Special Article

Executive Summary of JSMM Clinical Practice Guidelines for Diagnosis and Treatment of Cryptococcosis 2019

Chairman: Koichi Izumikawa
Vice chairman: Hiroshi Kakeya
Committee members: Fumikazu Sakai, Kazutoshi Shibuya, Takashi Sugita, Takahiro Takazono, Tohru Takata, Masato Tashiro, Katsuji Teruya, Shigeki Nakamura, Hiromitsu Noguchi, Masataro Hiruma, Koichi Makimura, Taiga Miyazaki, Yoshitsugu Miyazaki, Yuka Yamagishi, Koichiro Yoshida, and Akira Watanabe

1 Department of Infectious Diseases, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki
2 Department of Infection Control Science, Osaka City University Graduate School of Medicine, Osaka
3 Department of Diagnostic Radiology, Saitama Medical University International Medical Center, Saitama
4 Department of Pathology, Omori Hospital, Toho University School of Medicine, Tokyo
5 Department of Microbiology, Meiji Pharmaceutical University, Tokyo
6 Department Oncology, Hematology, and Infectious Diseases, Fukuoka University Hospital, Fukuoka
7 AIDS Clinical Center, National Center for Global Health and Medicine, Tokyo
8 Department of Chemotherapy and Mycoses, National Institute of Infectious Diseases, Tokyo
9 Department of Microbiology, Tokyo Medical University, Tokyo
10 Noguchi Dermatology Clinic, Kumamoto
11 Ochanomizu Institute for Medical Mycology and Allergology, Tokyo
12 Medical Mycology, Graduate School of Medicine, Teikyo University, Tokyo
13 Department of Clinical Infectious Diseases, Aichi Medical University Graduate School of Medicine, Aichi
14 Department of Medical Safety Management, Division of Infection Control and Prevention, Kindai University Hospital, Osaka
15 Division of Clinical Research, Medical Mycology Research Center, Chiba University, Chiba

Preface

The Japanese Society for Medical Mycology published “JSMM Clinical Practice Guidelines for Diagnosis and Treatment of Invasive Candidiasis 2013” in 2013 and “JSMM Clinical Practice Guidelines for Diagnosis and Treatment of Aspergillosis 2015” in 2015, and has now published the “JSMM Clinical Practice Guidelines for Diagnosis and Treatment of Cryptococcosis 2019.”

As for infections caused by cryptococcus, an abundance of evidence is available regarding diagnosis and treatment, particularly for human immunodeficiency virus (HIV) -infected patients around the world. On the other hand, evidence from non-HIV-infected patients is limited. In Japan, scant evidence exists since there are fewer HIV-infected patients compared to other countries. Unlike candidiasis and aspergillosis, cryptococcosis is a mycosis that can develop even in healthy people, and this fact further limits the collection of evidence from patients with such a background.

In preparing the current guidelines, we started with close examination of the latest evidence from HIV-infected patients, and then collected evidence from so-called non-HIV-infected patients, including healthy people in and outside Japan to the greatest extent possible. Recommendation and evidence levels regarding diagnosis and treatment have been determined by comparing evidence from non-HIV and HIV-infected patients. If sufficient evidence was unavailable in some fields, the Guideline Preparation Committee repeated discussions and made efforts to reach a consensus.

In preparing the guidelines, the lack of evidence from non-HIV-infected patients was clearly evident not only in Japan.
but also in other countries. Further collection of evidence and updating the guidelines will be required in the future. Presently, however, we consider that we can present practical recommendations and descriptions of standard diagnoses and therapies for cryptococcosis applicable to the current clinical settings in Japan by incorporating currently available data into the guidelines.

We firmly believe the “JSMM Clinical Practice Guidelines for Diagnosis and Treatment of Cryptococcosis 2019” will surely help many medical professionals in clinical settings.

December 2018
Koichi Izumikawa, Chairman,
The Guideline Preparation Committee of the “JSMM Clinical Practice Guidelines for Diagnosis and Treatment of Cryptococcosis 2019”,
The Japanese Society for Medical Mycology

Setting criteria on recommendation levels and evidence levels

| Recommendation level | Evidence level |
|----------------------|----------------|
| A Strongly recommended | I Evidence is available in one or more proper randomized controlled trials. |
| B Generally recommended | II While no randomized controlled trial is conducted, well-designed trials are conducted, and evidence is obtained from cohort analysis studies, case-control analysis studies (preferably at several sites), or multiple-time-series uncontrolled trials showing dramatic results. Proper randomized controlled trials are conducted on patients with different backgrounds. |
| C At the discretion of primary physicians | III Evidence is available from opinions of the authorities, clinical experience, descriptive studies, or reports from expert committees. |

1. Cryptococcosis in HIV-infected patients

A) Cryptococcal meningoencephalitis
I. Characteristics of cryptococcal meningoencephalitis
- The number of HIV-infected patients who develop disseminated cryptococcosis is estimated to be around 10 per year in Japan.
- Since antiretroviral therapy (ART) was introduced, the incidence rate of cryptococcosis has been reduced among HIV-infected patients in advanced nations, and the disease is generally only found in patients who have not been diagnosed with HIV infection and remain untreated, or HIV-infected patients who are placed in a situation where they cannot undergo medical care.
- While the mortality rate was 39.3% (11/28 cases) from 1995 to 1997 before the advent of ART in Japan, the rate has steadily shown improvement in vital prognosis over time, reaching 29.8% (14/47 cases) from 1998 to 2003, 17.6% (12/68 cases) from 2004 to 2009, and 9.1% (7/77 cases) from 2010 to 2016.
- In hyperepidemic areas such as areas south of the Sahara on the African continent, cryptococcal meningoencephalitis is ranked as the fourth cause of opportunistic infections observed among HIV-infected patients. The associated mortality rate (14%) is the second highest behind that of tuberculosis (16%) in the area.
- Cryptococcosis in HIV-infected patients is considered to be transmitted via the airway, but is frequently developed from a disseminated lesion (meningoencephalitis) without forming a clinical pulmonary lesion.
- When ART is introduced during the treatment of cryptococcal meningoencephalitis, the recovered immune system may cause an overreaction, possibly resulting in fatal immune reconstitution inflammatory syndrome (IRIS).

II. Diagnosis of cryptococcal meningoencephalitis
- Due to a weak immune response caused by cell-mediated immune deficiency, typical meningeal irritation symptoms do not appear until the disease progresses to a certain stage.
- In the diagnosis of cryptococcal meningoencephalitis in HIV-infected patients, serum glucuronoxylomannan (GXM) antigen may be detected before the onset of neurologic manifestation, and an extremely high sensitivity and specificity reaching 95% can be attained with serum GXM antigen testing.
- If an HIV patient with a CD4-positive lymphocyte count less than 200/μL shows symptoms such as unexplained headache, fever, or nausea, a serum GXM antigen test is recommended.
- If serum GXM antigen is confirmed positive, cerebrospinal fluid testing is recommended even if no symptoms have been identified.
- Cerebrospinal fluid testing often results in poor findings, and an increase of cerebrospinal fluid pressure (> 15 cm-H2O) is usually the only finding.
- HIV-infected patients show a higher positive rate in cerebrospinal fluid culture than non-HIV-infected patients, with the majority of HIV-infected patients showing positive results.
- HIV-infected patients also show a higher positive rate in blood cultures than non-HIV-infected patients, with approximately half to two-thirds of patients showing positive results.
If cryptococcal meningoencephalitis is suspected, a blood culture test should be conducted.
- Since drug resistance against azole is rare, the drug sensitivity test is not usually conducted.
- In patients with positive blood cultures, β-D-glucan may be positive.
- Regardless of the findings from general cerebrospinal fluid testing, a patient is diagnosed with meningoencephalitis when 1) the presence of fungus in the cerebrospinal fluid is confirmed using the India ink stain method, 2) the cerebrospinal fluid culture shows a positive result, and 3) cerebrospinal fluid GXM antigen shows a positive result.
- A characteristic finding (gelatinous pseudocyst) showing high signal intensity without a mass effect in the basal ganglia of the T2-weighted image in the MRI can be regarded as a rationale for the diagnosis.

III. Treatment of cryptococcal meningoencephalitis

Treatment plan with regard to antifungal medication
- The treatment of cryptococcal meningoencephalitis in HIV-infected patients consists of three major aspects: treatment with antifungals, management of cerebrospinal pressure, and recovery of immune function by ART. The optimum combination of these three aspects is essential for the success of the treatment and a reduction in the mortality rate.
- Treatment using antifungals should be conducted in three steps: Induction therapy, consolidation therapy, and maintenance therapy.
- Drug interaction between ART medicines and azole should be taken into consideration.
- When the clinical condition improves during induction therapy for two weeks or more and the cerebrospinal fluid culture is confirmed negative, the induction therapy can be terminated and consolidation therapy should be commenced.
- Intrathecal or intraventricular administration of amphotericin B (AMPH-B) is not recommended.
- Consolidation therapy should be conducted for at least 8 weeks, followed by the commencement of maintenance therapy.

