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Healthcare burden of probable and proven invasive mucormycosis: a multi-centre cost-of-illness analysis of patients treated in tertiary care hospitals between 2003 and 2016

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SUMMARY

Background: Invasive mucormycosis (IM) is a rare invasive fungal infection with a high mortality rate. However, data concerning the clinical and economic burden of IM are scarce.

Aim: To evaluate the direct treatment costs and additional expenditures of patients with IM.

Methods: A retrospective cost-of-illness analysis of cases with IM extracted from FungiScope – Global Registry for Emerging Fungal Infections, accessible through the epidemiological research platform www.ClinicalSurveys.net, was undertaken. Results of patients with IM were compared with those of matched patients with similar underlying conditions based on the German Diagnosis Related Group (G-DRG) coding.

Findings: Out of 46 patients with probable/proven IM, 31 (67%) patients were male and the median age was 53 years (range 11–88 years). Forty-two patients (92%) had haematological diseases as the most common risk factor. Analysis of cost factors identified antifungal treatment due to IM as the primary cost driver [€22,816, 95% confidence interval (CI) €15,036–32,346], with mean overall direct treatment costs of €53,261 (95% CI €39,660–68,825). Compared with matched patients, patients with IM were treated in hospital for 26.5 additional days (standard deviation 31.8 days; $P < 0.001$), resulting in mean additional costs of €32,991 (95% CI €21,558–46,613; $P < 0.001$). Probable IM, as well as absence of chemotherapy, surgical measures due to IM, and antifungal prophylaxis

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were associated with lower overall costs. Nineteen patients (41.3%) died during hospitalization.

Conclusion: This study demonstrates the considerable healthcare burden of IM. The choice of antifungal agent for treatment of IM had no impact on overall cost.

Introduction

Invasive mucormycosis (IM) is a rare invasive fungal infection with an incidence rate of <0.1 per 10,000 patients per year in the European Union [1]. Although the epidemiology of IM is difficult to study due to its low incidence rate and diagnostic limitations, European nation-wide and single-centre studies have shown an increase in incidence rate over the past decades [2,3]. Immunocompromised patients with haematological diseases are at particular risk of IM, with mortality rates up to 91%. IM mainly starts within the respiratory system or the sinuses, from where it may spread locally or through the bloodstream [4–7]. The current European Society for Clinical Microbiology and Infectious Diseases (ESCMID) and European Confederation of Medical Mycology (ECMM) guidelines for diagnosis and management of mucormycosis recommend liposomal amphotericin B (LAmB) followed by oral posaconazole for targeted first-line treatment of mucormycosis [8]. As an additional antifungal agent for IM, isavuconazole was approved by the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) in 2015, after matched comparison had shown similar response rates to isavuconazole compared with amphotericin-B-based treatments [9]. Early antifungal treatment is crucial in reducing mortality [7]. Furthermore, surgical procedures in addition to adequate antifungal therapy seem to improve patient outcome [4,10].

The considerable economic burden of IM, especially due to prolonged hospitalization, has been reported previously by Zilberberg *et al.* [11]. This study, conducted in acute care US hospitals, reported a significantly higher hospital length of stay (LOS) (+16.5 days) as well as mean additional costs of US$ 64,526 per patient if IM was diagnosed. A further study from US hospitals showed mean additional costs for patients with IM of US$ 31,849 and mean excess LOS of 10.6 days [12]. Based on a macro-costing approach without detailed analysis of antifungal drug costs, both studies reported total costs of patients with IM to be up to three-fold higher than those of control patients. Another recently published cost-of-illness analysis by Kontoyiannis *et al.* demonstrated mean daily and overall hospitalization costs per patient with IM of US$ 4096 and US$ 112,419, respectively [13]. To the authors' knowledge, no European data on the health economic burden of IM have been published. As such, a micro-costing cost-of-illness analysis of patients with IM treated in tertiary care centres in Germany was performed.

