Treatment and economic burden of mucormycosis in China: Case report review and burden estimation

Yifei Jian MS1 | Minggui Wang PhD2 | Yue Yu PharmD1 | Yongjia Zhuo MS1 | Dunming Xiao PhD3 | Sisi Lin MS4 | Jianwei Xuan PhD1

Abstract
What is known and Objective: Mucormycosis is an opportunistic fungal infection associated with low incidence but high mortality. Few studies have shown the treatment and disease burden of mucormycosis in China. This study aims at collecting all the reported cases to describe the characteristics and treatment patterns and to assess the economic burden of mucormycosis in China.

Methods: We conducted a literature review of mucormycosis case reports in Chinese patients to summarize the characteristics and treatment patterns of the disease in China. An economic model was built to evaluate the total cost of mucormycosis per person, including direct medical cost, direct non-medical cost and indirect cost.

Results and Discussion: A total of 676 case reports showed that the most common type of mucormycosis was pulmonary mucormycosis (299/676, 44.2%), and rhinocerebral mucormycosis had the highest case fatality rate (122/185, 68.5%). Among those who used empiric therapies, 48.8% (231/473) did not include anti-mucor drugs; 79.8% (336/421) of the therapies included amphotericin B (AMB) or AMB-lipo after detection of mucormycetes; 98.6% (69/70) of the reported adverse events were associated with AMB and AMB-lipo. The duration of treatment ranged from 90 to 180 days; the length of stay ranged from 22 to 95 days. The average total cost per patient was 166 thousand Chinese Yuan (CNY), of which 93.1% was the direct medical cost (155 thousand CNY).

What is new and Conclusion: There are a limited number of antifungal treatment options for mucormycosis in China. This study highlights the critical need to introduce innovative and broader spectrum antifungal drugs with improved safety, better clinical efficacy, easier administration and reduced economic burden to Chinese mucormycosis patients.

KEYWORDS
clinical burden, clinical pharmacy, economic burden, mucormycosis, treatment pattern, zygomycosis
1 | WHAT IS KNOWN AND OBJECTIVE

Mucormycosis is a rare, aggressive and usually life-threatening fungal infection that is difficult to diagnose. It usually leads to long hospital stays and high case fatality. Even with recent advances in the treatment of mucormycosis, the mortality rate still remains high worldwide from 30% to 90%. The epidemiology of mucormycosis in China has not been fully elucidated. In other Asian countries, South Korea has an estimated prevalence of mucormycosis at about 9 people per million based on their national health insurance data; the estimated incidence of mucormycosis in Thailand and Vietnam is about 2 people per million and 1.2 people per million, respectively, based on disease burden estimates.

Several types of fungi from order Mucorales can cause mucormycosis, most commonly Rhizopus, Mucor and Lichtheimia species. Mucormycetes are present throughout the environment, particularly in soil and decaying organic matter. They are usually harmless to most people but the immunocompromised. Patients with underlying conditions including diabetes, ketoacidosis, neutropenia, transplantation, tumours, haematologic diseases and tuberculosis, as well as those with long-term use of broad-spectrum antibiotics, glucocorticoids and immunosuppressive drugs, are at higher risk of mucormycosis. When mucormycosis is acquired, the fungal pathogens can cause necrotizing inflammation and granulomas, then invading the brain through blood to cause meningitis. Mucormycosis is classified into five clinical forms based on the organs affected: rhino-orbito-cerebral, pulmonary, cutaneous, gastrointestinal and disseminated. Global guideline for the diagnosis and management of mucormycosis from European Confederation of Medical Mycology (ECMM) strongly recommends surgical intervention upon suspicion of mucormycosis after proper imaging. High-dose liposomal amphotericin B (AMB-lipo) is strongly recommended as a first-line treatment, whereas intravenous isavuconazole and intravenous or delayed-release tablet posaconazole (POSA) are recommended with moderate strength; amphotericin B deoxycholate (AMB) is not recommended due to substantial toxicity, but it may be the only option in resource-limited settings.

The aim of this study was to analyse the management strategies of mucormycosis, to assess the clinical and economic burden in China from the patient’s perspective and to provide scientific advice for rational drug use and allocation of health resources.

