Changes in Mortality and Length of Stay for Aspergillosis-Related Hospitalizations in the United States from 2001 to 2011

A thesis

Submitted by

Masako Mizusawa

In partial fulfillment of the requirements

for the degree of

Master of Science

in

Clinical and Translational Science Institute

TUFTS UNIVERSITY

Sackler School of Graduate Biomedical Sciences

May, 2016

Advisor:

Thesis Chair: David R. Snydman, MD

Program Mentor: Jessica K. Paulus, ScD

Statistical Mentor: Lori Lyn Price, MAS

Project Mentor: Helen W. Boucher, MD

Project Mentor: Jennifer K. Chow, MD

ABSTRACT

Aspergillosis is a life-threatening infection associated with significant morbidity and mortality. In the last 15 years there have been major changes in the clinical management of aspergillosis. Most epidemiological studies of the burden of aspergillosis to date have been based on data from single centers or multicenter registries of invasive aspergillosis or transplant-associated infections. The objective of our study is to evaluate changes in mortality and length of stay in aspergillosis-related hospitalizations in the United States from 2001 to 2011 using a national inpatient administrative database. Using the 2001, 2006 and 2011 Nationwide Inpatient Sample, we analyzed changes in in-hospital mortality and length of stay over time using 16,323 adult hospitalizations with aspergillosis (ICD-9 117.3) or pulmonary aspergillosis (ICD-9 484.6) as a primary or secondary diagnosis. The main outcomes of our study were changes in in-hospital mortality and length of stay over time with adjustment for age, sex, renal failure and traditional and non-traditional risk factors for aspergillosis. From 2001 to 2011 there was 50% increase in the absolute number of the aspergillosis-related hospitalizations as well as in the annual rate of aspergillosis cases per 100,000 hospitalizations. The crude in-hospital mortality rate for aspergillosis-related hospitalizations was 18.7% in 2001, 11.7% in 2006 (43% relative odds reduction), and 7.8% in 2011 (63% relative odds reduction since 2001, p for trend < 0.0001). The risk of spending one additional day in the hospital was also reduced by 7% in 2006, and by 15% in 2011 compared to 2001 (p for trend < 0.0001). These significant reductions in in-hospital mortality and length of stay persisted after multivariable adjustment for demographic and clinical factors. Significant time trends in reduced in-hospital mortality and length of stay were also observed when limited to the subgroup of aspergillosis-related hospitalizations with any of the traditional risk factors for aspergillosis. In the United States, mortality and length of stay for aspergillosis-related hospitalizations have significantly decreased from 2001 to 2011 while

the number of these hospitalizations have increased over time.

ACKNOWLEDGEMENT

The authors thank Dr. Angie Mae Rodday for the technical support with R.

Table of Contents

List of Tables

List of Figures

List of Abbreviations

ABPA: Allergic bronchopulmonary aspergillosis

AHRQ: The Agency for Healthcare Research and Quality

CCI: The Charlson comorbidity index

CI: Confidence interval

CPA: Chronic pulmonary aspergillosis

COPD: Chronic obstructive pulmonary disease

DM: Diabetes mellitus

FDA: The US Food and Drug Administration

HIV: Human immunodeficiency virus disease

HCUP: The Health Care Utilization and Cost

IA: Invasive aspergillosis

ICU: Intensive care unit

NIS: Nationwide Inpatient Sample

OR: Odds ratio

RR: Risk ratio

TB: Tuberculosis

TRANSNET: The Transplant Associated Infection Surveillance Network

INTRODUCTION

Aspergillosis is a life-threatening infection with significant associated morbidity and mortality, particularly in immunocompromised hosts such as those with prolonged neutropenia or transplantation.[1–5] Higher mortality related to aspergillosis is observed in stem cell transplant recipients and patients with hematological malignancy compared to those with AIDS or underlying lung disease.[6–10] Given the development of more potent immunosuppressing chemotherapies, the expansion of organ and stem cell transplantation as treatment modalities for a number of disease indications, and improvement in diagnostic testing, an increased incidence of invasive aspergillosis (IA) has been observed over the past three decades.[11–13]

There have been three major changes in the management of aspergillosis in the past 15 years. First, voriconazole, a triazole anti-fungal medication, was approved by the US Food and Drug Administration (FDA) in 2002.[14] Voriconazole was the first anti-fungal agent for the primary treatment of IA that could be administered orally and the first to demonstrate a reduction in mortality. Until the advent of voriconazole, the only effective anti-aspergillosis agent was amphotericin B which is only available in parenteral formulation and predictably causes nephrotoxicity. Clinical trials demonstrated improved outcomes, better survival and fewer severe side effects among patients with aspergillosis treated with voriconazole as compared to amphotericin B-based therapy for IA.[15,16] Tolerability of voriconazole in patients with renal insufficiency has also been demonstrated.[17–19] One year after voriconazole's approval, the galactomannan antigen detection test, which detects aspergillus exoantigen and serves as a biomarker for the presence of aspergillosis, was approved by the FDA.[20] This test was intended to offer improved diagnostic accuracy for IA and it was recommended by global clinical trial guidelines for the study of IA.[21] Lastly, in January 2008, the Infectious Disease Society of America (IDSA) introduced

aspergillosis treatment guidelines that recommended voriconazole for the primary treatment of aspergillosis and the galactomannan test as a useful adjunctive test to establish an early diagnosis, particularly for serial screening in patients at high risk of infection.[22]

Several studies conducted in the United States suggest that mortality has been decreasing in immunocompromised patients with IA since 2002. One study of 405 stem cell transplant patients with IA from a single cancer center reported that the probability of survival at 30 days, 90 days, and 1 year for patients given diagnosis of IA during 2002–2004 was significantly higher than in the preceding years (1990–2001).[23] Another study of 605 IA cases from a multicenter registry of transplant recipients showed that there was a significant linear trend in decreased 12-week all-cause mortality from 2001 and 2006 for both stem cell transplant and solid organ transplant recipients who were diagnosed with IA.[24] These improvements in mortality may be explained by earlier diagnosis and better treatment of IA, as well as introduction of treatment guidelines for aspergillosis.[22] The most recent population-based analysis of burden in the United States was conducted in 2006[25] and the majority of the epidemiological studies have used data from single centers or multicenter registries of IA or transplant-associated infections.

We therefore aimed to evaluate changes in mortality and length of stay in aspergillosis-related hospitalizations over the 2001 - 2011 time period in both immunocompromised and apparently immunocompetent individuals in the United States using a national inpatient administrative database.

METHODS

Database

We used data from the Health Care Utilization and Cost - Nationwide Inpatient Sample (HCUP-NIS) from 2001, 2006 and 2011 to evaluate changes in in-hospital mortality (primary outcome) and length of stay (secondary outcome) in aspergillosis-related hospitalizations over time. HCUP was established by the Agency for Healthcare Research and Quality (AHRQ) to provide multistate, administrative, population-based data that includes information on both insured and uninsured patients in a uniform format. The Nationwide Inpatient Sample (NIS) is a representative sample of all US inpatient stays in acute-care non-federally funded institutions. Hospitals are stratified by ownership/control, bed size, teaching status, urban/rural location and geographic region. A sample weight is assigned to each hospitalization to calculate the national estimates. [26]

Patient Population

Hospitalizations of patients aged 18 years or older and who had aspergillosis (ICD-9 code 117.3) or pulmonary aspergillosis (ICD-9 code 484.6) as a primary or secondary diagnosis based on the first or second listed diagnosis were included. Allergic bronchopulmonary aspergillosis (ABPA) (ICD-9 code 518.6) cases were excluded because the management of ABPA differs from other types of aspergillosis.

Demographics and Clinical Risk Factors

Demographics and clinical factors that may be associated with aspergillosis were selected *a priori* based on clinical expertise and the published literature.[16,27,28] The risk factors were identified in the NIS sample using corresponding ICD9-codes and classified as "traditional" risk factors and "non-traditional" risk factors. Traditional risk factors for IA were defined as commonly identified and recognized risk factors for IA that were described in the literature. Traditional risk factors included stem cell transplantation, hematological malignancy, neutropenia, long-term corticosteroid therapy, solid organ transplantation,

human immunodeficiency virus disease (HIV), immunodeficiency other than HIV and rheumatological disease.[11,29] Non-traditional risk factors were defined as risk factors identified in mildly immunocompromised or apparently immunocompetent individuals that have been considered potential risk factors for IA, and those reported as predisposing factors for chronic pulmonary aspergillosis (CPA) or aspergilloma. Non-traditional risk factors included chronic obstructive pulmonary disease (COPD), asthma, cystic fibrosis, other underlying lung diseases, lung cancer, solid tumors other than lung cancer, diabetes mellitus (DM), pulmonary tuberculosis (TB), non-TB mycobacterial infection, cirrhosis and lung infarction.[30–34] *Pseudomonas aeruginosa* has been reported as a predominant bacterial co-pathogen for pulmonary aspergillosis among stem cell transplant recipients with GVHD.[35] Aspergillosis has also been frequently isolated from the respiratory tract of cystic fibrosis patients with *Pseudomonas aeruginosa*; the potential interplay between these two organisms in the pathogenesis of lung damage has been suggested.[36,37] As the proportion of anti-microbial resistance to *Pseudomonas aeruginosa* has increased,[38] eradication of *Pseudomonas* infection and colonization has become more and more challenging over time, which could have affected mortality and length of stay. Therefore, *Pseudomonas* infection was also included as a potential confounder. The definition of each risk factor and corresponding ICD-9 codes are described in the next section. Although renal failure is not commonly listed as a risk factor for developing aspergillosis, it was included in the analyses because it is a dose-limiting factor for amphotericin B-based therapy and has a significant impact on mortality in patients with aspergillosis.[23,24,39] The Charlson comorbidity index (CCI)[40] was also used to adjust for severity of co-morbid conditions other than aspergillosis-related risk factors.

Definitions of each risk factor and corresponding ICD9-codes

1. Stem cell transplantation

Bone marrow or peripheral stem cell transplantation.

279.50, 279.52, 279.53, 996.85, V42.81, V42.82

2. Hematologic malignancy

Leukemia, lymphoma, multiple myeloma, myelodysplastic syndrome, myelofibrosis or myeloproliferative disorder.

200.00, 200.01, 200.08, 200.10, 200.11, 200.13, 200.18, 200.20, 200.23, 200.51, 200.80, 200.84, 201.41, 201.50, 201.52, 201.58, 201.60, 201.90, 202.00, 202.08, 202.10, 202.18, 202.40, 202.80, 202.81, 202.82, 202.83, 202.84, 202.86, 202.87, 202.88, 202.90, 203.00, 203.01, 203.02, 203.10, 203.80, 204.00, 204.01, 204.02, 204.10, 204.11, 204.80, 205.00, 205.01, 205.02, 205.10, 205.11, 205.30, 207.00, 207.21, 207.80, 208.00, 208.80, 208.90, 238.7, 238.75, 238.76, 238.79, 289.83, V10.61, V10.62, V10.63, V10.72, V10.79

3. Neutropenia

Neutropenia or pancytopenia of any causes.

284.0, 284.1, 284.11, 284.12, 284.19, 284.8, 284.89, 284.9, 288.0, 288.00, 288.03, 288.04, 288.09

4. Long-term corticosteroid therapy

Long-term steroid use or equivalent conditions such as glucocorticoid deficiency and corticoadrenal insufficiency which require long-term corticosteroid therapy or Cushing syndrome.

255.0, 255.4, 255.41, V58.65

5. Solid organ transplantation

Transplantation of kidney, liver, heart, lung, pancreas or intestine.

996.81, 996.82, 996.83, 996.84, 996.86, V42.0, V42.1, V42.6, V42.7, V42.83, V42.84

6. Human immunodeficiency virus infection (HIV)

Human immunodeficiency virus disease or infection.