Methods

Source

The primary aims of this cost-of-illness analysis were to detect additional treatment costs and the most important cost drivers in the treatment of IM. Patients with probable/proven IM based on EORTC/MSG criteria [14], treated in tertiary care centres in Germany, were extracted from the FungiScope – Global Registry for Emerging Fungal Infections [15]. The FungiScope registry, set up in 2003 by researchers at the University Hospital of Cologne (UHC), collects comprehensive data on demography, diagnostics, pathogen biology, site of infection, treatment and outcome of patients with rare invasive fungal infections, including mucormycosis [9,16,17]. As no detailed direct treatment cost items are documented in FungiScope, a separate registry was set up and physicians were invited to provide additional information concerning direct cost data of treatment they had previously documented in FungiScope. For health economic evaluation, a comprehensive data collection was performed, including duration of mechanical ventilation, duration of stay on specific hospital wards [general ward, intermediate care unit, bone marrow transplant ward, intensive care unit (ICU)], antifungal treatment (indication, agent, dose, and duration), main and secondary diagnosis International Classification of Diseases (ICD) codes, main German Diagnosis Related Groups (G-DRG) code, and German Procedure Classification (OPS) codes for additional diagnostic and/or treatment measures due to IM. All data were documented retrospectively after the patients had completed treatment. The electronic case report forms were available on the online platform www.ClinicalSurveys.net, which was developed in cooperation with Globalpark AG, Hürth, Germany (now QuestBack GmbH, Cologne, Germany). Time to follow-up was restricted until the end of hospitalisation.

Cost analysis

The cost-of-illness analysis was performed in the context of the German healthcare system and based on national guidelines [18,19], whereby direct treatment costs alone were analysed because of the severity of underlying diseases. Based on the collected data items, the following direct treatment cost factors were analysed: (i) treatment on general ward; (ii) treatment on intermediate care unit; (iii) treatment on bone marrow transplant ward; (iv) treatment on ICU; (v) imaging; (vi) diagnostic measures; (vii) laboratory tests; and (viii) use of antifungal agents for empirical and/or targeted treatment. Direct treatment cost parameters i–vii were calculated based on the G-DRG system, known as the official reimbursement system for inpatient treatment in German hospitals (InEK GmbH, Siegburg, Germany). Thus, by using the nationwide G-DRG InEK matrix, direct personnel costs (medical, nursing and technical service) as well as direct material costs (e.g. medical products) were considered in the cost-of-illness analysis. The InEK matrix is the largest publicly available inpatient health care database in Germany. It contains data from more than 250 hospitals in Germany with over 4.4 million inpatient stays per year, and represents a 20–25% sample of all inpatient stays in Germany [20]. Out of these data, approximately 1200

individual G-DRGs have been developed since introduction of the G-DRG system in Germany in 2003, which are scaled into 25 major diagnostic categories (MDCs). Each G-DRG encompasses patients who have similar underlying conditions, and whose care regularly requires a similar amount of resources to treat. Identification of specific individuals is not possible because the InEK matrix only represents cumulative values of anonymized patient data provided by the participating hospitals. Direct treatment costs for antifungals (cost factor viii) were calculated using WEBAPO LAUER-Taxe (Lauer-Fischer GmbH, Fürth, Germany). This database offers comprehensive information on pharmaceutical products (e.g. drug prices, changes of drug prices, vendor, manufacturer).

