*J Antimicrob Chemother* 2015; **70**: 1175–1181
doi:10.1093/jac/dku506 Advance Access publication 21 December 2014

Journal of Antimicrobial Chemotherapy

# Prospective evaluation of the cost of diagnosis and treatment of invasive fungal disease in a cohort of adult haematology patients in the UK

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*Received 30 June 2014; returned 7 September 2014; revised 13 October 2014; accepted 17 November 2014*

**Objectives:** The direct cost of invasive fungal disease (IFD) includes antifungal drugs as well as diagnostic tests. The aim of this study was to determine these costs.

**Methods:** A total of 203 haematology patients were enrolled into the study and followed for a median of 556 days. Data were prospectively collected on antifungal drugs, diagnostic tests, length of stay and antibiotic usage.

**Results:** The overall mean (IQR) cost of care per patient (using UK-based reference costs) was £88 911 (45 339–121 594), £61 509 (39 748–78 383), £50 332 (23 037–72 057) and £34 075 (19 928–43 900) for proven/probable IFD, possible IFD, not classified and no evidence of IFD, respectively ($P<0.001$). The attributable cost of IFD was £54 836. Inpatient hospital stay accounted for nearly 74% of costs. In proven/probable IFD inpatient care, antifungals, antibiotics and IFD status accounted for 68%, 25%, 5% and 2%, respectively, compared with 85%, 11%, 2% and 2%, respectively, for no IFD ($P<0.001$). Among the allogeneic transplant patients, £36 914 (60%) of the total cost (£60 917) was used during the first 100 days.

**Conclusions:** IFD was associated with longer length of stay and higher total overall cost of care, with attributable costs greater than £50 000 per case of IFD. Costs for inpatient stay far outstrip the cost of antifungal agents.

**Keywords:** attributable cost, antifungals, diagnostic tests, length of stay

## Introduction

Invasive fungal disease (IFD), in particular invasive aspergillosis (IA), is associated with high morbidity and mortality.[1–3] Current guidelines recommend prophylaxis in patients at moderate or high risk of developing IFD.[4,5] Lack of standardized routine diagnostic criteria often results in empirical treatment and prolonged antifungal treatment is often required for a successful treatment outcome.[6] Although inpatient care is not always necessary during this period, there is evidence that patients with IFD have a longer inpatient admission and higher associated hospital costs compared with those without IFD with similar underlying diagnoses.[7] This suggests that IFD contributes to longer length of stay due to poor clinical state.[8]

However, data on the cost of managing IFD are largely retrospective or based on assumed length of treatment and primarily focused on drug costs.[9–11] While this is important, the true cost of IFD also includes the cost of diagnosis and monitoring, inpatient and outpatient care and various interventions that are difficult to capture in retrospectively collected data. We recruited a cohort of haematology patients likely to be rendered neutropenic during treatment for various haematological diagnoses and who were followed up prospectively for up to 2 years. The incidence of IFD in this cohort has already been reported.[12] The primary aim of the current study was to determine the costs associated with IFD and the pattern of antifungal usage including inpatient and outpatient care, antifungal prophylaxis and treatment, and diagnostic and monitoring costs. This will provide invaluable information for providers planning treatment services for immunocompromised patients and offer valuable insight into current patient care.

## Methods

### *Patient population*

Two hundred and three consecutive adult haematology patients likely to be rendered neutropenic ($<0.5\times10^9$/L) during treatment were prospectively enrolled from a single hospital site, King's College Hospital, London,

between December 2008 and May 2010. The inclusion criteria were one or more of the following: autologous or allogeneic HSCT, high-dose chemotherapy, and immunosuppressive therapy (IST) with a combination of antithymocyte globulin and cyclosporine in aplastic anaemia (AA). Children and adults unable or unwilling to sign informed consent were excluded. Patients' demographic details, haematological diagnosis, antifungal drug history, final IFD status and clinical management while enrolled in the study were recorded.