- When all termination criteria as listed below are satisfied, maintenance therapy may be discontinued.
  □ One year or more of maintenance therapy has been completed.
  □ Symptoms are resolving and are maintaining a stable state.
  □ HIV-RNA level is suppressed by ART, and a CD4-positive lymphocyte count of 100/μL or more continues for at least 3 months.
- If the CD4-positive lymphocyte count becomes 100/μL or less after discontinuation of maintenance therapy, the therapy should be resumed.

Management other than antifungal medication such as management of cerebrospinal fluid pressure
- With cryptococcal meningoencephalitis, cerebrospinal fluid pressure increases with the quantity of fungi present in cerebrospinal fluid.
- If the initial cerebrospinal fluid pressure is extremely high (25 cmH2O or more), cerebrospinal fluid should be drained (for 20 to 30 mL) until the pressure lowers to 20 cmH2O or below or to approximately half of the initial pressure.
- Lumbar puncture should be conducted every day until the cerebrospinal fluid pressure stabilizes and the symptoms continue to resolve for two consecutive days.
- Administration of a steroids or mannitol to control cerebrospinal fluid pressure is not recommended.
- Administration of acetazolamide to control cerebrospinal fluid pressure should be avoided.
- Alternative options to control cerebrospinal fluid pressure other than therapeutic lumbar puncture include insertion of an intrathecal drain, ventriculostomy, and V-P shunt.
- In severe cases that require repeated lumbar punctures for an extended period of time, percutaneous drainage or ventricular fenestration should be considered as a treatment option.
- If high cerebrospinal fluid pressure persists even with treatment using proper antifungal medication and the above-mentioned cerebrospinal fluid drainage, a V-P shunt should be considered as a treatment option.

Antifungal medication regimen for cryptococcal meningoencephalitis
1) Induction therapy (For two weeks or more and until a negative cerebrospinal fluid culture is confirmed)

| Regimen                  | Antifungals | Dose     | Number of doses per day | Administration route |
|--------------------------|-------------|----------|-------------------------|----------------------|
| Drug of first choice     |             |          |                         |                      |
| Combination of L-AMB + 5-FC (A-I) | L-AMB      | 3 to 4 mg/kg | 1                       | Drip infusion        |
|                          | 5-FC        | 25 mg/kg | 4                       | Oral                 |
In the case where L-AMB cannot be used

| Combination of (F-)FLCZ + 5-FC (B-I) | Use one of the FLCZs listed below. |
|-------------------------------------|----------------------------------|
| FLCZ 800 to 1,200 mg* 1 Oral        |                                  |
| FLCZ 800 mg 1 Drip infusion         |                                  |
| F-FLCZ 800 mg 1 IV                  |                                  |
| 5-FC 25 mg/kg 4 Oral                |                                  |

In the case where 5-FC cannot be used.

| Combination of L-AMB + (F-)FLCZ (B-I) | Use one of the FLCZs listed below. |
|--------------------------------------|----------------------------------|
| L-AMB 3 to 4 mg/kg 1 Drip infusion   |                                  |
| FLCZ 800 to 1,200 mg* 1 Oral         |                                  |
| FLCZ 800 mg 1 Drip infusion          |                                  |
| F-FLCZ 800 mg 1 IV                   |                                  |

L-AMB (B-I) monotherapy

| L-AMB 3 to 4 mg/kg 1 Drip infusion   |                                  |

In the case where either 5-FC or L-AMB cannot be used

| (F-)FLCZ (C-I) monotherapy | Use one of the FLCZs listed below. Continue at least 10 to 12 weeks. |
|---------------------------|---------------------------------------------------------------------|
| FLCZ 1,200 mg* 1 Oral     |                                                                      |
| FLCZ 1,200 mg 1 Drip infusion |                                                      |
| F-FLCZ 1,200 mg* 1 IV     |                                                                      |

VRCZ (C-III) monotherapy

| VRCZ 6 mg/kg on the 1st day 2 Drip infusion | FLCZ 3 to 4 mg/kg from the 2nd day onward 2 Drip infusion |
|--------------------------------------------|----------------------------------------------------------|

Note: Limited evidence of the efficacy of VRCZ is available. As with FLCZ, continue administration for at least 10 to 12 weeks. Adjust dosage by therapeutic drug monitoring (TDM).

* As for once-daily dosing of 1,200 mg of FLCZ, only limited evidence is available for long-term usage in Japanese patients, and safety has not been established.

2) Consolidation therapy (8 weeks or more)

| Regimen | Antifungals | Dose | Number of doses per day | Administration route |
|---------|-------------|------|-------------------------|----------------------|
| Drug of first choice |

| (F-)FLCZ (A-I) monotherapy | Use one of the FLCZs listed below. |
|-----------------------------|----------------------------------|
| FLCZ 400 mg 1 Oral          |                                  |
| FLCZ 400 mg 1 Drip infusion |                                  |
| F-FLCZ 400 mg 1 IV          |                                  |

In the case where (F-)FLCZ cannot be used

| ITCZ oral solution (B-I) monotherapy | ITCZ oral solution 200 mg (20 mL) 2 Oral (Taken between meals) |
|--------------------------------------|----------------------------------------------------------------|
| ITCZ capsule (C-I) monotherapy      | ITCZ capsule 200 mg 2 Oral (Taken immediately after meals)      |
| VRCZ (B-III) monotherapy            | VRCZ 300 mg on the 1st day 150 mg for those under 40 kg 2 Oral (Taken between meals) |

150 to 200 mg from the 2nd day onward 100 mg for those under 40 kg 2 Oral (Taken between meals)

Note: Limited evidence of the efficacy of VRCZ is available. Adjust dosage by TDM.
3) Maintenance therapy (until the discontinuation criteria for the maintenance therapy specified in the executive summary are satisfied)

| Regimen Antifungals | Dose | Number of doses per day | Administration route |
|---------------------|------|-------------------------|----------------------|
| Drug of first choice |      |                         |                      |
| FLCZ (A-I) monotherapy | FLCZ | 200 mg | 1 | Oral |
| In the case where FLCZ cannot be used | VRCZ | 300 mg on the 1st day 150 mg for those under 40 kg | 2 | Oral (Taken between meals) |
| VRCZ (B-III) monotherapy | VRCZ | 150 to 200 mg from the 2nd day onward 100 mg for those under 40 kg | 2 | Oral (Taken between meals) |

Note: Limited evidence of the efficacy of VRCZ is available. Adjust dosage by TDM.

IV. Management of persistent (refractory) cryptococcal meningoencephalitis
- While the definition of persistent infection has not been established, it generally refers to a state in which clinical symptoms have not improved and a positive cerebrospinal fluid culture persists even after the 4th week of treatment with the proper induction therapy and cerebrospinal fluid pressure under control (Fig. 1).
- The treatment rarely fails due to drug resistance. The factors as described below should be confirmed: Improper initial treatment (in terms of dose or administration duration), interaction between medicines used for treating this disease and other medicines, and evaluation of medication adherence (oral medicines in consolidation or maintenance therapy, or ART medicines in patients who are undergoing ART).
- Drug susceptibility testing should be conducted on a cerebrospinal fluid isolate.
- The dose of L-AMB should be increased (5 to 6 mg/kg/day), and the induction therapy should be continued until the cerebrospinal fluid culture turns negative (A-II).
- In principle, concomitant therapy with 5-FC or FLCZ should be conducted (B-III).
- Even after the cerebrospinal fluid culture turns negative, the induction therapy should be extended to approximately the 10th week from the start of treatment in total.
- For patients with persistent infection who started induction therapy with azole, the effect of increased dose using the same azole is not recommended.
- Even in the case of persistent infection, intrathecal or intraventricular administration of AMPH-B is not recommended.
- For consolidation therapy, the dose of (F-)FLCZ should be...
increased to 800 to 1,200 mg/day (A-III), and the treatment duration should also be extended to 10 to 12 weeks (B-III).
- For maintenance therapy, the dose of FLCZ should be increased up to 400 mg/day (A-III).

- If FLCZ resistance is suspected from the sensitivity test result, treatment with VRCZ should be taken into consideration as a treatment option (A-III).

Antifungal medication regimen in the case of persistent infection of cryptococcal meningoencephalitis

1) Induction therapy (extended until a negative cerebrospinal fluid culture is confirmed, and for approximately 10 weeks)

| Regimen | Drug of first choice | Antifungals | Dose | Number of doses per day | Administration route |
|---------|----------------------|-------------|------|------------------------|---------------------|
| Drug of first choice | Combination of L-AMB + 5-FC (A-II) | L-AMB | 5 to 6 mg/kg (increased) | 1 | Drip infusion |
| | | 5-FC | 25 mg/kg | 4 | Oral |
| In the case where 5-FC cannot be used | Combination of L-AMB + (F-)FLCZ (B-III) | L-AMB | 5 to 6 mg/kg (increased) | 1 | Drip infusion |
| | | Use one of the FLCZs listed below. | FLCZ | 800 to 1,200 mg* | 1 | Oral |
| | | | FLCZ | 800 mg | 1 | Drip infusion |
| | | | F-FLCZ | 800 mg | 1 | IV |
| In the case where L-AMB cannot be used | Combination of (F-)FLCZ + 5-FC (C-III) | Use one of the FLCZs listed below. | FLCZ | 800 to 1,200 mg* | 1 | Oral |
| | | | FLCZ | 800 mg | 1 | Drip infusion |
| | | | F-FLCZ | 800 mg | 1 | IV |
| | | | 5-FC | 25 mg/kg | 4 | Oral |

* As for once-daily dosing of 1,200 mg of FLCZ, only limited evidence is available for long-term usage in Japanese patients, and safety has not been established.