In combination with a calculation of overall direct treatment costs of patients with IM, results concerning overall LOS and overall direct treatment costs of patients with IM were compared with cumulative data of patients with similar G-DRG as stated in the G-DRG InEK matrix [20]. Besides a detailed overview of personnel and material costs as mentioned above, patient demographics (e.g. distribution of age and sex), mean cumulative values of overall LOS, as well as direct cost factors for inpatient treatment are given within the G-DRG InEK matrix for each G-DRG. To avoid biased results due to changes in treatment costs and LOS between the years, each patient with IM was matched with cumulative data of patients with similar G-DRG within the same year of treatment. For the analysis of LOS and direct treatment costs, data and calculated values of the patients with IM documented in the FungiScope registry, as well as the additional cost registry, were compared with the mean cumulative values of LOS and direct treatment costs as presented in the G-DRG InEK matrix. The LOS and direct treatment costs attributable to IM were estimated as the difference between the mean values of each patient with IM and the matched patients with similar G-DRG.

This micro-costing cost-of-illness analysis observed a timeframe of 14 years. Discounting of all costs was performed with a discount rate of 5% per year. A sensitivity analysis of different annual discount rates (0%, 3%, 10%) was performed, and annual variations in drug prices as well as each coded G-DRG were considered [21]. All direct treatment costs were expressed in Euros (€; 2016 values). In addition, a further sensitivity analysis of LOS, duration of empirical antifungal treatment, overall direct treatment costs, and direct treatment costs for empirical antifungal treatment prior to definitive diagnosis of probable/proven IM was undertaken.

Statistical analysis

Statistical analyses were performed using SPSS Version 23.0 (IBM Corp., Armonk, NY, USA). For descriptive purposes, treatment duration and cost data are presented as median [range or interquartile range (IQR)] and/or mean [95% confidence interval (CI) or standard deviation (SD)], as appropriate. Non-parametric Mann-Whitney U-test was applied to test the statistical significance of overall LOS, and Welch's bootstrapped *t*-test for non-normally distributed costs was used for comparison of patient groups. Bootstrapping was performed using 10,000 samples, and the starting point for the Mersenne Twister was 1000. A *P*-value <0.05 was considered significant. In addition, a multi-variate generalized linear model (GLM) with gamma distribution and log-link was used to analyse variables influencing overall direct treatment costs of patients with IM [22]. Prior to GLM, a univariate analysis was performed, and all variables with $P < 0.1$ were included in the model. The GLM reported odds ratios (OR) as well as 95% CI, and the level of significance was <0.05.

Ethical considerations

The cost-of-illness analysis was a strictly non-interventional retrospective chart review with a limited dataset. The FungiScope registry was approved by the ethics committee of UHC (local approval: 05-102) and is registered with ClinicalTrials.gov (No. NCT01731353). Data documentation was performed anonymously, such that informed consent from patients was waived.

Results

Patient characteristics

Overall, 46 patients (22 patients with probable IM and 24 patients with proven IM) from five German tertiary care centres were included in the cost-of-illness analysis. All patients were hospitalized between 2003 and 2016, no patient was included twice, and no outbreaks of nosocomial IM were reported during the observed timeframe. Most patients were male ($N = 31$; 67.4%), and acute myeloid leukaemia ($N = 21$; 45.7%) was the predominant primary underlying disease. Median age was 53 years (range 11–88 years), and the most common risk factors for IM were haematological disorders ($N = 42$; 91.3%), chemotherapy ($N = 29$; 63.0%) and allogeneic stem cell transplantation ($N = 17$; 37.0%). The majority of patients were coded in MDC group 17 ('haematological and solid neoplasms'). IM was mainly restricted to pulmonary involvement ($N = 25$; 54.3%). Thirty patients (65.2%) received antifungal prophylaxis prior to diagnosis of IM, and posaconazole was used most frequently ($N = 11$; 23.9%). Further demographics and baseline characteristics are summarized in Table I.

