Antifungal therapy in European hospitals: data from the ESAC point-prevalence surveys 2008 and 2009

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Abstract

The study aimed to identify targets for quality improvement in antifungal use in European hospitals and determine the variability of such prescribing. Hospitals that participated in the European Surveillance of Antimicrobial Consumption Point Prevalence Surveys (ESAC-PPS) were included. The WHO Anatomical Therapeutic Chemical (ATC) classification for 'antimycotics for systemic use' (J02) 2009 version was used. Demographic data and information about indications and diagnoses were collected in 2008 and 2009. From 99 053 patients, 29 324 (29.6%) received antimicrobials. Antifungals represented 1529 of 40 878 (3.7%) antimicrobials. Antifungals were mainly (54.2%) administered orally. Hospital-acquired infections represented 44.5% of indications for antifungals followed by medical prophylaxis at 31.2%. The site of infection was not defined in 36.0% of cases but the most commonly targeted sites were respiratory (19.2%) and gastrointestinal (18.8%). The most used antifungal was fluconazole (60.5%) followed by caspofungin (10.5%). Antifungal–antibacterial combinations were frequently used (77.5%). The predominance of fluconazole use in participating hospitals could result in an increase in prevalence of inherently resistant fungi, increasing the need for newer antifungals. Although acknowledging that antifungal prophylaxis in the immunocompromised host needs further exploration, repetitive surveys using ESAC-PPS methodology may help to monitor the effects of interventions set to regulate antifungal use.

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Introduction

The use of antifungal drugs, including newer agents, has increased in the last two decades, escalating concern about the development of resistance [1]. Most published data report on specific departments such as haematology–oncology and intensive-care units [2–4]. Publications reporting on whole hospital use of systemic antifungals are limited [1,5,6]. Furthermore, these reports were limited to either a single institution or a few hospitals from the same country. In addition, no point-prevalence-survey specifically dedicated to antifungal use could be identified on PubMed. In point-prevalence-surveys on antimicrobial consumption the proportion of antifungals ranged from 3.8% (eight antimycotics for systemic use out of 211 antimicrobials) plus another eight (3.8%) 'antifungals for dermatological use' giving a total of 7.6% in a paediatric hospital in north-western Russia [7] to 6.7% (88 of 1317 antimicrobials) in Turkish paediatric hospitals [8]. This shows that different inclusion and exclusion criteria can give rise to different values being reported.

The epidemiology of invasive fungal infections varies by geographic region, age and time [9]. The improvement in quality of health care has increased the population at risk for

developing invasive fungal infections. The most common yeast infections are caused by *Candida* spp. and *Cryptococcus* spp. whereas *Aspergillus* spp. remain the most frequently isolated moulds, although other filamentous fungi (*Fusarium* spp., *Scedosporium* spp., *Penicillium* spp. and *Zygomycetes*) are becoming more common [10–12]. For example, *Candida albicans* is the major pathogen in candidaemia, found in between 50% of candidaemia in Spain to 70% in Finland and Norway [9,13,14]. In a Spanish hospital the proportion of non-albicans candidaemia was greater than that caused by *C. albicans* [15]. The ARTEMIS DISK global antifungal susceptibility surveillance programme for 1997–2007 and other smaller studies have reported an increase in the proportion of *Candida glabrata*, a less susceptible species than *C. albicans* [16,17]. Despite non-albicans candidaemia being more likely to be fluconazole resistant, the crude and 14-day mortality rates from a Brazilian intensive-care unit were comparable [18]. Furthermore, the incidence of candidaemia caused both by *C. albicans* and non-albicans *Candida* spp. was reported to have increased in a report from Austria [6]. Therefore, rational use of antifungal agents is an important aspect of any antimicrobial stewardship programme. Antifungals are prescribed as an empiric or targeted therapeutic indication, as pre-emptive treatment, or as long-term medical prophylaxis in immunocompromised patients (e.g. in neutropenic patients [19], liver transplant patients [20] or haematopoietic stem cell transplantation [21,22]). Shifting from empirical to pre-emptive therapy may reduce the number of patients treated unnecessarily [23]. A recent systematic review suggested that some drugs may be superior to others depending on the specific indications (empiric vs. pre-emptive vs. directed therapy) [24]. Therefore, validation of pre-emptive strategies will probably lead to the development of evidence-based guidelines for targeted use of antifungals [25].

