Research Article

For reprint orders, please contact: reprints@futuremedicine.com

Future MICROBIOLOGY

Lumbar drainage for the treatment of refractory intracranial hypertension in HIV-negative cryptococcal meningitis

Qilong Zhang[‡,1], Hang Li[‡,1,2], Keming Zhang[‡,2,3], Amir Arastehfar[4], Farnaz Daneshnia[4], Wenjie Fang[2,3], Peijuan He[1], Weifeng Kuang[1], Guoqiang Jiang[1], Min Chen[2,3], Teun Boekhout[2,4,5], Shuai Li[6], Weiwei Jiang[**,2,3], Wanqing Liao[2,3] & Weihua Pan[*,2,3]

[1]Department of Internal Neurology, Jiangxi Chest Hospital, Jiangxi 330000, PR China

[2]Shanghai Key Laboratory of Molecular Medical Mycology, Shanghai Institute of Mycology, Shanghai Changzheng Hospital, Second Military Medical University, Shanghai 200003, PR China

[3]Department of Dermatology, Shanghai Changzheng Hospital, Second Military Medical University, Shanghai 200003, PR China

[4]Westerdijk Fungal Biodiversity Institute, Utrecht, The Netherlands

[5]Institute of Biodiversity & Ecosystem Dynamics, University of Amsterdam, Amsterdam 1012 WX, The Netherlands

[6]Department of Clinical Laboratory, Yan'an People's Hospital, Shanxi 716000, PR China

*Author for correspondence: Tel.: +86 021 81885594; panweihua@smmu.edu.cn

**Author for correspondence: Tel.: +86 021 81885592; jiangxuejiangwei@qq.com

‡ Authors contributed equally

Aim: This study aims to evaluate lumbar drainage (LD) for controlling refractory intracranial hypertension among non-HIV cryptococcal meningitis patients. **Patients & methods:** A case–control study was designed to compare LD (case) with repeated lumbar puncture (control). **Results:** Both LD and repeated lumbar puncture can efficiently control refractory intracranial hypertension. LD group showed better clinical symptom remission, such as lower rate of headache, vision disorders, signs of meningeal irritation and conscious disturbance, than control group. LD group was reported with higher intracranial pressure reduction (173.75 ± 17.72 mmH_2O) than those among control group (113.50 ± 14.94 mmH_2O; $p < 0.05$). **Conclusion:** LD is an effective and safe alternative to control refractory intracranial hypertension in HIV-negative cryptococcal meningitis patients.

First draft submitted: 20 March 2019; Accepted for publication: 20 May 2019; Published online: 5 June 2019

Keywords: cryptococcal meningitis • lumbar drainage • lumbar puncture • refractory intracranial hypertension

Cryptococcal meningitis (CM) is a systemic infection caused by the pathogenic yeast species belonging to the *Cryptococcus neoformans* and *Cryptococcus gattii* complexes [1]. *Cryptococcus* yeasts are ubiquitous and it is generally accepted that the primary infection is acquired by inhalation and first infects the lungs, then disseminates to other organs, most notably the CNS, which is responsible for CM. CM is the leading cause of death among adults living with HIV/AIDS, especially in sub-Saharan Africa [2]. It is estimated that CM was responsible for 624-700 annual HIV/AIDS-related deaths globally in 2008, while the number has dramatically decreased to 181–100 per year in 2014 [3]. However, we have witnessed an increasing population of non-HIV patients with CM, such as those with other immunocompromised conditions, for example, cancer, systemic lupus erythematosus, nephrotic syndrome, diabetes mellitus II, tuberculosis and those undergoing extensive use of broad-spectrum antibiotics [4–8]. Approximately, 80% of CM cases were reported in the HIV-negative populations in China and America [9,10].

Intracranial hypertension (ICH) is one of the most important risk factors for prognosis of CM patients [11], and is associated with high fungal burden, and, consequently difficulty in treatment [12]. Approximately 60% and 30% of CM patients reported have intracranial pressure (ICP) of more than 250 mmH_2O and ICP more than 350 mmH_2O (malignant), respectively [13]. Patients with persistent elevated ICP had a shorter survival time, compared with those with baseline opening pressures of less than 250 mmH_2O [13]. HIV-negative CM patients are associated with more severe inflammatory reactions, potentially leading to ICH and cerebral herniation [14]. The clinical practice guidelines of Infectious Diseases Society of America (IDSA) strongly recommended adequate

Future Medicine

management of ICP by repeated lumbar puncture, lumbar drainage (LD), use of ventriculoperitoneal shunt or pharmacologic approaches [14].