Treatment durations

On average, patients with IM were treated on a general ward for 36.9 days (SD 29.9 days), on an intermediate care unit for 1.5 days (SD 5.8 days), on a bone marrow transplant ward for 9.7 days (SD 20.6 days), and on an ICU for 8.6 days (SD 17.6 days) (Table II). Mean duration of mechanical ventilation was 154.8 h (SD 378.9 h). Forty-four patients (95.6%) received empirical and/or targeted antifungal therapy due to IM. LAmB was the most commonly prescribed antifungal agent (34 patients received LAmB for at least 96 h), followed by posaconazole (28 patients), caspofungin (14 patients) and voriconazole (11 patients) for at least 96 h. Concerning the most important additional medical procedures performed in association with IM, 17 patients (37.0%) underwent surgery (primarily lung resection). Furthermore, the mean number of IM-related computed tomography and/or magnetic resonance tomography scans per patient was 4.3 (SD 3.6). Nineteen patients (41.3%) with IM died during their hospital stay. Group comparison demonstrated a mean additional LOS of 26.5 days for patients with IM (Table IV).

Table I
Patient characteristics

Item	Probable/proven IM ($N = 46$)
Age (median; range)	53 (11–88)
Female gender (*N*; %)	15 (32.6)
Primary underlying disease (*N*; %)	
ALL	6 (13.0)
AML	21 (45.7)
Multiple myeloma	5 (10.9)
NHL	4 (8.7)
Other	10 (21.7)
Risk factors for IM (*N*; %)	
Allogeneic SCT	17 (37.0)
Chemotherapy	29 (63.0)
Haematological disease	42 (91.3)
Neutropenia (<500 neutrophils/μL)	25 (54.3)
Solid organ transplantation	2 (4.3)
Type of IM (*N*; %)	
Probable	22 (47.8)
Proven	24 (52.2)
Pathogen (*N*; %)	
Cunninghamellaceae spp.	2 (4.3)
Lichtheimiaceae spp.	12 (26.1)
Mucoraceae spp.	5 (10.9)
Mucorales moulds[a]	13 (28.3)
Rhizopodaceae spp.	14 (30.4)
Location of IM (*N*; %)	
Lungs only	25 (54.3)
Lungs and other organs	13 (28.3)
Other than lungs	8 (17.4)
Patients with surgical measures due to IM (*N*; %)	17 (37.0)
Antifungal prophylaxis prior to diagnosis of IM (*N*; %)	
Fluconazole alone	4 (8.7)
Posaconazole alone	11 (23.9)
Voriconazole alone	7 (15.2)
Other/combination	8 (17.4)
No antifungal prophylaxis	16 (34.8)
Inpatient mortality rate 14 days following diagnosis of IM (*N*; %)	8 (17.4)
Inpatient mortality rate 30 days following diagnosis of IM (*N*; %)	12 (26.1)
Inpatient mortality rate at the end of hospitalization (*N*; %)	19 (41.3)

ALL, acute lymphatic leukaemia; AML, acute myeloid leukaemia; IM, invasive mucormycosis; NHL, non-Hodgkin's lymphoma; SCT, stem cell transplantation.
[a] No species differentiation available.