042, V08

7. Immunodeficiency other than HIV

Any congenital or acquired immunodeficiency other than HIV.

279.00, 279.01, 279.03, 279.04, 279.06, 279.10, 279.19, 279.2, 279.3, 279.9, 288.1

8. Rheumatological disease

Any autoimmune or connective tissue disease.

245.2, 099.3, 135, 279.49, 517.2, 555.9, 556.2, 556.8, 556.9, 571.42, 695.4, 696.0, 696.1, 710.0, 710.1, 710.2, 710.3, 710.4, 710.9, 714.0, 714.1, 714.2,714.30, 714.81, 720.0, 725, 729.0

9. Chronic obstructive pulmonary disease (COPD)

All the conditions directly associated with COPD regardless of types or severity.

273.4, 491.20, 491.21, 491.22, 491.8, 491.9, 492.8, 496, 518.1

10. Asthma

All the conditions directly associated with asthma regardless of types or severity.

493.00, 493.01, 493.02, 493.10, 493.20, 493.21, 493.22, 493.90, 493.91, 493.92

11. Cystic fibrosis

All the conditions directly associated with cystic fibrosis regardless of types or severity.

277.00, 277.02, 277.03, 277.09

12. Other underlying lung diseases

Structural lung abnormalities such as bronchiectasis or previous resection surgery, radiation pneumonitis, pneumoconiosis, asbestosis, interstitial lung disease and other lung pathology with chronicity.

490, 492.0, 494.0, 494.1, 495.0, 495.4, 495.8, 495.9, 500, 501, 502, 508.0, 508.1, 515, 516.0, 516.3, 516.8, 516.9, 517.8, 518.0, 518.3, 518.6, 518.89, 748.3, 748.5, V45.76

13. Lung cancer

Primary or secondary malignant neoplasm of bronchus or lung.

162.2, 162.3, 162.4, 162.5, 162.8, 162.9, 197.0, V10.11

14. Solid tumor other than lung cancer

All the primary and secondary malignant solid tumors except for lung cancer.

141.0, 146.0, 149.0, 150.9, 153.3, 154.0, 155.0, 157.0, 157.9, 159.9, 161.0, 161.1, 161.9, 164.0, 170.2, 170.9, 171.0, 172.9, 173.2, 173.3, 173.6, 174.4, 174.9, 179, 180.0, 180.8, 180.9, 182.0, 184.4, 185, 186.9, 188.9, 189.0, 191.1, 191.2, 191.8, 191.9, 193, 194.0, 195.0, 195.3, 196.0, 196.1, 196.2, 196.5, 196.6, 197.1, 197.2, 197.3, 197.5, 197.6, 197.7, 197.8, 198.0, 198.2, 198.3, 198.5, 198.7, 198.89, 199.1, 237.5, 239.1, V10.01, V10.02, V10.03, V10.05, V10.06, V10.09, V10.21, V10.29, V10.3, V10.41, V10.42, V10.43, V10.44, V10.46, V10.47, V10.51, V10.52, V10.81, V10.82, V10.83, V10.87, V10.89

15. Diabetes mellitus (DM)

All the conditions directly associated with DM regardless of types or severity.

249.00, 249.01, 249.80, 250.00, 250.01, 250.02, 250.03, 250.12, 250.13, 250.22, 250.23, 250.40, 250.41, 250.42, 250.43, 250.50, 250.51, 250.60, 250.61, 250.62, 250.63, 250.70, 250.73, 250.80, 250.81, 250.82, 250.83, 250.92, 250.93, 362.01, V58.67

16. Cirrhosis

Cirrhosis of any causes.

571.2, 571.5, 571.6

17. History of tuberculosis (TB)

History of any infections caused by *Mycobacteria tuberculosis*.

011.20, 011.22, 011.24, 011.30, 011.40, 011.50, 011.90, 01.193, 012.80, 137.0, 137.4, V12.01

18. History of non-TB mycobacterial infection

History of any infections caused by non-TB mycobacteria.

031.0, 031.2, 031.8, 031.9

19. Lung infarction

Any pulmonary embolism or infarction.

415.11, 415.19

20. Pseudomonas infection

Any infections caused by Pseudomonas.

038.43, 041.7, 380.14, 482.1

21. Renal failure

Acute renal failure, chronic kidney disease or end stage renal disease.

403.00, 403.10, 403.90, 403.91, 404.90, 404.91, 404.93, 584.5, 584.8, 584.9, 585, 585.1, 585.2, 585.3, 585.4, 585.5, 585.6, 585.9, 586

Statistical Analysis

Demographic and clinical characteristics for each hospitalization year were described and compared by hospitalization year. Continuous variables were expressed as mean ± standard deviation or median and the 25^{th} and 75^{th} percentiles, as appropriate. Weighted data were used for all analyses and descriptive results. For the primary outcome, univariate logistic regression was used to assess the relationship between in-hospital mortality and hospitalization year as a categorical variable. For the secondary outcome, a univariate negative binomial regression model was used to assess the relationship between length of stay and hospitalization year, both including and excluding hospitalizations with death. A crude odds ratio was generated in the univariate analysis. In multivariable analysis three adjustment models were performed: a model adjusted for age, sex and traditional risk factors (Model 1), a model adjusted for age, sex and all risk factors (Model 2) and a model adjusted for age, sex, all risk factors and renal failure (Model 3). Additionally, CCI was categorized into 4 levels (0, 1, 2 and ≥ 3) and two multivariable adjustment models including CCI were performed: a model adjusted for age, sex, CCI and all risk factors that were not included in CCI (Model 4) and a model adjusted for age, sex

and CCI (Model 5). Although HCUP-NIS contained up to 15 diagnoses for each hospitalization until 2008 and up to 25 diagnoses from 2009, we used up to the first 15 diagnoses for 2011 to be consistent with the data collection methods used in 2001 and 2006 for the main analysis and performed a sensitivity analysis using up to 25 diagnoses for 2011. To evaluate trends over time, hospitalization year (2001, 2006 and 2011) was treated as a continuous variable and used to assess the relationship of time with each of the outcomes using logistic regression. Subgroup analyses for the primary and secondary outcomes were performed for hospitalizations grouped by each traditional risk factor and for those which had at least one risk factor from any of the traditional risk factors using the same methods as the main analysis. The impact of including *Pseudomonas* infection in multivariable statistical models as well as including up to 25 diagnoses for 2011 data were explored as sensitivity analyses. SAS 9.4 (SAS Institute, Cary, NC) was used for data preparation and all statistical analyses were performed using R, version 3.1.3.

RESULTS

Baseline Characteristics and Overall Trends

A total of 3,329 aspergillosis-related hospitalizations from 2001, 2006 and 2011 were identified from HCUP-NIS, resulting in an estimated 16,323 hospitalizations after the weights were applied. Baseline characteristics of these hospitalizations are summarized in Table 1. There were no missing data except for race/ethnicity. For each hospitalization year, the mean age of patients with aspergillosis was approximately 60 years, approximately 50% were male and 75% were white. The most frequent traditional risk factor was hematological malignancy followed by neutropenia. The most frequent non-traditional risk factor was COPD followed by other lung disease. Overall, there was a 50% increase in the absolute number of the aspergillosis-related hospitalizations as well as in the annual rate of aspergillosis cases per 100,000 hospitalizations from 2001 to 2011.

In-Hospital Mortality

The crude in-hospital mortality rate was 18.7% in 2001, 11.7% in 2006 (43% relative odds reduction) and 7.8% in 2011 (63% relative odds reduction since 2001, p for trend < 0.0001) (Figure 1). Mean age at death was 62.4 years in 2001, 65.7 years in 2006 and 65.3 years in 2011. Reduction in in-hospital mortality persisted after multivariable adjustment for age, sex and traditional risk factors (Model 1) and age, sex and all risk factors (Model 2) (Table 2).

Table 1. Clinical and demographic characteristics of aspergillosis-related hospitalizations in 2001, 2006 and 2011*

	2001 N = 4,537	2006 N = 4,954	2011 N = 6,832
Number of cases per 100,000 hospitalizations	12.0	12.6	17.7
Age, mean ± SD years	58.6 ± 15.8	61.2 ± 15.3	60.5 ± 15.7
Male, n (%)	2,434 (53.6)	2,700 (54.5)	3,597 (52.6)
Race/ethnicity, N**			
White, n (%)	2,545 (76.2)	2,686 (72.4)	4,658 (72.4)
Black, n (%)	348 (10.4)	513 (13.8)	1,024 (15.9)
Hispanic, n (%)	231 (6.9)	280 (7.5)	438 (6.8)
Others, n (%)	218 (6.5)	233 (6.3)	314 (4.9)
Missing†	1,195	1,242	398
Risk factors			
Any traditional risk factor	1,832 (40.4)	1,904 (38.4)	3,207 (47.0)
Non-traditional risk factor only	2,300 (50.7)	2,653 (53.6)	3,246 (47.5)
No risk factor	405 (8.9)	397 (8.0)	379 (5.5)
Traditional risk factors‡, n (%)			
Hematological malignancy	942 (20.8)	759 (15.3)	1,230 (18.0)
Neutropenia	594 (13.1)	484 (9.8)	945 (13.8)
Stem cell Transplantation	319 (7.0)	112 (2.3)	260 (3.8)
Solid organ transplantation	258 (5.7)	332 (6.7)	562 (8.2)
Rheumatological disease	285 (6.3)	378 (7.6)	899 (13.2)
Human immunodeficiency virus (HIV) infection	152 (3.4)	142 (2.9)	135 (2.0)
Immunodeficiency other than HIV	96 (2.1)	102 (2.1)	179 (2.6)
Long-term corticosteroid therapy	63 (1.4)	290 (5.9)	569 (8.3)
Non-traditional risk factors‡, n (%)			
Chronic obstructive pulmonary disease (COPD)	1,479 (32.6)	1,851 (37.4)	2,381 (34.9)
Asthma	395 (8.7)	647 (13.1)	764 (11.2)
Cystic fibrosis	90 (2.0)	109 (2.2)	263 (3.8)
Other lung disease	1,032 (22.7)	1,382 (27.9)	2,047 (30.0)
Lung cancer	345 (7.6)	360 (7.3)	562 (8.2)
Solid tumor other than lung cancer	421 (9.3)	467 (9.4)	775 (11.3)

Diabetes mellitus	586 (12.9)	814 (16.4)	1,487 (21.8)
Cirrhosis	13 (0.3)	62 (1.3)	141 (2.1)
History of tuberculosis (TB)	229 (5.0)	191 (3.9)	172 (2.5)
History of non-TB mycobacterial infection	73 (1.6)	125 (2.5)	269 (3.9)
Pulmonary infarction	50 (1.1)	107 (2.2)	157 (2.3)
Pseudomonas infection	205 (4.5)	303 (6.1)	347 (5.1)
The Charlson Comorbidity Index (CCI), n (%)			
0	1,000 (22.0)	790 (15.9)	987 (14.4)
1	1,484 (32.7)	1,791 (36.2)	2,072 (30.3)
2	1,120 (24.7)	1,162 (23.5)	1,675 (24.5)
≥ 3	933 (20.6)	1,211 (24.4)	2,098 (30.7)
Median [range]	1 [0-12]	1 [0-10]	2 [0-11]

* Unweighted total numbers of aspergillosis-related hospitalizations each year were 892 (2001), 1,017 (2006) and 1,420 (2011).

** The numbers of hospitalizations with race/ethnicity data were 3,342 (2001), 3,712 (2006) and 6,434 (2011).

† The proportions of missing data for race/ethnicity were 26.3% (2001), 25.1% (2006) and 5.8% (2011).

‡ Risk factors are not mutually exclusive.