IFD was diagnosed according to the revised EORTC/MSG criteria.[13] Standard diagnostic and monitoring tests included CT scan, galactomannan (GM), β-D-glucan (BDG) and blood culture. GM surveillance testing was done on sera twice weekly during inpatient admission and once during each outpatient visit, while BDG was performed on all possible IFD, GM-positive cases and a selection of negative controls on patients with no evidence of IFD. Routine tests included full blood count (FBC), liver function test (LFT), urea and electrolytes and C-reactive protein (CRP). Extended tests were bronchoscopy and biopsy. Patients were followed up for ≥4 months from last chemotherapy, IST or HSCT and up to 2 years or death, whichever was first. Data collected included the dose and duration of antifungal prophylaxis and treatment, incidence of side effects, reason for switching antifungal treatment, standard and routine tests, other diagnostic procedures (bronchoscopy and biopsy) and hospital bed days (ward or ICU). All data were anonymized for analysis and no patient-identifiable information was included. The study was approved by the hospital ethics committee and conducted in accordance with the Helsinki protocol (2008 revision) for medical research involving human subjects and registered with ClinicalTrials.gov (NCT00816088).

### Antifungal protocol

All patients received antifungal drugs according to local protocol using recommended dosages (Table S1, available as Supplementary data at *JAC* Online). Mould-active primary prophylaxis was given to high-risk patients [allogeneic HSCT, AML/myelodysplastic syndrome (MDS) and salvage lymphoma chemotherapies] who received itraconazole solution (200 mg twice/day). Umbilical cord allogeneic HSCT recipients were given posaconazole (200 mg three times/day) instead of itraconazole. Autologous HSCT was considered low risk and patients received oral fluconazole (200 mg daily). Voriconazole (200 mg twice/day) was used as secondary prophylaxis. Prophylaxis was initiated at admission and continued until unsupported neutrophils were $\geq 1.0 \times 10^9$/L for two consecutive days and immunosuppression weaned off and no signs of graft versus host disease (GVHD) in the case of allogeneic HSCT recipients. First-line empirical antifungal therapy was liposomal amphotericin B (3 mg/kg/day) while voriconazole was used for the treatment of proven/probable IFD. Duration of antifungal therapy was clinically determined, but proven/probable IFD was treated for ≥4 weeks, starting with intravenous therapy and changing to an oral agent (voriconazole as first line) whenever possible.

### Analysis

Age, sex, main treatment, IFD status, duration of antifungal therapy and number of patients given each agent were examined according to their primary diagnosis. Chi-squared *P* values were obtained to test for differences in categorical variables by primary diagnosis. For continuous variables, we examined the median and IQR according to the primary diagnosis, testing for differences using the Kruskal–Wallis test for equality of distributions, due to skewed or otherwise non-normal distributions.

### Costs

The cost analysis took a hospital perspective, with the costs of treating IA in neutropenic patients considered in four broad categories: (i) antifungal prophylaxis; (ii) antifungal treatments; (iii) diagnostic and monitoring tests and procedures; and (iv) inpatient stay and outpatient visits. UK and published reference costs relevant to the study period were used.[14–17] Antifungal drugs were costed using the *British National Formulary*[18] at the recommended doses (Table S1). Lengths of stay in hospital (ward, ICU and outpatient visits) were also costed using national unit costs from the *Department of Health NHS Reference Costs 2010–11* (Table S2).[19]

We reported resource use and costs per patient over the study period. We compared each component of costs and total costs of episode according to haematological diagnosis, antifungal drugs, IFD status and main treatment. Attributable cost was defined as the cost difference between proven/probable IFD and no evidence of IFD. For allogeneic HSCT recipients, we also examined costs/patient within 100 days of stem cell infusion (Table S3). The differences in the distribution of costs across groups were compared using the Kruskal–Wallis test. Other costs such as those related to various chemotherapy agents and autologous and allogeneic transplantation were not included in this study.

