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INCIDENCE OF SYSTEMIC MYCOSES IN AUTOPSY MATERIAL INZIDENZ VON SYSTEMISCHEN MYKOSEN IM AUTOPSIE MATERIAL

St. Koch[1], F.-M. Hohne[1] und H.-J. Tietz[2]

[1] Institut fűr Pathologic, HUMAINE Klinikum Bad Saarow,

[2] Klinik für Dermatologie, Venerologie und Allergologie, Universitutätsklinikum Charite, Medizinische Fakultät der Humboldt-Universität, Campus Charite Mitte, Berlin, Germany

The incidence of systemic mycoses was investigated in the autopsy material of the Institute of Pathology of the HUMAINE Hospital in Bad Saarow. This hospital provides qualified standard care in east Brandenburg with a wide spectrum of medical disciplines caring for patients with acute medical conditions as well as oncological cases (660 beds). Between 1973 and 2001, 47 systemic mycoses were diagnosed in 4,813 autopsies of deceased adults, corresponding to 0.98 %. During the period of investigation, both the care provided by the hospital and the organization of the health service changed. The autopsy frequency fell from about 80 % (1973 - 1991) to about 28 % (1992 - 2001). This is thus still far higher than the average of about 3 % assumed for the Federal Republic of Germany. Although the incidence of systemic mycoses increased during the entire 29-year period of investigation, the number of cases in whom this was the immediate cause of death decreased. Whereas candidiases predominated from 1973 - 1991, a shift in favor of aspergilioses was noticed in the period from 1992 - 2001. Systemic mycosis was diagnosed intravitally in only three out of 47 cases. The present study therefore underscores the significance of clinical autopsy as a diagnostic method and means of medical quality control.

Key words: aspergillosis, autopsy, Candidosis, cryptococcosis, endomycoses, epidemiology, incidence, systemic mycoses

Im Autopsiematerial des Institute fur Pathologic des HUMAINE Klinikums Bad Saarow, einem Versorgungskrankenhaus der qualifizierten Regelversorgung in Ostbrandenburg mit weitgefuchertem Disziplinenspektrum und akut-medizmischem sowie onkologischen Patientengut (660 Betten), wurde die HSufigkeit systemischer Mykosen untersucht. In der Zeit von 1973-2001 wurden unter 4813 Autopsien verstorbener Erwachsener 47 systemische Mykosen diagnostiziert. Das entspricht einem Anteil von etwa 0,98 %. Wabrend des Untersuchungszeitraumes anderte sich sowohl der Versorgungsauftrag des Klinikums, als auch die Organisation des Gesundheitswesens. Die Autopsiefrequenz sank von ca. 80 % (1973-1991) auf etwa 28 % (1992-2001). Sie liegt damit noch weit uber dem flir die Bundesrepublik Deutschland mit ca. 3 % angenommenen Durchschnittswert. Obwohl die Haufigkeit der systemischen Mykosen wShrend des gesamten 29jabrigen Untersuchungszeitraumes zunahm, reduzierte sich die Anzahl von Fallen, in denen diese die unmittelbare Todesursache war. Dominierten von 1973-1991 die Candidosen, war ein Wandel zugunsten von Aspergillosen im Zeitraum 1992-2001 feststellbar. Da lediglich in 3/47 Fallen intravital die systemische Mykose diagnostiziert wurde, unterstreicht die vorliegende Arbeit erneut die Bedeutung der klmischen Autopsie als Methode der Diagnostik und arztlichen Qualitatskontrolle.

