found that 64% of their patients with proven invasive aspergillosis at autopsy did not meet any of the criteria for diagnosis before death.

In a large epidemiological study of Yamazaki *et al.* [50] the retrospective autopsy data from 1969 to 1994 were compiled by the Japanese Society of Pathology from data gathered from university hospitals, public hospitals, and large private hospitals all over Japan. There were 594 263 autopsies and 17 775 found mycoses (2.99%). The frequency of visceral mycoses among the annual total number of pathological autopsy cases increased noticeably from 1.60% in 1969 to a peak of 4.66% in 1990. Among them, the incidences of candidosis and aspergillosis increased the most. After 1990, however, the frequency of visceral mycoses decreased gradually. Until 1989, the predominant causative agent was *Candida*, followed in order by *Aspergillus* and *Cryptococcus*. Although the rate of candidosis decreased by degrees from 1990, the rate of aspergillosis increased, and then surpassed that of candidosis in 1991. Leukaemia was the major disease underlying the visceral mycoses, followed by solid cancers and other blood and haematopoietic system diseases. Severe mycotic infection has increased over the reported 25-year period, from 6.6% of the total visceral mycosis cases in 1969 to 71% in 1994.

We have to conclude that in different countries most autopsy-proven fungal infections were not diagnosed ante mortem. Especially during the recent 20 years, the incidence of candidosis and aspergillosis increased first of all. In some studies, infections by *Aspergillus* had passed those by *Candida* in this period.

Some rare fungal disorders and courses diagnosed by autopsy

Yeasts (Candida, Cryptococcus, Trichosporon)

Mai *et al.* [51] reported four cases of mycotic arteritis caused by *C. albicans* after renal transplantation but which have been inoculated during organ harvesting or conservation. In two cases, the diagnosis of fungal arteritis was confirmed only during autopsy after the patient's death because of massive bleeding.

Rimek *et al.* [52] gave the first report of a case of meningitis caused by *Cryptococcus adeliensis* in a patient with acute myeloid leukaemia undergoing allogenic peripheral blood stem cell transplantation. They found the fungus in cerebrospinal fluid and the patient received liposomal amphotericin, flucytosine and additional amphotericin B. Fourteen days later, the patient died. Autopsy, including histopathological examinations by Grocott stain, did not reveal any fungal elements in the leptomeninx or brain at the time of death.

Nine patients with haematological malignancies were reported positive for *Trichosporon cutaneum* in their blood culture or at the time of autopsy.[53] Koyanagi *et al.* [54] presented an autopsy case of disseminated trichosporonosis caused by *Trichosporon inkin* in a 30-year-old man with allogenic peripheral blood stem cell transplantation for acute myelocytic leukaemia.

Zygomycosis

A 61-year-old man died of rare gastrointestinal basidiobolomycosis with an obstructing colon tumour and a large hepatic mass.[55] *In vivo* review of colon and liver biopsy samples showed extensive necrosis and histiocytes, multinucleated giant cells and numerous eosinophils. Grocott-stained sections contained unusually large hyphae surrounded by strongly eosinophilic material in haematoxylin and eosin stained sections (Splendore-Hoeppli phenomenon). A presumptive diagnosis of *Basidiobolus* spp. infection was made. Autopsy showed signs of extensive fungal infection of the liver, gallbladder and sigmoid colon. Culture of liver, gallbladder and sigmoid colon yielded *Basidiobolus ranarum*.

Phaeohyphomycosis

Heveling *et al.* [56] presented the case of a 75-year-old immunocompetent patient with a cardiogenic embolic anterior cerebral artery infarction and abscess formation. Autopsy revealed the clinically supposed *Exophiala* spp. endocarditis with metastatic cerebral abscesses.

Exserohilum rostratum is a dematiaceous fungus that rarely causes infection in humans. A patient with severe aplastic anaemia developed fatal disseminated disease caused by this fungus.[57] The clinical course and histopathologic findings at autopsy were similar to those seen in cases of invasive aspergillosis or mucormycosis.