Figure 1. The numbers of hospitalizations and in-hospital deaths, in-hospital mortality and median length of stay for all aspergillosis-related hospitlizations in 2001, 2006 and 2011

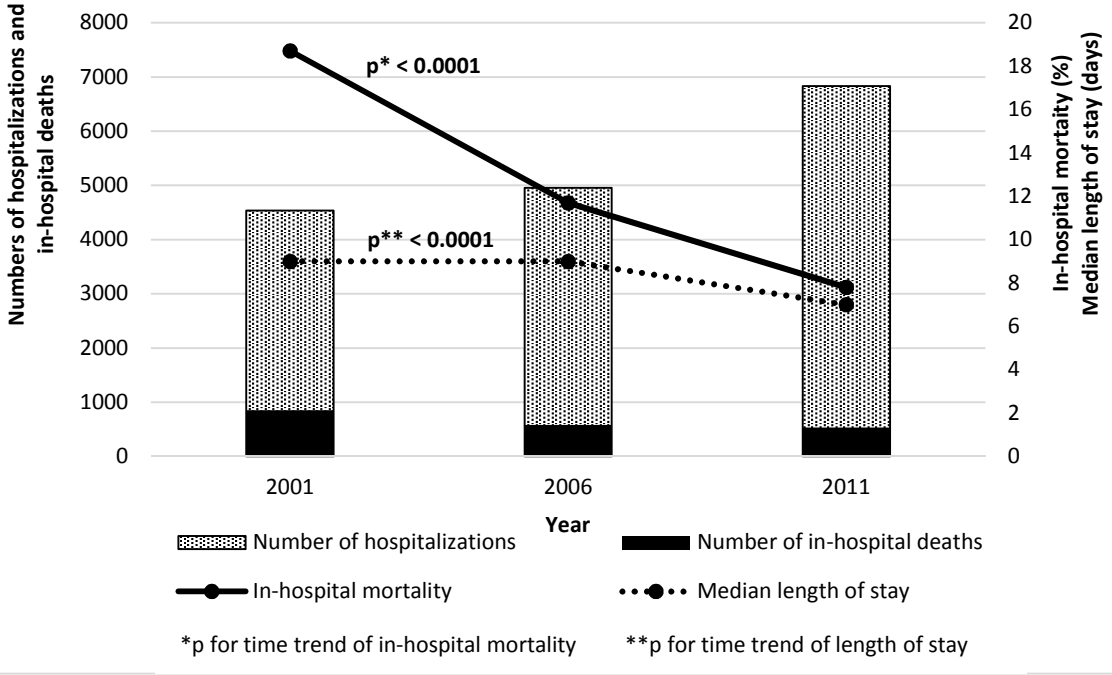


Table 2. Univariate and multivariable analyses for in-hospital mortality for aspergillosis-related hospitalizations in 2001, 2006 and 2011

Year	Univariate analysis N = 16,323		Multivariable analysis N = 16,323					
			Model 1		Model 2		Model 3	
	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
2001	Reference		Reference		Reference		Reference	
2006	0.57 (0.51 – 0.64)	< 0.0001	0.57 (0.51 – 0.64)	< 0.0001	0.59 (0.52 – 0.66)	< 0.0001	0.52 (0.46 – 0.59)	< 0.0001
2011	0.37 (0.33 – 0.41)	< 0.0001	0.33 (0.30 – 0.38)	< 0.0001	0.35 (0.31 – 0.40)	< 0.0001	0.27 (0.24 – 0.31)	< 0.0001
Time trends*	p < 0.0001		p < 0.0001		p < 0.0001		p < 0.0001	

Model 1: adjusted for age, sex and traditional factors

Model 2: adjusted for age, sex and all risk factors

Model 3: adjusted for age, sex, all risk factors and renal failure

* p-value from trend test from 2001, 2006 and 2011

Length of Stay

Median length of stay (25^{th}, 75^{th}) was 9 (5, 17) days in 2001, 9 (5, 16) days in 2006 and 7 (4, 14) days in 2011 for all aspergillosis-related hospitalizations (Figure 1), and 8 (4, 15) days in 2001, 8 (5, 14) days in 2006 and 7 (4, 13) days in 2011 for those with no death. In univariate analysis, the risk of spending one additional day in the hospital was reduced by 7% in 2006, and by 15% in 2011 compared to 2001 (p for trend < 0.0001). The risk ratio reduction in length of stay did not persist between 2001 and 2006 after multivariable adjustment for age, sex and traditional risk factors (Model 1), or age, sex and all risk factors (Model 2). However, significant risk ratio reduction in length of stay was maintained between 2001 and 2011 after adjustment for age, sex and traditional risk factors (Model 1), and age, sex and all risk factors (Model 2) (Table 3). These results were similar when the hospitalizations were restricted to those who survived (Table 4). Multivariable analyses for time trends also indicated that risk ratio for length of stay have decreased from 2001 to 2011 (p for trend < 0.0001).

Table 3. Univariate and multivariable analyses for length of stay (days) for all aspergillosis-related hospitalizations in 2001, 2006 and 2011

Year	Univariate analysis		Multivariable analysis					
			Model 1		Model 2		Model 3	
	RR (95% CI)	p-value	RR (95% CI)	p-value	RR (95% CI)	p-value	RR (95% CI)	p-value
2001	Reference		Reference		Reference		Reference	
2006	0.93 (0.90 – 0.96)	< 0.0001	0.98 (0.94 – 1.01)	0.16	0.97 (0.94 – 1.01)	0.15	0.95 (0.92 – 0.99)	0.01
2011	0.85 (0.79 – 0.91)	< 0.0001	0.86 (0.83 – 0.89)	< 0.0001	0.85 (0.83 – 0.88)	< 0.0001	0.80 (0.78 – 0.83)	< 0.0001
Time trends*	p < 0.0001		p < 0.0001		p < 0.0001		p < 0.0001	

Model 1: adjusted for age, sex and traditional factors

Model 2: adjusted for age, sex and all risk factors

Model 3: adjusted for age, sex, all risk factors and renal failure

* p-value from trend test from 2001, 2006 and 2011

Table 4. Univariate and multivariable analyses for length of stay for aspergillosis-related hospitalizations with no death

N=14,362 Year	Univariate analysis		Multivariable analysis					
			Model 1		Model 2		Model 3	
	RR (95% CI)	p-value	RR (95% CI)	p-value	RR (95% CI)	p-value	RR (95% CI)	p-value
2001	Reference		Reference		Reference		Reference	
2006	0.95 (0.92– 0.99)	0.01	0.98 (0.94 – 1.01)	0.24	0.97 (0.94 – 1.01)	0.12	0.95 (0.92 – 0.98)	0.005
2011	0.86 (0.83 – 0.89)	< 0.0001	0.87 (0.84 – 0.90)	< 0.0001	0.86 (0.83 – 0.89)	< 0.0001	0.81 (0.78 – 0.84)	< 0.0001
Time trends*	p < 0.0001		p < 0.0001		p < 0.0001		p < 0.0001	

Model 1: adjusted for age, sex and traditional risk factors
Model 2: adjusted for age, sex and all risk factors
Model 3: adjusted for age, sex, all risk factors and renal failure
* p-value from trend test from 2001, 2006 and 2011

Renal Failure

The number of aspergillosis-related hospitalizations with renal failure was 468 (10.3%) in 2001, 812 (16.4%) in 2006 and 1,555 (22.8%) in 2011. In univariate analysis, renal failure had the second highest odds ratios for in-hospital mortality (OR 2.69, 95% CI 2.42 – 2.99, $p < 0.0001$) and the second highest risk ratios for length of stay (RR 1.53, 95% CI 1.48 – 1.58, $p < 0.0001$) after neutropenia (Table 5, 6). In multivariable analysis, adjusting for renal failure further decreased the odds ratios for in-hospital mortality (Model 3, 2001 vs. 2006: OR 0.52, 95% CI 0.46 – 0.59, $p < 0.0001$, 2001 vs. 2011: OR 0.27, 95% CI 0.24 – 0.31, $p < 0.0001$) and the risk ratios for length of stay (Model 3, 2001 vs. 2006: RR 0.95, 95% CI 0.92 – 0.99, $p = 0.01$, 2001 vs. 2011: RR 0.80, 95% CI 0.78 – 0.83, $p < 0.0001$).

Table 5. Univariate analyses of demographics, traditional risk factors, non-traditional risk factors and renal failure for in-hospital mortality for aspergillosis-related hospitalizations from 2001 to 2011

	Univariate analysis	
	OR (95% CI)	p-value
Age	1.02 (1.01 – 1.02)	< 0.0001
Male sex	1.10 (1.00 – 1.20)	0.06
Risk factors		
Traditional risk factors		
Hematological malignancy	1.86 (1.66 – 2.07)	< 0.0001
Neutropenia	2.76 (2.46 – 3.10)	< 0.0001
Stem cell transplantation	2.25 (1.87 – 2.70)	< 0.0001
Solid organ transplantation	0.72 (0.58 – 0.88)	0.002
HIV	0.47 (0.30 – 0.68)	0.0002
Immunodeficiency other than HIV	0.53 (0.35 – 0.78)	0.002
Rheumatological disease	0.84 (0.71 – 1.00)	0.05
Long-term corticosteroid therapy	0.68 (0.53 – 0.85)	0.001
Any traditional risk factor	1.55 (1.41 – 1.70)	< 0.0001
Non-traditional risk factors		
COPD	1.14 (1.03 – 1.25)	0.01
Asthma	0.40 (0.32 – 0.49)	< 0.0001
Cystic fibrosis	0.32 (0.20 – 0.49)	< 0.0001
Other lung disease	0.70 (0.62 – 0.78)	< 0.0001
Lung cancer	1.14 (0.96 – 1.35)	0.13
Solid tumor other than lung cancer	0.91 (0.77 – 1.06)	0.24
Diabetes mellitus	0.46 (0.39 – 0.53)	< 0.0001
Cirrhosis	0.73 (0.44 – 1.13)	0.19
History of tuberculosis (TB)	0.52 (0.37 – 0.70)	< 0.0001
History of Non-TB mycobacterial infection	0.75 (0.54 – 1.01)	0.07
Pulmonary infarction	0.86 (0.59 – 1.22)	0.43
Pseudomonas infection	0.98 (0.79 – 1.21)	0.84
Renal failure	2.69 (2.42 – 2.99)	< 0.0001

Table 6. Univariate analyses of demographics, traditional risk factors, non-traditional risk factors and renal failure for length of stay for all aspergillosis-related hospitalizations from 2001 to 2011

	Univariate analysis	
	RR (95% CI)	p-value
Age	0.997 (0.996 – 0.998)	< 0.0001
Male sex	1.04 (1.01 – 1.06)	0.01
Risk factors		
Traditional risk factors		
Hematological malignancy	1.45 (1.40 – 1.50)	< 0.0001
Neutropenia	1.99 (1.91 – 2.07)	< 0.0001
Stem cell transplantation	1.43 (1.34 – 1.53)	< 0.0001
Solid organ transplantation	1.17 (1.11 – 1.24)	< 0.0001
HIV	1.11 (1.02 – 1.21)	0.017
Immunodeficiency other than HIV	1.02 (0.93 – 1.11)	0.71
Rheumatological disease	0.83 (0.79 – 0.87)	< 0.0001
Long-term corticosteroid therapy	0.84 (0.79 – 0.89)	< 0.0001
Any traditional risk factor	1.31 (1.27 – 1.34)	< 0.0001
Non-traditional risk factors		
COPD	0.90 (0.87 – 0.92)	< 0.0001
Asthma	0.82 (0.79 – 0.86)	< 0.0001
Cystic fibrosis	0.88 (0.81 – 0.95)	0.002
Other lung disease	0.86 (0.83 – 0.88)	< 0.0001
Lung cancer	0.76 (0.72 – 0.80)	< 0.0001
Solid tumor other than lung cancer	0.82 (0.78 – 0.85)	< 0.0001
Diabetes mellitus	0.95 (0.92 – 0.99)	0.009
Cirrhosis	0.89 (0.79 – 1.00)	0.05
History of tuberculosis (TB)	0.68 (0.63 – 0.73)	< 0.0001
History of Non-TB mycobacterial infection	1.15 (1.06 – 1.24)	0.0009
Pulmonary infarction	1.43 (1.29 – 1.57)	< 0.0001
Pseudomonas infection	1.25 (1.17 – 1.32)	< 0.0001
Renal failure	1.53 (1.48 – 1.58)	< 0.0001

The Charlson Comorbidity Index (CCI)

From 2001 to 2011 the proportion of aspergillosis-related hospitalizations with CCI of 0 decreased and the proportion of those with CCI of ≥ 3 increased although the median CCI remained stable over time (Table 1). In multivariable analysis adjusted for age, sex, CCI and aspergillosis-related risk factors that were not included in CCI (Model 4), the odds ratios for in-hospital mortality were similar to those of other multivariable models (Table 7). However, the risk ratios for length of stay were further decreased using Model 4 compared to other multivariable models (2001 vs. 2006: RR 0.61, 95% CI 0.55 – 0.68, 2001 vs. 2011: RR 0.38, 95% CI 0.34 – 0.42, p for trend < 0.0001) (Table 8). Using multivariable analysis adjusted for age, sex and CCI (Model 5) resulted in similar odds ratios for both in-hospital mortality and length of stay as Model 4.