2 | METHODS

2.1 | Data collection

2.1.1 | Literature search

Search strategies were applied to 3 electronic bibliographic databases (China National Knowledge Infrastructure/CNKI, Wanfang (China) and PubMed) for publications from January 1990 to April 2021, using search terms (mucormycosis) or (mucor) in title, abstract or keywords, and (China) or (Chinese) in title, abstract, keywords or affiliation. Studies were included if they reported a case or case series of mucormycosis patients. Studies were excluded if they were: (1) retrospective studies or reviews without any report of details in treatment or patient outcome; (2) pharmacokinetic and pharmacodynamic studies; (3) clinical practice guidelines; (4) clinical trials; (5) animal or plant studies; (6) patients not adult; and (7) patients not Chinese. This systematic review was carried out in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement.6

The following information was extracted from the case reports: author, year of publication, patient characteristics (age, gender and organs infected), admission and discharge dates, date of mucor detection (microbiological or histopathological), mucormycosis classification, treatment before and after confirmation of mucor infection, days of treatment (DOT, approximately equal to duration of anti-mucor medication), length of stay (LOS), frequency of hospitalization, adverse drug reaction and outcomes. Two investigators independently and in duplicate collected data from each case report and then cross-checked. Disagreements were resolved by discussion or consensus involving a third investigator. Calculation of percentages and case fatality rates was performed using Microsoft Office Excel 2016.

2.1.2 | Ad hoc survey

An ad hoc survey of 25 experts from 19 hospitals who have rich experience in the treatment of mucormycosis was performed. These hospitals are from six tier 1 or tier 2 cities in China [6 hospitals from Beijing, 7 from Shanghai, 8 from Guangzhou, 1 from Hangzhou, 1 from Tianjin and 2 from Hefei]. The survey questionnaire was composed of three parts including the clinical information of mucormycosis management, the treatment pattern and the cost (direct medical cost, direct non-medical cost and indirect cost) of mucormycosis treatment (Figure 1). Direct medical cost is the follow-up costs for medication and medical service in Chinese healthcare system; direct non-medical cost is the cost for personal care worker during hospitalization. Indirect cost was investigated through the human capital approach, defined as personal production loss due to disease, and it was calculated by per capita disposable income multiplied by the length of first hospitalization.

2.2 | Economic burden model

An economic burden model of mucormycosis was constructed in Microsoft Office Excel 2016 (Figure 2). The unit cost (cost per day, CNY/d) of each item, and LOS, DOT, frequency and proportions were determined by the mean values of the data from the ad hoc survey.
3 | RESULTS

3.1 | Summary of the Literature

The flow chart in Figure 3 displays the detailed screening and selection process of study inclusion and exclusion. The literature search identified 292 articles that met the criteria, from which 676 cases reported outcomes (with or without treatment information), 512 cases reported both the outcomes and disease progression or clinical management details, and 421 cases reported treatment after mucormycosis detection with generic drug names listed.

3.2 | Types of mucormycosis

Table 1 shows the percentage results of the 8 clinical forms of mucormycosis by site of infection. Pulmonary mucormycosis was the most common form (44.2%), followed by rhinocerebral (27.3%), gastrointestinal (12.4%), cutaneous (10.5%), disseminated (2.5%), and hepatic or renal (2.1%). Case fatality rate calculation excluded loss to follow-up from the denominator. Rhinocerebral mucormycosis had the highest case fatality rate (68.5%), followed by disseminated (58.8%), pulmonary (41.6%), hepatic or renal (23.1%), cutaneous (21.0%), other sites (11.1%) and gastrointestinal (6.4%).

The diagnosis of invasive fungal infection is classified into three categories^7,8 (Table S1). Based on the ad hoc survey, diagnostic categories of the cases and proportions of the clinical forms of mucormycosis in each department are shown in Tables S2 and S3.

3.3 | Underlying conditions

A total of 421 cases had at least one comorbidity reported in literature (Table 2). The most common underlying conditions were diabetes (38.2%) and hematologic malignancy (11.3%), followed by diseases of lung, kidney and liver or solid organ transplantation.

Underlying conditions of mucormycosis patients in each department based on the ad hoc survey are shown in Table S4.

