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The economic impact of aspergillosis: analysis of hospital expenditures across patient subgroups

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Summary

Objective: To measure the impact of invasive aspergillosis infection on US hospital costs and financial performance across different patient populations.

Methods: Hospital discharge data for patients with a primary or secondary diagnosis of aspergillosis were extracted from the 2003 Nationwide Inpatient Sample (NIS) and the fiscal year 2003 (FY03) Medicare Provider Analysis and Review (MedPAR) file. The data on patient demographics, length of stay (LOS), hospital charges, estimated costs, and reimbursement levels were reported. After controlling for comorbidities, operative procedures, and diagnosis-related group (DRG) assignment, the clinical and economic outcomes were compared for patients with and without aspergillosis.

Results: The NIS contains a total of over 38 million projected hospital discharges. From these, 10 400 aspergillosis cases were identified across 171 DRGs, resulting in a US incidence rate of 36 per million per year. The mean age of aspergillosis patients was 55.6 years, with 53.4% male and 67.9% Caucasian. The median (mean) LOS per aspergillosis patient was 10 (17.7) days, with a median (mean) total hospital charge (THC) of \$44 845 (\$96 731). Among the patient subgroups analyzed, the median (mean) THC per patient ranged from \$47 252 (\$82 946) for HIV to \$413 200 (\$442 233) for bone marrow transplant (BMT). When compared to the non-aspergillosis patient population, the data showed a significant increase in LOS, THC, and hospital costs. Furthermore, the higher hospital costs associated with aspergillosis patients were not matched by similar increases in reimbursements, resulting in a greater financial loss for hospitals. The mean reimbursement-to-cost ratio for aspergillosis cases across the DRGs analyzed was 0.80.

Conclusions: Aspergillosis affects a wide range of patient groups and has a negative economic impact across many DRGs. Improved prevention, diagnosis, and patient management strategies can help mitigate these effects on hospital financial performance.

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Introduction

Aspergillosis is associated with high morbidity and mortality, particularly in immunocompromised patients with risk factors such as bone marrow transplantation (BMT), solid organ transplantation, neutropenia, hematologic malignancy, HIV, immune dysfunction, chemotherapy, or corticosteroid therapy.^{1,2} Studies have reported a mortality rate of over 80% in BMT recipients with invasive aspergillosis, 90% in liver transplant recipients, and 49% in patients with leukemia or lymphoma.^{3,4} In an interim analysis conducted by the Transplant Associated Infections Surveillance Network (TransNet), the researchers reported hematopoietic stem cell and solid organ transplant estimated case incidence rates ranging from 0.5% to 3.9% among different types of stem cell transplants, and 0.1% to 2.4% among different solid organ transplants.⁵

Research also suggests that the incidence of aspergillosis is increasing. Groll et al. documented a rise in the rate of invasive mycoses from 1% to 7% of all autopsies performed between 1978 and 1992, and a proportional increase of invasive aspergillosis from 17% to 60% of all mycoses found on autopsy.⁶ Another study estimated that in 1996, rates of aspergillosis infections had risen to 38 per million hospital discharges.⁷ This trend may be attributed in part to the growing incidence of HIV infection, intensity of chemotherapy regimens, and increased number of bone marrow and solid organ transplants.^{8,9} At one major bone marrow transplant center, the risk of invasive aspergillosis grew from 4% to 12%.¹⁰ Treatment guidelines have addressed the growing concern for aspergillosis infection in immunocompromised hosts. In BMT, for example, attention has shifted from traditional anti-yeast prophylaxis to include anti-mold prophylaxis in high-risk patients.^{11,12}

As part of a study on the direct costs of systemic fungal infection, Wilson et al. demonstrated that costs associated with aspergillosis are high, with total inpatient and outpatient costs of \$674.1 million and an overall incremental hospitalization cost of \$36 867 per incident.¹³ However, the need remains for an in-depth evaluation of the impact of aspergillosis on healthcare and economic outcomes. While previous studies have estimated the total costs of aspergillosis, few attempts have been made to characterize the clinically relevant subgroups of patients affected. Because of the focus on overall costs alone, the economic impact of aspergillosis in certain patients may be underestimated. Identifying clinically relevant subgroups is a requisite step in being able to quantify the full cost of aspergillosis and to develop targeted therapeutic interventions for both the prevention and treatment of this disease.

This study examines the economic impact of aspergillosis in a variety of clinically relevant patient subgroups from the hospital inpatient perspective. To understand the impact of aspergillosis on hospital expenditures, interactions between aspergillosis and the diagnosis-related group (DRG) system are described. DRGs provide the basis for the hospital inpatient prospective payment system (PPS) to reimburse hospitals for care of Medicare, Medicaid, and an increasing number of commercially insured patients. Utilizing DRGs as the denominator for analysis provides a natural framework to understand the burden of disease from the hospital point of view.

Methods

Databases

Two databases were utilized as data sources for analysis. The 2003 Nationwide Inpatient Sample (NIS) was developed as part of the Healthcare Cost and Utilization Project, and is the largest all-payer inpatient care database publicly available in the US.¹⁴ The 2003 NIS consists of approximately 7.5 million hospital stays from 994 hospitals in 28 states, representing a stratified sample of 20% of all US community hospitals. Each record in the NIS contains information about a patient's hospital stay, documenting demographics, specific diagnoses and procedures, patient disposition, payer type, and overall hospital charges. All analyses were performed on the NIS, with the exception of those involving specific hospital charges and amounts reimbursed.