The first step in rationalizing prescription is the surveillance of use with the aim of identifying areas of practice that could be improved. In fact, the objectives of this report were to determine the variability or predictability of antifungal use in participating hospitals, and to identify targets for quality improvement for antifungal use in hospitalized patients.

Patients and Methods

The methodology used was the standardized European Surveillance of Antimicrobial Consumption Point Prevalence Surveys (ESAC-PPS) methodology [26]. In brief, this methodology required participating hospitals to carry out the survey, in a maximum of 2 weeks, within a given time window (May–June 2008 for the first survey and May–June 2009 for the second survey). Each department (e.g. Medical) had to be completed in a single day. All inpatients, i.e. patients whose total hospital stay was at least 24 h, on the respective ward census at 08:00 h on the survey date had to be assessed and included in the denominator. This information was recorded on the 'department form'.

Patients receiving antimicrobials at 08:00 h on the day of the survey were identified and the details of prophylaxis or therapy were recorded using the 'patient-form'. Antimicrobials in J01, J02, A07AA, P01AB, D01BA, and J04AB02 according to the World Health Organization (WHO) Collaborating Centre for Drug Statistics anatomical therapeutic chemical (ATC) classification were included in the survey. Rifampicin was recorded for any indication excluding tuberculosis. Those patients on systemic antifungal agents (J02) were extracted from the respective databases of ESAC-PPS of 2008 and 2009 for the purpose of this analysis. These were merged into one database for systemic antifungals. All antimicrobial treatment for the same indication in these same patients was taken into consideration for analysis of combination therapy of antifungal with antibacterial agent(s).

Hospitals that participated in both PPS were considered only once taking into account the most recent year of participation (2009). Fifty hospitals (from 28 European countries) participated in ESAC-PPS 2008, 36 of which formed part of the 172 (from 23 countries) hospitals that participated in ESAC-PPS 2009 so the total number of hospitals was 186. For those hospitals that participated in both surveys a comparison of antifungal prevalence was performed.

Statistical analysis

To determine the validity of differences between proportions, the exact binomial 95% confidence interval was calculated. Whenever the upper limit of the lower proportion did not overlap with the lower limit of the higher proportion the difference was unlikely to be due to chance. The *Z*-test was used to compare proportions of antibacterial versus antifungal use in different age groups.

Results

Hospitals

Out of 186 hospitals, 39 (21.5%) did not record any use of antifungal agents on the survey date. For the remaining 147 hospitals the median proportion of antifungals was 2.5% (interquartile range 0.8–4.6%) of all anti-infective agents. The 28 hospitals that participated in both surveys and recorded use of antifungals showed only marginal differences between the

two surveys. Indeed a lower total number of antifungal prescriptions with a higher median was observed in 2008 (2008: 258 prescriptions—median 6.5, interquartile range 2.0–11.3; 2009: 317 prescriptions—median 6.0, interquartile range 2.0–11.0).

Patients

From a total of 99 053 admitted patients, 29 324 (29.6%) received antimicrobials. Antifungals represented 3.7% (1529 prescriptions in 1499 patients) of all 40 878 antimicrobial prescriptions (Fig. 1). Hence, 5.1% (1499 of 29 324) of all treated patients received antifungals. The number and proportion of antifungal prescriptions increased up to the 60–75-year age group (31.2% of total antifungal prescriptions) and decreased in patients >75 years, unlike antibacterials, the proportion of which kept on increasing with age (Fig. 2). (The data shown in this figure were presented during an oral presentation during the 20th European Congress of Clinical Microbiology and Infectious Diseases: Vienna, Austria on 13 April 2010 without the p values). The proportions were significantly different in all age groups except the younger two groups.