3.4 | Treatment patterns

3.4.1 | Empiric therapy

A total of 448 cases in literature had medication records after mucormycosis detection (some without generic names of the drugs received). Mucor was not detected until post-mortem in 26 cases, accounting for 13.61% (26/191) of the total number of deaths.
Twelve cases reported medication use before mucor detection but no medications after detection; among them, only one survived possibly due to surgical debridement, and other cases died quickly after detection of mucormycetes without time for treatment. It showed that patients whose mucormycetes were not detected in time had rapid deterioration and, most likely, ultimate death.

Of the 473 cases with records of initial medication use after hospitalization (regardless of mucor detection status), 48.8% (231 cases) did not receive anti-mucor drugs recommended in ECCM, and their fatality rate was 44.0% (95/216). Among the 231 cases who failed to receive anti-mucor treatment in the initial medication use, 56.3% (130/231) received treatments recommended by the guidelines after therapy switch, fatality rate 37.4% (46/123); 42.4% (98/231) never received any anti-mucor treatment, fatality rate 50.5% (46/91).

Empiric therapy is defined as the initial treatment before detection of mucor. There were 197 (41.6%) records of empirical therapy among 473 records with initial medication use (Table 3). Among those with empiric therapy, 58 cases (29.4%) received azole antifungals such as fluconazole, itraconazole or voriconazole; 17 cases (8.6%) received caspofungin or micafungin; 42 cases (21.3%) received fluoroquinolone antibiotics, such as levofloxacin or moxifloxacin; 12 cases received AMB; 5 cases (2.5%) received AMB-lipo; and 1 case (0.51%) received POSA. The 17 cases (8.6%) who received anti-mucor drugs on the guidelines as empiric therapy had a mortality rate of 68.8% (11/16). Because only the oral tablet and

| Types of infection   | Number of patients | Proportion (%) | Number of deaths | Case fatality rate (%) |
|----------------------|--------------------|----------------|------------------|-----------------------|
| Pulmonary            | 299                | 44.2           | 117              | 41.6                  |
| Rhinocerebral        | 185                | 27.3           | 122              | 68.5                  |
| Gastrointestinal     | 84                 | 12.4           | 5                | 6.4                   |
| Cutaneous            | 71                 | 10.5           | 13               | 21.0                  |
| Disseminated         | 17                 | 2.5            | 10               | 58.8                  |
| Hepatic or renal     | 14                 | 2.1            | 3                | 23.1                  |
| Other sitesb         | 6                  | 0.9            | 1                | 11.1                  |
| Total                | 676                | 100            | 272              | 42.7                  |

*aCase fatality rate = number of death/ (total number of patients – loss to follow-up).

*bOther sites: heart, lumbar, eyes and cervix."
suspension forms of posaconazole are available in China, all POSA in our research were administered orally.

### 3.4.2 Therapy after detection of mucormycetes

There were 421 mucormycosis cases with records of generic drug names after detection of mucormycetes, all-cause case fatality rate 37.2% (145/390).

As shown in **Table 4**, AMB was the most commonly prescribed anti-mucor drug. Treatments involving AMB or AMB-lipo account for 79.8% (336/421) of all the first-line or sequential treatment plans, and few patients received liposomes due to poor availability of AMB-lipo in Chinese hospitals.

Some cases received antifungal drugs not recommended for mucormycosis treatment by the guidelines despite the detection of mucormycetes. According to the ad hoc survey, this was mainly due to the severe nephrotoxicity of AMB or AMB-lipo suspension and insufficient efficacy of POSA for invasive mucormycosis.

For first-line therapy, the fatality rate of cases on combination therapies was generally higher than those on monotherapy, probably because combination therapies are usually used for patients in serious condition. Among those who received AMB or AMB-lipo for first-line therapy, 8.0% (27/336) switched to second-line therapy and discontinued AMB or AMB-lipo, mainly because of the severe adverse effects and the high cost of liposomes.