Because the NIS is a sample of hospital discharges, it is possible to create national estimates based on the data using discharge weights that are defined for every discharge record. This was particularly useful for the purposes of generating a socio-demographic profile of aspergillosis with incidence rates at the national level (see below, Incidence and disease profile).

The Medicare Provider Analysis and Review (MedPAR) file for fiscal year 2003, acquired from the Centers for Medicare and Medicaid Services (CMS), contains detailed charge information for 100% of Medicare beneficiaries using hospital inpatient services (approximately 11.5 million records).¹⁵ Particularly useful to this study were data elements in each record that were not captured by the NIS, including specific categories of hospital charges as well as reimbursement amounts. While the patient populations represented by the NIS and MedPAR data were distinct, preliminary analysis of median and mean total hospital charges (THC) within various DRGs generally showed agreement between the two databases. Therefore, the MedPAR file was primarily used to examine specific hospital charges and reimbursed amounts.

Definition of aspergillosis patient population

For all analyses, patients were considered to have aspergillosis if they had a primary or secondary discharge diagnosis of aspergillosis, using the International Classification of Diseases, Ninth Revision, Clinical Modifications (ICD-9-CM) code 117.3. Discharge diagnoses are reported on hospital claim forms according to the healthcare provider's clinical assessment of the patient's condition.

Incidence and disease profile

A socio-demographic profile of aspergillosis patients as a whole was generated by examining patient age, race, gender, and payer mix. In addition, outcome-related variables including length of stay (LOS) and THC were analyzed. NIS weighted estimates were used to calculate US national aspergillosis incidence projections, assuming a 2003 US population of 290 788 976.¹⁶

While limitations of the data available precluded the possibility of performing a full analysis based on the location

Table 1 The economic impact of aspergillosis: analysis of hospital expenditures across patient subgroups from the 2003 Nationwide Inpatient Sample

Characteristic	Aspergillosis patients		Non-aspergillosis patients	
	Mean or <i>n</i>	SD or %	Mean or <i>n</i>	SD or %
Number of cases, unweighted	2143		7 975 585	
Number of cases, weighted	10 400		38 210 191	
Aspergillosis diagnosis				
Primary	3060	29.4%		
Secondary	7340	70.6%		
Mortality rate	1778	17.1%	847 489	2.2%
Mean age	55.6 years	± 19.0 years	48.2 years	± 21.8 years
Age distribution				
<18 years	493	4.7%	60 635	11.7%
18–44 years	2109	20.3%	147 823	28.6%
45–64 years	3929	37.8%	177 625	34.4%
65+ years	3869	37.2%	130 016	25.2%
Gender				
Male	5557	53.4%	290 113	56.3%
Female	4843	46.6%	225 340	43.7%
Race				
White	5418	67.9%	240 436	58.1%
Black	1359	17.0%	88 054	21.3%
Hispanic	741	9.3%	60 154	14.5%
Other	456	5.7%	25 365	6.1%
Payer				
Medicare	4656	44.8%	181 691	35.2%
Medicaid	1468	14.1%	100 882	19.6%
Private insurance	3734	35.9%	192 693	37.4%
Self-pay	220	2.1%	18 493	3.6%
Other	311	3.0%	21 898	4.2%
Mean length of stay	17.7 days	± 21.9 days	7.9 days	± 11.4 days
Mean total hospital charges	\$96 731	± \$134 073	± \$44 318	± \$78 670

SD, standard deviation. Note: Values are weighted to project national estimates. Missing values resulted in sample variations across certain variables; percentages were calculated after omitting missing values.

or severity of *Aspergillus* infection, stratification of the aspergillosis patient population based on the presence or absence of a secondary ICD-9-CM code for pneumonia in aspergillosis (484.6) was possible. Because pulmonary aspergillosis represents a serious, systemic infection, it was expected that on average, aspergillosis patients classified with *Aspergillus* pneumonia would have poorer outcomes (defined by LOS, THC, and inpatient mortality) than those who did not.

Patient subgroup analysis

There has been some debate about the makeup of the aspergillosis population. In a study involving a series of 595 invasive aspergillosis patients, Patterson et al. retrospectively reported that almost 80% had BMT, hematologic disease, solid organ transplant, or AIDS.¹⁷ However, a separate study that reviewed hospital discharge data from 1998 found that the most commonly cited comorbidities for fungal infections – HIV, neoplasms, and transplants – accounted for only 45% of all infections.¹³ In light of this, the DRG analysis was

approached in two ways: (1) through the characterization of high-risk DRGs previously described in the literature, and (2) through the characterization of the DRGs most commonly assigned to aspergillosis patients, identified on the basis of frequency.

In the first method, clinically relevant conditions known to place patients at high risk for invasive aspergillosis were identified from the literature. DRGs corresponding to these risk factors included BMT (DRG 481), hematologic malignancy (DRG 400–405 and 473), immunity disorders (DRG 398–399), HIV infection (DRG 488–490), solid organ transplantation (DRG 103, 302, 480, 495), and chemotherapy (DRG 410 and 492). In addition, the same literature found that patients who have undergone transplantation remain at elevated risk for aspergillosis during the weeks and months following the transplant procedure.^{18–21} Therefore, it was of interest to analyze data from the population of post-transplant patients who contracted aspergillosis after their initial hospitalization. This cohort cannot be captured using the DRG system because there are no post-transplant DRGs. To overcome this limitation, ICD-9-CM codes corresponding to complications of

transplanted kidney (996.81), liver (996.82), heart (996.83), lung (996.84), and bone marrow (996.85) were used to define the post-transplant patient population. To eliminate any overlap with patients hospitalized for a transplantation procedure, we excluded admissions that were concurrently assigned a transplant DRG.