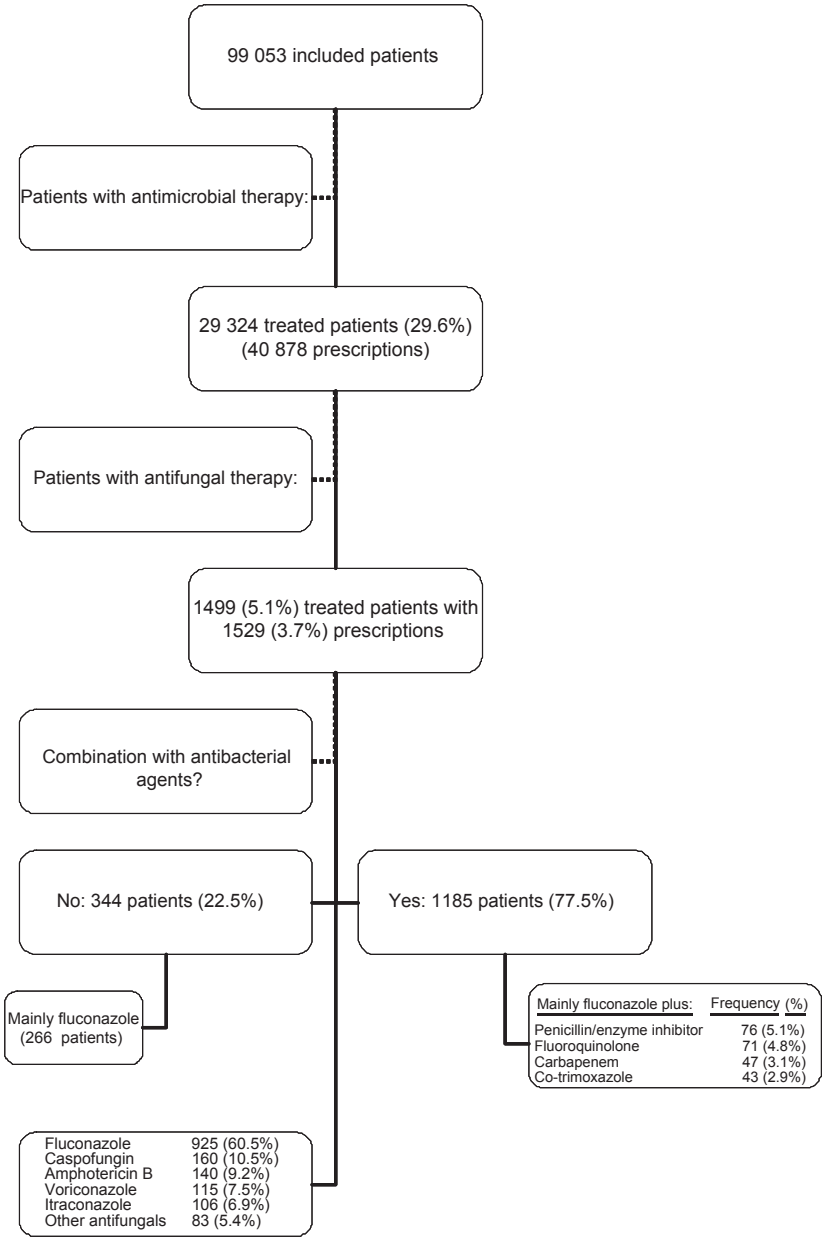

FIG. 1. Flowchart depicting a summary of: included patients; antifungal drugs used and combination of antibacterials with fluconazole.