Direct treatment costs

As presented in Table III, mean overall direct treatment costs of patients with IM were €53,261 (95% CI €39,660–68,825). The most important cost driver was antifungal treatment (€22,819 per patient; 95% CI €15,036–32,346), meaning that approximately 40% of mean overall direct treatment costs were attributed to antifungal drug acquisition. The second key cost driver was treatment on specialized care units (i.e. bone marrow transplant ward, ICU, intermediate care unit), accounting for €16,630 (95% CI €10,283–22,977) per patient. In addition, mean costs per patient were €6653 (95% CI €4615–8875) for treatment on a general ward, €4518 (95% CI: €3372–5755) for laboratory tests, €1362 (95% CI €1052–1720) for diagnostic measures and €1279 (95% CI €871–1769) for imaging. Sensitivity analysis of different annual discounting rates (0%, 3%, 10%) showed mean overall costs of €65,552 (95% CI €50,670–82,448), €57,648 (95% CI €43,578–73,656) and €44,577 (95% CI 31,882–59,183), respectively. Table IV gives an overview of direct treatment costs of 46 patients with IM, as well as those of matched patients with similar underlying conditions based on the G-DRG coding. Mean overall direct treatment costs of matched patients were €20,269 (95% CI €14,707–26,653). Additional direct treatment costs per patient with IM were calculated to be €32,991 (95% CI 21,558–46,613; $P < 0.001$). As demonstrated by a further sensitivity analysis, mean/median LOS prior to definitive diagnosis of probable/proven IM was 24.1 days (SD 21.1 days) and 19.5 days (IQR 6.5–38.3 days), respectively. Within this timeframe, the mean/median duration of empirical antifungal treatment prior to definitive diagnosis of probable/proven IM was 22.4 days (SD 27.3 days) and 13.5 days (IQR 0–40 days), respectively. With respect to the health economic burden, the mean/median direct treatment costs for empirical antifungal therapy due to IM were €6827 (95% CI €3680–9973) and €1660 (IQR €0–9519), resulting in mean/median overall direct treatment costs prior to definitive diagnosis of probable/proven IM of €18,582 (95% CI €12,811–24,353) and €11,414 (IQR €4493–27,453), respectively. Between hospital admission and initiation of empirical antifungal therapy due to probable/proven IM, the mean/median overall direct treatment costs were €1290 (95% CI €930–1649) and €891 (IQR €524–1780), respectively.

Next to the micro-costing calculation of overall direct treatment costs of patients with IM, the GLM showed several variables influencing overall direct treatment costs of patients with IM. The most important variables associated with a reduction in overall direct treatment costs were absence of antifungal prophylaxis (OR 0.490; 95% CI 0.324–0.740) and absence of chemotherapy (OR 0.578; 95% CI 0.337–0.990). Age <60 years was associated with 80% higher overall direct treatment costs (OR 1.804; 95% CI 1.251–2.601). The choice of primary antifungal treatment for IM, organ affected by IM, and allogeneic stem cell transplantation during hospitalization were found to have no influence on overall direct treatment costs. Further predictors for a reduction in overall direct treatment costs are given in Table V.

Discussion

Based on a micro-costing approach, the comprehensive cost-of-illness analysis demonstrates the economic burden of patients with IM treated in German tertiary care hospitals. Mean overall direct treatment costs of patients with IM were €53,261, and thus more than 2.5-fold higher than costs of matched patients with similar underlying conditions based on the G-DRG coding. Cases were treated for 26.5 additional in-hospital days ($P < 0.001$). The most important cost driver identified was antifungal treatment. To the authors' knowledge, this is the first study to analyse clinically relevant factors influencing overall direct treatment costs of patients with IM.

Table II
Treatment durations of patients with invasive mucormycosis (IM)

Item	Probable/proven IM ($N = 46$)
Duration (days) on different hospital wards, mean (SD); median (IQR)	
Bone marrow transplant ward	9.7 (20.6); 0 (0–6.3)
General ward	36.9 (29.9); 33.5 (10–58.5)
Intensive care unit	8.6 (17.6); 1 (0–7.8)
Intermediate care unit	1.5 (5.8); 0 (0–0)
Overall	56.4 (34.3)[a]; 46.5 (30.3–83.3)
Duration (h) of mechanical ventilation, mean (SD); median (IQR)	154.8 (378.9); 0 (0–72)
Duration (days) of empirical and/or targeted antifungal treatment due to IM, mean (SD); median (IQR)[b]	
Caspofungin	8.3 (18.2); 0 (0–6.5)
LAmB	25.2 (28.3); 15.5 (0–33.3)
Posaconazole (po and iv)	24.3 (36.7); 9 (0–33.5)
Voriconazole (po and iv)	5.9 (16.4); 0 (0–5.3)
Other	n.a.
Number of CT and/or MRT scans per patient due to IM (mean; SD)	4.3 (3.6)

CT, computed tomography; IQR, interquartile range; iv, intravenous; LAmB, liposomal amphotericin B; MRT, magnetic resonance tomography; po, per os; SD, standard deviation.
[a] Inconsistent sum due to rounding errors.
[b] Antifungal monotherapy and combination therapy included.