In the second method, all the DRGs found within the aspergillosis patient population were tabulated, and the most commonly assigned DRGs were identified based on frequency. This approach served two purposes. First, by identifying the number of DRGs associated with aspergillosis, it provided a context for the data obtained from each subgroup. Secondly, it provided a third subgroup solely based on raw data.

Subgroups of aspergillosis patients assigned to each of the DRG or ICD-9-CM categories above were analyzed and descriptive statistics generated for LOS and overall charges based on NIS data. For DRG defined subgroups, MedPAR data for specific and total hospital charges and costs as well as total amounts reimbursed were analyzed. Because the focus of this study was to describe costs from the hospital inpatient perspective, analysis was not performed for post-transplant ICD-9-CM categories, since each ICD-9-CM code would have represented a heterogeneous collection of DRGs. Each subgroup was compared to a reference population consisting of all patients within the same DRG or ICD-9-CM category who did not carry a diagnosis of aspergillosis.

CMS's 2004 Quarter 4 (Q4) hospital cost report data files were used to calculate provider-specific cost-to-charge ratios (RCC). For each discharge in MedPAR, the total charges were multiplied by the provider specific RCC to calculate an estimated cost. Incremental costs were determined by subtracting the median hospital costs of the non-aspergillosis reference population from the median hospital costs of patients with aspergillosis. Specific charges, particularly the expense categories of pharmacy, accommodation, intensive care unit (ICU), laboratory, and medical supplies were examined separately. All other specific charge categories were grouped as 'other'. When analyzing reimbursement amounts, a reimbursement-to-cost ratio (RCR) was calculated by dividing the median total amount reimbursed by the median hospital cost for each DRG examined. An incremental reimbursement-to-cost ratio (IRCR) was also defined for each DRG to determine to what extent incremental costs attributable to Aspergillus infection were reimbursed. The IRCR was

calculated by computing the difference between median reimbursed amounts for patients with and without aspergillosis and dividing this result by the difference between median hospital costs for patients with and without aspergillosis.

Chi-square tests were performed to describe statistically significant differences between categorical variables, except when small sample sizes made the Fisher's exact test more appropriate. Student's *t*-tests were performed to identify significant differences between means. The level of significance was set at 0.01. All analyses were performed using SPSS v12.

Results

Incidence of aspergillosis

Out of 38 million (weighted) hospital discharges in the 2003 NIS, 10 400 aspergillosis cases were identified across 171 DRGs. Aspergillosis was reported as the primary diagnosis for 29.4% of these cases. Assuming a 2003 US population of 290 million, we calculated a national incidence of 36 per million per year. Table 1 summarizes demographic characteristics as well as LOS and mean THC for aspergillosis patients as a whole. The mortality rate was 17.1%. The mean age of aspergillosis patients was 55.6 years. Approximately half (53.4%) were male and almost two-thirds (67.9%) were white. Medicare and private insurance were the largest payers of hospitalization expenses, each covering roughly 45% and 36%, respectively.

Aspergillosis patients with and without pneumonia

Of the 10 400 aspergillosis cases found in the NIS, 3910 (37.6%) were diagnosed with pneumonia in aspergillosis. Table 2 summarizes the median and mean LOS and THC, as well as hospital mortality rates for aspergillosis patients with and without the additional diagnosis of pneumonia in aspergillosis. The mean LOS, THC, and mortality were all significantly higher in those patients who had Aspergillus pneumonia compared with those patients who did not have Aspergillus pneumonia ($p < 0.01$). A complete list of the top ten commonly co-reported diagnosis codes for aspergillosis hospital discharges can be found in Appendix A.

Table 2 Length of stay, total hospital charges, and mortality in aspergillosis patients with and without Aspergillus pneumonia from the 2003 Nationwide Inpatient Sample

Aspergillosis patients (N = 10 400)	With Aspergillus pneumonia	Without Aspergillus pneumonia	p-Value
Number of cases (%)	3910 (37.6%)	6486 (62.4%)	
Median LOS, days (min–max)	13.0 (0.0–204.0)	9.0 (0.0–235.0)	
Mean LOS, days (SD)	20.8 (22.5)	15.8 (21.2)	<0.01
Median THC, \$ (min–max)	66 122 (658–941 043)	36 264.00 (51–864 986)	
Mean THC, \$ (SD)	120 910 (147 990)	82 406 (122 888)	<0.01
% Hospital mortality	25.1%	12.4%	<0.01

LOS, length of stay; SD, standard deviation; THC, total hospital charge. Note: Data from 2003 NIS. Missing values resulted in sample variations across variables; percentages were calculated after omitting missing values.