IDSA guideline recommended that LD could be an alternative to daily lumbar punctures, for patients with persistent ICP elevation ≥250 mmH_2O and continuous aggravation of ICH-related symptoms [14]. During two recent decades, LD has been successfully used in several medical centers to control ICH of HIV-positive CM patients [15–17]. For HIV-negative ones, the only study of LD evaluation was performed by Chen *et al.* in 2007, in which LD was used with intrathecal injection of amphotericin B (AmB) [18]. Herein, this study is the first case–control study to evaluate the efficacy of LD and make a comparison with repeated lumbar puncture in HIV-negative patients with ICP.

Patients & methods

This study protocol was approved by the ethical committee members of the Institutional Review Board of the Jiangxi Chest Hospital (no. 201712045). The informed consent was waived by the Institutional Review Board due to the nature of retrospective study design.

Study setting & participants

This retrospective case–control study was carried out at the Department of Internal Neurology, Jiangxi Chest Hospital, which is a 600-bed Tertiary Hospital specialized for treatment of infectious diseases. Between 1 January 2011 and 31 December 2017, 209 confirmed adult (>18 years) CM patients without HIV infection were enrolled. Diagnoses were based on positive results of cerebrospinal fluid (CSF) culture, or CSF cryptococcal antigen test (IMMY, OK, USA), or positive CSF India ink staining. Patients receiving temporary LD to reduce ICP were selected if they met the following criteria: persistent pressure elevation ≥250 mmH_2O and symptoms; absence of contraindications such as sign of brain hernia, intracranial space occupying lesion, skin or soft tissue infection at puncture site, lumbar deformity or bone destruction at puncture site; absence of neurological impairment caused by previous cerebral infarction, head injury or intracranial hemorrhage; follow-up data were available. Medical charts of CM patients with ICH who were treated with repeated lumbar puncture, were reviewed and potentially selected as control group.

Data collection

Medical charts were systematically reviewed independently by two authors. The following clinical data were collected from each medical record: admission date, gender, location, time of emergence of CM symptoms and time of confirmed CM, antifungal regime, device-days of LD, puncture time of patients from control group, clinical manifestations and laboratory findings at time of performed LD or lumbar puncture or LD removal, length of hospital stay (days) and outcome. Follow-up data were used to decide outcome, and the minimum follow-up duration should be at least 6 months after discharge. If follow-up was not complete, patients were contacted by the authors to collect relevant data. Two authors collected the clinical data and these data were checked by the third author. Disagreements were resolved by discussion between two authors and supervised by an expert.

Treatment

Antifungal therapy

We adopted the standardized antifungal induction therapy which lasted 4 weeks (AmB deoxycholate plus flucytosine) or 6 weeks (AmB deoxycholate for 2 weeks, and lipid formulation of AmB for 4 weeks, plus flucytosine) for CM patients with or without neurological complications, respectively. An 8-week treatment with fluconazole was used for consolidation and maintenance therapy subsequently [14].

All patients were tested with CT and MRI for preoperative evaluation.

In LD group, aiming to decrease the rate of CSF leakage-related infection, we adopted a modified LD (Figure 1). The invasive procedures of LD were performed at bedside. Patients took a lateral recumbent position, and L3/ L4 or L4/L5 intervertebral spaces were used as the puncture sites. The LD catheter was inserted into the subarachnoid space through needle. The other end of the catheter moves subcutaneously for 10 cm and comes out at the left or right of the back. The catheter was finally connected to a CSF-collecting system whose manometer was placed at 20 cm above the insertion site. The patients had activity restrictions during the drainage. The drainage device should be temporarily clamped if the patient wants to sit up or move any further. If the device was disconnected involuntarily during the drainage time, reinsertion was performed.