Table III
Direct treatment costs of patients with invasive mucormycosis (IM)

Direct treatment cost factors in Euros (€)	Probable/proven IM ($N = 46$)
Treatment on different hospital wards, mean (95% CI); median (IQR)	
Bone marrow transplant ward	7131 (3216–11,815); 0 (0–4386)
General ward	6653 (4615–8875); 3550 (880–9022)
Intensive care unit	7999 (3703–13,364); 922 (0–6159)
Intermediate care unit	1500 (258–3400); 0 (0–0)
Imaging, mean (95% CI); median (IQR)	1279 (871–1769); 693 (437–1480)
Diagnostic measures, mean (95% CI); median (IQR)	1362 (1052–1720); 1160 (533–1717)
Laboratory tests, mean (95% CI); median (IQR)	4518 (3372–5755); 3383 (1031–7624)
Drug costs for empirical and/or targeted antifungal treatment, mean (95% CI); median (IQR)	22,819 (15,036–32,346); 13,029 (5449–24,694)
Overall direct treatment costs, mean (95% CI); median (IQR)	53,261 (39,660–68,825); 35,765 (18,090–69,350)
Sensitivity analysis of overall direct treatment costs with different discount rates per year, mean (95% CI); median (IQR)	
0%	65,552 (50,670–82,448); 46,565 (25,657–88,000)
3%	57,648 (43,578–73,656); 40,905 (20,544–78,620)
10%	44,577 (31,882–59,183); 26,654 (12,763–59,947)

CI, confidence interval; IQR, interquartile range.

Table IV
Comparison of overall length of stay and overall direct treatment costs of patients with invasive mucormycosis (IM) vs matched patients based on similar German Diagnosis Related Group from the InEK matrix

Item	Probable/proven IM ($N = 46$)	InEK matrix data	Difference	*P*-value
Overall LOS in days mean (SD); median (IQR)	56.4 (34.3); 46.5 (30.3–83.3)	29.9 (17.5); 25.6 (17.9–40.4)	+26.5 (31.8); +20.9 (1.9–49.1)	<0.001*
Overall direct treatment costs in Euros (€), mean (95% CI); median (IQR)	53,261 (39,660–68,825); 35,765 (18,090–69,350)	20,269 (14,707–26,653); 12,587 (6601–30,762)	+32,991 (21,558–46,613); +23,178 (11,489–38,588)[a]	<0.001**

CI, confidence interval; IQR, interquartile range; LOS, length of stay; SD, standard deviation.
*Non-parametric Mann-Whitney U test.
**Welch's bootstrapped *t*-test.
[a] Inconsistent sum due to rounding errors.

Table V
Generalized linear model (GLM) of factors influencing overall direct treatment costs of patients with invasive mucormycosis (IM)

Covariates	*P* (univariate)*	*P* (multi-variable)**	Odds ratio	95% confidence interval
EORTC stage = probable	0.045	0.043	0.675	0.461–0.987
Age <60 years	0.002	0.002	1.804	1.251–2.601
Organ affected by IM	0.847	–	–	–
Underlying disease other than acute leukaemia	0.080	0.454	1.234	0.712–2.138
Absence of chemotherapy	0.057	0.046	0.578	0.337–0.990
Underwent aSCT	0.381	–	–	–
Absence of surgical measures due to IM	0.057	0.019	0.634	0.434–0.927
Absence of antifungal prophylaxis	0.019	0.001	0.490	0.324–0.740
Choice of antifungal agent for treatment of IM	0.172	–	–	–

EORTC, European Organization for Research and Treatment of Cancer; aSCT, allogeneic stem cell transplantation; GLM, generalized linear model.
*Kruskal-Wallis test.
**GLM with gamma distribution and log-link.
Further GLM information: Akaike information criterium: 1070; Bayes information criterium: 1084; deviation: 16.9; likelihood quotient Chi^2: 36.1 ($P < 0.001$); number of degrees of freedom: 39; Pearson Chi^2: 15.3.