Table 3 Contribution of various DRG and ICD-9-CM categories to total cases of aspergillosis for high-risk DRG categories and post-transplant ICD-9-CM categories in the 2003 Nationwide Inpatient Sample

	Number of cases		Rate of Asp cases in subgroup (%)	% of total Asp cases (N = 10 400)
	Asp	Non-Asp		
High-risk DRG categories				
Hematologic malignancy	503	124 924	0.40	4.8
HIV	380	87 854	0.43	3.7
Chemotherapy	283	140 315	0.20	2.7
BMT	114	10 517	1.1	1.1
Reticuloendothelial/immunity disorders	110	72 911	0.15	1.1
Total	1390	436 521	0.32	13.4
Post-transplant ICD-9-CM categories				
Complications of BMT	229	6584	3.4	2.2
Complications of lung transplant	285	5702	4.8	2.7
Complications of kidney transplant	63	36 561	0.17	0.61
Complications of heart transplant	29	5148	0.56	0.28
Complications of liver transplant	25	8597	0.29	0.24
Total	631	62 592	1.0	6.1

Asp, aspergillosis; DRG, diagnosis-related group; HIV, human immunodeficiency virus; BMT, bone marrow transplant.

Length of stay and hospital charges for high-risk DRG categories and post-transplant patients

Analysis was performed on 1390 patients in the following high-risk DRG categories: hematologic malignancy, HIV, chemotherapy, BMT, and reticuloendothelial and immunity disorders. The DRGs for solid organ transplantation were not analyzed due to low numbers (total $n = 68$). We also analyzed the following post-transplant patients ($n = 631$) grouped by ICD-9-CM code: bone marrow, lung, kidney, heart, and liver. Altogether, these high-risk patients comprised 19.4% of the aspergillosis population (Table 3). Approximately 1.1% of BMT hospitalizations were associated with a diagnosis of aspergillosis, 2.5 to 7 times higher than in other high-risk DRG categories. Within the identified post-transplant patient population, cases of aspergillosis were proportionally highest in hospitalizations related to complications of lung transplant (4.8%) and complications of BMT (3.4%).

Table 4 compares median and mean LOS and THC for these patient subgroups with and without aspergillosis. Compared to non-aspergillosis patients within the same DRG or ICD-9-CM category, median LOS was 1.8 to 12.4 times higher and the median THC per admission in aspergillosis patients was 2.3 to 12.7 times higher. These differences were significant in all patient subgroups except for post-heart and post-liver transplant patients, where small sample sizes were a concern. Among all patients, the mean THC of those with aspergillosis ranked above the 90th percentile for all high-risk DRG categories examined.

Among the high-risk DRG subgroup, Aspergillus-infected BMT patients stayed in the hospital the longest (median LOS 48 days), and had the most expensive hospitalizations (median THC = \$413 200). Within the post-transplant patient category, liver transplant patients with aspergillosis had the longest and most expen-

sive hospitalizations (median LOS = 62 days; median THC = \$291 158).

Length of stay and hospital charges for the top five most common DRGs

In determining the most commonly assigned DRGs among the aspergillosis patients, 171 different DRG classifications were found to be associated with an aspergillosis diagnosis. The five most commonly assigned DRGs among the aspergillosis patients in order of frequency were: infectious and parasitic diseases (DRG 423, $n = 2014$), operating room (OR) procedures for infectious and parasitic diseases (DRG 415, $n = 1087$), tracheostomy (DRG 483, $n = 567$), respiratory system diagnoses with ventilator support (DRG 475, $n = 471$), and chronic obstructive pulmonary disease (COPD; DRG 79, $n = 452$). Combined, these patients comprised 44.1% of the aspergillosis population (Table 5). Aspergillosis patients with tracheostomy (DRG 483) had the longest hospital stay (median LOS = 49.5) and the highest THC (median THC = \$309,351) of all DRG categories examined (Table 6).

Specific hospital charges and costs

Specific hospital charges and costs were also analyzed across high-risk DRGs and the five most commonly assigned DRGs. Pharmacy and accommodation charges represented the highest proportion (50–70%) of hospital charges in all DRGs examined. In general, specific charges within high-risk DRGs increased four to six times in aspergillosis patients; ICU charges increased tenfold.

With respect to the total hospital cost for aspergillosis patients, pharmacy, ICU, and laboratory expenditures were the most significant contributors across the DRGs analyzed. On average, pharmacy costs represented 30% of total

Table 4 Length of stay and total hospital charges by associated DRG or ICD-9-CM category, aspergillosis vs. non-aspergillosis patients for high-risk DRG categories and post-transplant ICD-9-CM categories in the 2003 Nationwide Inpatient Sample