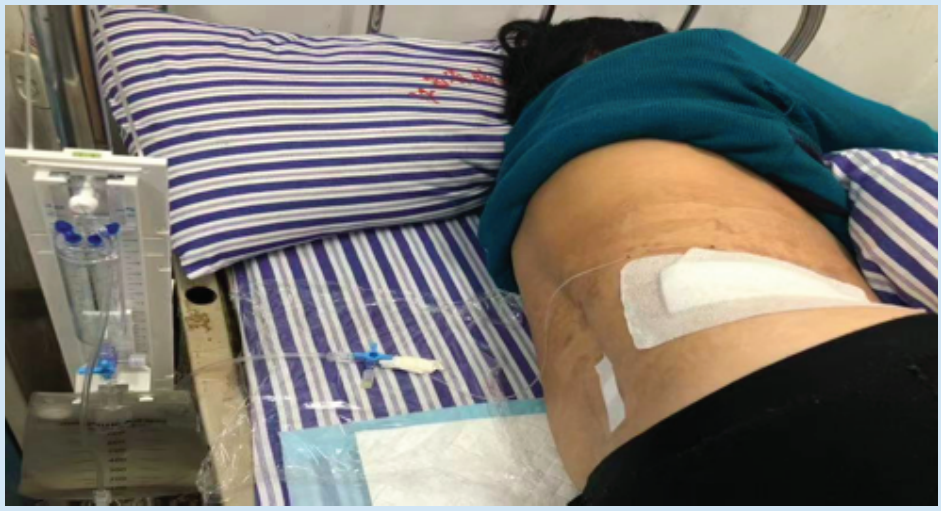

Figure 1. Modified lumbar drainage. The lumbar drainage catheter was inserted into the subarachnoid space through needle. The other end of the catheter moves subcutaneously for 10 cm and comes out from skin at the left or right of the back. The catheter was finally connected to a cerebrospinal fluid-collecting system whose manometer was placed at 20 cm above the insertion site.

In LD group, prophylactic antibiotics were not used before the procedure. We did not limit the number of device-days for LD within 7–14 days similar as in previous studies [15–17]. The period of device-days was decided by whether the patient adequate ICH control and clinical relief. If symptoms and signs continued to relieve, and a controlled ICH (<250 mmH_2O) has been stabilized for more than 3 days, the catheter could be clamped temporarily. Approximately 24–36 h later, if ICP is still lower than 250 mmH_2O and no evidence of ICH (e.g., nausea, vomiting, recurrent headache) was observed, the catheter was removed.

In the control group, the patients were first subject to lumbar puncture normally one- to two-times daily to control ICH, to achieve an adequate guideline recommended ICH control [14]. If ICP stays below 250 mmH_2O after 14 days of daily puncture and is stabilized for more than 3 days, the frequency of lumbar puncture can be decreased from every other day to once per week, depending on ICP and clinical symptoms.

Statistical analysis

IBM SPSS statistics 25 (International Business Machines Corporation, NY, USA) was used for data analysis. The categorical data were reported as percentages or proportions. Comparisons between groups were performed by χ^2 test or Mann-Whitney U test. P-values less than 0.05 were considered as statistically significant.

Results

Patient enrollment

The general information of the case and control groups is presented in Table 1, with no statistical significance observed ($p > 0.05$). Among the 32 included cases, only four patients declared being exposed to pigeon droppings.

Treatment outcomes

The remission of clinical symptoms and laboratory findings between the two groups were compared (Table 2). The LD group showed better clinical symptom remission, such as a higher improvement rate for headaches (93.75%), vision disorders (66.67%), signs of meningeal irritation (100%) and conscious disturbance (75%), than the control group. The LD group was reported with higher average ICP reduction (173.75 ± 17.72 mmH_2O) than those among control group (113.50 ± 14.94 mmH_2O; $p < 0.05$), and both case and control groups showed similar efficacy in decreasing cerebrospinal fluid protein ($p = 0.956$). In LD group, the median device-days were 33 days (range 10–66 days) during 75.25 ± 7.20 hospital days, and 16 patients experienced 18 placement procedures for a

Table 1. Patients' characteristics and laboratory findings on admission.