2) Consolidation therapy (extended to 10 to 12 weeks)

| Regimen | Drug of first choice | Antifungals | Dose | Number of doses per day | Administration route |
|---------|----------------------|-------------|------|------------------------|---------------------|
| Drug of first choice | (F-)FLCZ (A-III) monotherapy | Use one of the FLCZs listed below. | FLCZ | 800 to 1,200 mg* (increased) | 1 | Oral |
| | | | FLCZ | 800 mg (increased) | 1 | Drip infusion |
| | | | F-FLCZ | 800 mg (increased) | 1 | IV |
| In the case where (F-)FLCZ cannot be used | VRCZ (B-III) monotherapy | VRCZ | 300 mg on the 1st day | 2 | Oral (Taken between meals) |
| | | | 150 mg for those under 40 kg | | |
| | | | 150 to 200 mg from the 2nd day onward | 2 | Oral (Taken between meals) |
| | | | 100 mg for those under 40 kg | | |

Note: Little evidence of the efficacy of VRCZ is available. Adjust dosage by TDM.

* As for once-daily dosing of 1,200 mg of FLCZ, only limited evidence is available for long-term usage in Japanese patients, and safety has not been established.
3) Maintenance therapy (until the discontinuation criteria for the maintenance therapy specified in ordinary treatment are satisfied)

| Regimen                        | Antifungals | Dose               | Number of doses per day | Administration route |
|--------------------------------|-------------|--------------------|-------------------------|----------------------|
| Drug of first choice           |             |                    |                         |                      |
| FLCZ (A-III) monotherapy       | FLCZ        | 400 mg (increased) | 1                       | Oral                 |
| In the case where FLCZ cannot be used |             |                    |                         |                      |
| VRCZ (B-III) monotherapy       | VRCZ        | 300 mg on the 1st day |
|                                |             | 150 mg for those under 40 kg |
|                                |             | 150 to 200 mg from the 2nd day onward |
|                                |             | 100 mg for those under 40 kg |
|                                |             | 2                   | Oral (Taken between meals) |

Note: Little evidence of the efficacy of VRCZ is available. Adjust dosage by TDM.

V. Management of recurrence (exacerbation or reinfection) of cryptococcal meningoencephalitis

- If an associated symptom or sign such as headache develops again after the cerebrospinal fluid culture turns negative from the induction or consolidation/maintenance therapy, and cerebrospinal meningitis symptoms resolve, the possibility of recurrence should be considered and a cerebrospinal fluid culture test should be conducted. Once the cerebrospinal fluid culture is confirmed positive, it is judged as a recurrence.
- Since exacerbation due to failure of the consolidation/maintenance therapy cannot be precisely distinguished from a new re-infection during treatment, the guidelines collectively define them as a recurrence.
- When the cerebrospinal fluid culture is confirmed negative, IRIS, rather than a recurrence, should be suspected.
- Recurrence due to drug resistance is rare. The factors as described below should first be confirmed: Insufficient induction therapy, interaction between medicines used for treating this disease and other medicines, and evaluation of medication adherence.

- During a recurrence, drug susceptibility testing should be conducted on an isolate from the extracted cerebrospinal fluid.
- The induction therapy should be resumed. Increasing the dose or extending the treatment duration is not necessary.
- Medicines to be selected, doses, and treatment duration for consolidation or maintenance therapy after induction therapy should be determined for each case by taking the results of drug susceptibility testing during a recurrence into consideration.
- In consolidation therapy, the dose of FLCZ should be increased to 800 to 1,200 mg/day, and the duration should be extended to 10 to 12 weeks (B-III).
- The dose of FLCZ should be increased to 400 mg/day in maintenance therapy (A-III).
- If a recurrence is attributable to poor medication adherence and the isolate at the time of the recurrence demonstrates FLCZ sensitivity, FLCZ in the standard quantity for consolidation or maintenance therapy should be used for treatment as in the case of the initial treatment (B-III).

**Antifungal medication regimen in the case of recurrence (exacerbation or reinfection) of cryptococcal meningoencephalitis**

1) Induction therapy (For two weeks or more and until a negative cerebrospinal fluid culture is confirmed. Dose increase or extension of treatment duration is not necessary.)

| Regimen                        | Antifungals | Dose               | Number of doses per day | Administration route |
|--------------------------------|-------------|--------------------|-------------------------|----------------------|
| Drug of first choice           |             |                    |                         |                      |
| Combination of L-AMB + 5-FC (A-I) | L-AMB       | 3 to 4 mg/kg        | 1                       | Drip infusion        |
|                                | 5-FC        | 25 mg/kg            | 4                       | Oral                 |
| In the case where L-AMB cannot be used |             |                    |                         |                      |
| Combination of (F-)FLCZ + 5-FC (B-I) | Use one of the FLCZs listed below. | |                       |                      |
|                                | FLCZ        | 800 to 1,200 mg*    | 1                       | Oral                 |
|                                | FLCZ        | 800 mg              | 1                       | Drip infusion        |
|                                | F-FLCZ      | 800 mg              | 1                       | IV                   |
|                                | 5-FC        | 25 mg/kg            | 4                       | Oral                 |
In the case where 5-FC cannot be used

| Combination of L-AMB + (F-)FLCZ (B-I) | L-AMB 3 to 4 mg/kg | 1 | Drip infusion |
|---------------------------------------|--------------------|---|---------------|
| Use one of the FLCZs listed below. |
| FLCZ 800 to 1,200 mg* | 1 | Oral |
| FLCZ 800 mg | 1 | Drip infusion |
| F-FLCZ 800 mg | 1 | IV |

L-AMB (B-I) monotherapy

| L-AMB 3 to 4 mg/kg | 1 | Drip infusion |
|--------------------|---|---------------|

In the case where either 5-FC or L-AMB cannot be used

| (F-)FLCZ (C-I) monotherapy | Use one of the FLCZs listed below. Continue administration for at least 10 to 12 weeks. |
|-----------------------------|--------------------------------------------------------------------------------|
| FLCZ 1,200 mg* | 1 | Oral |
| FLCZ 1,200 mg* | 1 | Drip infusion |
| F-FLCZ 1,200 mg* | 1 | IV |

VRCZ (C-III) monotherapy

| VRCZ 6 mg/kg on the 1st day | 2 | Drip infusion |
|-------------------------------|---|---------------|
| 3 to 4 mg/kg from the 2nd day onward | 2 | Drip infusion |

Note: Little evidence of the efficacy of VRCZ is available. As with FLCZ, continue administration for at least 10 to 12 weeks. Adjust dosage by TDM.

* As for once-daily dosing of 1,200 mg of FLCZ, only limited evidence is available for long-term usage in Japanese patients, and safety has not been established.

2) Consolidation therapy (extended to 10 to 12 weeks)

| Regimen | Antifungals | Dose | Number of doses per day | Administration route |
|---------|-------------|------|-------------------------|---------------------|
| Drug of first choice |
| (F-)FLCZ (A-III) monotherapy | Use one of the FLCZs listed below. |
| FLCZ 800 to 1,200 mg* (increased) | 1 | Oral |
| FLCZ 800 mg (increased) | 1 | Drip infusion |
| F-FLCZ 800 mg (increased) | 1 | IV |

In the case where (F-)FLCZ cannot be used

| VRCZ (B-III) monotherapy | VRCZ 300 mg on the 1st day |
|--------------------------|---------------------------|
| 150 mg for those under 40 kg | 2 | Oral |
| 150 to 200 mg from the 2nd day onward |
| 100 mg for those under 40 kg | 2 | Oral |

Note: Little evidence of the efficacy of VRCZ is available. Adjust dosage by TDM.