## Results

### Patient characteristics

Table 1 shows the patient characteristics. The cohort was followed up for a median of 556 days and received 263 treatments for their haematological diagnosis during the study period: allografts (106), chemotherapy (77), autografts (67) and IST (13). The overall incidence of IFD in this cohort was 21% while the treatment-specific incidence per cycle of treatment was 16% (17/105), 3% (2/72), 12% (21/177) and 14% (4/29) for allograft, autograft, chemotherapy only and IST, respectively.[12]

### Antifungal prophylaxis and treatment

In total, there were 395 episodes of prophylactic treatments. The drugs used were itraconazole (215; 54%), fluconazole (59; 15%), posaconazole (68; 17%), voriconazole (23; 6%) and liposomal amphotericin B (30; 8%). Itraconazole was used mainly as

**Table 1.** Patient characteristics (*N* = 203)

| | |
|---|---|
| Age (years), median (range) | 54 (19–73) |
| Male/female, *n*/*n* | 123/80 |
| Primary diagnosis, *n* (%) | |
| AML | 55 (27) |
| MDS | 29 (14) |
| AA | 19 (10) |
| NHL | 29 (14) |
| multiple myeloma | 46 (23) |
| others[a] | 25 (12) |
| Main treatment, *n* (%) | |
| allogeneic HSCT | 99 (49) |
| autologous HSCT | 65 (32) |
| chemotherapy alone | 28 (14) |
| IST | 11 (5) |
| Follow-up (days), median (range) | 556 (12–730) |

[a]Others include acute lymphoblastic leukaemia (7), blastic plasmacytoid dendritic cell neoplasm (1), chronic lymphocytic leukaemia (1), chronic myeloid leukaemia (3), common variable immunodeficiency (1), Hodgkin lymphoma (8) and myeloproliferative neoplasm (4).

primary prophylaxis while voriconazole was used as secondary prophylaxis according to local protocol. The median duration of antifungal prophylaxis was 87 days (IQR 36–164 days). Eleven patients received no prophylaxis as they were receiving empirical antifungal treatment (9) or none (2) at the time of recruitment. The latter two patients were admitted for allograft, which was subsequently cancelled. The median duration of antifungal prophylaxis was similar across the different IFD categories (Figure S1) and primary haematological diagnoses (Figure S2).

Antifungal treatment was given to 101 (50%) patients during the course of the study for suspected IFD and 68 (33%) were treated for ≥2 weeks. The median duration of treatment was 32 days (IQR 8–80 days; range 1–456 days). This duration was similar between proven, probable and possible IFD, but shorter among not classified and no evidence of IFD cases (Figure S3). Similarly, treatment duration was shortest among autologous transplant patients (Figure S4). A total of 266 treatment episodes were administered with liposomal amphotericin B (101; 38%), caspofungin (74; 28%), posaconazole (50; 19%) and voriconazole (41; 15%). In patients who received antifungal treatment, there were differences in total duration receiving different antifungal treatments (Kruskal–Wallis, $P<0.001$) with posaconazole being given for the longest duration (median 88 days) and liposomal amphotericin B and caspofungin the shortest (median 12 and 16 days, respectively). Distributions of treatment duration are shown in Table S1.

### Antifungals at the time of IFD diagnosis

Itraconazole was the most commonly used antifungal drug, used in 65% of patients, within 2 weeks of the IFD classification (Figure S5). However, in patients with proven/probable and possible IFD, itraconazole was used in 52% and 53%, respectively, being displaced by the use of empirical therapy with liposomal amphotericin B, caspofungin and voriconazole. Based on these, the breakthrough proven/probable IFD was 5/23 (22%), 23/137 (17%) and 3/24 (13%) for posaconazole, itraconazole and fluconazole, respectively. Liposomal amphotericin B, caspofungin and voriconazole were used as empirical treatment.

### Diagnostic tests

Table 2 shows the frequency of diagnostic and monitoring tests. In addition, bronchoscopy and biopsies were obtained in some patients. The use of diagnostic tests was similar across different categories of haematological diagnosis, IFD status and main treatment.