Characteristic	LD group (n = 16)	Control group (n = 16)	p-value
Demography			
Mean age	42.94 ± 3.41	45.44 ± 5.33	0.780 ‡
Sex: male	7 (43.75%)	9 (56.25%)	0.480 †
Geographic location			
Rural area	12 (75.00%)	13 (81.25%)	0.669 †
Underlying diseases	5 (31.25%)	6 (37.50%)	0.710 †
The duration before confirmed diagnosis	33.14 ± 14.23	39.25 ± 11.86	0.381‡
Clinical parameters			
Headache	16 (100.00%)	16 (100.00%)	-
Fever	12 (75.00%)	14 (87.50%)	0.365 †
Nausea/vomiting	11 (68.75%)	10 (62.50%)	0.710 †
Anorexia	16 (100.00%)	14 (87.50%)	0.144 †
Seizure	3 (18.75%)	2 (12.50%)	0.626 †
Hearing loss	2 (12.50%)	3 (18.75%)	0.626 †
Vision disorders	6 (37.50%)	7 (43.75%)	0.719 †
Weight loss	9 (56.25%)	8 (50.00%)	0.723 †
Signs of meningeal irritation	7 (43.75%)	7 (43.75%)	1.000 †
Conscious disturbance	4 (25.00%)	3 (18.75%)	0.669 †
Dizziness	1 (6.25%)	2 (12.50%)	0.544 †
Deep reflexes	1 (6.25%)	3 (18.75%)	0.285 †
Papilledema	3 (18.75%)	2 (12.50%)	0.626 †
CSF examinations			
Open pressure (mmH_2O)	384.38 ± 100.40	387.75 ± 57.94	0.724‡
CSF glucose (mmol/l)	1.89 ± 1.11	1.64 ± 1.31	0.515‡
CSF protein (mg/l)	844.29 ± 681.54	905.49 ± 790.03	0.956‡
CSF chloride (mmol/l)	112.75 ± 10.69	113.44 ± 6.88	0.956 ‡

†p-value by $\chi 2$ test.
‡p-value by Mann-Whitney U test.
CSF: Cerebrospinal fluid; LD: Lumbar drainage.

total of 549 device-days of observation. While patients in the control group, averagely experienced repeated lumbar puncture for 32-times (range 28–41 times) during 89.68 ± 7.78 hospital days.

In LD group, 12 (75%) patients survived without sequela. Three patients survived with complications, including renal dysfunction (n = 1), secondary epilepsy (n = 1) and hearing loss (n = 1). One patient died due to *Staphylococcus aureus* infection.

In the control group, 10 (62.5%) patients survived without sequela. The most frequently observed complication was liver and kidney dysfunction (n = 3), followed by hypokalemia (n = 1) and anemia (n = 1). One patient died due to brain herniation caused by ICP.

Discussion

Elevated ICP is a common complication of CM and generally linked to a high fungal burden in the CSF [12]. Uncontrolled ICP will result in poor prognosis, such as brain herniation and death [19]. IDSA guideline recommended that LD could be an alternative to daily lumbar punctures, for patients with persistent ICH ≥250 mmH_2O and continuous aggravation of ICH-related symptoms [14]. However, limited data support the application of LD among HIV-negative patients with ICH. Our case–control study confirmed the efficacy of LD in relieving symptoms and reverting CSF index to normal.

Patients from both case and control groups suffered from refractory ICH, with an average ICP of 384.38 and 387.75 mmH_2O, respectively. Signs and symptoms related to ICH were serious in both groups before operation, such as headache (100%), vomiting (65.62%) and signs of meningeal irritation (43.75%). Currently, the mechanism of increased ICP among CM patients is not yet fully understood. Some investigators believed that the increased ICP

Table 2. Remission of clinical symptoms and laboratory findings between the two groups.

Variables	LD group (n = 16) remission	Control group (n = 16) remission	p-value
Clinical parameters			
Headache	15†/16‡ (93.75%)§	12†/16‡ (75.00%)§	0.144¶
Fever	12†/12‡ (100.00%)§	13†/14‡ (92.85%)§	0.345¶
Nausea/vomiting	10†/11‡ (90.90%)§	9†/10‡ (90.00%)§	0.943¶
Anorexia	14†/16‡ (87.50%)§	10†/11‡ (90.90%)§	0.782¶
Seizure	2†/3‡ (66.67%)§	1†/2‡ (50.00%)§	0.709¶
Hearing loss	1†/2‡ (50.00%)§	1†/3‡ (33.33%)§	0.709¶
Vision disorders	4†/6‡ (66.67%)§	3†/7‡ (42.85%)§	0.391¶
Weight loss	7†/9‡ (77.78%)§	6†/8‡ (75.00%)§	0.893¶
Signs of meningeal irritation	7†/7‡ (100.00%)§	6†/7‡ (85.71%)§	0.299¶
Conscious disturbance	3†/4‡ (75.00%)§	1†/3‡ (33.33%)§	0.270¶
Dizziness	1†/1‡ (100.00%)§	2†/2‡ (100.00%)§	-
Deep reflexes	1†/1‡ (100.00%)§	2†/3‡ (66.67%)§	0.505¶
Papilledema	3†/3‡ (100.00%)§	2†/2‡ (100.00%)§	-
CSF examinations			
Open pressure (mmH_2O)	173.75 ± 17.72††	113.50 ± 14.94††	0.021#
CSF glucose (mmol/l)	1.00 ± 0.35††	1.32 ± 0.22††	0.138#
CSF protein (mg/l)	483.75 ± 175.02††	480.88 ± 178.14††	0.956#
CSF chloride (mmol/l)	13.05 ± 2.89††	9.25 ± 2.46††	0.361#