Schlűsselwörter: *aspergillose, autopsie, endo-mykosen, epidemiologie, inzidenz, kandidose, kryptokokkose, systemische mykosen*

ЧАСТОТА СИСТЕМНЫХ МИКОЗОВ В МАТЕРИАЛАХ ВСКРЫТИЯ

С.Кох[1], Ф.-М. Хохн[1] и Х.-Дж. Титц[2]

[1] Институт патологии, Клиника, Бэд Сэроу,

[2] Клиника дерматологии, венерологии и аллергологии, Клиника Университета Шари, Медицинский факультет Университета Хумбольта, Университетский Городок Шарите, Берлин, Германия

Исследовали частоту системных микозов по материалам вскрытия института патологии (HUMAINE Hospital in Bad Saarow), расположенного на востоке Бранденбурга, где осуществляли стандартное широкоспектральное медицинское обследование пациентов с тяжелыми заболеваниями, например, онкологическими (660 коек). Между 1973 и 2001 годами при 4,813 вскрытиях умерших взрослых диагностировали 47 системных микозов (соответственно 0,98 %). За период исследования изменялась предусмотренная больницей организация услуг. Частота вскрытия упала от около 80 % (1973 - 1991) до приблизительно 28 % (1992 - 2001). Таким образом, это выше среднего числа (около 3 %), принятого для Федеральной Республики Германии. Хотя частота встречаемости системных микозов возрастала в течение 29-летнего периода исследования, количество случаев смерти больных уменьшалось. Поскольку кандидоз преобладал в 1973 - 1991, увеличение случаев аспергиллеза наблюдали в период от 1992 - 2001. Системный микоз был диагностирован прижизненно в только трех из 47 случаев. Следовательно, настоящий анализ подчеркивает значение клинического вскрытия как диагностического метода и средства медицинского контроля качества.

Ключевые слова: аспрегиллез, вскрытие, кандидоз, криптококкоз, системные микозы, частота, эндомикоз, эпидемиология

INTRODUCTION

New and very much more effective tumor chemotherapeutics, methods of surgery and irradiation but also complex treatment procedures such as autologous and allogenic bone marrow and blood stem cell therapy as well as organ transplantations have enabled treatment of various solid tumors and systemic hematological diseases that has long-term results. The use of chemotherapeutics and immunosuppressants entailed in these methods of treatment evidently also directly result in a general increase of bacterial, viral and mycotic infections [1].

Only a few large-scale studies have been published which report on the nature and incidence of systemic mycoses [2-6]. Some of the autopsy studies presented in the last ten years document that systemic mycoses do indeed occur more frequently in absolute terms. On the other hand, it is assumed that more mycoses are diagnosed today than in the past [4, 7], In patients with hematological-oncological neoplasias, an increase in the incidence of invasive fungal infections is observed. The pathogen-associated lethality is reported to be more than 80% in aspergilloses and more than 50% in candidiases [8].

In the present study, the incidence of systemic mycoses was investigated in autopsy material from the Institute of Pathology at the HUMAINE Hospital in Bad Saarow. This is a standard-care hospital in eastern Brandenburg with a broad spectrum of medical disciplines and patients with acute medical and oncological conditions. The hospital in Bad Saarow has existed since 1954 and was a central military medical care and research facility with the status of a medical teaching hospital that also provided medical care to parts of the population of adjacent towns and rural counties for several decades up to 1990. After a brief period of corporate administration by the medical service corps of the Federal German Army, the hospital with about 660 beds has been run since 1991 as a public medical care hospital of qualified standard care (15 specialist disciplines, 4 institutes). As a result of the foundation of the eastern Brandenburg Tumor Center located in Bad Saarow in 1992, the oncological profile of the facility was raised. In the last ten years, an average of about 23,000 cases of inpatient treatment have been recorded including treatment of 4000 patients with first diagnosis of malignant tumor. The frequency of autopsy was about 80 % in 1989. As a result of the restructuring of the health service in the area of the former GDR, there was a drastic decrease in the frequency of autopsy after the adaptation to bring the health service into line with that of the Federal Republic of Germany. From 1992 - 2002, this remained roughly constant at around 28 %. It is especially problematic that autopsies practically no longer take place in patients who died at home. Our own investigation results are compared with similar studies and discussed.