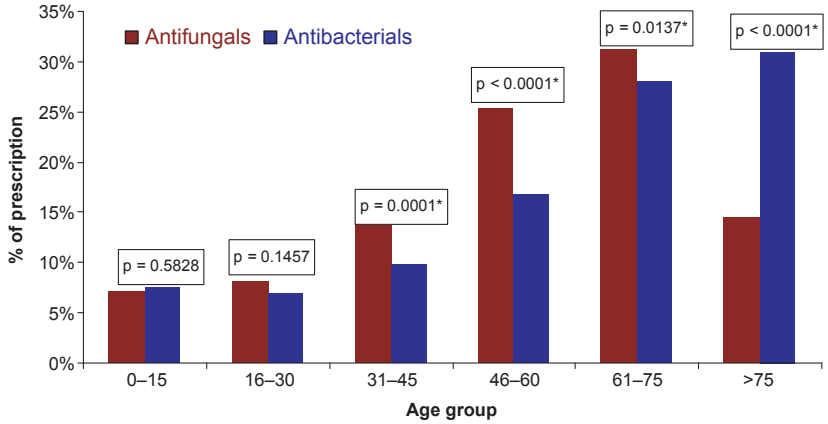

FIG. 2. Proportion of antimicrobial prescriptions (antifungals (dark red) and antibacterials (blue)) by different age group. The p-value is shown above each age group column pair and denote by an * whenever significant.

Prescriptions

The proportion of oral prescriptions was 54.2% (95% CI 51.6–56.7%) for all antifungal agents and 61.2% (95% CI 58.1–64.5%) for fluconazole. The latter was the most used antifungal agent accounting for 60.5% (95% CI 58.0–63.0%) of prescriptions (Fig. 1). Caspofungin, a relatively novel echinocandin, was the second most used antifungal agent (10.5%; 95% CI 9.0–12.1%). The relative proportion for the five most commonly prescribed antifungal agents is shown in Fig. 3.

Antifungals were mainly used in combination with antibacterial agents (77.1%; 95% CI 74.9–79.2%) and not as monotherapy. The most frequently used combinations included fluconazole plus either, a β-lactam (penicillin with enzyme inhibitor or carbapenem—50.5%; 95% CI 47.9–53.1%) or, a fluoroquinolone (ciprofloxacin or levofloxacin—16.3%; 95% CI 14.4–18.2%).

Hospital-acquired infections represented 44.5% (95% CI 42.0–47.1%) of indications for antifungals followed by medical prophylaxis at 31.2% (95% CI 28.9–33.6%). The overall proportion of antifungal use for HAI ranged from 1.2% in patients admitted in surgical departments to 5.8% in patients admitted in intensive-care units. The proportion of antifungal agents also varied by indication. These proportions ranged from 15.9% of antimicrobial agents used in medical prophylaxis to 0.2% of drugs used for surgical prophylaxis. The most commonly targeted sites were respiratory (19.2%) and gastrointestinal (18.8%). However, in 36.0% of cases no specific site was targeted. This was mainly attributed to 51.4% of medical prophylaxis and 33.9% of HAI. Figure 4 highlights differences in the actual antifungal agents by specialty and indication, respectively. For example, caspofungin was more frequently used in intensive-care units and for HAIs whereas itraconazole was mainly used as medical prophylaxis within medical departments.

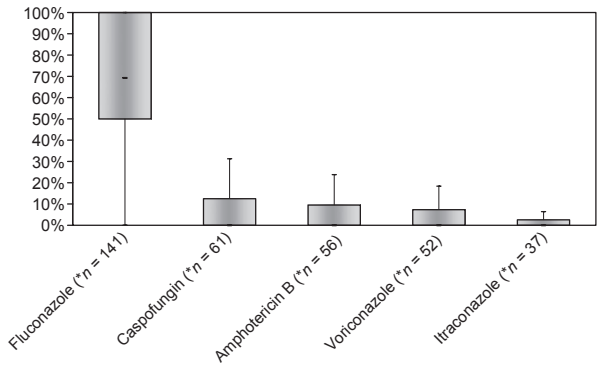

FIG. 3. Distribution of prescriptions for the five most used antifungal agents. *n denotes the number of hospitals in which the drug was prescribed on the survey date.