	Length of stay				p-Value	Total hospital charges				
	Median, days (min–max)		Mean, days (SD)			Median, \$ (min–max)		Mean, \$ (SD)		p-Value
	Asp	Non-Asp	Asp	Non-Asp		Asp	Non-Asp	Asp	Non-Asp	
High-risk DRG categories										
Hematologic malignancy	30.0 (1.0–172.0)	6.0 (0.0–351.0)	34.8 (31.7)	9.3 (11.4)	<0.01	149 912 (7519–747 897)	22 157 (73–957 245)	191 974 (163 535)	45 064 (69 220)	<0.01
HIV	11.0 (1.0–73.0)	6.0 (0.0–302.0)	14.2 (12.8)	8.6 (9.9)	<0.01	47 252 (2826–316 110)	20 115 (72–974 336)	82 946 (78 884)	38 173 (57 641)	<0.01
Chemotherapy	8.0 (0.0–92.0)	4.0 (0.0–153.0)	19.9 (20.5)	4.8 (6.1)	<0.01	50 196 (1979–525 848)	16 005 (158–942 096)	87 624 (97 349)	26 045 (38 298)	<0.01
BMT	48.0 (20.0–130.0)	23.0 (1.0–254.0)	56.9 (26.2)	28.1 (19.1)	<0.01	413 200 (60 386–808 002)	151 791 (5091–995 571)	442 233 (236 014)	203 603 (165 034)	<0.01
Reticuloendothelial/immunity disorders	9.0 (3.0–107.0)	4.0 (0.0–346.0)	18.9 (23.3)	5.0 (6.2)	<0.01	49 703 (9321–794 716)	11 574 (30–978 516)	112 892 (169 865)	20 811 (41 576)	<0.01
Post-transplant ICD-9 categories										
Complications of BMT	15.0 (2.0–107.0)	6.0 (0.0–145.0)	23.6 (22.1)	11.5 (15.9)	<0.01	93 857 (5100–794 716)	33 027 (1926–978 516)	180 843 (189 619)	80 513 (134 615)	<0.01
Complications of lung transplant	11.0 (2.0–190.0)	6.0 (0.0–260.0)	24.0 (38.8)	11.3 (16.6)	<0.01	90 622 (6144–534 184)	36 267 (2323–961 072)	153 796 (146 252)	81 558 (130 736)	<0.01
Complications of kidney transplant	14.0 (4.0–61.0)	5.0 (0.0–196.0)	25.8 (21.3)	7.5 (10.4)	<0.01	206 289 (15 957–511 774)	19 053 (548–957 763)	191 986 (136 382)	39 732 (70 425)	<0.01
Complications of heart transplant	14.6 (3.0–36.0)	5.0 (0.0–230.0)	15.1 (11.3)	8.3 (14.6)	<0.01	88 557 (48 800–768 054)	33 970 (1787–897 011)	210 128 (274 304)	68 808 (106 533)	<0.01
Complications of liver transplant	62.0 (4.0–138.0)	5.0 (0.0–241.0)	53.2 (50.9)	10.3 (17.5)	<0.01	291 158 (19 574–562 742)	22 821 (1023–917 140)	291 158 (286 294)	54 475 (95 895)	0.03

DRG, diagnosis-related group; SD, standard deviation; Asp, aspergillosis; BMT, bone marrow transplant. Note: Missing values resulted in sample variations across variables; percentages were calculated after omitting missing values.

Table 5 Contribution of various DRG and ICD-9-CM categories to total cases of aspergillosis for the top five most common DRGs in the 2003 Nationwide Inpatient Sample

	Number of cases		Rate of Asp cases in subgroup (%)	% of total Asp cases (N = 10 400)
	Asp	Non-Asp		
Top five most common DRGs				
Infectious and parasitic diseases	2014	22 552	8.2	19.4
OR procedures for infectious and parasitic diseases	1087	101 904	1.1	10.5
Tracheostomy	567	99 565	0.57	5.5
Respiratory system diagnoses with ventilator support	471	217 439	0.22	4.5
COPD	452	684 860	0.07	4.3
Total	4591	1 126 320	0.41	44.1

DRG, diagnosis-related group; Asp, aspergillosis; OR, operating room; COPD, chronic obstructive pulmonary disease.

expenditures, while ICU and laboratory costs represented roughly 12.2% and 11.8%, respectively.

Estimated total hospital cost and incremental hospital cost by DRG

Table 7 presents estimated total hospital costs by DRG in aspergillosis and non-aspergillosis patients and the incremental costs associated with aspergillosis. Within the high-risk DRG category, BMT patients with aspergillosis incurred the highest median estimated costs, \$74 945, over two times the amount for non-aspergillosis patients (\$33 055). However, in terms of incremental costs, both hematologic malignancy and chemotherapy patients experienced large relative increases in expenditures, over 600% and 800%, respectively. Although patients within the reticuloendothelial/immunity disorder DRG displayed the lowest median costs, the aspergillosis cases resulted in a 162% increase in hospital cost.

When examining cost by the five most common DRGs, tracheostomy procedures produced the highest median estimated costs in both aspergillosis and non-aspergillosis patient groups (\$87 729 and \$64 938, respectively). Infectious and parasitic diseases experienced the largest relative increase in cost (98.30%). Estimated costs associated with COPD were the lowest across the five most common DRGs, resulting in a median estimated cost of \$5924 for aspergillosis patients and \$3417 for non-aspergillosis patients. Hospitals managing patients within this subgroup experienced a 73.37% increase in costs.

Reimbursed amounts by DRG

Median and mean THC and reimbursed amounts for Medicare patients with aspergillosis are listed in Table 8. As would be expected, both median and mean reimbursed amounts were higher in cases involving aspergillosis than in those not involving aspergillosis. However, as shown in Table 9, cases involving aspergillosis were on average reimbursed a lower percentage of their total cost than non-aspergillosis cases (mean RCR, 0.80 vs. 1.43, respectively). Additionally, incremental costs associated with aspergillosis were reimbursed at a very low rate with a mean IRCR of 0.30. The IRCR for

individual DRG categories ranged from 0.08 (infectious and parasitic diseases) to 0.52 (chemotherapy and HIV). For aspergillosis patients, the RCRs were lower than the corresponding ratios for non-aspergillosis cases in all DRG categories.

Discussion

Aspergillosis is found in approximately 0.03% of all hospitalizations. The estimated US incidence rate of 36 per million per year confirms previous estimates of the incidence of aspergillosis.¹³ While the number of incident cases is fairly small, aspergillosis has a significant impact on: (1) patients – aspergillosis affects a diverse patient population, with the 10 400 cases in our dataset spread across 171 DRGs, and (2) hospitals – expenses associated with *Aspergillus* infection were disproportionately large.