3) Maintenance therapy (until the discontinuation criteria for the maintenance therapy specified in ordinary treatment are satisfied)

| Regimen | Antifungals | Dose | Number of doses per day | Administration route |
|---------|-------------|------|-------------------------|---------------------|
| Drug of first choice |
| FLCZ (A-III) monotherapy | FLCZ 400 mg (increased) | 1 | Oral |
B) Disseminated cryptococcosis (not associated with meningoencephalitis)

I. Characteristics of disseminated cryptococcosis (not associated with meningoencephalitis)
- Disseminated cryptococcosis, once developing local infection of the lung or skin, disseminates throughout the entire body as a blood stream infection and may form lesions in different organs possibly without meningoencephalitis.
- Skin lesions are developed most frequently, and dissemination has also been reported in other organs such as lymph nodes, digestive tract, eye, heart, urogenital organs, bone marrow, liver, mediastina, and vagina.
- Skin cryptococcosis can be divided to localized cutaneous cryptococcosis that develop due to Cryptococcus neoformans directly affecting the skin, and secondary cryptococcosis as a complication of disseminated cryptococcosis. If the latter is suspected, sufficient examinations should be conducted to determine the presence of skin lesions, which manifest in diversified disease types. Reports on skin lesions include papula, tumor mass, water blister, abscess, cellulitis, purpura, ulcer, and subcutaneous swelling (refer to Chapter 7 of “Particular Theories”).

II. Diagnosis of disseminated cryptococcosis (not associated with meningoencephalitis)
- If an HIV-infected patient develops an unexplained skin lesion, disseminated cryptococcosis should be proactively suspected, and blood culture, measurement of serum GXM antigen, skin biopsy and culture testing should be considered.
- Skin cryptococcosis demonstrates the typical finding of papula with umbilication at the center, and is similar to molluscum contagiosum in terms of form (refer to Chapter 7 “Skin cryptococcosis”).
- Since skin cryptococcosis may take on various forms, differential diagnoses may be necessary to distinguish it from Kaposi’s sarcoma or malignant lymphoma.
- If the blood culture alone shows a positive result and no other infected lesions, including meningoencephalitis, are observed, the patient should be treated as having disseminated cryptococcosis.
- If serum GXM antigen alone shows a positive result with no other infected lesions and the antigen dilution titer is high (512 times or higher), the patient should be treated as having disseminated cryptococcosis. If the antigen dilution titer is less than 512 times, management as with pulmonary cryptococcosis should be considered as a treatment option.

III. Treatment of disseminated cryptococcosis (not associated with meningoencephalitis)
- As for disseminated cryptococcosis with lesions other than meningoencephalitis, the same therapeutic medicines with the same treatment duration as cryptococcal meningoencephalitis should be applied.
- Even for patients without meningoencephalitis, it may be developed as a disseminated lesion in the clinical course after the start of treatment. Therefore, patients should be closely monitored for such a risk.
- Such patients require additional monitoring because they have a risk to develop meningoencephalitis as an IRIS after the commencement of ART.
- Assume that a disseminated lesion cannot be identified with the serum GXM antigen positive and the cerebrospinal fluid GXM antigen negative and the antigen dilution titer is high (512 times or higher). In such a case, we recommend treatment similar to that for disseminated cryptococcosis since another latent disseminated lesion is suspected.

Antifungal medication regimen
Treatment as with meningoencephalitis should be provided (B-III) (refer to the section describing treatment for cryptococcal meningoencephalitis).

C) Pulmonary cryptococcosis

I. Characteristics of pulmonary cryptococcosis
- Pulmonary cryptococcosis is frequently identified as pulmonary opacity with no symptoms during a health checkup or follow-up of another pulmonary disease.
- HIV-infected patients have a tendency to show higher severity and faster progression compared to non-HIV-infected patients.
- Pulmonary cryptococcosis showing specific symptoms and signs develops at a CD-4 positive lymphocyte count exceeding 100/µL. The severity of a lesion is inversely correlated with the CD4-positive lymphocyte count.
II. Diagnosis of pulmonary cryptococcosis
- Clinical symptoms are diversified, ranging from no symptoms to fever, coughing, dyspnea, or headache.
- As in non-HIV-infected patients, solitary or multiple nodular shadows can be observed as a finding from chest X-ray imaging. In the chest CT scan, nodular shadows are also observed at the pulmonary periphery several millimeters away from the pleura.
- HIV-infected patients with severe immunodeficiency typically present with ground glass opacity similar to pneumocystis pneumonia. They also develop symptoms such as consolidation, lobar opacity, mediastinal mass, pleural effusion, and cavitiation.
- A definite diagnosis is made by proving the existence of cryptococcus in specimens acquired from the airway (such as sputum, endotracheal sputum, bronchoalveolar lavage fluid, transbronchial lung biopsy, and percutaneous pulmonary aspirate) with direct microscopy or a culture test.
- If serum GXM antigen is confirmed positive, a blood culture should immediately be conducted to locate a disseminated lesion.
- When pulmonary cryptococcosis is diagnosed, the possibility of concomitant meningoencephalitis should be excluded. Examination of cerebrospinal fluid is recommended for all patients diagnosed as having pulmonary cryptococcosis regardless of the presence of neurologic symptoms or signs.

III. Treatment of pulmonary cryptococcosis
- FLCZ should be recommended (A-III).
- If FLCZ is not available, ITCZ or VRCZ should be used as an alternative medicine (B-III).
- Antifungals similar to those for cryptococcal meningoencephalitis should be used for severe cases with respiratory failure.
- If lung abnormalities are found in chest imaging and symptoms persist in spite of antifungals, surgical resection should be considered as a treatment option.
- Treatment may be discontinued if all completion criteria are satisfied:
  - Treatment with FLCZ is provided for 12 months or more.
  - Serum GXM antigen is 512 times or lower or shows no rising tendency.
  - HIV-RNA level is suppressed by ART, and the CD4-positive lymphocyte count is 100/μL or more.

### Antifungal medication regimen

| Regimen | Antifungals | Dose | Number of doses per day | Administration route |
|---------|-------------|------|-------------------------|----------------------|
| Severe cases with respiratory failure | | | | |
| Antifungals similar to those used for cryptococcal meningoencephalitis should be administered (B-III). (Refer to the section describing treatment for cryptococcal meningoencephalitis.) | | | | |
| Other than above | | | | |
| Drug of first choice | | | | |
| (F-)FLCZ (A-III) monotherapy | Use one of the FLCZs listed below. | | | |
| FLCZ | 400 mg | 1 | Oral |
| FLCZ | 400 mg | 1 | Drip infusion |
| F-FLCZ | 800 mg on the 1st and 2nd days 400 mg from the 3rd day onward | 1 | IV |
| In the case where (F-)FLCZ cannot be used | | | | |
| VRCZ (B-III) monotherapy | VRCZ | 300 mg on the 1st day 150 mg for those under 40 kg | 2 | Oral (Taken between meals) |
| | | 150 to 200 mg from the 2nd day onward 100 mg for those under 40 kg | 2 | Oral (Taken between meals) |
| Note: Adjust dosage of VRCZ by TDM. | | | | |
| ITCZ oral solution (B-III) monotherapy | ITCZ oral solution | 200 mg (20 mL) | 2 | Oral (Taken between meals) |
| ITCZ capsule (C-III) monotherapy | ITCZ capsule | 200 mg | 2 | Oral (Taken immediately after meals) |
D) Immune reconstitution inflammatory syndrome (IRIS)

I. Characteristic of IRIS
- There are two types of IRIS in HIV-infected patients with concomitant cryptococcosis. One is unmasking IRIS developed after commencement of ART for asymptomatic patients, and the other is paradoxical IRIS in which symptoms of cryptococcosis worsen by introducing ART during primary treatment.
- Meningoencephalitis caused by unmasking IRIS badly affects survival prognosis in hyperepidemic areas such as Africa.
- Measurement of serum GXM antigen should be considered for patients who have lived in hyperepidemic areas such as Africa prior to administration of ART.
- The incidence rate of paradoxical IRIS is high among HIV-infected patients with concomitant cryptococcal meningoencephalitis, and paradoxical IRIS is identified in approximately 30 to 40% of patients receiving ART.
- Since unmasking IRIS and paradoxical IRIS are both caused by excessive immune reaction (pathologically defined as nonsuppurative inflammation), adequate immunosuppression with steroids may theoretically improve prognosis.

II. Diagnosis of IRIS

[Unmasking IRIS]
- If a patient shows symptoms such as unexplained fever, headache or disturbance of consciousness after the commencement of ART (within 4 weeks after commencement in particular), cryptococcal meningoencephalitis should be considered, and a serum GXM antigen test and cerebrospinal fluid testing should be conducted.
- If a patient develops a new skin lesion or pulmonary lesion after the commencement of ART (within 4 weeks after commencement in particular), the lesion should be suspected as being a symptom of cryptococcosis, and serum GXM antigen measurement and collection of clinical specimens will be required.

[Paradoxical IRIS]
- Paradoxical IRIS should be suspected when patients with meningoencephalitis experience worsened clinical symptoms such as headache after the commencement of ART (within 4 weeks after commencement in particular).
- Cerebrospinal fluid pressure remarkably increases in meningoencephalitis-associated IRIS. In such a case, the cerebrospinal fluid culture remains negative. If the cerebrospinal fluid culture is confirmed positive, it should be diagnosed as a persistent infection or a recurrence.
- In cases other than meningoencephalitis, paradoxical IRIS should be suspected if an existing lesion worsens after the commencement of ART (within 4 weeks after commencement in particular). In such a case, it should be noted that meningoencephalitis not identified before the commencement of ART may become evident.