Barron *et al.* [58] reported two cases of invasive human mycoses caused by *Chaetomium perlucidum*. Fatal disseminated disease involving the brain, myocardium, lungs and spleen was described in an acute myelogenous leukaemia autopsied patient. A second patient with a history of asthma and chronic bronchiectasis was not autopsied. In each case, cultures were surgically obtained from lung tissue. A rare form of CNS infection was caused by *Chaetomium atrobrunneum* with fatal brain abscess in a bone marrow transplant patient.[59]

A case of multiple cerebral abscesses caused by *Cladophialophora bantiana* in a patient with probable Duncan's syndrome was noticed, too.[60] The patient also had extensive extra-cerebral disease, which is unusual for infection with this organism.

Moore *et al.* [61] described a premature infant with black, necrotic skin lesions as fungal infection identified as *Bipolaris spicifera*. A shave biopsy showed the fungi. On autopsy, fungal organisms found throughout the internal organs confirmed disseminated disease.

Dimorphic fungi as opportunistic pathogens

Reactive haemophagocytic syndrome (RHS) is an uncommon life-threatening disorder. A case presentation[62] describes a patient with a history of chronic hepatitis C, cryoglobulinaemia, renal failure and *Staphylococcus aureus* perinephric abscess and bacteraemia, who, at autopsy, was found to have disseminated histoplasmosis with fungal endocarditis and RHS.

Autopsies of two patients with AIDS revealed disseminated blastomycosis with massive pulmonary involvement, *Blastomyces* meningoencephalitis, and widespread dissemination.[63]

Hyalohyphomycosis

Trichoderma longibrachiatum was recovered from stool surveillance cultures and a perirectal ulcer biopsy specimen from a 29-year-old male who had received an allogenic bone marrow transplant for acute lymphoblastic leukaemia.[64] At autopsy, histological sections from the lungs, liver, brain and intestinal wall showed infiltration by branching septate hyphae. Cultures were

positive for *Trichoderma longibrachiatum*. This was the first report of probable acquisition through the gastro-intestinal tract.

A case of autopsy-proven fungal pneumonia in a relapsed leukaemia patient was reported.[65] A diagnosis of probable invasive aspergillosis was made. Then *Coprinus cinereus* (anamorph *Hormographiella aspergillata*) was cultured from two bronchoalveolar fluid samples. Culture of tissue specimens taken by autopsy was not performed.

Autopsy-proven therapeutic research

The consensus group of the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) published standard definitions for IFI for clinical and epidemiological research.[66,67] They assigned three levels of probability to the diagnosis, namely 'proven', 'probable' and 'possible' IFI. It is adopted in every scientific endeavour from validating diagnostic tests to evaluating antifungal agents for treating IFI. The 'proven' category consists of criteria that allow IFI to be diagnosed with certainty and that differentiates between deep-tissue infections and fungaemia. The highest level of certainty in diagnosing is attained by establishing the presence of fungi in tissue by biopsy or a needle aspirate and so includes autopsy.

Only some examples of manner to research therapeutic influences on mycoses proven by autopsy are presented in this review.

Van Burik *et al.* [68] reviewed 355 autopsies performed between 1990 and 1994 to determine whether fluconazole prophylaxis prevented visceral fungal infection. Fungal infection was found in 40% of patients transplanted and autopsied at the marrow transplant centre. Overall, the proportion of autopsies with any fungal infection was not different for those patients receiving no fluconazole prophylaxis vs. those with prophylactic fluconazole. With fluconazole prophylaxis, candidal infections were less frequent, decreasing from 27% to 8%, while *Aspergillus* infections were more frequent, increasing from 18% to 29%. No increase in deaths related to non-*Candida albicans* infections was seen. Of the 329 patients with livers examined, hepatic infection caused by *Candida* species was significantly less common in patients who had received fluconazole. Fungal liver infection was found in 31 patients (9%), 16% of those who were not treated with fluconazole and 3% of those who were treated with fluconazole. As patients with *Candida* infections died earlier after

marrow transplant than patients with mold infections, the authors speculate that a longer length of survival may dispose toward acquisition of mold infections. Fluconazole prophylaxis in this cohort of marrow transplant patients undergoing autopsy resulted in a significant reduction in infection caused by *Candida* species and an increase in mold infections.