Impact of aspergillosis

Diverse patient population

Clinical attention has naturally focused on well-known risk factors for invasive aspergillosis in immunosuppressed patients. The rates of aspergillosis we found among hospitalizations for BMT (1.1% and 3.4% for preoperative period and post-transplant, respectively), complications of lung transplant (4.8%), HIV (0.4%), and hematologic malignancy (0.4%) are consistent with what has previously been reported.⁸ However, patients assigned to high-risk DRGs and post-transplant ICD-9-CM categories comprised only 19.4% of aspergillosis hospitalizations. On the other hand, the top five most common DRGs comprised 44.1%, with none of the top five belonging to a readily identifiable high-risk category. Moreover, the finding that an additional 161 DRG classifications were associated with incidents of aspergillosis only further demonstrates the diversity of the population that aspergillosis has an impact on.

The top two most common DRGs found in our analysis: infectious and parasitic disease diagnoses (423, 415), appear largely to represent a general, chronically ill population without classic risk factors for invasive disease. The DRG for COPD (79) includes patients who had comorbid conditions

Table 6 Length of stay and total hospital charges by associated DRG or ICD-9-CM category, aspergillosis vs. non-aspergillosis patients for the top five most common DRGs in the 2003 Nationwide Inpatient Sample

	Length of stay					Total hospital charges				
	Median, days, (min–max)		Mean, days (SD)		p-Value	Median, \$ (min–max)		Mean, \$ (SD)		p-Value
	Asp	Non-Asp	Asp	Non-Asp		Asp	Non-Asp	Asp	Non-Asp	
Top five most common DRGs										
Infectious and parasitic diseases	8.0 (0.0–87.0)	4.0 (0.0–145.0)	10.4 (10.4)	6.8 (8.1)	<0.01	29 878 (658–766 488)	12 962 (35–854 046)	52 024 (78 471)	27 271 (45 161)	<0.01
OR procedures for infectious and parasitic diseases	13.0 (0.0–165.0)	9.0 (0.0–259.0)	16.9 (15.7)	12.7 (13.1)	<0.01	66 043 (6241–426 406)	32 882 (32–999 346)	94 569 (86 778)	58 692 (79 640)	<0.01
Tracheostomy	49.5 (1.0–63.0)	32.0 (0.0–265.0)	55.7 (38.0)	40.0 (32.2)	<0.01	309 351 (1765–185 101)	208 664 (48–933 005)	358 931 (226 806)	261 087 (194 973)	<0.01
Respiratory system diagnosis with ventilator support	15.0 (8.0–235.0)	8.0 (0.0–362.0)	20.2 (15.8)	11.0 (11.5)	<0.01	103 007 (56 205–941 043)	42 979 (35–999 945)	136 153 (105 923)	64 334 (72 905)	<0.01
COPD	7.0 (0.0–50.0)	4.0 (0.0–261.0)	11.0 (11.4)	4.6 (3.9)	<0.01	18 307 (2497–513 178)	9847 (94–916 925)	30 933 (37 084)	14 217 (15 965)	<0.01

DRG, diagnosis-related group; SD, standard deviation; Asp, aspergillosis; OR, operating room; COPD, chronic obstructive pulmonary disease. Note: Missing values resulted in sample variations across variables; percentages were calculated after omitting missing values.

Table 7 Total hospital costs by associated DRG, aspergillosis vs. non-aspergillosis patients in the 2003 MedPAR

	Median costs, \$ (min–max)		Mean costs, \$ (SD)		Incremental median cost	
	Asp	Non-Asp	Asp	Non-Asp	\$ Difference	% Increase
High-risk DRG categories						
Hematologic malignancy	47 949 (0–247 250)	6570 (0–962 484)	55 292.33 (47 425.67)	11 575.73 (16 883.29)	41 379.40	629.85%
HIV	15 944 (0–84 448)	5905 (0–465 763)	23 374.35 (20 885.76)	10 107.73 (14 794.25)	10 039.70	170.03%
Chemotherapy	45 214 (1297–175 800)	4917 (0–249 391)	48 830.36 (36 115.95)	7746.36 (11 457.99)	40 297.45	819.58%
BMT	74 945 (23 956–272 912)	33 056 (0–389 799)	109 013.59 (82 246.43)	43 306.94 (42 218.08)	41 889.07	126.72%
Reticuloendothelial/ immunity disorders	11 270 (0–278 987)	4301 (0–288 617)	40 289.82 (67 231.63)	6287.02 (8437.65)	6968.42	162.01%
Top five most common DRGs						
Infectious and parasitic diseases	9856 (0–163 019)	4970 (0–158 251)	15 042.64 (18 375.63)	8901.55 (12 327.88)	4886.06	98.30%
OR procedures for infectious and parasitic diseases	19 556 (0–176 771)	12 036 (0–2 129 893)	28 718.60 (26 856.63)	18 709.17 (23 719.57)	7520.49	62.48%
Tracheostomy	87 729 (0–430 429)	64 938 (0–1 593 666)	101 522.94 (69 196.48)	81 134.54 (66 399.87)	22 790.80	35.10%
Respiratory system diagnosis with ventilator support	26 252 (0–261 599)	13 474 (0–1 010 665)	33 787.87 (31 680.46)	18 548.40 (19 683.88)	12 777.20	94.83%
COPD	5924 (0–82 289)	3417 (0–288 989)	9485.55 (10 956.42)	4471.06 (4261.07)	2507	73.37%

DRG, diagnosis-related group; MedPAR, Medicare Provider Analysis and Review file; SD, standard deviation; Asp, aspergillosis; BMT, bone marrow transplant; OR, operating room; COPD, chronic obstructive pulmonary disease.