### Length of stay during admission

The average total length of stay in this study was 69 days, but there was considerable variation across diagnostic categories, treatment groups and IFD classifications (Table 3). Length of stay was highest among patients with proven/probable IFD (119 days) and lowest in those with no evidence of IFD (57 days) ($P<0.001$). Similarly, the proportion of the study period in inpatient care was 27% (119/439 days) in patients with proven/probable IFD compared with 9% (57/655 days) in those with no evidence of IFD ($P<0.001$). The length of stay in ICU was on average 1 day. The mean number of outpatient appointments ranged from three to seven. Patients with MDS had increased length of stay and more diagnostic tests than other diagnosis groups. The median (IQR) length of stay in

**Table 2.** Mean (IQR) number of diagnostic tests per patient

| | Standard tests | | | | Routine tests | | | |
|---|---|---|---|---|---|---|---|---|
| | GM | BDG | blood cultures | CT scan | FBC | LFT | U&E | CRP |
| Haematological diagnosis | | | | | | | | |
| AML | 18 (10–27) | 2 (0–2) | 8 (3–13) | 2 (0–3) | 23 (16–32) | 23 (15–31) | 24 (17–34) | 19 (10–27) |
| MDS | 27 (11–49) | 2 (0–2) | 13 (4–24) | 3 (0–4) | 25 (16–34) | 25 (16–36) | 26 (16–37) | 20 (10–29) |
| myeloma | 7 (5–8) | 1 (0–1) | 4 (3–4) | 1 (0–1) | 13 (9–14) | 13 (10–14) | 13 (10–15) | 10 (8–11) |
| NHL | 13 (7–16) | 1 (0–1) | 7 (3–10) | 3 (0–4) | 18 (11–22) | 18 (11–22) | 19 (11–22) | 15 (10–21) |
| AA | 15 (9–23) | 1 (0–2) | 8 (3–12) | 2 (0–3) | 22 (12–27) | 22 (12–29) | 24 (13–30) | 18 (11–26) |
| others[a] | 14 (9–27) | 2 (0–2) | 8 (5–10) | 3 (1–4) | 23 (13–32) | 24 (13–34) | 25 (14–35) | 20 (11–24) |
| IFD status | | | | | | | | |
| proven/probable IFD | 27 (13–37) | 3 (1–4) | 17 (9–25) | 4 (2–7) | 28 (16–38) | 28 (17–39) | 30 (17–41) | 25 (12–34) |
| possible IFD | 16 (9–19) | 2 (1–2) | 9 (4–12) | 3 (0–5) | 20 (11–28) | 21 (11–28) | 22 (11–30) | 18 (10–25) |
| not classified | 14 (7–17) | 1 (0–2) | 6 (3–8) | 1 (0–2) | 20 (11–26) | 20 (11–25) | 21 (12–27) | 16 (10–21) |
| no evidence | 9 (6–11) | <1 (0–0) | 4 (2–5) | 1 (0–1) | 16 (11–19) | 16 (11–19) | 12 (9–15) | <1 (0–0) |
| Main treatment | | | | | | | | |
| allogeneic HSCT | 18 (10–20) | 1 (0–2) | 9 (3–11) | 2 (0–3) | 23 (16–30) | 23 (15–30) | 24 (17–30) | 18 (10–23) |
| autologous HSCT | 7 (6–9) | 1 (0–1) | 5 (3–6) | 1 (0–1) | 13 (10–15) | 13 (10–15) | 14 (10–15) | 10 (9–11) |
| chemotherapy | 22 (10–30) | 2 (1–3) | 10 (5–15) | 3 (1–5) | 25 (14–36) | 26 (15–38) | 27 (15–41) | 22 (11–29) |
| IST | 16 (6–21) | 1 (0–2) | 8 (2–11) | 2 (0–3) | 22 (10–31) | 23 (10–33) | 24 (10–34) | 19 (9–28) |

U&E, urea and electrolytes (renal function tests).
[a]Others include acute lymphoblastic leukaemia (7), blastic plasmacytoid dendritic cell neoplasm (1), chronic lymphocytic leukaemia (1), chronic myeloid leukaemia (3), common variable immunodeficiency (1), Hodgkin lymphoma (8) and myeloproliferative neoplasm (4).