†Number of cases relieved after operation.
‡Number of cases with symptoms before operation.
§Remission rate.
¶p-value by $\chi 2$ test.
#p-value by Mann-Whitney U test.
††The average remission of CSF parameter.
CSF: Cerebrospinal fluid; LD: Lumbar drainage.

is a result of the increment of vascular permeability and cerebral edema due to cytokine-induced inflammation [13]. Others think that the main cause is that arachnoid villi and lymphatic vessels plugged with fungal cells cause mechanical obstruction to the flow of CSF by blocking the passage [20,21]. Whatever the mechanisms are, the timely and adequate management of ICH is of clinical significance. Both LD and repeated lumbar puncture are recommended by IDSA guideline for ICH control.

Although the LD group showed somehow better clinical symptom remission, both LD and repeated daily puncture showed efficacy in treating ICH-related symptoms among HIV-negative patients. However, patients with LD were reported with higher ICP reduction than those among control group ($p < 0.05$). Patients with refractory ICH, experienced a median of 32-times of puncture and longer hospital stay if a physician recommended repeated lumbar puncture. While LD showed more advantages over repeated lumbar puncture in adequate symptoms remission, controllable drainage rate, minimal injury, less pain and fewer in hospital days, LD allows for steadily drainage of CSF, dynamic monitoring of pressure and appearance, and readily withdrawing of CSF samples for biochemical or microbiological examination at any time. Additionally, compared with pharmacologic approaches, LD may decrease the risk of renal impairment and electrolyte disorders caused by high-dose mannitol.

In our study, we adopted an unlimited duration of drainage to achieve satisfactory relief of symptoms. The median device-day for LD was 33 days (range 10–66 days), and 16 patients experienced 18 placement procedures for a total of 549 device-days of observation. The number of LD device-days has not been defined by previous researches. Studies among HIV-positive populations recommend a short device-day for ICH control, considering the infection risks of immunocompromised hosts [15–17]. It is not yet clear whether longer device-days will increase the risk of infection among HIV-negative patients, and almost all the previous studies limit the device-days to 14 days or less, for HIV-positive ones [15–17]. However, according to our clinical observation, 14 days is not enough to achieve extubation indication for part of the HIV-negative patients. Hence, we extended the number of the device-days based on various conditions observed among individual patients. The CSF secondary infection rate in our study was 6.25%, which is similar to previously reported incidences (4–7%) [17,22–25]. We speculate that the difficult-to-control refractory ICH in HIV-negative patients could be due to an active and higher immune

response that, apart from protecting them from the acquirement of secondary infections, may also result in exacerbation of clinical conditions, and hence, longer period of device-days. It is noteworthy that, for HIV-negative patients with other severe immune-related underlying conditions, shorter drainage time is recommended to avoid further infection. Involuntary catheter disconnection is another risk for longer periods of device-days and as such requires frequent monitoring of the connection. Moreover, bacterial meningitis may occur when CSF or soft tissue are contaminated due to involuntary catheter disconnection, which is closely related to CSF leakage. Herein, physicians should emphasize the importance of postoperative activity restriction to patients, and a drainage device should be temporarily clamped if the patient wants to sit up or move any further. Catheter removal and tip culture should be done immediately if CSF color or turbidity changes, followed by initiation of appropriate early empirical treatment.

Conclusion

Our study demonstrated that LD is an effective and safe alternative for reducing refractory elevated ICP in non-HIV patients with CM. For LD group patients, although a longer period of device-days of LD can achieve better clinical relief and adequate control of RICH, there is a limited risk of infection acquirement that could be controlled by close monitoring and examination of the connection. Due to the limited number of cases and retrospective study design, multicenter and prospective studies are warranted to further evaluate our conclusions.

