mycoses
Diagnosis, Therapy and Prophylaxis of Fungal Diseases

Supplement article

Burden of serious fungal diseases in Hungary

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Summary

Valid data on the prevalence of serious fungal diseases are difficult to derive as in most countries these conditions are not reportable infections. To assess the burden of these infections in Hungary prevalence estimates from international peer-reviewed papers and population statistics were utilised. In the intensive care unit (ICU) population at least 370 cases of serious yeast and 52 mould infections can be expected yearly. The total number of candidaemia cases may be as high as 1110 annually. In patients with acute leukaemia and recipients of haematopoietic stem cell and solid organ transplants the predicted incidence is more than 55 every year. Recurrent vulvovaginal candidiasis – though not a life-threatening condition – can adversely affect the quality of life of more than 177 000 Hungarian women. According to organisation for economic co-operation and development (OECD), 4.7% of total population older than 15 will suffer from chronic obstructive pulmonary disease (COPD) and 4.4% from asthma, adding another very broad risk group to the aforementioned categories susceptible for mycotic complications. Here more than 17 000 can have severe asthma with fungal sensitisation (SAFS) and more than 13 000 are at risk for developing allergic bronchopulmonary aspergillosis (ABPA). The incidence of dermatomycoses and other superficial fungal infections is even more difficult to assess but – according to international estimations – can effect around 14.3% of the total population. More than 1.6 million Hungarians may suffer from fungal diseases annually, with 33 000 cases being life threatening or very serious. This is an underrecognised problem of special importance for public health.

Key words: Aspergillosis, candidiasis, epidemiology, invasive fungal disease.

Introduction

Hungary is a central-eastern European country with a long tradition of mycological research. The first papers from currently available medical literature date back to the 1950s and were published in local journals.[1–3] In the current era, research groups from Hungarian university institutions have contributed to our present understanding of fungal biology and pathogenesis.[4–6] The first data on epidemiology were published in 1958,[7] and were followed by publications including regional data mostly on superficial mycoses.[8,9] However, in the last two decades very few epidemiological studies have been done in Hungary or other neighbouring countries. Like in most countries of the world, in Hungary non-endemic fungal diseases are not listed as officially reportable infections, either. Sporadic data from individual centres have been published,[10–12] but no national database for surveillance has been set up so far. Therefore, true figures regarding the epidemiology of mycoses post the millennium are largely unknown, despite an interest in this topic stretching back to at least 1958.

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In association with the LIFE program at www.LIFE-worldwide.org.

Submitted for publication 20 March 2015
Revised 18 May 2015
Accepted for publication 20 May 2015

doi:10.1111/myc.12385

Many fungal infections occur only or almost only in defined populations. Data on these populations allow a crude estimation of the likely incidence and prevalence of fungal infections in each population. Data for many of these specific populations are available in Hungary and these were used to estimate some of the more serious fungal infections. Other uncommon, incidental infections such as fungal keratitis or imported infections could not be estimated.

Methods

To review relevant Hungarian publications PubMed and Hungarian Scientific Bibliography[13] databases have been accessed using search terms 'mycosis' or 'fungal infection' and 'Hungary' or 'Hungarian'. Population statistics downloaded from the website of the Hungarian Central Statistical Office[14] were used. To calculate the cohort size of certain patients at risk, country-specific data from OECD and World Health Organization (WHO) reports were utilised.[15–17] Estimations of incidence and prevalence were derived from relevant studies performed in other countries. Where available, recent epidemiological data from European countries (Italy, United Kingdom and France) published in peer-reviewed papers were accepted.[18–22] Fungal infections other than superficial/dermatological mycoses, recurrent vulvovaginal candidiasis, oropharyngeal and oesophageal candidiasis were considered as being serious or potentially life threatening.

Results

The population of Hungary in 2013 was about 9 908 798 and the gross domestic product $13 480 per person. Hungary is a low birth rate country with about 15% of the population under 16 years of age, and 22% over the age of 60 years.[14]

Incidence in patients treated in intensive care (ICU) or with renal support

With 22 452 yearly ICU admissions[23] and an estimated infection rate (derived from Italy) of 16.5/1000 admissions (for yeast) and 2.3/1000 admissions (for moulds),[18] 370 new cases of yeast infections and 52 mould infections can be expected. Approximately 33% of candidaemia cases occur in ICU, so a national total of about 1110 cases are estimated annually, a relatively high rate of 11 per 100 000. If the rate of *Candida* peritonitis in ICU is as in France,[19] then about 185 such cases are likely each year. Alternative estimates of candidaemia relate to total population estimates and range in Europe from 3 to 10 per 100 000[20,21] or 297 to 991 cases annually in Hungary.