Table 7. Multivariable analyses with the Charlson comorbidity index (CCI) adjustment for in-hospital mortality for aspergillosis-related hospitalizations

Year	Multivariable analysis			
	Model 4		Model 5	
	OR (95% CI)	p-value	OR (95% CI)	p-value
2001	Reference		Reference	
2006	0.54 (0.48 – 0.61)	< 0.0001	0.52 (0.46 – 0.58)	< 0.0001
2011	0.31 (0.28 – 0.35)	< 0.0001	0.32 (0.28 – 0.36)	< 0.0001
Time trends*	p < 0.0001		p < 0.0001	

Model 4: adjusted for age, sex, the Charlson comorbidity index (CCI) and risk factors not included in CCI
Model 5: adjusted for age, sex and CCI
* p-value from trend test from 2001, 2006 and 2011

Table 8. Multivariable analyses with the Charlson comorbidity index (CCI) for length of stay for all aspergillosis-related hospitalizations

Year	Multivariable analysis			
	Model 4		Model 5	
	RR (95% CI)	p-value	RR (95% CI)	p-value
2001	Reference		Reference	
2006	0.61 (0.55 – 0.68)	< 0.0001	0.58 (0.52 – 0.65)	< 0.0001
2011	0.38 (0.34 – 0.42)	< 0.0001	0.38 (0.34 – 0.42)	< 0.0001
Time trends*	p < 0.0001		p < 0.0001	

Model 4: adjusted for age, sex, the Charlson comorbidity index (CCI) and risk factors not included in CCI
Model 5: adjusted for age, sex and CCI
* p-value from trend test from 2001, 2006 and 2011

Subgroup Analyses of Aspergillosis-Related Hospitalizations with Traditional Risk Factors

The crude in-hospital mortality for the subgroup of aspergillosis-related hospitalizations in patients who had any traditional risk factor was 26.1% in 2001, 13.2% in 2006 (57% relative odds reduction) and 9.1% in 2011 (72% relative odds reduction since 2001, p for trend < 0.0001) (Table 9). This reduction persisted after multivariable adjustment for age, sex, non-traditional risk factors and renal failure (Figure 2-1). All the subgroups except for those who had rheumatological disease had significantly lower in-hospital mortality in 2006 and 2011 compared to 2001 in univariate and multivariable analyses adjusted for age, sex, all risk factors and renal failure (Figure 2-1). Between 2006 and 2011, in-hospital mortality for the subgroup of aspergillosis-related hospitalizations in patients who had any traditional risk factor was significantly reduced and reduction in in-hospital mortality persisted after multivariable adjustment with age, sex, non-traditional risk factors and renal failure (Figure 2-2). All the subgroups except for those who had neutropenia also had significantly decreased in-hospital mortality between 2006 and 2011 (Figure 2-2).

Table 9. Subgroup analyses for in-hospital mortality for aspergillosis-related hospitalizations

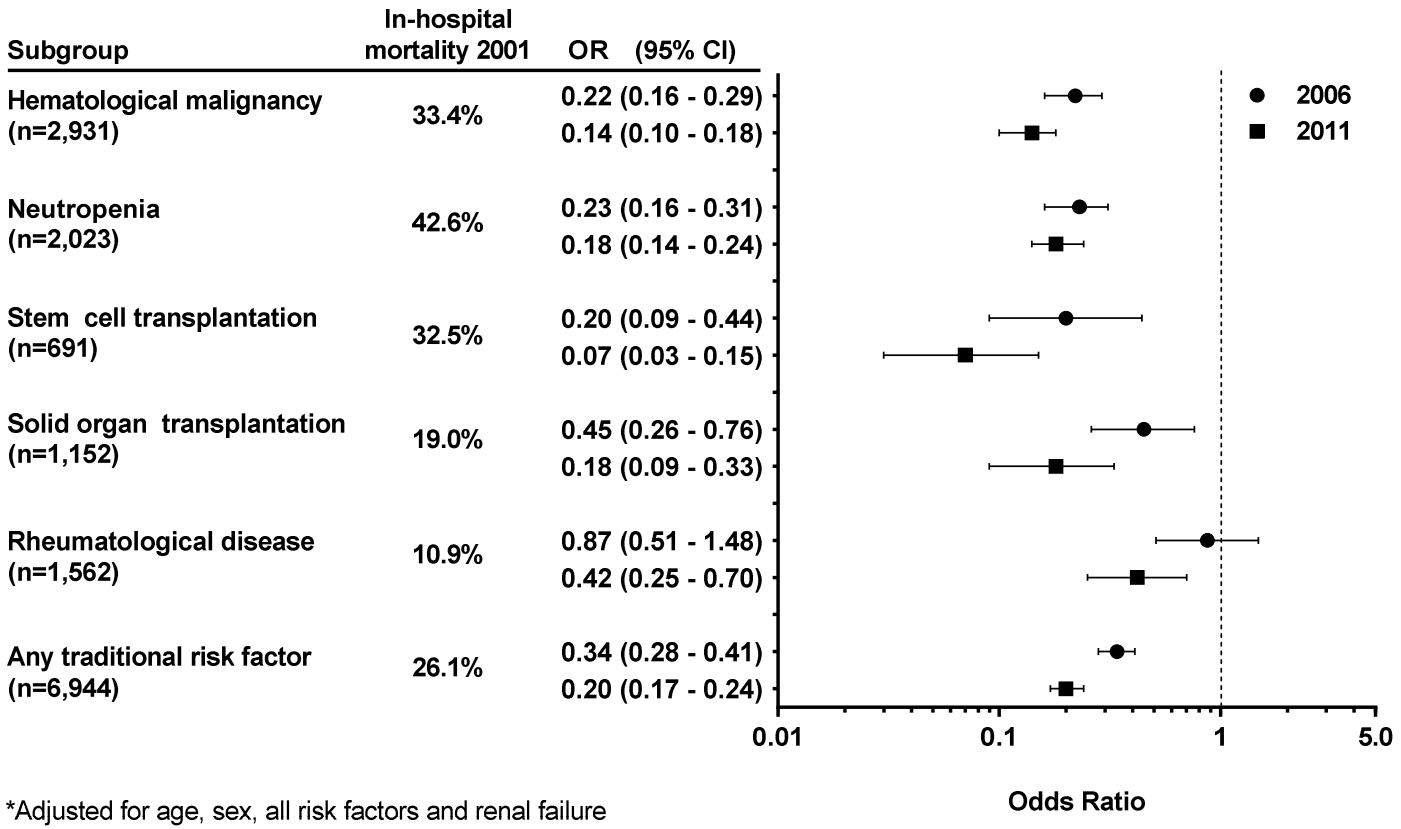
Subgroup	Year	Univariate analysis		Multivariable analysis (Model 3)	
		OR (95% CI)	p-value	OR (95% CI)	p-value
Hematological malignancy N = 2,931	2001	Reference		Reference	
	2006	0.29 (0.23 – 0.38)	< 0.0001	0.22 (0.16 – 0.29)	< 0.0001
	2011	0.21 (0.17 – 0.27)	< 0.0001	0.14 (0.10 – 0.18)	< 0.0001
Neutropenia N = 2,023	2001	Reference		Reference	
	2006	0.32 (0.24 – 0.42)	< 0.0001	0.23 (0.16 – 0.31)	< 0.0001
	2011	0.24 (0.19 – 0.31)	< 0.0001	0.18 (0.14 – 0.24)	< 0.0001
Stem cell transplantation N = 691	2001	Reference		Reference	
	2006	0.46 (0.26 – 0.78)	0.005	0.20 (0.09 – 0.44)	0.0001
	2011	0.30 (0.19 – 0.46)	< 0.0001	0.07 (0.03 – 0.15)	< 0.0001
Solid organ transplantation N = 1,152	2001	Reference		Reference	
	2006	0.48 (0.29 – 0.76)	0.002	0.45 (0.26 – 0.76)	0.004
	2011	0.18 (0.11 – 0.31)	< 0.0001	0.18 (0.09 – 0.33)	< 0.0001
Rheumatological disease N = 1,562	2001	Reference		Reference	
	2006	1.46 (0.92 – 2.35)	0.12	0.87 (0.51 – 1.48)	0.60
	2011	0.75 (0.49 – 1.18)	0.21	0.42 (0.25 – 0.70)	0.0008
Any traditional risk factor N = 6,944	2001	Reference		Reference	
	2006	0.43 (0.36 – 0.51)	< 0.0001	0.34 (0.28 – 0.41)	< 0.0001
	2011	0.28 (0.24 – 0.33)	< 0.0001	0.20 (0.17 – 0.24)	< 0.0001
	Time trends*	p < 0.0001		p < 0.0001	

Model 3: Adjusted for age, sex, all risk factors and renal failure

HIV and the immunodeficiency other than HIV group were excluded due to small numbers of hospitalizations. Long-term corticosteroid therapy as a group was also excluded because this group was very heterogeneous due to a wide variety of indications and dosing regimens for corticosteroid therapies. Analysis of this population was unlikely to provide informative results.

* p-value from trend test from 2001, 2006 and 2011

Figure 2-1. Odds ratios for in-hospital mortality for aspergillosis-related hospitalizations in multivariable subgroup analysis* comparing 2001 with 2006 or 2011 (reference group 2001)

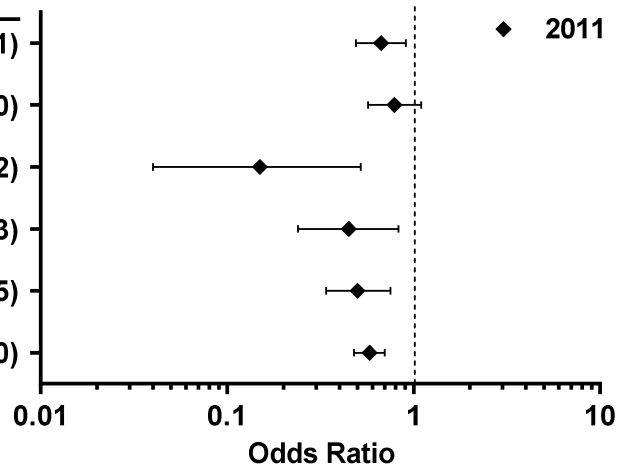


*Adjusted for age, sex, all risk factors and renal failure

HIV and immunodeficiency other than HIV group were excluded due to small numbers of hospitalizations. Long-term cordicosteroid therapy as a group was also excluded because this group was very heterogeneous due to a wide variety of indications and dosing regimens for corticosteroid therpies. Analsis of this population was unlikely to provide informative results.