Summary points

- This study is the first case–control study to evaluate the efficacy of lumbar drainage (LD) and make a comparison with repeated lumbar puncture in HIV-negative patients with intracranial pressure.
- The LD group showed better clinical symptom remission, such as a lower rate of headaches, vision disorders, signs of meningeal irritation and conscious disturbance, than the control group.
- We did not limit the number of device-days for LD to 7–14 days as in previous studies. The period of device-days was decided by whether the patient had an adequate intracranial hypertension control and clinical relief.
- Aiming to decrease the rate of cerebrospinal fluid leakage-related infection, we adopted a modified LD.
- For HIV-negative patients with other severe immune-related underlying conditions, shorter drainage time is recommended to avoid further infection.
- Involuntary catheter disconnection is another risk for longer periods of device-days that require frequent monitoring of the connection.
- Our study demonstrated that LD with longer device-days is an effective and safe alternative to control refractory intracranial hypertension in HIV-negative patients with cryptococcal meningitis.

Author contributions

WQ Liao, WW Jiang and WH Pan participated in study design. QL Zhang, H Li and KM Zhang draft the manuscript. WJ Fang, PJ He, WF Kuang, GQ Jiang have helped with data collection and analysis. All the authors contributed to the writing and revising the final manuscript.

Financial & competing interests disclosure

This work was supported by the National Health Department (2018ZX10101003), National Natural Science Foundation of China (31770161, 81471926, 81720108026), Beijing Medical and Health Public Welfare Foundation (B183062), Shanghai sailing Program (19YF1448000), Second Military Medical University (2017JZ47) and Shanghai Science and Technology Committee (17DZ2270900, 2017ZZ01024-001 and 16DZ0500401). The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

Ethical conduct of Research

This study protocol was approved by the ethical committee members of the Institutional Review Board (IRB) of the Jiangxi Chest Hospital (201712045). The informed consent was waived by the IRB due to the nature of retrospective study design.

References

Papers of special note have been highlighted as: • of interest; •• of considerable interest

1. Hagen F, Khayhan K, Theelen B *et al.* Recognition of seven species in the *Cryptococcus gattii*/*Cryptococcus neoformans* species complex. *Fungal Genet. Biol.* 78, 16–48 (2015).

• ***Cryptococcus neoformans* is a complex of important human pathogens.**

2. Park BJ, Wannemuehler KA, Marston BJ, Govender N, Pappas PG, Chiller TM. Estimation of the current global burden of cryptococcal meningitis among persons living with HIV/AIDS. *AIDS* 23(4), 525–530 (2009).

3. Rajasingham R, Smith RM, Park BJ *et al.* Global burden of disease of HIV-associated cryptococcal meningitis: an updated analysis. *Lancet Infect. Dis.* 17(8), 873–881 (2017).

4. Fang W, Chen M, Liu J *et al.* Cryptococcal meningitis in systemic lupus erythematosus patients: pooled analysis and systematic review. *Emerg. Microbes Infect.* 5(9), e95 (2016).

5. Fang W, Hong N, Li Y *et al.* Cryptococcosis in patients with nephrotic syndrome: a pooled analysis of cases. *Mycopathologia* 182(5–6), 517–525 (2017).

6. Fang W, Zhang L, Liu J *et al.* Tuberculosis/cryptococcosis co-infection in China between 1965 and 2016. *Emerg. Microbes Infect.* 6(8), e73 (2017).

7. Hong N, Chen M, Fang W *et al.* Cryptococcosis in HIV-negative patients with renal dialysis: a retrospective analysis of pooled cases. *Mycopathologia* 182(9-10), 887–896 (2017).

8. Li Y, Fang W, Jiang W *et al.* Cryptococcosis in patients with diabetes mellitus II in mainland China: 1993-2015. *Mycoses* 60(11), 706–713 (2017).

9. Yuchong C, Fubin C, Jianghan C *et al.* Cryptococcosis in China (1985-2010): review of cases from Chinese database. *Mycopathologia* 173(5–6), 329–335 (2012).

• **The epidemiology and therapy of cryptococcosis in China.**

10. Barragan NC, Sorvillo F, Kuo T. Cryptococcosis-related deaths and associated medical conditions in the United States, 2000–2010. *Mycoses* 57(12), 741–746 (2014).