Specialty and indication also influenced considerably the distribution of route of administration. The parenteral route was dominant in intensive-care units (88.3%; 95% CI 81.9–91.9% parenteral vs. 11.7%; 95% CI 8.1–16.1% oral) whereas the oral route was predominant in medical wards (66.3%; 95% CI 63.3–69.1% oral vs. 33.7%; 95% CI 30.9–26.7% parenteral). In surgical patients the predominance of the parenteral route (55.4%; 95% CI 47.5–53.0%) was not significantly different from the oral route (44.6%; 95% CI 37.0–52.5%). With respect to route of administration by indication, the treatment of community-acquired infections showed the least difference with 43.5% (95% CI 36.2–48.9%) parenteral and 56.5% (95% CI 51.1–61.8%) oral. In medical prophylaxis the oral route was used predominantly (76.5%; 95% CI 72.5–80.3%). Conversely, in the treatment of HAI the most used route of administration was the parenteral route (62.8%; 95% CI 59.1–66.5%).

Discussion

Antifungal agents represent a relatively small proportion of antimicrobial agents within the hospital setting. In our study

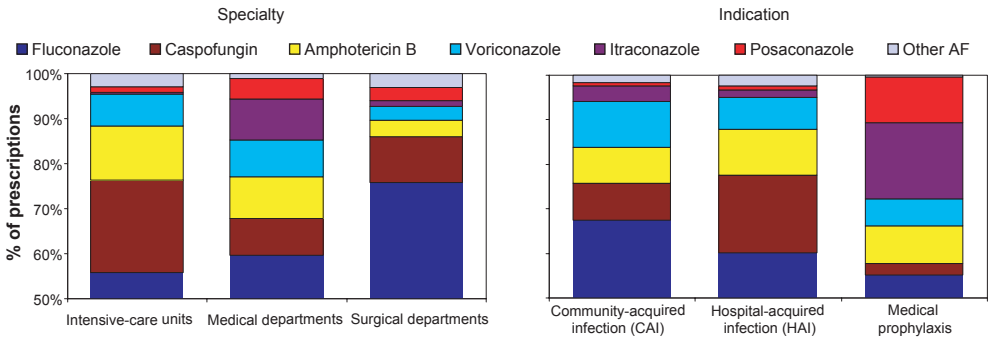

FIG. 4. Varying proportion of antifungals by specialty and by indication.

the proportion of antifungal agents was equivalent to a median of 2.5% or an overall proportion of 3.7%. However, certain departments (e.g. intensive-care and oncology–haematology units) are more intense users [1]. In our study medical prophylaxis accounted for >30% of antifungal use and could therefore be used as a quality indicator by specific institutions or health systems. The epidemiology of opportunistic invasive fungal pathogens varies by type of patient [27] so different departments would have specific consumption patterns. Therefore, prophylaxis in the immunocompromised host needs further exploration and should be studied in the specific context of this sub-population.

The use of empiric fluconazole in intensive-care units in adults with risk factors for invasive candidiasis is widely practised despite the fact that it is not clearly proven to improve outcome compared with placebo [28]. Furthermore, if used at all, it should be reserved for patients with a high risk of developing fungal infections [29] or in units with high incidence of candidaemia [30].

In our study the second most used antifungal for medical prophylaxis was itraconazole. Medical prophylaxis is widely practised in immunocompromised patients who are undergoing chemotherapy or radiotherapy or who are receiving immunosuppressant therapy following a transplant. Haematology–oncology units have already been identified as intense users of systemic antifungal agents in the early 2000s [1]. Case reports from Singapore reported that antifungal prophylaxis with newer agents (caspofungin and voriconazole) resulted in patients developing resistant invasive fungal infections [31]. This suggests that previous exposure to antifungal agents is a risk factor for resistant fungal infections. Therefore prophylaxis should not be used in all patients. Indeed in liver transplant patients without high-risk factors, antifungal prophylaxis does not seem to be justified [20] whereas, in haematopoietic stem cell transplantation the newer agent micafungin was reported to be more cost-effective than fluconazole [21,22].