III. Treatment of IRIS

[Unmasking IRIS]
- If a patient develops cryptococcal meningoencephalitis, ART should immediately be discontinued.
- If a patient develops a disease other than meningoencephalitis, ART may be continued in principle.
- The standard therapy for cryptococcosis should be provided.

[Paradoxical IRIS]
- Since paradoxical IRIS may spontaneously resolve within several days to several weeks regardless of disease type, mild paradoxical IRIS should simply be followed up (B-III).
- In the case of cryptococcal meningoencephalitis, proper induction as well as consolidation therapy should be conducted for at least two weeks. If ART is started after the cerebrospinal fluid culture is confirmed negative, ART should be continued in principle.
- For cases that do not satisfy the above criteria, discontinuation of ART should be considered.
- If significant worsening of symptoms due to IRIS is observed regardless of disease type, administration of a steroid (0.5 to 1.0 mg/kg/day as the converted dose of Prednisolone equivalence) should be considered as a treatment option while continuing ART.
- If the possibility of exacerbation due to poor medication adherence cannot be excluded, resumption of induction therapy for cryptococcal meningoencephalitis should be considered in addition to the steroid.
- If severe symptoms persist with a steroid at the initial dose, the possibility of interrupting ART (A-III) and increasing the dose of the steroid should be considered as a treatment option.
- Once symptoms can be suppressed, the steroid administered each week should be gradually decreased to approximately 15 to 20 mg/day (as the converted dose of Prednisolone equivalence). It should then be further gradually decreased for about 2 to 4 weeks while the symptoms are carefully observed, and the minimum dose at which the symptoms can be controlled should be carefully determined.
- In the case of IRIS from meningoencephalitis, normalized cerebrospinal fluid pressure may serve as an index to determine a decrease in the steroid.
- Exacerbation of symptoms associated with a decrease in the steroid occur with high frequency. When symptoms show no signs of resolution during observation for several days, increasing the steroid should be considered.

E) Timing to introduce antiretroviral therapy (ART)
- Appropriate timing of introduction of ART medicine has not been established with sufficient evidence and no consensus
has been achieved, either.
- Paradoxical IRIS after the introduction of ART is highly likely to relate to cryptococcal fungus bodies remaining at the beginning of ART and low immune function of the host.
- The serum GXM antigen dilution titer at the time of onset of cryptococcal meningoencephalitis and positive cerebrospinal fluid culture upon the introduction of ART are related to the risk of onset of paradoxical IRIS.
- Early introduction of ART should be avoided since it poses a high risk of paradoxical IRIS onset among meningoencephalitis patients with a low cell population in cerebrospinal fluid and a poor immune response, and may worsen survival prognosis.
- Introduction of ART should be withheld until treatment of cryptococcal meningoencephalitis shows a favorable response and clinical symptoms start to resolve.
- Once the cerebrospinal fluid pressure returns to the normal level and the cerebrospinal fluid culture is confirmed negative, the timing to introduce ART should be determined.
- The timing to commence ART administration should be carefully determined for each case by taking into consideration not only the risk of IRIS onset but also the degree of immune deficiency of the host and other complications.
- For patients with disseminated cryptococcosis but without meningoencephalitis, ART administration should commence after induction therapy is completed (after the second week or later).
- When patients with pulmonary cryptococcosis show no or mild symptoms, ART may be started immediately.
- If patients with pulmonary cryptococcosis show some symptoms, ART administration should commence after resolution of the symptoms via the initial treatment has been confirmed.

F) Prophylaxis
- If ART administration can commence, preventive therapy using antifungals as a primary prevention measure for cryptococcosis will not improve the overall survival rate and the therapy is not recommended in terms of drug interactions, side reactions, potential induction of antimicrobial resistance, and cost (A-II).

2. Characteristics of cryptococcosis in patients who underwent solid organ transplant

I. Characteristics of cryptococcosis in patients who underwent solid organ transplant
- Cryptococcosis accounts for 7 to 8% of deep-seated mycoses developed in patients who underwent solid organ transplant.
- The incidence rate of cryptococcosis after transplant is 0.2 to 5%.
- It often develops in the later period of the transplantation, or around 20 months after the transplantation.

- As for the disease types with regard to cryptococcosis following solid organ transplantation, 14 to 39% of patients present with only pulmonary cryptococcosis, while 45 to 68% present with cryptococcal meningoencephalitis, and 56 to 77% are reported to develop disseminated cryptococcosis.
- The mortality rate is reported as approximately 30% when disseminated lesions including meningoencephalitis are presented, and the mortality of pulmonary cryptococcosis is reported as 2.8 to 7%.
- Cryptococcosis cases attributable to donors’ organs have also been reported.

II. Diagnosis of cryptococcosis in patients who underwent solid organ transplant
- While symptoms include headache, disturbance of consciousness, vomiting, coughing, and fever, some patients present with no symptoms.
- Among pulmonary cryptococcosis patients, 38% are asymptomatic.
- If a cryptococcosis infection focus is identified in organs other than the central nervous system, presence or absence of meningoencephalitis should be confirmed by proactive cerebrospinal fluid testing.
- If a patient presents with meningoencephalitis, blood culture and urine culture should be proactively conducted in addition to serum and cerebrospinal fluid antigen tests.
- Findings from pulmonary cryptococcosis imaging vary, including multiple nodular shadows and infiltrative shadows (21% of patients), isolated nodular shadows, mass shadows, cavitary lesions and pleural effusion.
- Serum GXM antigen is positive in 83% of pulmonary cryptococcosis and 98% of cryptococcal meningoencephalitis and disseminated cryptococcosis, and thus is useful for diagnosis.
- No specific findings have been reported from cerebrospinal fluid testing of patients who underwent solid organ transplantation.
- If meningoencephalitis cannot be excluded in donors, cryptococcosis screening should be conducted from serum or cerebrospinal fluid GXM testing before transplantation.

III. Treatment of cryptococcosis in patients who underwent solid organ transplant
[Cryptococcal meningoencephalitis and disseminated cryptococcosis]
- Treatment should be provided in three steps: Induction, consolidation, and maintenance therapy.
- Combination of L-AMB and 5-FC should be provided in induction therapy (A-II).
- FLCZ should be administered for 8 weeks in consolidation therapy (A-II).
- FLCZ should be administered for 6 to 12 months in
maintenance therapy (A-II).
- L-AMB should be recommended instead of AMPH-B (A-II).
- Unless maintenance therapy is provided for a sufficient period, the exacerbation rate will be increased. Therefore, the maintenance therapy period should be extended depending on improvement of the clinical condition and the degree of immunosuppression.
- Exacerbation is frequently observed 3.5 months after the completion of treatment, and mostly within a year.
- The serum GXM antigen dilution titer should not be used as an index to determine the treatment discontinuation.
- The antifungals should be administered for at least 2 weeks, and until blood and cerebrospinal fluid cultures are confirmed negative.
- No evidence that decreased doses of immunosuppressant improve prognosis is available.
- IRIS is observed at an incidence of 14% around 1 to 2 months after the start of treatment.
- The existence of meningoencephalitis or discontinuation of calcineurin inhibitors is regarded as a risk factor for the onset of IRIS.

**[Pulmonary cryptococcosis]**
- FLCZ should be provided for 6 to 12 months (B-III).
- In severe cases with respiratory failure, use antifungals similar to those for cryptococcal meningoencephalitis.

**[Common subjects]**
- The dose of the calcineurin inhibitor should be decreased to commence administration of an azole. Therefore, the dose should be adjusted while monitoring the trough for the calcineurin inhibitor.
- No data for recommending prophylaxis is available.

### Antifungal medication regimen for cryptococcal meningoencephalitis in the case of solid organ transplant

**[Cryptococcal meningoencephalitis and disseminated cryptococcosis]**

1) Induction therapy (for at least 2 weeks and until the cerebrospinal fluid culture is confirmed negative)

| Regimen | Antifungals | Dose | Number of doses per day | Administration route |
|---------|-------------|------|-------------------------|----------------------|
| Drug of first choice | | | | |
| Combination of L-AMB + 5-FC (A-II) | L-AMB | 3 to 4 mg/kg | 1 | Drip infusion |
| | 5-FC | 25 mg/kg | 4 | Oral |
| In the case where L-AMB cannot be used | | | | |
| Combination of (F-)FLCZ + 5-FC (B-III) | FLCZ | 800 mg | 1 | Drip infusion |
| | F-FLCZ | 800 mg | 1 | IV |
| | 5-FC | 25 mg/kg | 4 | Oral |
| In the case where 5-FC cannot be used | | | | |
| L-AMB (B-III) monotherapy | L-AMB | 3 to 4 mg/kg | 1 | Drip infusion |
| In the case where either 5-FC or L-AMB cannot be used | | | | |
| VRCZ (C-III) monotherapy | VRCZ | 6 mg/kg on the 1st day | 2 | Drip infusion |
| | | 3 to 4 mg/kg from the 2nd day onward | 2 | Drip infusion |
| | | | | |
| | Note: Adjust dosage by TDM. |

2) Consolidation therapy (for 8 weeks)

| Regimen | Antifungals | Dose | Number of doses per day | Administration route |
|---------|-------------|------|-------------------------|----------------------|
| Drug of first choice | | | | |
| (F-)FLCZ (A-II) monotherapy | Use one of the FLCZs listed below. | | | |
| | FLCZ | 400 mg | 1 | Oral |
| | FLCZ | 400 mg | 1 | Drip infusion |
| | F-FLCZ | 400 mg | 1 | IV |
In the case where (F-)FLCZ cannot be used

| Antifungals | Dose | Number of doses per day | Administration route |
|-------------|------|-------------------------|----------------------|
| Itraconazole (ITCZ) oral solution (B-III) monotherapy | ITCZ oral solution 200 mg (20 mL) | 2 | Oral (Taken between meals) |
| ITCZ capsule (C-III) monotherapy | ITCZ capsule 200 mg | 2 | Oral (Taken immediately after meals) |
| VRCZ (B-III) monotherapy | VRCZ | 2 | Oral (Taken between meals) |

Note: Adjust dosage by TDM.