MATERIALS AND METHODS

The retrospective investigations were based on archived autopsy records of a total of 4,813 autopsies carried out from 1973 - 2001 at the Institute of Pathology in the Bad Saarow Hospital. In addition, the still completely preserved paraffin blocks and section preparations that have been kept as well as pertinent clinical data were available. The histological preparations were stained with hematoxylin-eosin (Riedel-de Haën, Hannover), with the periodic acid-Scruff reaction (PAS) and the Grocott method (Riedel-de Haen, Hanover; Fluka, Neu-Ulm, Germany). The sections were evaluated under the light microscope using dry and oil immersion objectives at about 40 - 1000 fold magnification. Fungal infections in the deep mucosal layers and the parenchymatous organs were diagnosed as systemic mycoses (endomycoses). Fungal findings on the mucosal surface of the upper gastrointestinal and the upper respiratory tracts up to the tracheal bifurcation were not considered. Dermatomycoses as well as mycoses of the buccal and vaginal cavities were not included in the evaluation. The occurrence of necroses and inflammatory reactions in the morphological detection of fungi was investigated as a criterion for demonstrating intravital fungal infection and used to distinguish it from postmortem fungal growth.

RESULTS

The investigation comprised the period from 1973 - 2001. 4,813 of the adults who died in this period were autopsied. The frequency of autopsy in the first 19 years (1973 - 1990) was about 80 % and that of the last ten years (1992 - 2001) of the investigation period was almost constant, averaging about 28 % per year.

In the period from 1973 - 1990, persons who died at home were also autopsied, Evaluation of the autopsies from 1992 - 2001 exclusively involves patients who were treated and died in hospital (Fig. 1).

Amongst the 4,813 autopsies, systemic mycoses were diagnosed in 47 cases (0.98 % of all autopsies). The incidence, age and sex of the patients and the fungal species or genera diagnosed (Fig. 2 and 3) and the organs in which they were found differed in the individual phases in the entire investigation period and are shown separately in Table 1.

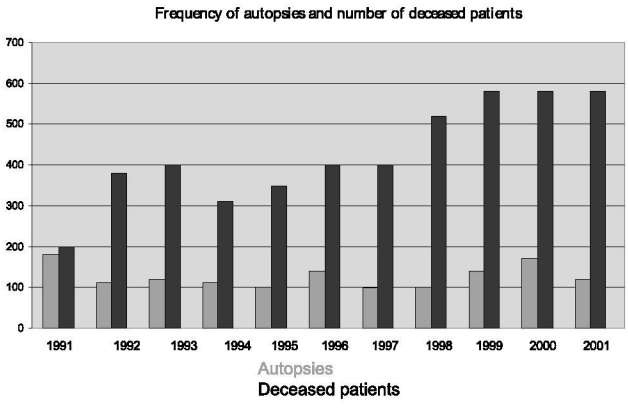


Figure 1: Frequency of autopsies and number of deceased patients, Institute of Pathology Bad Saarow (1973-2001)

Table 1.

Clinical and morphological characteristics of systemic mycoses in the autopsy material of the Institute of Pathology Bad Saarow (autopsies n 4813)

	1973-1980	1981-1991	1992-2001	1973-2001
Number	11	10	26	47
Incidence (%)				0,98
Age (years)	56,1 (22-87)	58,9 (20-82)	63,8 (41-88)	
Sex (m:f)	9:2	7:3	16:10	32:15
Preceding diseases				
Diabetes mellitus	3	1	7	11
Adipositas	0	0	7	7
Neutropenia	0	1	10	11
Fungal genus				
Candida	11	7	9	27
Aspergillus	0	2	16	18
Cryptococcus	0	0	1	1
Aureobasidium	0	1	0	1

The assignment of the systemic mycoses to a fungal genus is shown in Figures 4 to 7. In the period from 1973–1980, candidiases were found exclusively. From 1981–1991, some aspergilloses and an infection with Aureobasidium pullulans occurred in addition. From 1992–2001, aspergilloses predominate, although numerous candidiases were also observed. Furthermore, a case of cryptococcosis was verified.