**Table 3.** Mean (IQR) total number of days on antibiotics, hospital length of stay and outpatient appointments

| | Antibiotics | Total length of stay (days) | | Outpatient appointments |
|---|---|---|---|---|
| | | ward | ICU[a] | |
| Diagnosis | | | | |
| AML | 66 (22–93) | 85 (47–109) | 1 (0–0) | 4 (1–8) |
| MDS | 96 (28–164) | 115 (63–157) | 1 (0–0) | 7 (3–8) |
| multiple myeloma | 20 (12–26) | 62 (32–49) | 0 (0–0) | 3 (2–4) |
| NHL | 46 (21–67) | 79 (53–98) | 1 (0–0) | 3 (2–4) |
| AA | 58 (23–94) | 78 (34–95) | 1 (0–0) | 7 (4–10) |
| others[b] | 58 (34–83) | 67 (41–96) | 1 (0–0) | 5 (2–7) |
| IFD status | | | | |
| proven/probable IFD | 120 (71–181) | 119 (57–169) | 1 (0–0) | 5 (0–8) |
| possible IFD | 56 (30–87) | 89 (56–114) | 1 (0–0) | 4 (1–4) |
| not classified | 47 (21–61) | 76 (38–96) | 1 (0–0) | 5 (3–7) |
| no evidence | 23 (12–30) | 57 (34–68) | 0 (0–0) | 4 (2–6) |
| Main treatment | | | | |
| allogeneic HSCT | 62 (22–81) | 85 (44–110) | 1 (0–0) | 6 (3–8) |
| autologous HSCT | 25 (15–32) | 27 (13–35) | 0 (0–0) | 3 (2–4) |
| chemotherapy | 86 (34–104) | 97 (52–125) | 1 (0–0) | 4 (0–7) |
| IST | 62 (12–93) | 74 (24–107) | 1 (0–0) | 5 (2–8) |

[a]As 94% of patients had no ICU admission, the mean ICU length of stay is 0 and the IQR is 0–0.
[b]Others include acute lymphoblastic leukaemia (7), blastic plasmacytoid dendritic cell neoplasm (1), chronic lymphocytic leukaemia (1), chronic myeloid leukaemia (3), common variable immunodeficiency (1), Hodgkin lymphoma (8) and myeloproliferative neoplasm (4).

days per cycle of treatment was 32 (21–40), 26 (22–29), 26 (14–36) and 21 (11–23) for allograft, autograft, chemotherapy and IST, respectively.

The use of antibiotics was widespread among the study patients; 96% of patients had been given antibiotics. The average total duration of antibiotics was 56 days, which varied considerably by haematological diagnosis, IFD status and treatment group. Patients with proven/probable IFD were on antibiotics for longer (total duration 120 days) compared with those with no evidence of IFD (23 days) ($P<0.001$).

### *Cost of IFD*

The total costs of IFD varied substantially according to primary diagnosis, main treatment and IFD status (Table 4). Patients with MDS incurred the highest cost (£81338) while myeloma patients had the lowest (£33941) and the difference was statistically significant ($P<0.001$). Similarly, proven/probable IFD was associated with significantly higher total costs at £88911 compared with £34075 for no evidence of IFD ($P<0.001$). Therefore, the attributable cost of IFD was estimated to be £54836. However, it varied according to underlying haematological diagnosis and treatment (Figure S6). For example, among the AML/MDS/AA patients, the total attributable cost was £66523, but with allograft patients incurring higher cost (£81017) than chemotherapy/IST-only patients (£63163). On the other hand, the total attributable cost in myeloma/non-Hodgkin lymphoma (NHL) patients was £32997, which varied according to the treatment received: allograft (£67226), chemotherapy only (£48727) and autograft (£8900).

The costs of care across the different IFD classifications showed important differences. In general, inpatient care accounted for nearly 74% of costs. In proven/probable IFD inpatient care, antifungals, antibiotics and IFD diagnostics accounted for 68%, 25%, 5% and 2%, respectively, compared with 85%, 11%, 2% and 2%, respectively, for no evidence of IFD ($P<0.001$). The pattern of antifungal costs also showed significant differences between IFD categories. In proven/probable IFD, prophylaxis and treatment costs were £4226 (19%) and £17753 (81%), respectively, compared with £2568 (67%) and £1272 (33%), respectively, in patients with no evidence of IFD ($P<0.001$).