From 780 chronic ambulatory peritoneal dialysis (CAPD) patients, the estimated annual incidence of intra-abdominal candidiasis is about 40/year.[24]

Incidence in haematological and transplant recipients

The estimated incidence of invasive fungal disease (IFD) for patients with acute myeloid leukaemia, recipients of haematopoietic stem cell as well as solid organ transplants is summarised in Table 1. These risk groups account for about 55–57 severe and difficult to treat cases yearly. The estimates are derived from published literature from the USA and Italy of confirmed (proven) cases in the case of solid organ transplant recipients, so are likely to underestimate rates slightly.[22,25,26]

Recurrent vulvovaginal candidiasis

The exact rate of recurrent vulvovaginal candidiasis is not known, however up to 9% of women in their fertile years have reported yearly = >4 episodes of infection.[27] Some of these reflect other conditions, such as bacterial vaginosis,[28] so we have used a 'discounted' figure of 6% to estimate recurrent infection. The number of Hungarian women under 50 years is 2 954 882, thus the affected population size is likely to be 177 294.[15]

Chronic respiratory aspergillosis

An estimated 5.3% of adults have self-reported clinical asthma in Hungary, with an estimated 525 166 sufferers.[15] With around 33% of most severe asthma cases (assumed to be 10%) having hyper-reactivity to

Table 1 Invasive fungal disease (IFD) estimates for patients with acute myeloid leukaemia, recipients of haematopoietic stem cell and solid organ transplants.

	Patients at risk	% IFD	Incidence IFD cases/year
Acute myeloid leukaemia	303	12	36
Allogeneic stem cell transplantation	85	6–8	5–7
Lung transplantation	75	8.6	6
Heart transplantation	58	3.4	2
Liver transplantation	40	4.7	2
Renal transplantation	342	1.3	4
Total			55–57

fungal antigens, the estimated number of patients with severe asthma with fungal sensitisation (SAFS) is 17 330. Not all these patients will have been admitted to hospital and the OECD estimate of asthma admissions of those over 15 years of age of 35 per 100 000 indicates 2947 adult asthma admissions.[16]

Allergic bronchopulmonary aspergillosis (ABPA) affects adult asthmatics and those with cystic fibrosis. The rate of ABPA in asthma has been estimated from 0.7% to 3.5% in five studies, none from central Europe.[29] Using a figure of 2.5%, a cohort of 13 129 adults with ABPA can be estimated. There will be some overlap with SAFS because of *Aspergillus* sensitisation, perhaps 20% of ABPA patients having severe asthma. From the 576 registered individuals with cystic fibrosis, at least 15% (89 patients) are at risk of developing ABPA, although only 238 are older than 18 years, and in this group 40 cases are estimated, and another 84 with *Aspergillus* bronchitis.[30]

The number of admissions to hospital for COPD was 248 per 100 000 in 2009 (OECD),[16] 24 573 patients, some of whom will have had multiple admissions. Assuming a rate of 1.3%,[31] 319 COPD patients are likely to develop invasive aspergillosis annually.

In 2013, Hungary reported 999 cases of pulmonary tuberculosis to World Health Organisation (WHO), of which 430 were bacteriologically confirmed and almost all in non-HIV infected patients.[17] Using previously published means of estimation (a 12% rate in those with a cavity following TB and 2% in those without a cavity), the annual incidence of subsequent chronic pulmonary aspergillosis (CPA) is 32 cases and the 5-year period prevalence is 101 patients.[32] Assuming that tuberculosis is the underlying disease in only 20% of patients, as in the UK,[33] this would suggest there are about 504 patients with CPA in Hungary.

HIV-associated infections

As for HIV-related infections, Hungary remains a low-prevalence country. The number of HIV/AIDS-infected cases under regular medical follow-up is 1080, with 733 cases treated with anti-retrovirals. As up to 90% of untreated patients can have oral candidiasis,[34] this would account for a population size of 312. In the same risk group with a calculated 20% prevalence, 70 patients will likely develop *Candida* oesophagitis. Cryptococcal meningitis is rare. There are about five patients annually diagnosed with *Pneumocystis* pneumonia with AIDS.