With the exception of two cases between 1973 and 1980 in which an intravital diagnosis was already made, all systemic mycoses were detected exclusively at autopsy.

The underlying diseases in the deceased persons autopsied and data on the pathological relevance are given in Tables 2 and 3. In the first two phases of the investigation period (1973–1991), the underlying diseases are evenly distributed amongst various organ systems: benign diseases are the most frequent. In the last part of the investigation period (1992–2001), the malignant diseases of the hematopoietic and the lymphatic systems clearly predominate.

Table 2.

Systemic mycoses in the autopsy material of the Institute of Pathology Bad Saarow (1973-2001), Organ system location of underlying disease

Organ system	1973-1980	1981-1991	1992-2001
Heart	1	0	0
Lung	2	1	4
Vessels	1	3	2
Gastro-Intestinal-Tract	3	0	2
Liver	1	3	3
Pancreas	0	0	1
Kidney	1	0	0
Bladder	1	0	0
Hдmatopoiet. System	2	1	14
Other	0	0	2

Table 3.

Systemic mycoses in the autopsy material of the Institute of Pathology Bad Saarow (1973-2001), Dignity of underlying disease

Dignity	1973-1980	1981-1991	1992-2001
Benign	4	8	6
Malign	7	2	20

In the 47 patients with systemic mycoses, these were also the immediate cause of death in most cases (Tab. 4). However, it was interesting that the incidence of systemic mycosis as an immediate cause of death decreased over the entire period investigated. It amounted to 72.7 % (8/11) of the deceased patients in 1973 - 1980 and decreased to 60 % (6/10) in the period 1981 - 1991 and to only 46.1 % (12/26) between 1992 and 2001. Systemic mycoses could be detected in seven patients with septic shock and in two patients with bronchopneumonia as an immediate cause of death. However, a synoptic consideration of the clinical, macroscopic and histological findings revealed that systemic mycoses was not the immediate cause of death.

Table 4.

Systemic mycoses in the autopsy material of the Institute of Pathology Bad Saarow (1973-2001), Directly cause of death

	1973-1980			1981-1991			1992-2001		
Systemic mycosis [1)]	8	72,7	17,0	6	60	12,8	12	46,1	25,5
Malignant tumor	0			0			2		
Septic shock	0			0			2		
Acute myocardial infarction	1			0			2		
Bronchopneumonia	1			2			4		
Gastrointest. bleeding	0			0			1		
Pancreatitis	0			0			1		
Intracerebral bleeding	1			0			0		
Mesenterial infarction	0			1			1		
Cerebral infarction	0			1			0		
Pericarditis	0			0			1		

[1)] *1.Number: absolute number of cases, 2. Number: percent with regard to respective period of investigation, 3. Number: percent with regard to overall period of investigation*

DISCUSSION

In the entire investigation period, the health service and the care that the hospital was required to provide underwent fundamental changes. The adoption of the legal system of the old Federal Republic of Germany entailed a decrease in the frequency of autopsy from about 80 % (before 1989) to only about 28 % in the last ten years in the study period. Persons who died at home were practically no longer autopsied. In consequence of the transfer of the patient treatment to doctor's offices or the patient's homes, patients in the final stage of life-threatening diseases often die outside the hospital. These fatalities are generally not subject to autopsy investigations and verification. Consequently, in appraising the incidence of systemic mycoses and their significance as the immediate cause of death, a large number of undetected cases must be assumed. The frequency of autopsy in the Bad Saarow Hospital (about 28 %) is to be rated as relatively high for clinical facilities and therefore allows a more detailed interpretation of the investigation results. In the interests of autopsy quality assurance, a rate of autopsy of about 10 % of the total number of deceased persons is considered appropriate. An autopsy frequency of 20 % - 30 % for standard care hospitals and 50 % for

maximum care hospitals should be aimed for [9]. On average, an autopsy rate of about 3 % (1.2 % - 5.6 %) is reported for the Federal Republic of Germany [9,10].