In the allogeneic HSCT patients, £36914 (60%) of the total cost (£60917) was used during the first 100 days (Figure S7 and Table S3). However, this varied between 40% (£2180/£5417) for prophylaxis, 51% (£4394/£8557) for treatment, 75% (£1535/£2059) for antibiotics and 77% (£964/£1254) for diagnostic costs. The median cost of allogeneic transplantation within the first 100 days of HSCT per patient with proven/probable IFD was £43922 compared with £24227 with no evidence of IFD ($P<0.001$).

Antifungal prophylaxis and treatment costs are also reported by first-line and subsequent regimens in Table S4. There were significant differences in first-line and subsequent prophylaxis costs according to diagnosis and treatment groups. First-line treatment costs were similar across groups of haematological diagnosis, IFD status and main treatment, but again there were significant differences in the subsequent cost of treatment.

## Discussion

In a cohort of 203 haematology patients undergoing chemotherapy, IST or HSCT who were prospectively followed for a median of 18.5 months, we found that proven/probable IFD was associated with a significantly longer length of inpatient care and higher

**Table 4.** Mean (IQR) costs per patient by diagnosis, IFD status and main treatment (UK £2010)

| | | | Antifungal diagnosis | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Antifungal prophylaxis | Antifungal treatment | standard[a] | routine[a] | extended[a] | Antibiotic treatment | Hospital | Total costs |
| Diagnosis | | | | | | | | |
| AML | 5090 (474–8208) | 8208 (0–12903) | 575 (207–851) | 423 (276–564) | 33 (0–0) | 2177 (675–3120) | 43356 (23353–58990) | 59862 (27624–82954) |
| MDS | 5453 (371–9720) | 12478 (0–20273) | 889 (220–1315) | 454 (282–636) | 678 (0–460) | 3186 (1002–5761) | 58200 (32315–78412) | 81338 (46112–124826) |
| myeloma | 792 (10–755) | 746 (0–0) | 223 (144–249) | 233 (181–265) | 33 (0–0) | 647 (374–907) | 31248 (16252–24644) | 33941 (19788–28513) |
| NHL | 2115 (283–2899) | 4074 (0–5807) | 572 (256–732) | 329 (200–397) | 24 (0–0) | 1515 (732–2106) | 39975 (26314–50987) | 48603 (32383–61393) |
| AA | 5668 (858–6984) | 10816 (0–14058) | 569 (217–814) | 408 (216–510) | 197 (0–230) | 1953 (475–3174) | 39808 (17905–49175) | 59418 (26696–90988) |
| others[b] | 2616 (38–2689) | 11021 (0–15823) | 616 (329–822) | 427 (234–597) | 139 (0–230) | 1871 (853–2532) | 33574 (20448–47674) | 50264 (25355–69866) |
| *P*[c] | <0.001 | <0.001 | <0.001 | <0.001 | 0.006 | <0.001 | <0.001 | <0.001 |
| IFD status | | | | | | | | |
| proven/probable IFD | 4226 (0.52–6433) | 17753 (1231–28221) | 1114 (599–1567) | 515 (286–714) | 529 (0–230) | 4080 (2057–5668) | 60695 (28137–83799) | 88911 (45339–121594) |
| possible IFD | 2963 (51–3955) | 10455 (0–17030) | 699 (246–1034) | 373 (200–519) | 93 (0–0) | 1851 (1002–2918) | 45075 (27795–56730) | 61509 (39748–78383) |
| not classified | 4206 (225–4433) | 5065 (0–6153) | 407 (186–566) | 361 (203–460) | 111 (0–0) | 1509 (615–2055) | 38672 (19955–49060) | 50332 (23037–72057) |
| no evidence | 2568 (283–2638) | 1272 (0–0) | 274 (146–351) | 286 (196–335) | 4 (0–0) | 723 (374–966) | 28948 (17733–33871) | 34075 (19928–43900) |
| *P*[c] | 0.889 | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 |
| Main treatment | | | | | | | | |
| allogeneic HSCT | 5417 (640–8431) | 8557 (0–13464) | 606 (213–732) | 413 (286–529) | 235 (0–0) | 2059 (624–2878) | 43631 (22784–61210) | 60917 (27827–81163) |
| autologous HSCT | 1069 (24–1587) | 1499 (0–393) | 285 (155–350) | 236 (181–268) | 31 (0–0) | 831 (437–1046) | 33183 (17980–33871) | 37134 (20554–44750) |
| chemotherapy | 4045 (51–4698) | 9895 (0–15822) | 813 (429–1079) | 470 (264–702) | 220 (0–230) | 2773 (1199–3798) | 48702 (25669–62920) | 66917 (39464–95049) |
| IST | 2865 (530–4240) | 15710 (0–20607) | 544 (195–575) | 409 (176–575) | 180 (0–230) | 2086 (355–3172) | 37478 (12303–53560) | 59272 (19880–77823) |
| *P*[c] | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 |