### 3.4.3 Duration of treatment

Median days of treatment (mDOT) and median length of stay (mLOS) are shown in **Table 5**. The values (Table 5 in italics) obtained from a small case sample \((n \leq 3)\) were disregarded in calculation. LOS of all cases ranged from 18 to 107 days. Median LOS of the dead cases ranged from 9 to 58 days, and 4 to 19.5 days after detection of mucormycetes; time from first-time admission to use of anti-mucor medications ranged from 6 to 24 days. Median LOS of the cases alive ranged from 22 to 95 days, and 14 to 96 days after detection of mucormycetes; time from first-time admission to use of anti-mucor medications ranged from 7.5 to 25 days. Cases with less than 30 days of LOS were mainly cutaneous mucormycosis or those who received surgical debridement. It generally took more than 7 days to get a definite diagnosis, leading to delayed treatment and rapid deterioration. Most of the cases alive had a LOS over 30 days, longer than the LOS of the dead cases because cases that are more severe usually progress to death within 30 days of admission.

Information of treatment patterns obtained from the ad hoc survey is presented in Table S5. From the ad hoc survey, the mean DOT was 119 days, and the average length of first hospitalization was 38 days. AMB and AMB-lipo were mainly used in inpatient therapies, and POSA was taken orally post-discharge for about 90 days. Some patients received AMB or AMB-lipo intravenous infusion for about 54 days in primary hospital or community healthcare centre after their first discharge. Most experts said the total duration of treatment for mucormycosis was 3–12 months. Due to the high fatality rate of mucormycosis, severe cases may die within 14 to 30 days of hospitalization, whereas patients survived may have been hospitalized for 30 to 60 days.

### 3.5 Adverse effects

Adverse effects of 70 cases were reported in 54 articles, accounting for 18.8% (55/292) of the articles included and 16.6% (70/421) of the...
Among them, 45 cases (64.3%) had adverse events from AMB, 24 cases (34.3%) from AMB-lipo and 1 case (1.4%) from POSA. Most of the cases experienced adverse effects from AMB, such as hypokalaemia, elevated serum creatinine, kidney injury, arrhythmia and mental disorders, with a case fatality rate of 27.3% (18/66); 6 cases switched to AMB-lipo and 9 cases to POSA for second-line therapy due to severe intolerance to AMB. Although liposomes cause fewer adverse effects, there were cases intolerant to both and one case died as a result of drug discontinuation.10

A 58 of the cases with adverse events had records of underlying conditions, of which 18 cases had diabetes mellitus, 15 cases had respiratory diseases, 9 cases had haematologic malignancy, 5 cases had cardiovascular diseases, 5 cases had kidney diseases, 3 cases had liver diseases, 3 cases had systemic lupus erythematosus, and 2 cases had solid organ transplantation.

### 3.6 Economic burden

#### 3.6.1 Descriptive statistics

Mean cost and average economic burden per person of mucormycosis by department are shown in Table S6 and Figure S1, data based on the ad hoc survey. Because the sample size of experts was small and the cost data did not follow a normal distribution, we obtained the mean and 95% confidence interval with bootstrapping (Table 6). The mean total cost per patient was 154,506 CNY, composed of direct medical cost (145,887 CNY), direct non-medical cost (2669 CNY) and indirect cost (5950 CNY).