Clinical-pathology autopsies as well as the drafting of the autopsy reports were carried out in accordance with a standardised procedure applied without change over the entire period of investigation (1973- 2001). Furthermore, in all cases paraffin blocks were kept from all parenchymatous organs. These could be used for retrospective investigation. The findings presented in this study can therefore be compared over a period of 29 years. In addition, documents containing the relevant clinical findings were available and could be used to compare and interpret the results of the morphological investigation.

Comparable autopsy studies are relatively rare in the literature (Tab. 5), The incidence of systemic mycoses (0.98 %) determined in our investigations of autopsy material that has not been specifically selected is comparable to that reported by Boon et al. (1.4 %) [2] and by Tietz et al. (0.7 %) [6], However, the investigations carried out by Tietz et al. [6] on material of the Berlin Charite only covered the period up to a short time after the restructuring of the health service in the former GDR, whereas the results of the present study extend up to 2001, when the re-organization of the health service had been concluded. Groll et al. [4] found 278 cases with systemic mycoses amongst 8,124 autopsies analyzed. These also included patients with AIDS, whereas there were no HIV-positive patients or AIDS cases in our material. The investigations of Du et al. [3] comprised a very long period from 1953 to 1993 in which systemic mycoses had been detected in 85 out of 3,447 patients. A study on 36,509 autopsies published by Kehrer and Brandt [5] which extends back to 1901 also shows very much higher incidences of systemic mycoses than present-day studies. When interpreting these studies, it must be taken into consideration that with such long periods of investigation the newly introduced or optimized diagnostic and treatment techniques or more effective medication in themselves already restrict the comparability with present-day studies.

Table 5.

Systemic mycoses in the autopsy material of the Institute of Pathology Bad Saarow (1973-2001), frequency of systemic mycoses (overview to literature)

Authors	Autopsies (n)	Systemic mycoses (n)	%	Period of investigation
Kehrer u. Brandt (1979)	36509	273	2,3	1901-1976
Boon, O'Brien u. Adams (1991)	2315	32	1,4	1980-1989
Du, Zhang u. Chen (1996)	3447	85	2,5	1953-1993
Groll et al.(1996)	8124	278	3,4	1978-1992
Tietz, Martin u. Koch (2001)	13275	93	0,7	1970-1993
Eigene Untersuchungen	4813	47	0,98	1973-2001

In our own material, the absolute number of patients with systemic mycoses increases by about 2.5 fold over the 29-year-old period of observation. However, the significance of systemic mycoses as the cause of death clearly runs counter to this. In the first period investigated (1973 - 1980), as many as 72.7 % of autopsied patients still died as a result of their systemic mycoses. This compares with 60 % in the period from 1981 - 1991, and only 46.1% in the most recent years investigated (1992 - 2001). Another remarkable feature of this development is that in the lethality attributable to systemic mycoses the number of patients with advanced age and malignant underlying diseases rose from 14.9 % in the period from 1973 - 1980 and to 4.3 % in the period from 1981 - 1991 and to 42.6 % in the period from 1992 - 2001 in parallel to the reduction. The reduction in lethality is most likely to be attributable to improved diagnostics and better progress observation of patients with malignant diseases and to more effective pharmacotherapy, especially in consequence of the specific and early use of fluconazole.

In agreement with Groll et al. [4], we found a pronounced change in the spectrum of causative organisms of systemic mycoses. Aspergilloses now predominate, whereas more candidiases were observed initially. With constant autopsy and histological investigation technique, an absolute increase in the number of aspergilloses in the autopsy material can be assumed. The change is possibly also attributable to the better treatability of systemic candidiases, so that these are now encountered less frequently in autopsy material.