Medical prophylaxis is also encountered in the community setting as most patients receiving antifungal prophylaxis during their immunosuppression are admitted as day-cases for administration of their chemotherapy. However, this use in the community is minimal. In fact, antifungal consumption in the community relies on terbinafine (>50% of prescriptions) [32]. Our results showed a predominance of a different drug (fluconazole >50%), whereas terbinafine was only used in nine of our patients so it was not included in this analysis.

This high predominance of fluconazole use is another potential quality indicator. Its use has been reported to remain unchanged with the introduction of new antifungal classes [1]. Indeed, following the introduction of the first novel antifungal agent, voriconazole, in 2003, the latter was being used instead of amphotericin B rather than fluconazole. Our results, which are similar to those from an intensive-care units study from the USA, [33] showed that caspofungin was the second most used antifungal agent but voriconazole ranked lower than amphotericin B. This predominance of fluconazole could lead to a rise in the prevalence of inherently resistant fungi (e.g. *Candida krusei* and *Candida glabrata*) [34]. Fluconazole prophylaxis in a French hospital decreased the cases of candidaemia but increased the prevalence of *C. glabrata* isolation [5]. Over-reliance on fluconazole could also promote the development of resistance in *Candida* spp. that are usually considered to be fluconazole susceptible (e.g. *C. albicans*). However, increased consumption of newer antifungals also has its untoward effects. Increased caspofungin usage was associated with an increased incidence of *Candida parapsilosis* candidaemia, as well as, a reduction in *Candida tropicalis* and *C. glabrata* candidaemia [35]. Certain laboratories only carry out species identification for *Candida* spp. as standard practice because this is usually synonymous with a specific susceptibility profile. Antifungal susceptibility testing might become a necessary standard practice in clinical practice for *Candida* spp.

Unnecessary or inappropriate antifungal use is another indicator of quality because, apart from selecting for resistance, it contributes to elevated pharmacy costs [36]. In various settings, such as the intensive-care setting, more costly second-line antifungal agents are often started based on isolation of *Candida* spp. from respiratory secretions, which should be regarded as contaminants [1]. Indeed inappropriate antifungal therapy has been reported as being 'frequent' and associated with increased length of stay in intensive-care units [33].

Another possible performance indicator is the route of administration. This has to be based on specific departments because there is no universal standard quantifying what the appropriate percentage of oral antifungal use might be in different settings. For instance, a high proportion of parenteral fluconazole in haematology–oncology patients could be inappropriate because this drug has 90% oral bioavailability [37]. In addition, haematology–oncology patients would be prone to opportunistic fungal infections including moulds (e.g. *Aspergillus* spp.) [38]. Therefore, fluconazole would not be the best drug because it is not active against these opportunistic pathogens.

A possible improvement on our methodology could be the inclusion of specific fungal infection identification to enable comment on the drugs used in the treatment of such infection. This was, however, not possible in our study because we did not collect such detailed information on the infections. However, the spin-off PPS organized by the European Centre for Disease Prevention and Control will collect data on HAI, microorganisms as well as antimicrobials used [39]. This could possibly analyse data for correlation between fungal infections and antifungal use.

The lower proportion of antifungals prescribed in patients aged 75 years or more compared with that of antibacterial agents was not anticipated. These patients have a lower level of immunity and are more likely to acquire not only bacterial but also fungal infections. Therefore, it would have been expected that the respective prescription distribution for both antibacterial and antifungal agents would follow similar trends.

In conclusion, continual surveillance of antifungal consumption using the ESAC-PPS methodology is feasible and could identify lacunae in guidance or practice. In turn, targeted interventions to encourage appropriate antifungal prescribing could be put in place. The effectiveness of such interventions in improving the quality of antifungal prescriptions could be evaluated by means of repeated surveys. This is important both from the epidemiological aspect of slowing down development of resistance as well as reducing costs because novel antifungal agents account for a considerable proportion of pharmacy costs.

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Transparency Declaration

The authors have no conflicts of interest to declare.

Disclaimer

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