#### 3.6.2 Economic burden model

We used mean data from the ad hoc survey as values of the parameters in the economic burden model (Table S7). The values were put into the model (Figure 2) for basic analysis, results shown in Figure 4 (mean costs). Through model calculation, the mean total personal economic burden of mucormycosis was 166,300 CNY: direct medical cost was 154,800 CNY (93.1%), direct non-medical cost was 5700 CNY (3.4%), and indirect cost was 5800 CNY (3.5%). More than 90% of the total cost was direct medical cost, and drug cost was the highest (63.9%) of them followed by inpatient charges during first hospitalization at almost 20%. The proportion of test costs was higher than surgery costs since not every patient underwent a surgery. Proportions of both surgery cost and adverse effects cost were low at about 1%, because the model calculation uses the total number of patients rather than the actual subgroup number of patients who underwent surgery or had adverse effects for cost
| Treatment pathways                  | Medication after detection of mucormycetes | Median length of stay (days) | Median time from admission to use of anti-mucor<sup>a</sup> drugs (days) | Median length of stay after detection of mucormycetes (days) | Median days of treatment (days)<sup>b</sup> |
|------------------------------------|-------------------------------------------|-----------------------------|-------------------------------------------------------------------------|-----------------------------------------------------------------|------------------------------------------|
| Monotherapy                        | AmB                                       | 10                          | 9                                                                       | 4                                                              | 30                                       |
|                                   | AmB- lipo                                 | 9                           | 6                                                                       | 8                                                              | 30                                       |
|                                   | POSA                                      | -                           | -                                                                       | -                                                              | -                                        |
|                                   | Other antifungals<sup>c</sup>             | 29                          | -                                                                       | 11                                                             | 34.5 NO/YES                              |
| Combination or sequential therapy  | AMB + AMB- lipo                           | 12                          | -                                                                       | -                                                              | 12                                       |
|                                   | AMB/AMB- lipo + POSA (combination)        | 58                          | 24                                                                     | 14                                                             | 56                                       |
|                                   | AMB/AMB- lipo + other antifungals         | 24                          | 7                                                                      | 6.5                                                            | 70                                       |
|                                   | Multiple other antifungals                | 4.5                         | -                                                                      | 2                                                              | 14                                       |
|                                   | AMB/AMB- lipo + POSA (sequential)         | -                           | 25                                                                     | -                                                              | 30                                       |
| Therapy switch (from first-line to second-line) | AMB/AMB- lipo → POSA (due to ADR); AMB- lipo + POSA → POSA only (due to ADR) | 36                          | 7                                                                      | 11.5                                                           | 24                                       |
|                                   | AMB/AMB- lipo → AMB/AMB- lipo + POSA      | -                           | -                                                                      | -                                                              | -                                        |
|                                   | Other antifungals → AMB/AMB- lipo only or combined with other antifungals | 28                          | 15                                                                     | 19.5                                                           | 76                                       |
|                                   | AMB- lipo → AMB- lipo + other antifungals | -                           | 365                                                                    | -                                                              | -                                        |
|                                   | AMB only (due to high cost of AMB- lipo)  | 218                         | 32                                                                     | 7.5                                                            | 57                                       |
|                                   | AMB/AMB- lipo → other antifungals         | -                           | 66                                                                     | 107                                                            | 96                                       |

Abbreviations: AmB, amphotericin B deoxycholate; AMB- lipo, liposomal amphotericin B; POSA, posaconazole.

<sup>a</sup>Anti-mucor drugs: anti-mucor drugs recommended in the global guideline for the diagnosis and management of mucormycosis from European Confederation of Medical Mycology (ECMM) including AmB, AMB- lipo and POSA.

<sup>b</sup>Median days of treatment: total duration of inpatient and discharge medication use based on information from literature.

<sup>c</sup>Other antifungals: mono-antifungal drugs not recommended in the global guideline for the diagnosis and management of mucormycosis from European Confederation of Medical Mycology (ECMM).

<sup>d</sup>Numbers in italics indicate that sample size used for this median calculation is <3.


### TABLE 6

| Types of cost                                      | Mean cost (CNY) | 95% confidence interval (CNY) |
|---------------------------------------------------|-----------------|-----------------------------|
| Drug cost                                         | 98,648          | 82,545–118,061              |
| First hospitalization                              |                 |                             |
| Tests                                             | 20,040          | 15,873–24,619               |
| Surgery                                           | 1404            | 761–2,122                   |
| Adverse effects                                   | 1903            | 945–3237                    |
| Medical service and materials                      | 6631            | 15,155–24,357               |
| Outpatient charges (except for drug cost)         | 8290            | 7145–9294                   |
| Cost of rehospitalization                         | 8971            | 5800–12,674                 |
| Direct medical cost                               | 145,887         | 123,913–171,110             |
| Direct non-medical cost†                           | 2669            | 1867–3575                   |
| Indirect cost‡                                     | 5950            | 4852–7195                   |
| Mean total cost                                   | 154,506         | 131,825–81,279              |

†Direct non–medical cost: salary paid for care worker during first hospital.
‡Indirect cost: personal production loss.

### Figure 4

Pie chart showing components of the total cost (cost/10,000 CNY, type of cost, proportion%): basic analysis of the mucormycosis economic burden. The total cost was divided into drug cost, inpatient charges during 1st hospitalization (except for drug cost), outpatient charges (except for drug cost), cost of rehospitalization, direct non-medical cost and indirect cost. Inpatient charges during 1st hospitalization (except for drug cost) were divided into test cost, medical service and material cost, adverse effect-related cost and surgery cost.