Taking the entire 29-year period of observation, there is agreement with various other groups of authors in Europe, America, Canada and Japan, especially with Bodey et al. [7], who found 58 % candidiases in their investigation material. In our own material, the percentage of candidiases was 77.4 %. Considering only the last ten years in which the structure of care provided by the Bad Saarow Hospital was almost identical, with priority care of patients with acute diseases and oncological conditions with an autopsy rate of about 28 %, 34.6 % candidiases (9/26) and 61.5 % aspergilloses (16/26) were found.

Nosari et al. [11] found an infection as the cause of death in 63 % of the cases in an autopsy study comprising 95 patients with hematological conditions. 25 % of the yeast infections were mycoses. Pfaffenbach et al. [12] showed that systemic mycoses were present in 17.5 % of 1,053 autopsied patients with hematological neoplasias. Aspergilloses predominated (85 cases), whereas candidiases only accounted for 75 cases. In an autopsy study on tumor patients, Bodey et al. [7] showed that 25 % of the mycoses detected occurred in patients with leukemia, and 25 % in patients with transplantations. Srivastava et al. [13] found systemic mycoses in 29 % of autopsies carried out in 72 patients with hematological neoplasias: ten patients had aspergilloses and ten patients had candidiases.

It is especially problematical that systemic mycosis was diagnosed when the patient was still alive in only 6.4 % (3/47) of cases in our own material. In two patients, the autopsy revealed candidiasis, and in one patient aspergillosis. Despite improved intravital monitoring of patient groups at special risk of developing systemic mycoses, the results indicate that autopsies are still valuable as an original medical quality control method. Sarode et

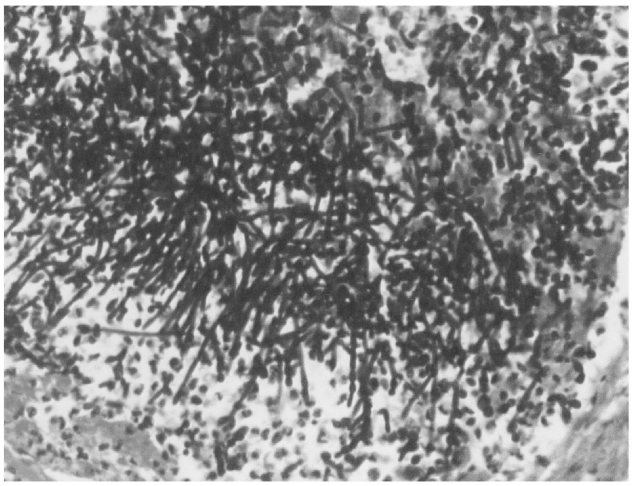


Figure 2
Hepatic infiltrate in candidiasis. Necrotic liver tissue with non-branching fungal hyphae. Periodic acid staining, 20fold microscopic magnification

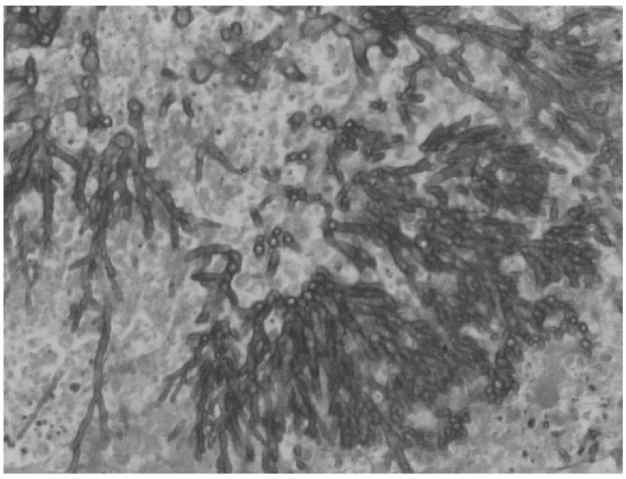


Figure 3
Aspergillus pneumonia. Lung tissue is invaded by septated, dichotomously branched aspergillus hyphae. Periodic acid staining, 20fold microscopic magnification