Figure 2-2. Odds ratios for in-hospital mortality for aspergillosis-related hospitalizations in multivariable subgroup analysis* comparing 2006 with 2011 (reference group 2006)

Subgroup	In-hospital mortality 2006	OR (95% CI)
Hematological malignancy (n=1,989)	12.8%	0.67 (0.49 - 0.91)
Neutropenia (n=1,429)	19.0%	0.79 (0.57 - 1.10)
Stem cell transplantation (n=372)	17.9%	0.15 (0.04 - 0.52)
Solid organ transplantation (n=894)	9.9%	0.45 (0.24 - 0.83)
Rheumatological disease (n=1,277)	15.1%	0.50 (0.34 - 0.75)
Any traditional risk factor (n=5,110)	13.2%	0.58 (0.48 - 0.70)



*Adjusted for age, sex, all risk factors and renal failure

HIV and immunodeficiency other than HIV group were excluded due to small numbers of hospitalizations. Long-term cordicosteroid therapy as a group was also excluded because this group was very heterogeneous due to a wide variety of indications and dosing regimens for corticosteroid therpies. Analsis of this population was unlikely to provide informative results.

Median length of stay for the subgroup of aspergillosis-related hospitalizations in patients who had any traditional risk factor was 10 days in 2001, and the risk of spending one additional day in the hospital was reduced by 15% in 2006, and by 25% in 2011 compared to 2001 (p for trend < 0.0001) (Table S7). This risk ratio reduction persisted after multivariable adjustment for age, sex, non-traditional risk factors and renal failure (Figure 3-1, Table S7). In multivariable analysis adjusted for age, sex, all risk factors and renal failure, rheumatological disease had significant risk ratio reduction in length of stay in 2006 and in 2011 compared to 2001 (Figure 3-1), and between 2006 and 2011 (Figure 3-2). Solid organ transplantation also had significant risk ratio reduction in length of stay in 2006 and in 2011 compared to 2001. Hematological malignancy and neutropenia had significant risk ratio reduction in length of stay in 2011 compared to 2001 and between 2006 and 2011. There was no significant risk ratio reduction in length of stay in stem cell transplantation from 2001 to 2011.

Table 10. Subgroup analyses for length of stay for all aspergillosis-related hospitalizations

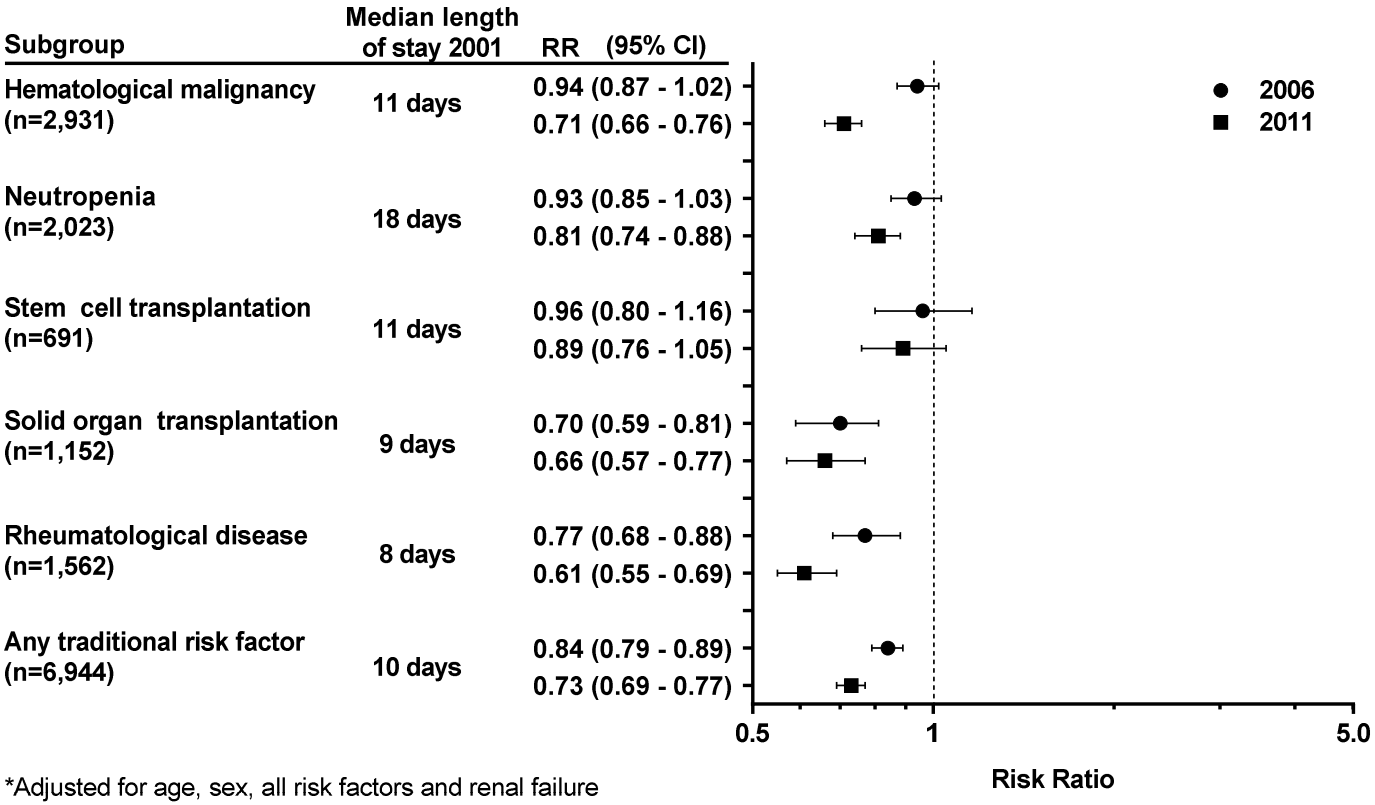
Subgroup	Year	Univariate analysis		Multivariable analysis (Model 3)	
		RR (95% CI)	p-value	RR (95% CI)	p-value
Hematological malignancy N = 2,931	2001	Reference		Reference	
	2006	0.94 (0.86 – 1.02)	0.15	0.94 (0.87 – 1.02)	0.11
	2011	0.79 (0.73 – 0.84)	< 0.0001	0.71 (0.66 – 0.76)	< 0.0001
Neutropenia N = 2,023	2001	Reference		Reference	
	2006	0.90 (0.24 – 0.42)	0.04	0.93 (0.85 –1.03)	0.16
	2011	0.82 (0.76 – 0.89)	< 0.0001	0.81 (0.74 – 0.88)	< 0.0001
Stem cell transplantation† N = 691	2001	Reference		Reference	
	2006	0.85 (0.69 – 1.03)	0.11	0.96 (0.80 – 1.16)	0.65
	2011	1.04 (0.89 – 1.21)	0.62	0.89 (0.76 – 1.05)	0.14
Solid organ transplantation† N = 1,152	2001	Reference		Reference	
	2006	0.86 (0.29 – 0.76)	0.07	0.70 (0.59 – 0.81)	< 0.0001
	2011	0.77 (0.66 – 0.89)	0.0004	0.66 (0.57 – 0.77)	< 0.0001
Rheumatological disease† N = 1,562	2001	Reference		Reference	
	2006	0.89 (0.77 – 1.01)	0.08	0.77 (0.68 – 0.88)	< 0.0001
	2011	0.89 (0.79 – 1.00)	0.06	0.61 (0.55– 0.69)	< 0.0001
Any traditional risk factor N = 6,944	2001	Reference		Reference	
	2006	0.85 (0.80 – 0.90)	< 0.0001	0.84 (0.79 – 0.89)	< 0.0001
	2011	0.75 (0.72 – 0.79)	< 0.0001	0.73 (0.69 – 0.77)	< 0.0001
	Time trends*	p < 0.0001		p < 0.0001	

Model 3: Adjusted for age, sex, all risk factors and renal failure

HIV and the immunodeficiency other than HIV group were excluded due to small numbers of hospitalizations. Long-term corticosteroid therapy as a group was also excluded because this group was very heterogeneous due to a wide variety of indications and dosing regimens for corticosteroid therapies. Analysis of this population was unlikely to provide informative results.

* p-value from trend test from 2001, 2006 and 2011

Figure 3-1. Risk ratios for length of stay for all aspergillosis-related hospitalizations in multivariable subgroup analysis* comparing 2001 with 2006 or 2011 (reference group 2001)

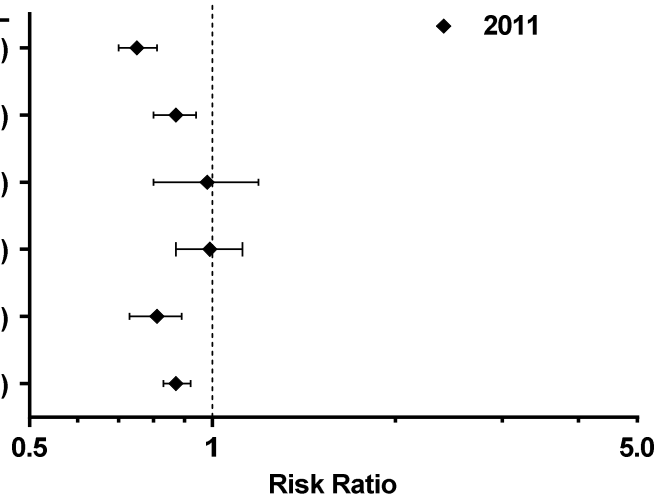


*Adjusted for age, sex, all risk factors and renal failure

HIV and immunodeficiency other than HIV group were excluded due to small numbers of hospitalizations. Long-term cordicosteroid therapy as a group was also excluded because this group was very heterogeneous due to a wide variety of indications and dosing regimens for corticosteroid therpies. Analsis of this population was unlikely to provide informative results.

Figure 3-2. Risk ratios for length of stay for all aspergillosis-related hospitalizations in multivariable subgroup analysis* comparing 2006 with 2011 (reference group 2006)

Subgroup	Median length of stay 2006	RR (95% CI)
Hematological malignancy (n=1,989)	12 days	0.75 (0.70 - 0.81)
Neutropenia (n=1,429)	18 days	0.87 (0.80 - 0.94)
Stem cell transplantation (n=372)	13 days	0.98 (0.80 - 1.19)
Solid organ transplantation (n=894)	8 days	0.99 (0.87 - 1.12)
Rheumatological disease (n=1,277)	7 days	0.81 (0.73 - 0.89)
Any traditional risk factor (n=5,110)	9 days	0.87 (0.83 - 0.92)



*Adjusted for age, sex, all risk factors and renal failure

HIV and immunodeficiency other than HIV group were excluded due to small numbers of hospitalizations. Long-term cordicosteroid therapy as a group was also excluded because this group was very heterogeneous due to a wide variety of indications and dosing regimens for corticosteroid therpies. Analsis of this population was unlikely to provide informative results.

Sensitivity Analyses of Potential Effects from *Pseudomonas* Infection or Using Up to 25 Diagnoses in 2011

Adding *Pseudomonas* infection to multivariable analyses adjusted for age, sex and all risk factors (Model 2) or age, sex, all risk factors and renal failure (Model 3) as an additional risk factor did not change the odds ratios for in-hospital mortality and the risk ratios for length of stay or length of stay for those who survived (Table 11-1, 11-2 and 11-3). Using up to 25 instead of the first 15 diagnoses to identify the risk factors and renal failure for 2011 data increased the number of aspergillosis-related hospitalizations with each risk factor from 0 to 32 % (Table 12). However, the results for in-hospital mortality, length of stay or length of stay for those who survived in the multivariable analyses remained similar to those of the main analyses (Table 13-1, 13-2 and 13-3).