3) Maintenance therapy (for 6 to 12 months)

| Regimen | Antifungals | Dose | Number of doses per day | Administration route |
|---------|-------------|------|-------------------------|----------------------|
| Drug of first choice |
| FLCZ (A-II) monotherapy | FLCZ | 200 mg | 1 | Oral |

In the case where FLCZ cannot be used

| Antifungals | Dose | Number of doses per day | Administration route |
|-------------|------|-------------------------|----------------------|
| VRCZ (B-III) monotherapy | VRCZ | 2 | Oral (Taken between meals) |

Note: Adjust dosage by TDM.

[Pulmonary cryptococcosis] (Provide treatment for 6 to 12 months.)

| Regimen | Antifungals | Dose | Number of doses per day | Administration route |
|---------|-------------|------|-------------------------|----------------------|
| Severe cases with respiratory failure |
| Antifungals similar to those for cryptococcal meningoencephalitis should be administered. (Refer to the section describing treatment for cryptococcal meningoencephalitis.) |
| Other than above |
| Drug of first choice |
| (F-)FLCZ (A-III) monotherapy | Use one of the FLCZs listed below. |
| FLCZ | 400 mg | 1 | Oral |
| FLCZ | 400 mg | 1 | Drip infusion |
| F-FLCZ | 800 mg on the 1st and 2nd days 400 mg from the 3rd day onward | 1 | IV |

In the case where (F-)FLCZ cannot be used

| Antifungals | Dose | Number of doses per day | Administration route |
|-------------|------|-------------------------|----------------------|
| VRCZ (B-III) monotherapy | VRCZ | 2 | Oral (Taken between meals) |

Note: Adjust dosage of VRCZ by TDM.
3. Characteristics of cryptococcosis in other immunosuppressive patients

I. Characteristics of cryptococcosis in other immunosuppressive patients
- Patients with malignancy (both hematological and non-hematological) are susceptible to cryptococcosis.
- Factors impairing cell-mediated immunity such as cirrhosis, diabetes, or steroid-administered cases pose a risk of onset.
- Administration of biologics centered on anti-TNF-α inhibitors may pose a risk of onset.
- The mortality rate for all disease types is reported to be 16.7%.
- Patients administered steroids (30 mg/day or more as the converted dose of Prednisolone equivalence) are reported to increase the risk of mortality.
- There is little evidence demonstrating the rationale for the steroids in meningoencephalitis patients.

II. Diagnosis of cryptococcosis in other immunosuppressive patients
- Approximately 40% of non-HIV-infected patients who develop pulmonary cryptococcosis are asymptomatic, while approximately 20% show symptoms such as cough, sputum or fever.
- Radiological findings of pulmonary cryptococcosis show more bilateral multiple nodule shadows and consolidations than those in healthy individuals.
- Studies of non-HIV-infected patients showed that those with shadows 20 mm or less had decreased sensitivity to serum GXM antigen testing to 52.4% (compared to 92.3% for 21 mm or more).

III. Treatment of other immunosuppressive patients
- Cryptococcal meningoencephalitis or disseminated cryptococcosis is basically treated with therapies used for HIV-infected patients, but FLCZ is administered to patients with pulmonary cryptococcosis for 6 to 12 months (A-III).
- Attention should be paid to complications, such as immune reconstitution inflammatory syndrome (IRIS), after biologics are discontinued.
- No data supporting preventive administration or secondary prevention is available.
- When biologics are resumed, careful follow-up is required by conducting GXM antigen testing, routine chest X-ray, and CT scan.

Antifungal medication regimen of cryptococcal meningoencephalitis among other immunosuppressive patients
[Cryptococcal meningoencephalitis and disseminated cryptococcosis]
1) Induction therapy (for at least 2 weeks and until the cerebrospinal fluid culture is confirmed negative)

| Regimen | Antifungals | Dose          | Number of doses per day | Administration route |
|---------|-------------|---------------|-------------------------|----------------------|
| Drug of first choice | | | | |
| L- Combination of AMB + 5-FC (A-III) | L-AMB | 3 to 4 mg/kg | 1 | Drip infusion |
| | 5-FC | 25 mg/kg | 4 | Oral |

In the case where L-AMB cannot be used

Combination of (F-)FLCZ + 5-FC (B-III)
Use one of the FLCZs listed below.

| | | |
|-----------------|-----------------|-----------------|
| FLCZ            | 800 mg          | 1               |
| F-FLCZ          | 800 mg          | 1               |
| 5-FC            | 25 mg/kg        | 4               |

In the case where 5-FC cannot be used

| | | |
|-----------------|-----------------|-----------------|
| L-AMB (B-III) monotherapy | L-AMB | 3 to 4 mg/kg | 1 | Drip infusion |
In the case where either 5-FC or L-AMB cannot be used

| Regimen                  | Antifungals | Dose                        | Number of doses per day | Administration route |
|--------------------------|-------------|-----------------------------|-------------------------|----------------------|
| **VRCZ (C-III) monotherapy** | VRCZ        | 6 mg/kg on the 1st day      | 2                       | Drip infusion        |
|                          |             | 3 to 4 mg/kg from the 2nd day onward | 2                       | Drip infusion        |

Note: Adjust dosage by TDM.

2) Consolidation therapy (for 8 weeks)

| Drug of first choice | Antifungals | Dose                        | Number of doses per day | Administration route |
|----------------------|-------------|-----------------------------|-------------------------|----------------------|
| **(F-)FLCZ (A-III) monotherapy** | Use one of the FLCZs listed below. |                           |                         |                      |
| FLCZ                 | 400 mg      | 1                           | Oral                    |                      |
| FLCZ                 | 400 mg      | 1                           | Drip infusion           |                      |
| F-FLCZ               | 400 mg      | 1                           | IV                      |                      |

In the case where (F-)FLCZ cannot be used

| Drug of first choice | Antifungals | Dose                        | Number of doses per day | Administration route |
|----------------------|-------------|-----------------------------|-------------------------|----------------------|
| **ITCZ oral solution (B-III) monotherapy** | ITCZ oral solution | 200 mg (20 mL) | 2 | Oral (Taken between meals) |
| **ITCZ capsule (C-III) monotherapy** | ITCZ capsule | 200 mg | 2 | Oral (Taken immediately after meals) |
| **VRCZ (B-III)** | VRCZ        | 300 mg on the 1st day       | 2                       | Oral (Taken between meals) |
|                      |             | 150 mg for those under 40 kg |                         |                      |
|                      |             | 150 to 200 mg from the 2nd day onward | 2                       | Oral (Taken between meals) |
|                      |             | 100 mg for those under 40 kg |                         |                      |

Note: Adjust dosage by TDM.

3) Maintenance therapy (for 6 to 12 months)

| Drug of first choice | Antifungals | Dose                        | Number of doses per day | Administration route |
|----------------------|-------------|-----------------------------|-------------------------|----------------------|
| **FLCZ (A-III) monotherapy** | FLCZ        | 200 mg                      | 1                       | Oral                 |

In the case where FLCZ cannot be used

| Drug of first choice | Antifungals | Dose                        | Number of doses per day | Administration route |
|----------------------|-------------|-----------------------------|-------------------------|----------------------|
| **VRCZ (B-III) monotherapy** | VRCZ        | 300 mg on the 1st day       | 2                       | Oral (Taken between meals) |
|                      |             | 150 mg for those under 40 kg |                         |                      |
|                      |             | 150 to 200 mg from the 2nd day onward | 2                       | Oral (Taken between meals) |
|                      |             | 100 mg for those under 40 kg |                         |                      |

Note: Adjust dosage by TDM.