Figures 4-7: Diagnosed fungal genus in different periods of the complete period of investigations in 1973-2001, Institute of Pathology Bad Saarow

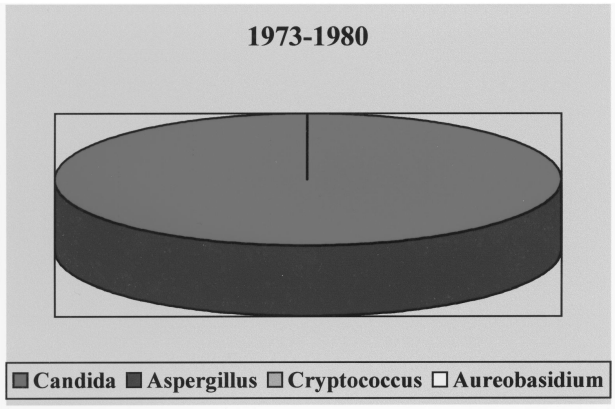


Figure 4

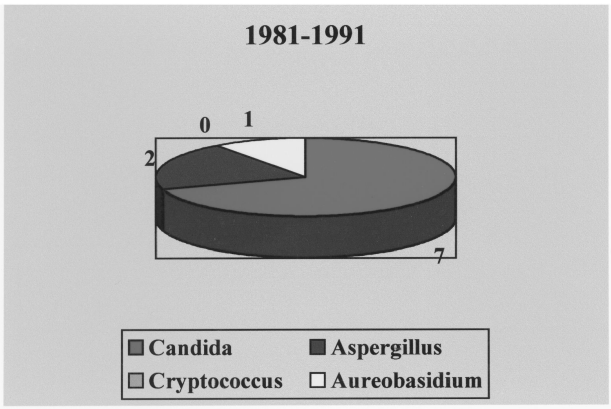
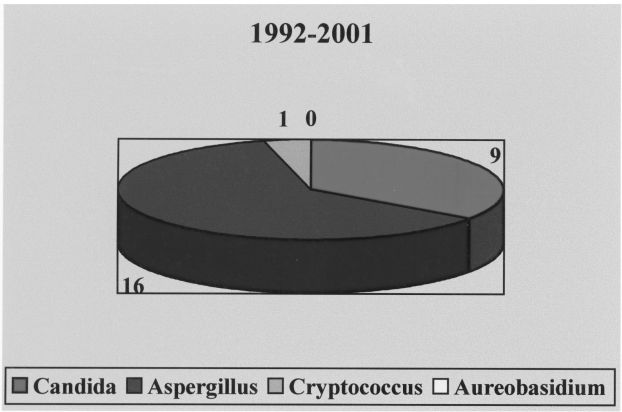


Figure 5



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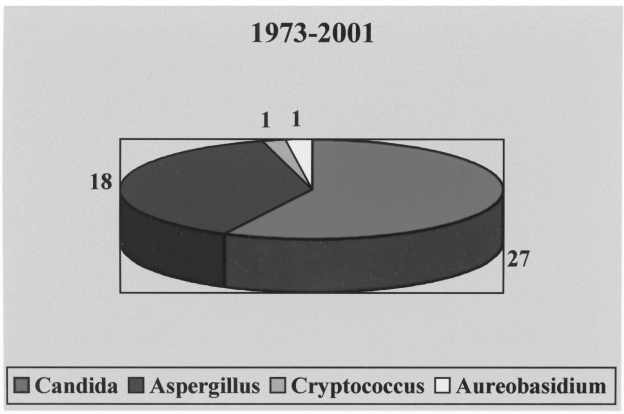

Figure 7

al. [14] found that mycoses were not detected intravitally in 89 % of cases in a comparison of clinical and autopsy findings in 1,000 patients. Salonen and Nlkarkeleinen [15] found systemic mycoses in 25.9 % of 410 patients with hematological conditions. Of these, only two out of 29 cases were diagnosed while the patients were still alive.

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