Since 1987, chemoprophylaxis and empiric therapy with antifungal drugs have been used routinely in neutropenic children with neoplasm in a Japanese study.[69] The incidence of terminal IFI diagnosed by autopsy findings was compared in two groups: group A, consisting of 25 patients autopsied between 1982 and 1986, and group B, consisting of 14 patients autopsied between 1987 and 1991. There was no difference in the incidence of IFI between the two groups, but the characteristics of infections appeared to differ. With the recent intensification of chemotherapy, the patients in group B had more risk factors. It might therefore have been anticipated that group B patients may have shown an increase in fungal infections. No such increase was observed, suggesting that the prophylaxis was effective. Autopsy findings also showed that the target organs of infections were localized and that systemic candidosis was decreased in group B. It is thus concluded that the present antifungal countermeasures are effective.

The purpose of a histological study[70] was to present postmortem findings in the eyes of a 53-year-old male with liver dysfunction 2 weeks after a short-time oral treatment with 200 mg/day fluconazole for metastatic *Candida* endophthalmitis due to intravenous hyperalimentation for 18 days. *Candida* had been demonstrated in the venous blood and on the tip of the intravenous catheter. The bilateral fungal endophthalmitis with hypopyon responded well to fungistatic therapy, but the patient suddenly died of heart failure. Both eyes were obtained at autopsy. *Candida* was demonstrated only in vitreous puffballs but not in the retina or uvea. Fluconazole administered for a short period had little effect in eliminating fungus from vitreous puffballs, which have no blood supply. The authors stated that prolonged administration of the antifungal drug or vitrectomy should be considered when treating an eye with vitreous puffballs in the presence of fungal endophthalmitis.

Scedosporium prolificans was isolated at autopsy from the lungs of two patients, in the one case also from postmortem samples of kidney and liver.[71] One patient was treated with oral fluconazole and the second with intravenous amphotericin B. Despite this therapy, they died. *In vitro* susceptibility testing of all isolates suggests that they were resistant to these antifungal drugs.

Conclusions

There is a need for autopsies also in the management of fungal disease:

• With respect to the reliability of real causes of death and morbidity, statistics and other epidemiological studies in mycology, there have to be a considerable increase in autopsies. The number of clinical diagnostic errors is inversely proportional to that of carried out autopsies.[72]

• Autopsy remains an important tool for quality control in medical diagnostic and therapeutic activity. A high medical standard is associated with a high autopsy rate.

• Only an exact death statistic makes specific health care possible. Specific health care means cost saving in a public health system in the long term for instance by investment in preventive programmes. Autopsies are essential for solid epidemiologic findings.

• Autopsies help evaluate new diagnostic and therapeutic measures.

• A final consideration of validity on modern diagnostic methods as an alternative to autopsy is still waiting for an answer. Despite modern methods, about 10% of autopsies generally revealed a misdiagnosis.[26] More as the same applies to mycoses.

• Autopsies improve fundamental medical education and further training. The autopsy remains a valuable diagnostic and teaching tool. It is safe for infectious diseases in particular, but it requires adequate training of pathologists. Today, it is possible to use some modern computer-aided teaching media and to abandon some autopsies.

• The clear aim should be to raise the frequency of hospital autopsies to 30–40%, a figure considered to enable a valuable quality control.[2,4,73]

• The necessary legal, personnel and financial regulations to facilitate and sustain the autopsy service at a sufficiently high rate are to be demanded.

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