Dermatomycoses and other superficial fungal infections

Although not life threatening, these conditions will adversely impact the quality of life of up to 14.3% of total population.[35] Therefore, in Hungary 1 416 958 individuals may be affected.

Discussion

Although patient groups with fungal disease may overlap, it can be estimated that at least 1.6 M people (16% of the total population) might be affected in Hungary (Table 2). The number of difficult to treat and potentially life-threatening mycoses is at least 33 000 annually. This result is significantly higher than previously predicted and an underestimation of the true burden of illness can still be assumed.

Table 2 Yearly incidence estimates for fungal diseases in Hungary.

Condition	Number	Per 100 000
Superficial/dermatological mycoses	1 416 958	14 300.0
Recurrent vulvovaginal candidiasis	177 294	1789.3
Severe asthma with fungal sensitisation	17 330	174.9
Allergic bronchopulmonary aspergillosis	13 129	132.5
Candidaemia	1110	11
Chronic pulmonary aspergillosis total	504	6
Yeast infection in ICU patients	370	3.7
Invasive aspergillosis in COPD	319	3.2
Oropharyngeal candidiasis in HIV	312	3.1
Post-surgical *Candida* peritonitis	185	1.9
Chronic pulmonary aspergillosis post TB	101	1.2
Aspergillus bronchitis in CF	84	0.8
Candida oesophagitis in HIV	70	0.7
IFD in haematology and transplant patients	55–57	0.56–0.58
Mould infection in ICU patients	52	0.5
Intra-abdominal candidiasis in CAPD patients	40	0.4
Allergic bronchopulmonary aspergillosis in CF patients	40	0.4
Pneumocystis pneumonia in HIV	5	0.1
Total affected	1 600 000[1]	16 147
Severe or life threatening	33 000[2]	333

CAPD, chronic ambulatory peritoneal dialysis; CF, cystic fibrosis; COPD, chronic obstructive pulmonary disease; ICU, intensive care unit; IFD, invasive fungal disease; TB, tuberculosis.

[1]Some duplication included.

[2]Infections other than superficial/dermatological mycoses, recurrent vulvovaginal candidiasis, oropharyngeal and oesophageal candidiasis.

The methods used suffer from several limitations. When calculating with incidence rates from studies performed in other countries results should be regarded with caution and should be viewed as approximations. A more precise insight into the fungal epidemiology of Hungary could be gained by collecting relevant local data in a prospective manner. Less severe cases visiting private healthcare providers cannot be captured through central databases. According to OECD data, Hungary had the highest rate of self-reported COPD prevalence in the region (4.7% of total population older than 15 years). To evaluate the true rate of fungus-related complications within this heterogeneous and vulnerable population is extremely difficult. In the highly immunocompromised setting, a steep decrease in autopsy rate of patients deceased in hospitals will also leave more and more fatal mycoses undiscovered. Indeed, the commonest major error for missed infection at autopsy is aspergillosis.[12,36,37] Decision makers and offices responsible for strategic decisions and development of the healthcare system should be aware of the significant burden of serious fungal diseases.

Conflict of interest

JS has received speakers fees and consulting honoraria from Astellas Pharma, Merck Sharp and Dohme, Pfizer and Lilly. MS has no funding to disclose. DWD holds Founder shares in F2G Ltd a University of Manchester spin-out antifungal discovery company, in Novocyt which markets the Myconostica real-time molecular assays and has current grant support from the National Institute of Allergy and Infectious Diseases, National Institute of Health Research, NorthWest Lung Centre Charity, Medical Research Council, Astellas and the Fungal Infection Trust. He acts as a consultant to T2 Biosystems, GSK, Sigma Tau, Oxon Epidemiology and Pulmicort. In the last 3 years, he has been paid for talks on behalf of Astellas, Dynamiker, Gilead, Merck and Pfizer. He is also a member of the Infectious Disease Society of America Aspergillosis Guidelines and European Society for Clinical Microbiology and Infectious Diseases Aspergillosis Guidelines groups. He is also President of the Global Action Fund for Fungal Infections.

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