11. De Vedia L, Arechavala A, Calderon MI *et al.* Relevance of intracranial hypertension control in the management of *Cryptococcus neoformans* meningitis related to AIDS. *Infection* 41(6), 1073–1077 (2013).

•• **Evaluated the relationship between intracranial hyperpressure and mortality in patients with cryptococcal meningitis related to AIDS.**

12. Bicanic T, Brouwer AE, Meintjes G *et al.* Relationship of cerebrospinal fluid pressure, fungal burden and outcome in patients with cryptococcal meningitis undergoing serial lumbar punctures. *AIDS* 23(6), 701–706 (2009).

13. Graybill JR, Sobel J, Saag M *et al.* Diagnosis and management of increased intracranial pressure in patients with AIDS and cryptococcal meningitis. The NIAID Mycoses study Group and AIDS Cooperative Treatment Groups. *Clin. Infect. Dis.* 30(1), 47–54 (2000).

• **The clinical importance of increased intracranial pressure management.**

14. Perfect JR, Dismukes WE, Dromer F *et al.* Clinical practice guidelines for the management of cryptococcal disease: 2010 update by the infectious diseases society of America. *Clin. Infect. Dis.* 50(3), 291–322 (2010).

15. Fessler RD, Sobel J, Guyot L *et al.* Management of elevated intracranial pressure in patients with cryptococcal meningitis. *J. Acquir. Immune Defic. Syndr. Hum. Retrovirol.* 17(2), 137–142 (1998).

16. Macsween KF, Bicanic T, Brouwer AE, Marsh H, Macallan DC, Harrison TS. Lumbar drainage for control of raised cerebrospinal fluid pressure in cryptococcal meningitis: case report and review. *J. Infect.* 51(4), e221–e224 (2005).

17. Manosuthi W, Sungkanuparph S, Chottanapund S *et al.* Temporary external lumbar drainage for reducing elevated intracranial pressure in HIV-infected patients with cryptococcal meningitis. *Int. J. STD AIDS* 19(4), 268–271 (2008)

•• **Temporary external lumbar drainage for the treatment of refractory intracranial hypertension in HIV-infected patients with cryptococcal meningitis.**

18. Yuchong C, Jianghan C, Hai W, Julin G. Lumbar puncture drainage with intrathecal injection of amphotericin B for control of cryptococcal meningitis. *Mycoses* 54(4), e248–e251 (2011).

•• **The role of the lumbar drainage and lumbar intrathecal injection of amphotericin B in the management of elevated intracranial pressure with non-HIV cryptococcal meningitis.**

19. Manley GT, Dillon W. Acute posterior fossa syndrome following lumbar drainage for treatment of suboccipital pseudomeningocele. Report of three cases. *J. Neurosurg.* 92(3), 469–474 (2000).

20. Denning DW, Armstrong RW, Lewis BH, Stevens DA. Elevated cerebrospinal fluid pressures in patients with cryptococcal meningitis and acquired immunodeficiency syndrome. *Am. J. Med.* 91(3), 267–272 (1991).

21. Malessa R, Krams M, Hengge U *et al.* Elevation of intracranial pressure in acute AIDS-related cryptococcal meningitis. *Clin. Investig.* 72(12), 1020–1026 (1994).

22. Shapiro SA, Scully T. Closed continuous drainage of cerebrospinal fluid via a lumbar subarachnoid catheter for treatment or prevention of cranial/spinal cerebrospinal fluid fistula. *Neurosurgery* 30(2), 241–245 (1992).

- **Possible complications of continuous lumbar drainage and its preventive measures.**

23. Coplin WM, Avellino AM, Kim DK, Winn HR, Grady MS. Bacterial meningitis associated with lumbar drains: a retrospective cohort study. *J. Neurol. Neurosurg. Psychiatry* 67(4), 468–473 (1999).

24. Schade RP, Schinkel J, Visser LG, Van Dijk JM, Voormolen JH, Kuijper EJ. Bacterial meningitis caused by the use of ventricular or lumbar cerebrospinal fluid catheters. *J. Neurosurg.* 102(2), 229–234 (2005).

25. Acikbas SC, Akyuz M, Kazan S, Tuncer R. Complications of closed continuous lumbar drainage of cerebrospinal fluid. *Acta Neurochir.* 144(5), 475–480 (2002).