The GLM found absence of chemotherapy, antifungal prophylaxis, and surgical measures due to IM to be associated with reduction of overall direct treatment costs.

A study by Menzin *et al.* presented mean additional direct medical costs for patients with IM of US$31,849, which is within the range of the present analysis [12]. Interestingly, the mean additional LOS of patients with IM compared with the control group was only 10.6 days, whereas the present study identified an additional LOS of 26.5 days per patient. Additionally, inpatient mortality of patients with IM was relatively low (14%) compared with the present results (41.3%). However, the study by Menzin *et al.* was based on the Healthcare Cost and Utilization Project – Nationwide Inpatient Sample (HCUP-NIS), a US database for inter alia (i.a.) hospital charges and LOS, such that no micro-costing analysis was possible and no classification in possible, probable and proven IM based on EORTC/MSG criteria was performed [14], which limits comparability of the respective populations. A further study based on the HCUP-NIS database analysed data of patients with different types of risk for mucormycosis [11]. Mean additional costs of patients with IM were US$ 64,526, which is substantially higher than the €32,991 identified in the present study, likely associated with different cost values for inpatient services in US and German hospitals. Again, no micro-costing analysis was performed, meaning that a comparison of, for example, antifungal drug acquisition costs and level of certainty of IM between the studies by Menzin *et al.* and Zilberberg *et al.*, as well as the present study was impossible. Nevertheless, the strength of this study is its sample size of 5346 cases of mucormycosis. However, the overall mortality rate (22.1%) and the mean excess LOS (+16.5 days) were considerably lower than the results of the analysis would suggest. Looking at other studies from the German healthcare system analysing costs of invasive fungal disease (IFD), a recently published study demonstrated mean overall direct treatment costs for candidaemia of €28,432 per patient, whereas mean antifungal drug acquisition costs were €3775 for treatment with echinocandins and €1758 for treatment with fluconazole [23]. Another study by Rieger *et al.* analysed mean additional direct treatment costs per patient with IFD of €21,063 compared with controls, primarily caused by *Aspergillus* spp. [24]. Additionally, this study calculated mean antifungal drug acquisition costs of €13,685 per patient and a mean excess LOS for patients with IFD of 12.2 days. Compared with the current analysis, results from both studies emphasize substantial treatment costs for patients with IM, based on the high antifungal drug acquisition costs of €22,819 per patient due to prolonged treatment duration. Furthermore, 17 patients (37.0%) underwent surgical procedures for IM, highly likely resulting in additional LOS and excess costs.

Several limitations of the cost-of-illness analysis should be noted. As IM is a rare IFD, only a small dataset of 46 patients with probable/proven IM was included. The majority of patients in this analysis had haematological malignancy as the primary underlying disease, and the lung was the dominant site of infection. Both criteria may be biased by the participating centres, meaning that associated costs may vary, for example, in the case of primarily surgical IM patients. Furthermore, treatment costs for IM and for underlying diseases are sometimes inseparable, such that the possibility that comorbidities may have influenced the calculated costs cannot be ruled out. For example, the inpatient treatment prior to definite diagnosis of probable/proven IM could be assessed as a time-dependent bias for overestimation of direct treatment costs. However, probable/proven IM remains difficult to diagnose, and definite diagnosis of IM requires direct sampling of infected tissue, which is most often hampered due to difficulties in patients with haematological underlying diseases (e.g. because of severe thrombocytopenia). As a result, a substantial number of diagnostic and medical measures during inpatient stay are needed prior to the definite diagnosis of probable/proven IM. Additionally, empirical antifungal treatment is a well-known method to improve patient outcome. As the study dataset shows a substantial number of days on empirical treatment prior to definite diagnosis of probable/proven IM, an exclusion of these inpatient days would have resulted in a significant underestimation of LOS and (antifungal drug) costs, which was also demonstrated in the sensitivity analysis. As the duration between hospital admission and initiation of empirical antifungal therapy was relatively short, it was assumed that several patients might have been transferred to a tertiary care hospital due to the severity of the underlying diseases and multimorbidity.