Table 11-1. Sensitivity analyses with *Pseudomonas* infection for in-hospital mortality for aspergillosis-related hospitalizations

Year	Multivariate analysis			
	Model 2 + *Pseudomonas*		Model 3 + *Pseudomonas*	
	OR (95% CI)	p-value	OR (95% CI)	p-value
2001	Reference		Reference	
2006	0.59 (0.52 – 0.66)	< 0.0001	0.52 (0.46 – 0.59)	< 0.0001
2011	0.35 (0.31 – 0.40)	< 0.0001	0.27 (0.24 – 0.31)	< 0.0001
Time trends*	p < 0.0001		p < 0.0001	

Model 2: adjusted for age, sex and all risk factors
Model 3: adjusted for age, sex, all risk factors and renal failure

Table 11-2. Sensitivity analyses with *Pseudomonas* infection for length of stay for all aspergillosis-related hospitalizations

Year	Multivariate analysis			
	Model 2 + *Pseudomonas*		Model 3 + *Pseudomonas*	
	RR (95% CI)	p-value	RR (95% CI)	p-value
2001	Reference		Reference	
2006	0.97 (0.94 – 1.01)	0.12	0.95 (0.92 – 0.99)	0.006
2011	0.85 (0.83 – 0.88)	< 0.0001	0.80 (0.78 – 0.83)	< 0.0001
Time trends*	p < 0.0001		p < 0.0001	

Model 2: adjusted for age, sex and all risk factors
Model 3: adjusted for age, sex, all risk factors and renal failure

Table 11-3. Sensitivity analyses with *Pseudomonas* infection for length of stay for aspergillosis-related hospitalizations with no death

N = 14,362 Year	Multivariate analysis			
	Model 2 + *Pseudomonas*		Model 3 + *Pseudomonas*	
	RR (95% CI)	p-value	RR (95% CI)	p-value
2001	Reference		Reference	
2006	0.97 (0.94 – 1.01)	0.11	0.95 (0.92 – 0.98)	0.005
2011	0.86 (0.83 – 0.89)	< 0.0001	0.81 (0.78 – 0.84)	< 0.0001
Time trends*	p < 0.0001		p < 0.0001	

Model 2: adjusted for age, sex and all risk factors
Model 3: adjusted for age, sex, all risk factors and renal failure

Table 12. Risk factors of aspergillosis-related hospitalizations in 2011 using up to 15 diagnoses vs. 25 diagnoses

	2011 N = 6,832 Up to 15 diagnoses	2011 N = 6,832 Up to 25 diagnoses	Increased number of hospitalizations (% increase)
Traditional risk factors			
Hematological malignancy, n (%)	1,230 (18.0)	1,248 (18.2)	18 (1.5)
Neutropenia, n (%)	945 (13.8)	973 (14.2)	28 (3.0)
Stem cell Transplantation, n (%)	260 (3.8)	264 (3.9)	4 (1.5)
Solid organ transplantation, n (%)	562 (8.2)	572 (8.4)	10 (1.8)
HIV, n (%)	135 (2.0)	135 (2.0)	0 (0)
Immunodeficiency other than HIV, n (%)	179 (2.6)	198 (2.9)	19 (10.6)
Rheumatological disease, n (%)	899 (13.2)	946 (13.8)	47 (5.2)
Long-term corticosteroid therapy, n (%)	569 (8.3)	751 (11.0)	182 (32.0)
Any traditional risk factor, n (%)	3,207 (46.9)	3,324 (48.7)	117 (3.6)
Non-traditional risk factors			
COPD, n (%)	2,381 (34.9)	2,484 (36.4)	103 (4.3)
Asthma, n (%)	764 (11.2)	819 (12.0)	55 (7.2)
Cystic fibrosis, n (%)	263 (3.8)	263 (3.8)	0 (0)
Other lung disease, n (%)	2,047 (30.0)	2,196 (32.1)	149 (7.3)
Lung cancer, n (%)	562 (8.2)	605 (8.9)	43 (7.7)
Solid tumor other than lung cancer, n (%)	775 (11.3)	919 (13.5)	144 (18.6)
Diabetes mellitus, n (%)	1,487 (21.8)	1,677 (24.5)	190 (12.8)
Cirrhosis, n (%)	141 (2.1)	164 (2.4)	23 (16.3)
History of tuberculosis (TB), n (%)	172 (2.5)	205 (3.0)	33 (19.2)
History of Non-TB mycobacterial infection, n (%)	269 (3.9)	269 (3.9)	0 (0)
Pulmonary infarct, n (%)	157 (2.3)	157 (2.3)	0 (0)
Pseudomonas infection, n (%)	347 (5.1)	357 (5.2)	10 (2.9)
Renal failure, n (%)	1,555 (22.8)	1,569 (23.0)	14 (0.9)

Table 13-1. Multivariable analyses for in-hospital mortality for aspergillosis-related hospitalizations using up to 25 diagnoses in 2011

Year	Multivariable analysis					
	Model 1		Model 2		Model 3	
	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
2001	Reference		Reference		Reference	
2006	0.57 (0.50 – 0.64)	< 0.0001	0.58 (0.51 – 0.65)	< 0.0001	0.51 (0.45 – 0.58)	< 0.0001
2011	0.33 (0.29 – 0.37)	< 0.0001	0.34 (0.30 – 0.39)	< 0.0001	0.26 (0.23 – 0.30)	< 0.0001
Time trends*	p < 0.0001		p < 0.0001		p < 0.0001	

Model 1: adjusted for age, sex and traditional risk factors
Model 2: adjusted for age, sex and all risk factors
Model 3: adjusted for age, sex, all risk factors and renal failure
* p-value from trend test from 2001, 2006 and 2011

Table 13-2. Multivariable analyses for length of stay for all aspergillosis-related hospitalizations using up to 25 diagnoses in 2011

Year	Multivariable analysis					
	Model 1		Model 2		Model 3	
	RR (95% CI)	p-value	RR (95% CI)	p-value	RR (95% CI)	p-value
2001	Reference		Reference		Reference	
2006	0.97 (0.94 – 1.00)	0.15	0.97 (0.94 – 1.00)	0.08	0.95 (0.92 – 0.98)	0.004
2011	0.85 (0.82 – 0.88)	< 0.0001	0.84 (0.81 – 0.86)	< 0.0001	0.79 (0.76 – 0.82)	< 0.0001
Time trends*	p < 0.0001		p < 0.0001		p < 0.0001	

Model 1: adjusted for age, sex and traditional risk factors
Model 2: adjusted for age, sex and all risk factors
Model 3: adjusted for age, sex, all risk factors and renal failure
* p-value from trend test from 2001, 2006 and 2011

Table 13-3. Multivariable analyses for length of stay for aspergillosis-related hospitalizations with no death using up to 25 diagnoses in 2011

Year	Multivariable analysis					
	Model 1		Model 2		Model 3	
	RR (95% CI)	p-value	RR (95% CI)	p-value	RR (95% CI)	p-value
2001	Reference		Reference		Reference	
2006	0.98 (0.94 – 1.01)	0.2	0.97 (0.94 – 1.01)	0.10	0.95 (0.92 – 0.98)	0.004
2011	0.87 (0.84 – 0.90)	< 0.0001	0.85 (0.82 – 0.88)	< 0.0001	0.80 (0.77 – 0.83)	< 0.0001
Time trends*	p < 0.0001		p < 0.0001		p < 0.0001	

Model 1: adjusted for age, sex and traditional risk factors
Model 2: adjusted for age, sex and all risk factors
Model 3: adjusted for age, sex, all risk factors and renal failure
* p-value from trend test from 2001, 2006 and 2011

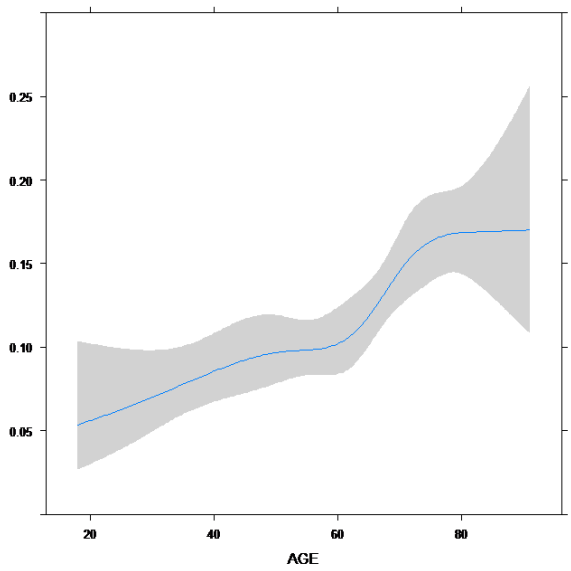
Model diagnostics

For logistic regression model, linearity of the continuous variable (age) was met (1-a). Model 3 also had good C-statistic (1-b) and Hosmer-Lemeshow test was non-significant (1-c). Although deviance residuals with weighted data were relatively high, those with unweighted data were ± 3 and the odds ratios for the year of hospitalization with unweighted data were the same as those with weighted data (1-d).

For negative binominal regression model, the lowess curves for age – LOS plot suggests linearity of the continuous variable (age) (2-a). There were three influential points in the multivariable analysis model (model 3). However, removal of each point did not change the risk ratios (2-b).

1. Logistic regression model

a. Linearity of the continuous variable (age)



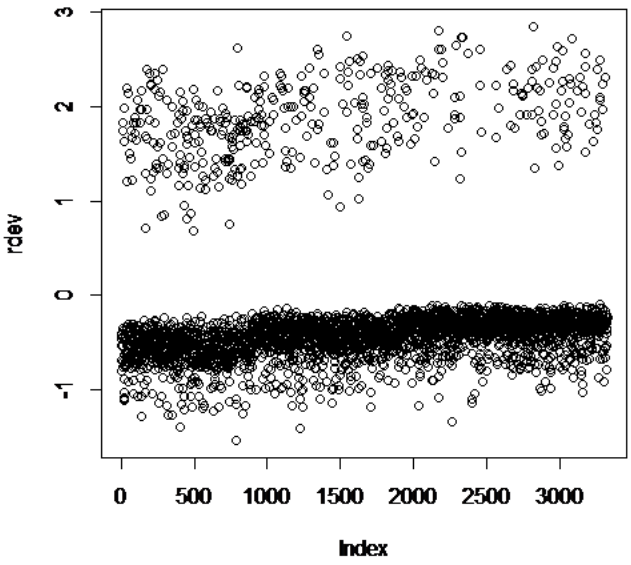
b. C-statistic: 0.746

c. Hosmer-Lemeshow test for the main analysis using model 3: p-value 0.49

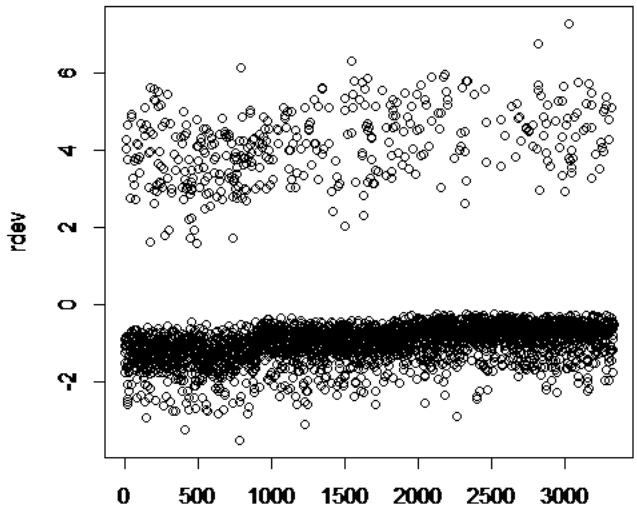
d. Deviance residuals for the main analysis using model 3

Odds ratios for year of hospitalization with unweighted data were the same as those with weighted data.