[Pulmonary cryptococcosis] (Provide treatment for 6 to 12 months.)

| Severe cases with respiratory failure | Antifungals | Dose                        | Number of doses per day | Administration route |
|--------------------------------------|-------------|-----------------------------|-------------------------|----------------------|
| Antifungal medication similar to that for cryptococcal meningoencephalitis should be administered (B-III). (Refer to the section describing treatment for cryptococcal meningoencephalitis.) |             |                             |                         |                      |

Other than above
Drugs of first choice

| (F-)FLCZ (A-III) monotherapy | Use one of three types of FLCZ listed below. |
|------------------------------|---------------------------------------------|
| FLCZ 400 mg 1 Oral           |                                             |
| FLCZ 400 mg 1 Drip infusion  |                                             |
| F-FLCZ 800 mg on the 1st and 2nd days |
| 400 mg from the 3rd day onward |
| IV                           |                                             |

In the case where (F-)FLCZ cannot be used

| VRCZ (B-III) monotherapy | VRCZ 300 mg on the 1st day |
|--------------------------|---------------------------|
|                          | 150 mg for those under 40 kg |
|                          | 150 to 200 mg from the 2nd day onward |
|                          | 100 mg for those under 40 kg |
|                          | Oral (Taken between meals) |

| ITCZ oral solution (B-III) monotherapy | ITCZ oral solution |
|---------------------------------------|-------------------|
|                                       | 200 mg (20 mL)    |
|                                       | Oral (Taken between meals) |

| ITCZ capsule (C-III) monotherapy | ITCZ capsule |
|----------------------------------|-------------|
|                                  | 200 mg      |
|                                  | Oral (Taken immediately after meals) |

Note: Adjust dosage of VRCZ by TDM.

4. Characteristics of cryptococcosis in healthy individuals

I. Characteristics of cryptococcosis in healthy individuals
- Even healthy people with no underlying disease may develop cryptococcosis.
- Major disease types include pulmonary cryptococcosis and cryptococcal meningoencephalitis.
- Among non-HIV-infected patients who developed pulmonary cryptococcosis, 44% were healthy.
- Among healthy people who developed pulmonary cryptococcosis, 9% also developed cryptococcal meningoencephalitis.
- Among patients with disseminated cryptococcosis including meningoencephalitis, 15% were healthy.
- A report shows that healthy people who developed cryptococcal meningoencephalitis developed more strokes and brain herniation than patients with underlying disease (non-HIV-infected patients).
- The mortality due to cryptococcal meningoencephalitis, treatment success rate, and prognosis of healthy individuals showed no difference from patients with underlying disease (non-HIV-infected patients).
- *C. gattii* has a higher incidence of cryptococcal meningoencephalitis in healthy people than *C. neoformans*.

II. Diagnosis of cryptococcosis in healthy individuals
- A report showed that 64% of patients with pulmonary cryptococcosis are asymptomatic, while other symptoms include cough (22%), sputum (6%), chest pain (10%), and fever (3%).
- Many with asymptomatic pulmonary cryptococcosis are unexpectedly identified during a health checkup or detailed examination for other pulmonary diseases.
- It is reported that findings of pulmonary cryptococcosis from imaging consist of solitary nodular shadow in 33% of patients, multiple nodular shadow in 60%, multiple nodular shadow localized to a lobe in the lung in 24%, multiple nodular shadow spreading to several lobes in the lung in 36%, and consolidation in 7%.
- Serum GXM antigen testing shows high sensitivity and specificity and is useful for the screening of pulmonary cryptococcosis. If a nodular shadow in imaging is small (major axis ≤ 20 mm), however, the result may not become positive.
- For pulmonary cryptococcosis patients with a negative or low serum GXM antigen dilution titer and minimal symptoms suspected for cryptococcal meningoencephalitis, determination on whether to conduct a cerebrospinal fluid test must be made based on clinical judgement.
- Among healthy people who develop disseminated cryptococcosis, symptoms are presented as fever in 50%, disturbance of consciousness in 56%, headache in 44%, respiratory symptoms in 28% and nuchal rigidity in 17%.
- Patients with cryptococcal meningoencephalitis may present with mild central nervous symptoms such as personality disorder and changes in character in addition to fever or meningeal irritation syndrome.
- Microscopic examination by applying the India ink stain method to cerebrospinal fluid, mycology culture, and GXM antigen testing are useful for the diagnosis of cryptococcal meningoencephalitis.
Findings from cerebrospinal fluid testing include an increase in initial pressure, protein concentration, and the number of monocytes. When a patient presents with meningoencephalitis, a blood culture should be conducted in addition to serum and cerebrospinal fluid GXM antigen testing.

III. Treatment of cryptococcosis in healthy individuals

- Treatment should be provided in three steps: Induction, consolidation, and maintenance therapies.
- Combination of L-AMB and 5-FC should be employed in induction therapy (A-III).
- FLCZ should be administered for 8 weeks in consolidation therapy (A-III).
- FLCZ should be administered for 6 to 12 months in maintenance therapy (A-III).
- If AMPH-B is not available or a patient is intolerant to AMPH-B, VRCZ should be used for treatment (C-III).

Antifungal medication regimen for cryptococcal meningoencephalitis among healthy people

1) Induction therapy (for at least 2 weeks and until the cerebrospinal fluid culture is confirmed negative)

| Drug of first choice | Antifungals | Dose | Number of doses per day | Administration route |
|----------------------|-------------|------|-------------------------|----------------------|
| L- Combination of AMB + 5-FC (A-III) |  |  |  | |
| L-AMB | 3 to 4 mg/kg | 1 | Drip infusion |
| 5-FC | 25 mg/kg | 4 | Oral |
| In the case where L-AMB cannot be used | Use one of the FLCZs listed below. |  |  | |
| FLCZ | 800 mg | 1 | Drip infusion |
| F-FLCZ | 800 mg | 1 | IV |
| 5-FC | 25 mg/kg | 4 | Oral |
| In the case where 5-FC cannot be used | L-AMB (B-III) | 3 to 4 mg/kg | 1 | Drip infusion |
| In the case where either 5-FC or L-AMB cannot be used | VRCZ (C-III) | VRCZ | 6 mg/kg on the 1st day | 2 | Drip infusion |
| | | | 3 to 4 mg/kg from the 2nd day onward | 2 | Drip infusion |

Note: Adjust dosage of VRCZ by TDM.

2) Consolidation therapy (for 8 weeks)

| Drug of first choice | Antifungals | Dose | Number of doses per day | Administration route |
|----------------------|-------------|------|-------------------------|----------------------|
| (F-)FLCZ (A-III) | Use one of the FLCZs listed below. |  |  | |
| FLCZ | 400 mg | 1 | Oral |
| FLCZ | 400 mg | 1 | Drip infusion |
| F-FLCZ | 400 mg | 1 | IV |
| In the case where (F-)FLCZ cannot be used | ITCZ oral solution (B-III) | ITCZ oral solution | 200 mg (20 mL) | 2 | Oral (Taken between meals) |
| | ITCZ capsule (C-III) | ITCZ capsule | 200 mg | 2 | Oral (Taken immediately after meals) |
| VRCZ (B-III) | VRCZ | 300 mg on the 1st day 150 mg for those under 40 kg | 2 | Oral (Taken between meals) |
| | | 150 to 200 mg from the 2nd day onward 100 mg for those under 40 kg | 2 | Oral (Taken between meals) |

Note: Adjust dosage of VRCZ by TDM.

3) Maintenance therapy (for 6 to 12 months)

| Regimen | Antifungals | Dose | Number of doses per day | Administration route |
| --- | --- | --- | --- | --- |
| Drug of first choice | | | | |
| FLCZ (A-III) | FLCZ | 200 mg | 1 | Oral |

In the case where FLCZ cannot be used

| VRCZ (B-III) | VRCZ | 300 mg on the 1st day 150 mg for those under 40 kg | 2 | Oral (Taken between meals) |
| | | 150 to 200 mg from the 2nd day onward 100 mg for those under 40 kg | 2 | Oral (Taken between meals) |

Note: Adjust dosage of VRCZ by TDM.

[Pulmonary cryptococcosis] (Provide treatment for 3 months.)

| Regimen | Antifungals | Dose | Number of doses per day | Administration route |
| --- | --- | --- | --- | --- |
| Severe cases with respiratory failure | | | | |
| Antifungal medication similar to that for cryptococcal meningoencephalitis should be administered. (Refer to the section describing treatment for cryptococcal meningoencephalitis.) | | | | |
| Other than above | | | | |
| Drug of first choice | | | | |
| (F-)FLCZ (A-III) | Use one of three types of FLCZ listed below. | | | |
| FLCZ | 400 mg | 1 | Oral |
| FLCZ | 400 mg | 1 | Drip infusion |
| F-FLCZ | 800 mg on the 1st and 2nd days 400 mg from the 3rd day onward | 1 | IV |

In the case where (F-)FLCZ cannot be used

| VRCZ (B-III) | VRCZ | 300 mg on the 1st day 150 mg for those under 40 kg | 2 | Oral (Taken between meals) |
| | | 150 to 200 mg from the 2nd day onward 100 mg for those under 40 kg | 2 | Oral (Taken between meals) |

Note: Adjust dosage of VRCZ by TDM.

| ITCZ oral solution (B-III) | ITCZ oral solution | 200 mg (20 mL) | 2 | Oral (Taken between meals) |
| ITCZ capsule (C-III) | ITCZ capsule | 200 mg | 2 | Oral (Taken immediately after meals) |
5. Characteristics of cryptococcosis in pregnant and lactating patients

I. Characteristics of cryptococcosis in pregnant and lactating patients
- Severity increases with decreased immunity caused by pregnancy.
- Attention should be paid to IRIS after delivery.
- Cryptococcosis frequently manifests as cryptococcal meningoencephalitis or pulmonary cryptococcosis.
- The mortality of expectant and nursing mothers who develop meningoencephalitis is approximately 25%.
- A report shows that prognosis differs depending on race.