Nevertheless, the authors tried to use a micro-costing approach that was as detailed as possible, including all related cost factors based on the G-DRG InEK matrix, for the

most comprehensive view on inpatient burden of IM. Additionally, only inpatient costs for the initial inpatient stay were included in the analysis. Outpatient costs (e.g. visits to primary care physician, outpatient clinic) were disregarded, such that overall costs of IM treatment are potentially underestimated. However, it is believed that these limitations are unlikely to have had a relevant impact on the major findings on the health economic burden of IM.

In conclusion, further health economic analyses are of interest, as most of the patients analysed in this study were treated with LAmB and posaconazole. Since the approval of isavuconazole for treatment of IM and invasive aspergillosis by FDA and EMA in 2015, physicians have a new IFD treatment option with fewer drug-related adverse events [9,25], and a favourable safety and tolerability profile [26]. This new treatment strategy may also have an economic impact in the treatment of IM.

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Conflict of interest statement

S.M.H. has received research and travel grants from Astellas and Merck; research grants from Basilea, Gilead and 3M; travel grants from Pfizer; lecture honoraria from Astellas and Merck; and is a consultant to Basilea, Gilead and Merck. M.J.G.T.V. has served at the speakers' bureau of Pfizer, Merck/MSD, Gilead Sciences, Astellas Pharma and Organobalance; received research funding from 3M, Astellas Pharma, Da Volterra, Merck/MSD, Morphochem, Seres Therapeutics, Organobalance and Gilead Sciences; and is a consultant to Alb Fils Kliniken GmbH, Merck/MSD and MaaT Pharma. O.A.C. is supported by the German Federal Ministry of Research and Education (BMBF Grant 01KN1106); has received research grants from 3M, Actelion, Astellas, Basilea, Bayer, Celgene, Cubist/Optimer, Genzyme, Gilead, GSK, Merck/MSD, Miltenyi, Pfizer, Quintiles, Shionogi and Viropharma; is a consultant to 3M, Astellas, Basilea, Cidara, Cubist/Optimer, Da Volterra, Daiichi Sankyo, F2G, Genentech, Gilead, GSK, Merck/MSD, Merck Serono, Pfizer, Rempex, Sanofi Pasteur and Summit/Vifor; and has received lecture honoraria from Astellas, Gilead, Merck/MSD and Pfizer. W.J.H. has received research grants from MSD Sharp & Dohme/Merck and Pfizer; serves on the speakers' bureaus of Alexion, Astellas, Basilea, Bristol-Myers Squibb, Gilead Sciences, Janssen, MSD Sharp & Dohme and Pfizer; and has received travel grants from Alexion, Astellas, Lilly, MSD Sharp & Dohme, Novartis and Pfizer. J.K. has received travel grants from Astellas and Gilead Sciences. G.S. has received grants from MSD Sharp & Dohme, Pfizer, Gilead Sciences, Astellas and Basilea; and serves as a consultant for MSD Sharp & Dohme and Basilea. J.J.V. is supported by the German Federal Ministry of Research and Education (BMBF Grant 01KI0771) and the German Centre for Infection Research. J.J.V. has received research grants from Astellas, Basilea, Gilead Sciences, Infectopharm, Merck/MSD and Pfizer; and has served on the speakers' bureau of Astellas, Basilea, Gilead Sciences, Merck/MSD and Pfizer. B.G. declares no conflict of interests.

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