(Unweighted)

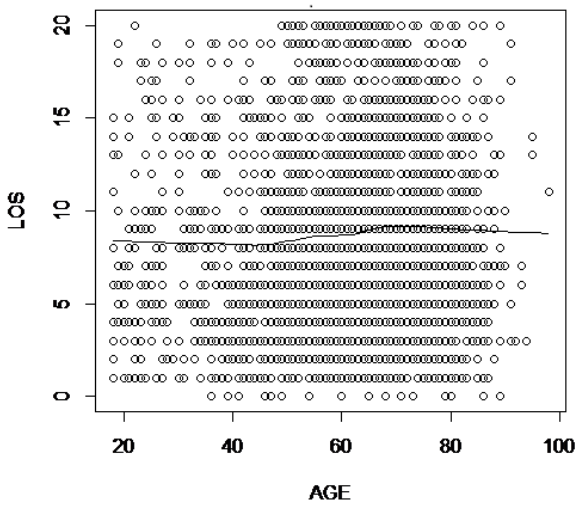


(Weighted)

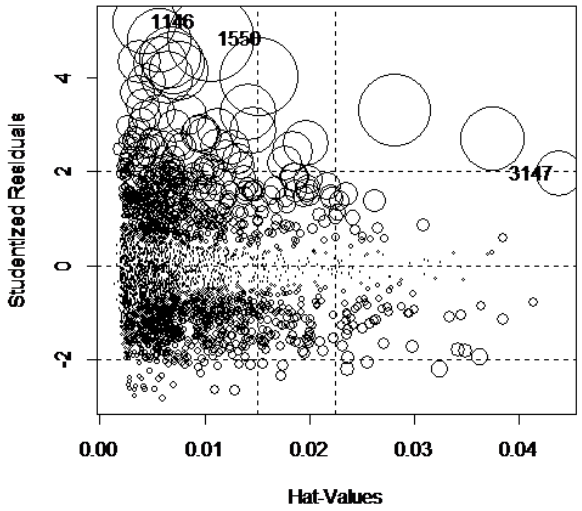


2. Negative binominal regression model

a. Lowess for age – LOS plot



b. Influential points



ID	StudRes	Hat	CookD
1146	5.181531	0.004280593	0.3991088
1550	4.811781	0.010647315	0.5377887
3147	1.953143	0.043794237	0.2801046

Original data: RR (95% CI)
2006: 0.95 (0.92 - 0.99)
2011: 0.80 (0.78 - 0.83)

Without 1146: RR (95% CI)
2006: 0.94 (0.91 - 0.97)
2011: 0.80 (0.77 - 0.83)

Without 1550: RR (95% CI)
2006: 0.94 (0.91 - 0.98)
2011: 0.80 (0.77 - 0.83)

Without 3147: RR (95% CI)
2006: 0.95 (0.92 - 0.99)
2011: 0.80 (0.78 - 0.83)

DISCUSSION

Our study of aspergillosis-related hospitalizations in the United States over the 2001 - 2011 time period demonstrates significantly decreased in-hospital mortality and length of stay while the number of aspergillosis-hospital admissions increased. To our knowledge, this

is the first population-based study with a large sample size that has evaluated trends in aspergillosis outcomes over the recent period of major changes in the management of aspergillosis.

Reduction in in-hospital mortality was also observed in the immunocompromised populations, which is consistent with previous studies on IA among severely immunocompromised patients such as transplant recipients or patients with hematological malignancy.[3,5,23] Over the last four decades allogeneic stem cell transplantation has evolved as a curative modality and significant improvement in survival has been reported from a large stem cell transplant registry including 38,060 patients who underwent allogeneic stem cell transplantation in the U.S. or Canada from 1994 to 2005.[41] Among our subgroups, stem cell transplantation showed the most dramatic mortality reduction and this may be associated with overall survival improvement in this population. The mortality rates for stem cell transplantation, solid organ transplantation and hematological malignancy in our study appear lower than the reported mortality for IA in other studies which may be because we evaluated in-hospital mortality instead of 6-week or 12-week mortality.[3,5,23,42–47]

Several studies have shown that renal insufficiency is a potential prognostic factor for mortality from IA.[23,24,39] Renal toxicity is predictable, common and the dose limiting factor for use of amphotericin B as well as a common complication from amphotericin B-based formulations, which used to be the standard of care for treatment of aspergillosis. The fact that the mortality reduction persisted even when adjusted for renal failure suggests that renal failure alone did not likely contribute to the observed difference.

Reduction in in-hospital mortality is possibly the result of more effective and less toxic

treatment with voriconazole,[15] intensive monitoring and earlier diagnoses with the serum galactomannan antigen detection test[48,49] and recommendations on their use from published guidelines.[22] Improved in-hospital mortality is unlikely a reflection of less severe aspergillosis infection since the Charlson comorbidity index remained stable over time. In addition, not only has the mortality rate decreased but the absolute number of deaths has also decreased over time despite the increased incidence of aspergillosis-related hospitalizations, which may suggest that decreasing mortality was attributed to the new treatment rather than the diagnosis of less severe cases over time with the new diagnostic testing.

Although the potential explanations for shortened length of stay include changes in clinical practice, social support system and healthcare utilization, voriconazole may have played an important role in this trend. A subgroup study from the Transplant Associated Infection Surveillance Network (TRANSNET) analyzed factors associated with hospital length of stay including 361 transplant patients with IA enrolled from 2001 to 2005 and reported that initial voriconazole use was associated with decreased length of stay.[50] Another study of 475 COPD patients with IA using a large U.S. hospital-based database (Premier Perspective database) from 2005 to 2008 also showed that those who received voriconazole as the first-line treatment had significantly shorter length of stay compared to those who received other anti-fungal agents.[51] Of note, intravenous to oral conversion on voriconazole was common in this study with 48% of first-line voriconazole IV patients switching to voriconazole oral (average conversion on day 4). Availability of effective oral anti-fungal therapy for aspergillosis might have enabled early transition to outpatient care and contributed to the reduction in length of stay.

Surprisingly, more than half of aspergillosis-related hospitalizations did not have any

traditional risk factors for IA identified. There are no existing epidemiological data to corroborate this observation. The most common non-traditional risk factor in our study was COPD which has been increasingly reported as a risk factor for IA among critically ill patients without apparent severe immunosuppression in the intensive care unit (ICU).[52,53] Although most of these COPD patients were on steroid therapy, those who were not on steroid therapy also developed IA in the ICU. ICU patients are an emerging population at risk for IA with high mortality (60 to 90%) [52–55] and the reported incidence is variable ranging from 0.3 to 5.8%.[56] The true incidence of IA in the ICUs is difficult to describe because of differences in underlying patient characteristics, definitions of IA cases and autopsy policies. Population-based studies on aspergillosis occurring in patients without apparent immunosuppression could be an opportunity for future research.

Our study has several limitations. First, this is a descriptive study of time trends in rates of aspergillosis-related hospitalizations, and we are not able to make any direct inferences about the specific causes of observed trends. Second, HCUP-NIS is an administrative database based on ICD-9 codes with no information on laboratory tests, radiographic images, microbiological data or treatment. Therefore, there is the potential for influence by unmeasured risk factors and misclassification bias. Third, there are no ICD9-codes that indicate specific types of aspergillosis (except for ABPA). We were not able to exclude hospitalizations with aspergilloma, which sometimes can be cured by surgical excision alone. We expect that including these hospitalizations would have led to underestimation of time trends for in-hospital mortality or length of stay because uneventful surgical hospitalizations would have had no benefit from improved medical treatment for aspergillosis. However, surgery as the treatment of choice for symptomatic aspergilloma has been questioned since major postoperative complications such as respiratory failure, bronchopleural fistulas, resistant air space problems, pleural aspergillosis, and

disseminated disease[57–59] may occur. Furthermore, in many patients underlying structural lung disease and low pulmonary reserve preclude operative intervention.[29] It is likely that the impact from including hospitalizations with aspergilloma may be relatively small.

Our study reports the most updated epidemiological trends in aspergillosis-related hospitalizations in the United States with decreases found in both in-hospital mortality and length of stay over time despite increased incidence in aspergillosis. Our results can be used as the basis for future studies to investigate epidemiology of aspergillosis among apparently immunocompetent and mildly immunocompromised patients as well as to determine specific causes for improved mortality and length of stay among patients with aspergillosis.

REFERENCES

1. Lin SJ, Schranz J, Teutsch SM. Aspergillosis case-fatality rate: systematic review of the literature. *Clin Infect Dis Off Publ Infect Dis Soc Am*. 2001;32(3):358-366. doi:10.1086/318483.

2. Singh N, Singh NM, Husain S, AST Infectious Diseases Community of Practice. Aspergillosis in solid organ transplantation. *Am J Transplant Off J Am Soc Transplant Am Soc Transpl Surg*. 2013;13 Suppl 4:228-241. doi:10.1111/ajt.12115.

3. Neofytos D, Horn D, Anaissie E, et al. Epidemiology and outcome of invasive fungal infection in adult hematopoietic stem cell transplant recipients: analysis of Multicenter Prospective Antifungal Therapy (PATH) Alliance registry. *Clin Infect Dis Off Publ Infect Dis Soc Am*. 2009;48(3):265-273. doi:10.1086/595846.

4. Neofytos D, Fishman JA, Horn D, et al. Epidemiology and outcome of invasive fungal infections in solid organ transplant recipients. *Transpl Infect Dis Off J Transplant Soc*. 2010;12(3):220-229. doi:10.1111/j.1399-3062.2010.00492.x.

5. Kriengkauykiat J, Ito JI, Dadwal SS. Epidemiology and treatment approaches in management of invasive fungal infections. *Clin Epidemiol*. 2011;3:175-191. doi:10.2147/CLEP.S12502.

6. Yeghen T, Kibbler CC, Prentice HG, et al. Management of invasive pulmonary aspergillosis in hematology patients: a review of 87 consecutive cases at a single institution. *Clin Infect Dis Off Publ Infect Dis Soc Am*. 2000;31(4):859-868. doi:10.1086/318133.

7. Russo A, Giuliano S, Vena A, et al. Predictors of mortality in non-neutropenic patients with invasive pulmonary aspergillosis: does galactomannan have a role? *Diagn Microbiol Infect Dis*. 2014;80(1):83-86. doi:10.1016/j.diagmicrobio.2014.05.015.

8. Fukuda T, Boeckh M, Carter RA, et al. Risks and outcomes of invasive fungal infections in recipients of allogeneic hematopoietic stem cell transplants after nonmyeloablative conditioning. *Blood*. 2003;102(3):827-833. doi:10.1182/blood-2003-02-0456.

9. Moreno A, Perez-Elías M, Casado J, et al. Role of antiretroviral therapy in long-term survival of patients with AIDS-related pulmonary aspergillosis. *Eur J Clin Microbiol Infect Dis Off Publ Eur Soc Clin Microbiol*. 2000;19(9):688-693.

10. Dai Z, Zhao H, Cai S, Lv Y, Tong W. Invasive pulmonary aspergillosis in non-neutropenic patients with and without underlying disease: a single-centre retrospective analysis of 52 subjects. *Respirol Carlton Vic*. 2013;18(2):323-331. doi:10.1111/j.1440-1843.2012.02283.x.

11. Helen W. Boucher, Thomas F. Patterson. Aspergillosis. In: *Diagnosis and Treatment of Fungal Infections*. Second. Springer; 2015:129-140.

12. Al-Badriyeh D, Heng SC, Neoh CF, Slavin M, Stewart K, Kong DCM. Pharmacoeconomics of voriconazole in the management of invasive fungal infections. *Expert Rev Pharmacoecon Outcomes Res*. 2010;10(6):623-636. doi:10.1586/erp.10.69.