U&E, urea and electrolytes (renal function tests).
Note: for many values, especially for extended tests, a large proportion of patients had low or zero costs, but a small proportion may have relatively high costs; this leads to the mean being outside the IQR, and in many cases a non-zero mean and an IQR of 0–0.
[a]Standard tests were CT, GM, BDG and blood cultures, routine tests were FBC, CRP U&E and LFT (Table 2) and extended tests were biopsy and bronchoscopy.
[b]Others include acute lymphoblastic leukaemia (7), blastic plasmacytoid dendritic cell neoplasm (1), chronic lymphocytic leukaemia (1), chronic myeloid leukaemia (3), common variable immunodeficiency (1), Hodgkin lymphoma (8) and myeloproliferative neoplasm (4).
[c]Kruskal–Wallis *P* values.

overall costs, with an attributable cost of £54 836 per patient, which was higher in high-risk AML/MDS/AA patients (£66 523) than low-risk NHL/MM patients (£32 997). In general, 74% of the cost of care was due to inpatient care. Among allograft recipients, 60% of the costs occurred during the first 100 days post-allograft.

Antifungal therapy was received by 50% of patients during the study. Although this may seem excessive in a cohort with a proven/probable IFD incidence of 21%,[12] a closer look at patients who had therapy for ≥2 weeks revealed a figure of 33%, which is similar to the incidence of IFD from autopsy data in the study by Chamilos *et al.*[3] However, it is important to note that in the Chamilos *et al.*[3] study, the autopsy rate decreased from 63% to 27% over the course of the three time periods studied, but IFD prevalence remained similar at 30%–32%. In our study, the combined incidence of proven, probable and possible IFD was 34%. Possible IFD with antibacterial-refractory neutropenic sepsis is usually treated in the same way as proven/probable IFD in clinical practice.[20]

The cost of care in patients admitted for haematological therapy is an important issue for clinicians and payers. In this study, we describe one of the largest prospective studies with long follow-up and individual patient-level data, which captured the various components of care relevant to IFD. The length of stay was the biggest determinant of the cost of care, in agreement with some previous studies,[7,8,11,21–23] but contrary to Ananda-Rajah *et al.*,[24] who found pharmacy costs as the key determinant of cost. The study by Ananda-Rajah *et al.*[24] was a matched case–control study that included pharmacy staff salaries as well as medications and this approach might have accounted for the difference compared with our study. The longer length of stay associated with proven/probable IFD (119 days compared with 57 days with no evidence of IFD) is important not only as a cost determinant but is also relevant in tackling the true cost of IFD. It means that in order to truly make an impact in the reduction of IFD-attributable costs, efforts must be directed at reducing IFD incidence and length of stay. It is important to note that length of stay was not determined by the need for intravenous antifungal therapy alone, but by the overall clinical condition of the patients. Patients were discharged as soon as they were well enough and intravenous therapy changed to oral agents.