Per capita. Rehospitalization cost, outpatient charges, direct non-medical cost, and indirect cost were all less than 10,000 CNY (drug costs excluded), each only accounted for less than 5%.

### 3.6.3 Sensitivity analysis

A one-way sensitivity analysis was performed to estimate the range of personal cost of mucormycosis (Figure 5). Maximum and minimum values on the interval of parameters were obtained from the ad hoc survey (Table S8). Economic burden of mucormycosis is estimated from 99,247 to 321,295 CNY, which is 3–10 times of annual disposable income per capita of China. Sensitivity analysis suggested that drug cost per day, duration of medication treatment and length of first hospitalization are factors that have the most impact.

### 4 Discussion

Mucormycosis is a rare infection, but common in people with weakened immune systems due to health conditions or medications, such as diabetes mellitus (especially with diabetic ketoacidosis), long-term...
corticosteroid use, haematologic malignancy, solid organ transplant and lung diseases. The mortality rate of mucormycosis is higher than 40% and even higher for patients without surgical debridement. This study indicates that pulmonary type is the most common clinical form in Chinese mucormycosis patients. Patients are at highest risk of death when infection occurs in the sinuses and brain, whereas the survival rate is higher for mild cutaneous infection. It is often difficult for mucormycosis to be accurately diagnosed in time, especially when based on clinical symptoms only. Therefore, patients may easily miss the best time for treatment and increase their risk of death. Treatment duration for patients with mucormycosis ranges from 3 to 6 months and up to 1 year. The mean days of treatment for mucormycosis was 119 days. Overall, the length of stay of patients who used multiple drugs and had a second-line therapy was longer than that of patients who received monotherapy. This is probably because the former are usually in more severe condition and have a poor tolerance to adverse drug reactions, thereby requiring longer treatment duration.

This is the first disease burden research of mucormycosis in China. Drug cost has the highest proportion of total cost because of the expensive anti-mucor drugs and long treatment duration. During first hospitalization, test costs accounted for more than half of the total cost in addition to drug cost, since mucormycosis is difficult to diagnose and patient condition needs to be closely monitored to ensure the safety and efficacy of drug use. The test costs could have been higher if therapeutic drug monitoring services of anti-mucor drugs were available in Chinese hospitals. Good adherence to long-term treatment is of great importance for the cure of mucormycosis, and poor adherence to medication or treatment termination usually leads to death. However, the high cost of anti-mucor drugs placed such a heavy financial burden on some patients that they had to give up treatment, leading to poor prognosis. It is necessary to reduce the economic burden of patients with mucormycosis.

The ad hoc survey of many experts suggested the unmet need in mucormycosis treatment in China: (1) most patients with mucormycosis are immunocompromised and suffer from renal insufficiency, so they cannot tolerate the nephrotoxicity of AMB or even AMB-lipo; (2) AMB-lipo has a lower risk of nephrotoxicity and is recommended in patients with cerebral mucormycosis (crosses the blood–brain barrier), but it is unfortunately not available in many hospitals in China; (3) POSA is not labelled for mucormycosis, so there is no more effective option if patients are intolerant to both AMB and AMB-lipo or when AMB-lipo is unavailable. A wider variety of antifungal medications are needed for the treatment of mucormycosis.

**WHAT IS NEW AND CONCLUSION**

The mortality of mucormycosis remains high, and the number of antifungal treatment options for mucormycosis is limited in China. The personal economic burden of mucormycosis is 3–10 times of the annual disposable income per capita of China, so the long duration and high cost of mucormycosis treatment with few safe and effective drug options have brought heavy financial burden to patients. There is a critical need to introduce innovative and broader spectrum
antifungal drugs with improved safety, better clinical efficacy, easier administration, and reduced economic burden for Chinese mucormycosis patients.

CONFLICT OF INTEREST
The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT
The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID
Yifei Jian https://orcid.org/0000-0002-0250-0637

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SUPPORTING INFORMATION
Additional supporting information may be found in the online version of the article at the publisher’s website.

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