Table 8 Total hospital charges and reimbursed amounts by associated DRG category, aspergillosis vs. non-aspergillosis from the 2003 MedPAR

	Number of cases		Total hospital charges				Reimbursed amounts						p-Value
			Median, \$ (min–max)		Mean, \$ (SD)		Median, \$ (min–max)		Mean, \$ (SD)				
	Asp	Non-Asp	Asp	Non-Asp	Asp	Non-Asp	Asp	Non-Asp	Asp	Non-Asp			
High-risk DRG categories													
Hematologic malignancy	117	60 517	123 139 (4678–1 736 649)	19 556 (5–2 276 578)	183 166 (232 394)	36 522 (56 293)	23 371 (0–517 679)	9568 (0–830 478)	44 371 (62 841)	12 316 (12 594)	<0.01		
HIV	81	20 214	46 499 (5920–400 156)	17 690 (114–1 644 000)	77 924 (74 262)	33 289 (54 133)	14 512 (0–55 480)	9328 (0–505 669)	17 992 (13 102)	11 366 (11 529)	<0.01		
Chemotherapy	64	33 435	111 335 (3248–544 893)	14 817 (293–890 563)	150 513 (126 946)	24 484 (37 184)	26 703 (0–138 785)	5647 (0–242 910)	35 121 (26 847)	8131 (9404)	<0.01		
BMT	24	20 328	245 598 (53 867–878 671)	97 948 (3063–830 109)	101 820 (129 528)	19 567 (29 755)	60 929 (42 214–261 860)	47 057 (0–318 297)	26 348 (39 328)	6288 (6749)	0.02		
Reticuloendothelial/immunity disorders	19	993	40 494 (2564–469 379)	12 433 (15–1 779 806)	306 449 (244 879)	128 792 (105 638)	7103 (0–162 817)	5763 (0–558 998)	97 022 (68 825)	50 478 (29 622)	0.03		
Top five most common DRGs													
Infectious and parasitic diseases	843	8179	28 193 (1452–600 417)	14 673 (17–981 571)	46 644 (57 134)	28 097 (41 321)	8813 (0–200 004)	8420 (0–196 958)	11 567 (12 952)	9774 (7955)	<0.01		
OR procedures for infectious and parasitic diseases	398	46 811	63 114 (3827–1 012 735)	35 911 (67–7 453 037)	91 291 (98 185)	61 117 (90 854)	20 549 (0–237 714)	18 320 (0–2 961 377)	25 599 (19 649)	21 617 (21 505)	<0.01		
Tracheostomy	175	45 745	262 790 (17 172–1 987 949)	195 583 (40–5 881 797)	333 252 (297 415)	260 736 (249 904)	97 807 (0–459 114)	88 230 (0–1 503 270)	110 004 (65 152)	99 461 (62 565)	0.03		
Respiratory system diagnosis with ventilator support	248	120 419	82 628 (5852–1 061 907)	42 395 (8–2 790 084)	119 824 (116 700)	64 195 (75 677)	20 620 (0–236 424)	18 175 (0–735 914)	27 534 (23 723)	21 287 (14 326)	<0.01		
COPD	317	418 414	19 440 (1765–514 010)	9773 (9–1 075 344)	32 475 (46 186)	14 388 (16 646)	4016 (0–115 118)	3780 (0–213 937)	6486 (9802)	4199 (2846)	<0.01		

DRG, diagnosis-related group; MedPAR, Medicare Provider Analysis and Review file; SD, standard deviation; Asp, aspergillosis; BMT, bone marrow transplant; OR, operating room; COPD, chronic obstructive pulmonary disease.

Table 9 Reimbursement-to-cost ratio (RCR) and incremental reimbursement-to-cost ratio (IRCR) by DRG category, aspergillosis vs. non-aspergillosis hospitalizations from the 2003 MedPAR

DRG category	RCR		IRCR
	Asp	Non-Asp	
Hematologic malignancy	0.49	1.46	0.33
HIV	0.91	1.58	0.52
Chemotherapy	0.59	1.15	0.52
BMT	0.81	1.42	0.33
Reticuloendothelial/immunity disorders	0.63	1.34	0.19
Infectious and parasitic diseases	0.89	1.69	0.08
OR procedures for infectious and parasitic diseases	1.05	1.52	0.30
Respiratory system diagnosis with ventilator support	1.11	1.36	0.42
Tracheostomy	0.79	1.35	0.19
COPD	0.68	1.11	0.09
Mean	0.80	1.43	0.30

DRG, diagnosis-related group; MedPAR, Medicare Provider Analysis and Review file; Asp, aspergillosis; BMT, bone marrow transplant; OR, operating room; COPD, chronic obstructive pulmonary disease.

that are pulmonary in nature. The relatively low expenditures found in these DRGs may reflect a significant percentage of patients with localized or chronic disease within these subgroups. According to the literature, mild-to-moderate degrees of immunosuppression such as in the setting of diabetes, advanced COPD, or low-dose corticosteroid therapy, may place patients at risk for developing acute and chronic forms of aspergillosis.