IFD was associated with higher antifungal drug costs, but similar diagnostic costs, compared with non-IFD cases. The cost of diagnosis largely depends on the diagnostic strategy used. For example, in this study the use of BDG as a surveillance tool would have increased the diagnostic costs >2-fold. Antifungal policy is also crucial. In our cohort, itraconazole was used in 65% of all cases. Replacing this with posaconazole, a drug that has been shown to be cost-effective,[25,26] but which is also >6-fold the cost of itraconazole (Table S2), would have increased prophylaxis costs significantly. It is also important to note that while the attributable cost of IFD was £54 836 based on the difference between the cost of proven/probable IFD (£88 911) and no evidence of IFD (£34 075), the latter category still represents a significant cost of care. This attributable cost varied according to the haematological diagnosis and treatment and was highest among AML/MDS/AA patients undergoing allograft and lowest in myeloma/NHL patients undergoing autograft. However, the number of patients in the latter group was small (Figure S6) with only one proven invasive candidiasis and three probable IFDs. This difference reflects the significantly longer duration of stay and higher proportion of proven/probable cases in the allograft/chemotherapy/IST patients. About one-third of the cost spent on patients with no evidence of IFD (£1272) was on antifungal treatment (Table 4), which argues strongly for antifungal stewardship to ensure adherence to protocol and minimum standards of prescribing these expensive drugs.[27,28]

The strength of this study lies in its prospective cohort design with long-term follow-up data and reflects real-life clinical practice. Many previous studies in this area are often based on retrospective data collected from hospital records and primarily focused on drug costs.[7,9–11,23] The single-centre nature of our study facilitates consistent clinical assessment and completion of data collection across a whole spectrum of haematological malignancies and AA. However, the different models of healthcare delivery elsewhere with different reimbursement systems may limit the applicability of our findings. Moreover, local discounts may be available at individual hospitals, but this is not addressed here. The low rate of bronchoscopy in this study undoubtedly underestimates the contribution of this procedure to diagnostic costs, but is counterbalanced by the high rate of biopsy and tissue diagnosis and serial CT scans.

In conclusion, IFD is associated with longer length of stay and higher overall costs with attributable costs greater than £50 000 per case of IFD. The length of stay in hospital is the key determinant of costs. This study will inform clinicians who manage patients undergoing treatment of haematological malignancies and marrow failure syndromes and help inform payers for allocation of resources for these patients.

## Funding

This work was supported by Gilead Sciences, Pfizer and Merck Sharp & Dohme (MSD) Limited who provided unrestricted educational grants for the project.

## Transparency declarations

Gilead Sciences provided funds to Aquarius Population Health to support this project. Aquarius Population Health has a Gilead Fellowship Grant for HIV and Gilead has funded other work on liposomal amphotericin B and HIV. E. J. A. is an employee of Aquarius Population Health and A. E. and Z. S. were contracted by Aquarius Population Health for this project. M. M. C. and A. P. acknowledge honoraria from Gilead Sciences for lectures, advisory boards and conference sponsorships. E. J. A. reports funding from Aquarius Population Health (from Gilead) to conduct this study and has received grants and personal fees from Gilead, outside the submitted work. Z. S., R. H. and A. E. report personal fees from Aquarius Population Health during the conduct of the study. However, none of these authors played any decision-making role in this research.

### *Author contributions*

M. M. C. designed the study, recruited and followed up patients, acquired data and wrote the manuscript. Z. S. conducted the economic analyses and drafted the economic sections of the manuscript. R. H. conducted the statistical analyses and drafted the analysis sections of the manuscript. A. E. supported the work and drafted initial parts of the manuscript. E. J. A. led the work, supervised the analysis, contributed to the input parameters, contributed to drafting the manuscript and supported the submission process. A. P. designed the study, supported the project and reviewed the manuscript.

## Supplementary data

Tables S1 to S4 and Figures S1 to S7 are available as Supplementary data at *JAC* Online (http://jac.oxfordjournals.org/).

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