13. Lewis RE, Cahyame-Zuniga L, Leventakos K, et al. Epidemiology and sites of involvement of invasive fungal infections in patients with haematological malignancies: a 20-year autopsy study. *Mycoses*. 2013;56(6):638-645. doi:10.1111/myc.12081.

14. U.S. Food and Drug Administration. *Drug Approval Package; Vfend (Voriconazole) Tablets & Injection*.; 2002. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2002/21-266_21-267_Vfend.cfm.

15. Herbrecht R, Denning DW, Patterson TF, et al. Voriconazole versus amphotericin B for primary therapy of invasive aspergillosis. *N Engl J Med*. 2002;347(6):408-415. doi:10.1056/NEJMoa020191.

16. Denning DW, Ribaud P, Milpied N, et al. Efficacy and safety of voriconazole in the treatment of acute invasive aspergillosis. *Clin Infect Dis Off Publ Infect Dis Soc Am*. 2002;34(5):563-571. doi:10.1086/324620.

17. Lashof AMLO, Sobel JD, Ruhnke M, et al. Safety and Tolerability of Voriconazole in Patients with Baseline Renal Insufficiency and Candidemia. *Antimicrob Agents Chemother*. 2012;56(6):3133-3137. doi:10.1128/AAC.05841-11.

18. Lilly CM, Welch VL, Mayer T, Ranauro P, Meisner J, Luke DR. Evaluation of intravenous voriconazole in patients with compromised renal function. *BMC Infect Dis*. 2013;13:14. doi:10.1186/1471-2334-13-14.

19. Alvarez-Lerma F, Allepuz-Palau A, Garcia MP, et al. Impact of intravenous administration of voriconazole in critically ill patients with impaired renal function. *J Chemother Florence Italy*. 2008;20(1):93-100. doi:10.1179/joc.2008.20.1.93.

20. U.S. Food and Drug Administration. *51O(k) SUMMARY*.; 2003. http://www.accessdata.fda.gov/cdrh_docs/pdf2/k023857.pdf.

21. De Pauw B, Walsh TJ, Donnelly JP, et al. Revised Definitions of Invasive Fungal Disease from the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group. *Clin Infect Dis Off Publ Infect Dis Soc Am*. 2008;46(12):1813-1821. doi:10.1086/588660.

22. Walsh TJ, Anaissie EJ, Denning DW, et al. Treatment of aspergillosis: clinical practice guidelines of the Infectious Diseases Society of America. *Clin Infect Dis Off Publ Infect Dis Soc Am*. 2008;46(3):327-360. doi:10.1086/525258.

23. Upton A, Kirby KA, Carpenter P, Boeckh M, Marr KA. Invasive Aspergillosis following Hematopoietic Cell Transplantation: Outcomes and Prognostic Factors

Associated with Mortality. *Clin Infect Dis*. 2007;44(4):531-540. doi:10.1086/510592.

24. Baddley JW, Andes DR, Marr KA, et al. Factors associated with mortality in transplant patients with invasive aspergillosis. *Clin Infect Dis Off Publ Infect Dis Soc Am*. 2010;50(12):1559-1567. doi:10.1086/652768.

25. Kim A, Nicolau DP, Kuti JL. Hospital costs and outcomes among intravenous antifungal therapies for patients with invasive aspergillosis in the United States. *Mycoses*. 2011;54(5):e301-e312. doi:10.1111/j.1439-0507.2010.01903.x.

26. Agency for Healthcare Research and Quality Healthcare Cost and Utilization Project (HCUP). INTRODUCTION TO THE HCUP NATIONWIDE INPATIENT SAMPLE (NIS) 2011. June 2013. https://www.hcup-us.ahrq.gov/db/nation/nis/NIS_Introduction_2011.pdf.

27. Segal BH, Walsh TJ. Current approaches to diagnosis and treatment of invasive aspergillosis. *Am J Respir Crit Care Med*. 2006;173(7):707-717. doi:10.1164/rccm.200505-727SO.

28. Cornillet A, Camus C, Nimubona S, et al. Comparison of epidemiological, clinical, and biological features of invasive aspergillosis in neutropenic and nonneutropenic patients: a 6-year survey. *Clin Infect Dis Off Publ Infect Dis Soc Am*. 2006;43(5):577-584. doi:10.1086/505870.

29. Cadena J, Thompson III GR, Patterson TF. Invasive Aspergillosis: Current Strategies for Diagnosis and Management. *Infect Dis Clin North Am*. 2016;30(1):125-142. doi:10.1016/j.idc.2015.10.015.

30. Kosmidis C, Denning DW. The clinical spectrum of pulmonary aspergillosis. *Thorax*. 2015;70(3):270-277. doi:10.1136/thoraxjnl-2014-206291.

31. Kousha M, Tadi R, Soubani AO. Pulmonary aspergillosis: a clinical review. *Eur Respir Rev*. 2011;20(121):156-174. doi:10.1183/09059180.00001011.

32. Soubani AO, Chandrasekar PH. The clinical spectrum of pulmonary aspergillosis. *Chest*. 2002;121(6):1988-1999.

33. Smith NL, Denning DW. Underlying conditions in chronic pulmonary aspergillosis including simple aspergilloma. *Eur Respir J*. 2011;37(4):865-872. doi:10.1183/09031936.00054810.

34. Huang C-W, Lee M-A, Lu R-H, Peng H-C, Chao H-S. A case of pulmonary aspergilloma and actinomycosis. *J Med Microbiol*. 2011;60(Pt 4):543-546. doi:10.1099/jmm.0.026427-0.

35. Alangaden GJ, Wahiduzzaman M, Chandrasekar PH, Group TBMT. Aspergillosis: The Most Common Community-Acquired Pneumonia with Gram-Negative Bacilli as Copathogens in Stem Cell Transplant Recipients with Graft-versus-Host Disease. *Clin Infect Dis*. 2002;35(6):659-664. doi:10.1086/342061.

36. Bakare N, Rickerts V, Bargon J, Just-Nübling G. Prevalence of Aspergillus fumigatus and other fungal species in the sputum of adult patients with cystic fibrosis. *Mycoses*. 2003;46(1-2):19-23.

37. Smith K, Rajendran R, Kerr S, et al. Aspergillus fumigatus enhances elastase production in Pseudomonas aeruginosa co-cultures. *Med Mycol*. 2015;53(7):645-655. doi:10.1093/mmy/myv048.

38. Driscoll JA, Brody SL, Kollef DMH. The Epidemiology, Pathogenesis and Treatment of Pseudomonas aeruginosa Infections. *Drugs*. 2012;67(3):351-368. doi:10.2165/00003495-200767030-00003.

39. Nivoix Y, Velten M, Letscher-Bru V, et al. Factors Associated with Overall and Attributable Mortality in Invasive Aspergillosis. *Clin Infect Dis*. 2008;47(9):1176-1184. doi:10.1086/592255.

40. Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. *J Clin Epidemiol*. 1992;45(6):613-619.

41. Hahn T, McCarthy PL, Hassebroek A, et al. Significant Improvement in Survival After Allogeneic Hematopoietic Cell Transplantation During a Period of Significantly Increased Use, Older Recipient Age, and Use of Unrelated Donors. *J Clin Oncol*. 2013;31(19):2437-2449. doi:10.1200/JCO.2012.46.6193.

42. Steinbach WJ, Marr KA, Anaissie EJ, et al. Clinical epidemiology of 960 patients with invasive aspergillosis from the PATH Alliance registry. *J Infect*. 2012;65(5):453-464. doi:10.1016/j.jinf.2012.08.003.

43. Marr KA, Schlamm HT, Herbrecht R, et al. Combination antifungal therapy for invasive aspergillosis: a randomized trial. *Ann Intern Med*. 2015;162(2):81-89. doi:10.7326/M13-2508.

44. Jacobs F, Selleslag D, Aoun M, Sonet A, Gadisseur A. An observational efficacy and safety analysis of the treatment of acute invasive aspergillosis using voriconazole. *Eur J Clin Microbiol Infect Dis Off Publ Eur Soc Clin Microbiol*. 2012;31(6):1173-1179. doi:10.1007/s10096-011-1425-5.

45. Garcia-Vidal C, Peghin M, Cervera C, et al. Causes of death in a contemporary cohort of patients with invasive aspergillosis. *PloS One*. 2015;10(3):e0120370. doi:10.1371/journal.pone.0120370.

46. Wingard JR, Ribaud P, Schlamm HT, Herbrecht R. Changes in causes of death over time after treatment for invasive aspergillosis. *Cancer*. 2008;112(10):2309-2312. doi:10.1002/cncr.23441.

47. Neofytos D, Treadway S, Ostrander D, et al. Epidemiology, outcomes, and mortality predictors of invasive mold infections among transplant recipients: a 10-year, single-center experience. *Transpl Infect Dis*. 2013;15(3):233-242. doi:10.1111/tid.12060.

48. Pfeiffer CD, Fine JP, Safdar N. Diagnosis of Invasive Aspergillosis Using a Galactomannan Assay: A Meta-Analysis. *Clin Infect Dis*. 2006;42(10):1417-1727. doi:10.1086/503427.

49. Leeflang MMG, Debets-Ossenkopp YJ, Wang J, et al. Galactomannan detection for invasive aspergillosis in immunocompromised patients. *Cochrane Database Syst Rev*. 2015;12:CD007394. doi:10.1002/14651858.CD007394.pub2.

50. Baddley JW, Andes DR, Marr KA, et al. Antifungal therapy and length of hospitalization in transplant patients with invasive aspergillosis. *Med Mycol*. 2013;51(2):128-135. doi:10.3109/13693786.2012.690108.

51. Patel DA, Gao X, Stephens JM, Forshag MS, Tarallo M. US hospital database analysis of invasive aspergillosis in the chronic obstructive pulmonary disease non-traditional host. *J Med Econ*. 2011;14(2):227-237. doi:10.3111/13696998.2011.564246.

52. Vandewoude KH, Blot SI, Depuydt P, et al. Clinical relevance of Aspergillus isolation from respiratory tract samples in critically ill patients. *Crit Care Lond Engl*. 2006;10(1):R31. doi:10.1186/cc4823.

53. Baddley JW, Stephens JM, Ji X, Gao X, Schlamm HT, Tarallo M. Aspergillosis in Intensive Care Unit (ICU) patients: epidemiology and economic outcomes. *BMC Infect Dis*. 2013;13:29. doi:10.1186/1471-2334-13-29.

54. Vincent J-L, Rello J, Marshall J, et al. International study of the prevalence and outcomes of infection in intensive care units. *JAMA*. 2009;302(21):2323-2329. doi:10.1001/jama.2009.1754.

55. Meersseman W, Vandecasteele SJ, Wilmer A, Verbeken E, Peetermans WE, Van Wijngaerden E. Invasive aspergillosis in critically ill patients without malignancy. *Am J Respir Crit Care Med*. 2004;170(6):621-625. doi:10.1164/rccm.200401-093OC.

56. Meersseman W, Lagrou K, Maertens J, Wijngaerden EV. Invasive Aspergillosis in the Intensive Care Unit. *Clin Infect Dis*. 2007;45(2):205-216. doi:10.1086/518852.

57. Babatasi G, Massetti M, Chapelier A, et al. Surgical treatment of pulmonary aspergilloma: current outcome. *J Thorac Cardiovasc Surg*. 2000;119(5):906-912. doi:10.1016/S0022-5223(00)70085-7.

58. Daly RC, Pairolero PC, Piehler JM, Trastek VF, Payne WS, Bernatz PE. Pulmonary aspergilloma. Results of surgical treatment. *J Thorac Cardiovasc Surg*. 1986;92(6):981-988.

59. Massard G, Roeslin N, Wihlm JM, Dumont P, Witz JP, Morand G. Pleuropulmonary aspergilloma: clinical spectrum and results of surgical treatment. *Ann Thorac Surg*. 1992;54(6):1159-1164.