The DRGs for tracheostomy (483) and respiratory diagnoses with ventilator support (475) represent gravely ill patients, many of whom require substantial care in the ICU. This is consistent with other studies in which cases of aspergillosis in the ICU were reported.²²

Increased hospital expenditures

These findings reinforce that aspergillosis has a critical impact on expenditures and length of stay in high-risk patient groups. Each of these variables was many times higher in patients with aspergillosis than in patients without infection. The impact of aspergillosis was found to be particularly high in the setting of BMT. Additionally, these findings demonstrate that aspergillosis is a devastating complication in the ICU population, associated with very high costs. A separate sub-analysis of aspergillosis patients using artificial ventilation as a proxy for intensive care confirmed these conclusions. These results are consistent with the findings of previous studies: Pelz and colleagues reported high attributable ICU costs in critically ill patients with *Candida* infections,²³ while a study conducted by Vandewoude et al. found that stays in ICU were associated with patients with invasive aspergillosis.²⁴

Furthermore, the high monetary costs of treating aspergillosis were reimbursed at a low level. For the DRGs that were analyzed, hospital charges involving patients with aspergillosis were reimbursed at an average rate of 7% lower than hospitalizations without aspergillosis (35% vs. 42%, respectively). In addition, aspergillosis-related incremental hospital expenditures were generally reimbursed at well below 30% of charges.

Limitations

One concern about performing an analysis based on DRGs was that high-risk patients could potentially be hidden within non-specific DRG categories due to the rules of patient DRG assignment. To explain this, the number of aspergillosis patients within the top five most common DRGs, who had a primary or secondary diagnosis of HIV, hematologic malignancy, solid organ transplantation, BMT, chemotherapy, or neutropenia based on an ICD-9-CM code, were identified and counted. Relevant diagnoses were found in 23.5% of patients, which suggests that while there is indeed some overlap, such patients are in the minority.

Another limitation of the current study is the single ICD-9-CM code for aspergillosis (117.3), which did not allow differentiation between invasive aspergillosis and other more chronic forms of *Aspergillus* infection. However, by utilizing the secondary code of pneumonia in aspergillosis (484.6) to stratify cases, aspergillosis patients with this secondary diagnosis were found to incur higher costs and have worse outcomes than those who do not carry this diagnosis. This level of analysis was not carried throughout the entire study due to sample size constraints. Instead, most of these results are based on a sample of the entire aspergillosis patient population, including those with localized disease as well as acute systemic infection. It is probable, however, that observations for per-case mortality, LOS, and hospital charges and estimated costs underestimated those of patients who have had invasive, systemic disease.

Under-diagnosis of invasive aspergillosis has also been cited as a major issue in previous studies. This analysis is also subject to these limitations as the study populations were identified using the clinical diagnosis reported with hospital discharge data, which is subject to the discretion of the treating physician and the diagnostic tools available to them. Current estimates of the rate of under-diagnosis vary; however, one study of BMT patients found that upon postmortem evaluation, 45% had gone untreated for aspergillosis.²⁵ These trends may understate the total cost of care estimated in this analysis. Future analyses of more recent data may lend a more accurate

assessment of total costs, as newer molecular diagnostics will probably increase diagnostic rates for aspergillosis. Our estimates also do not account for the additional costs associated with follow-up treatment in the hospital outpatient and home health setting. However, previous studies have suggested that hospital costs represent 90% of the total mean cost associated with invasive aspergillosis.²⁶

Concluding remarks

The present study demonstrates that aspergillosis has a strong economic impact across many DRGs. The broad, heterogeneous nature of the population affected by aspergillosis makes it challenging to direct healthcare resources effectively, in order to address the problem that the disease imposes on healthcare outcomes. In addition to determining and improving guidelines for both prophylaxis and treatment of fungal infections, it is necessary to expand consideration to groups not considered to be typically at high risk.

Aspergillosis particularly affects drug, accommodation (LOS), and ICU expenditures. While much of the attention paid to aspergillosis has been directed towards patients who are severely immunocompromised, more should be directed towards other subgroups such as the chronically ill or ICU patients in terms of both preventative and therapeutic interventions.

With reimbursement of aspergillosis-related cases at less than a third of hospital expenditures, providers are placed in the unenviable position of confronting a life-threatening and costly disease with poor outcomes while facing difficult economic constraints. We recommend a strong focus on the development of more cost-effective approaches to the disease, including new therapies as well as prophylactics, which may reduce the onset of infection. The findings of this study underscore the critical need for more research to identify settings of care and specific risk factors that drive increased expenditures.

Conflict of interest: This study was supported by Astellas Pharma US Inc. Authors Tong, Lau, Murtagh, and Layton are consultants to Astellas. Author Seifeldin is an employee of Astellas. However, this study does not focus on any specific product; it examines the burden of illness with aspergillosis.

Appendix A. Top ten most common diagnoses reported with aspergillosis

ICD-9-CM	Description	Percent of aspergillosis discharges
484.60	Pneumonia in aspergillosis	37.2%
401.90	Hypertension (not otherwise specified)	21.0%
518.81	Acute respiratory failure	16.5%
496.00	Chronic airway obstruction (not elsewhere classified)	13.4%
428.00	Chronic heart failure (not otherwise specified)	13.2%
491.21	Obstructive chronic bronchitis with (acute) exacerbation	12.3%

427.31	Atrial fibrillation	11.7%
284.80	Aplastic anemia (not elsewhere specified)	11.1%
276.50	Volume depletion unspecified	9.6%
285.90	Anemia (not otherwise specified)	9.1%

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