II. Diagnosis of cryptococcosis in pregnant and lactating patients
- While symptoms include headache, disturbance of consciousness, vomiting, cough, and fever, some patients are asymptomatic.
- Among pulmonary cryptococcosis patients, 38% are asymptomatic.
- If a cryptococcosis infection focus is identified in organs other than the central nervous system, presence or absence of meningoencephalitis should be confirmed by proactive cerebrospinal fluid testing.
- If a patient presents with meningoencephalitis, blood culture and urine culture should be proactively conducted in addition to serum and cerebrospinal fluid antigen tests.
- Findings from pulmonary cryptococcosis imaging include multiple nodular shadows and infiltrative shadows in 21% of patients, and are diverse, including isolated nodular shadows, mass shadows, cavitary lesions and pleural effusion.
- Serum GXM antigen is positive in 83% of pulmonary cryptococcosis and 98% of cryptococcal meningoencephalitis and disseminated cryptococcosis, and thus is useful for diagnosis.

III. Treatment of cryptococcosis in pregnant and lactating patients
- If an expectant mother develops cryptococcal meningoencephalitis or disseminated cryptococcosis, antifungals should be considered as a treatment option even during pregnancy.
- If an expectant mother develops stable pulmonary cryptococcosis without presenting with a disseminated lesion, treatment should not be provided during pregnancy but will be considered after delivery.
- If cryptococcosis is treated during pregnancy, L-AMB should be used in principle (B-III).
- If pregnancy is completed and breastfeeding can be discontinued, initiate combination of 5-FC with L-AMB if cryptococcal meningoencephalitis or disseminated cryptococcosis are being treated for induction (C-III).
- If pregnancy is completed and breastfeeding can be discontinued, change the medication to FLCZ if cryptococcal meningoencephalitis and disseminated cryptococcosis are being treated for consolidation and maintenance, or if the patient is being treated for pulmonary cryptococcosis (C-III).
- FLCZ, VRCZ, ITCZ, and 5-FC is contraindicated for pregnant patients.
- No data available recommend prophylactic administration.
- The clinical course, serum GXM antigen, and CD4-positive T cell counts should be monitored over time in HIV-infected pregnant patients after maintenance therapy is completed (or discontinued).

Antifungal medication regimen for cryptococcal meningoencephalitis among expectant and nursing mothers
[Cryptococcal meningoencephalitis and disseminated cryptococcosis]
1) Induction therapy (for at least 2 weeks and until the cerebrospinal fluid culture is confirmed negative)

| Regimen          | Antifungals | Dose       | Number of doses per day | Administration route |
|------------------|-------------|------------|-------------------------|---------------------|
| Drug of first choice |             |            |                         |                     |
| L-AMB (B-III) monotherapy | L-AMB       | 3 to 4 mg/kg | 1                       | Drip infusion       |

2) Consolidation therapy (for 8 weeks)

| Regimen          | Antifungals | Dose       | Number of doses per day | Administration route |
|------------------|-------------|------------|-------------------------|---------------------|
| During pregnancy |             |            |                         |                     |
| Drug of first choice |             |            |                         |                     |
| L-AMB (C-III) monotherapy | L-AMB       | 3 to 4 mg/kg | 1                       | Drip infusion       |

In the case where the pregnancy period is completed and nursing can be interrupted
6. Characteristics of Cryptococcus gattii infections

1. Characteristics of Cryptococcus gattii infections
- Cryptococcus gattii infections were considered as infections in tropical or subtropical zones in the past. However, mass infection broke out on Vancouver Island, Province of British Columbia, Canada, and spread to adjacent areas including the States of Washington and Oregon in the US.
- Healthy individuals mainly develop Cryptococcus gattii infections. Unlike C. neoformans, fewer HIV-infected patients contract Cryptococcus gattii infections.
- The epidemic strain in North America is characterized by high pathogenicity, low response to therapy and a high mortality of 10 to 40% due to meningoencephalitis.
- While two cases were considered to have developed in Japan (with the genotype VGIIa for both cases) (as of January 2016), details of the actual incidence are still unknown in Japan.

### Drug of first choice

| (F-)FLCZ (A-III) monotherapy | Use one of the FLCZs listed below. |
|------------------------------|-----------------------------------|
| FLCZ (internal medicine)     | 400 mg                            |
|                              | 1                                 |
|                              | Oral                              |
| FLCZ                         | 400 mg                            |
|                              | 1                                 |
|                              | Drip infusion                      |
| F-FLCZ                       | 400 mg                            |
|                              | 1                                 |
|                              | IV                                |

### 3) Maintenance therapy (for 6 to 12 months)

| Regimen | Antifungals | Dose | Number of doses per day | Administration route |
|---------|-------------|------|-------------------------|----------------------|
| During pregnancy | | | | |
| Drug of first choice | | | | |
| L-AMB (C-III) monotherapy | L-AMB | 3 to 4 mg/kg | 1 | Drip infusion |

In the case where the pregnancy period is completed and nursing can be interrupted

| Drug of first choice |
|----------------------|
| FLCZ (A-III) monotherapy |
| FLCZ (internal medicine) | 200 mg |
|                         | 1 |
|                         | Oral |

### [Pulmonary cryptococcosis] (Provide treatment for 6 to 12 months.)

| Regimen | Antifungals | Dose | Number of doses per day | Administration route |
|---------|-------------|------|-------------------------|----------------------|
| Severe cases with respiratory failure | | | | |
| Antifungal medication similar to that for cryptococcal meningoencephalitis should be administered. (Refer to the section describing treatment for cryptococcal meningoencephalitis.) |
| Other than above | | | | |
| During pregnancy | | | | |
| When the pregnancy period is completed and nursing can be interrupted, proceed to the FLCZ described below to complete the treatment period. |
| Drug of first choice |
| L-AMB (C-III) monotherapy |
| L-AMB | 3 to 4 mg/kg |
|       | 1 |
|       | Drip infusion |

In the case where the pregnancy period is completed and nursing can be interrupted

| Drug of first choice |
|----------------------|
| (F-)FLCZ (B-III) monotherapy |
| Use one of three types of FLCZ listed below. |
| FLCZ                   | 400 mg |
|                        | 1 |
|                        | Oral |
| FLCZ                   | 400 mg |
|                        | 1 |
|                        | Drip infusion |
| F-FLCZ                 | 800 mg on the 1st and 2nd days |
|                        | 400 mg from the 3rd day onward |
|                        | 1 |
|                        | IV |
II. Diagnosis of Cryptococcus gattii infections
- When lesions are limited to the lung alone, fever is observed in 22% patients, cough in 61%, sputum in 35%, and chest pain in 31%.
- When central nervous system infections are concomitantly developed, headache is observed in 81% patients, vomiting in 53%, photophobia in 34%, disturbance of consciousness in 26%, nuchal rigidity in 23%, and visual disorder in 13%. Convulsions are observed more frequently than with C. neoformans. Visual disorder is observed in 13% patients.
- When the culture, microscopic examination, and pathological examination are confirmed positive, cryptococcal infections are definitively diagnosed, while color change of L-canavanine glycine bromothymol blue (CGB) medium and genetic identification are used to make a differential diagnosis from C. neoformans.
- Serum GXM antigen testing has a slightly lower sensitivity than with C. neoformans but is useful as an auxiliary diagnosis since 90% or more become positive in clinical settings.

III. Treatment of Cryptococcus gattii infections

1) Induction therapy (for at least 4 weeks and until the cerebrospinal fluid culture is confirmed negative)

| Regimen                  | Antifungals | Dose         | Number of doses per day | Administration route |
|--------------------------|-------------|--------------|-------------------------|---------------------|
| Drug of first choice     |             |              |                         |                     |
| Combination of L-AMB + 5-FC (A-II) | L-AMB       | 3 to 4 mg/kg | 1                       | Drip infusion       |
|                          | 5-FC        | 25 mg/kg     | 4                       | Oral                |

2) Consolidation therapy (for 8 weeks)

| Regimen                  | Antifungals | Dose         | Number of doses per day | Administration route |
|--------------------------|-------------|--------------|-------------------------|---------------------|
| Drug of first choice     |             |              |                         |                     |
| (F-)FLCZ (A-III) monotherapy | FLCZ       | 400 mg       | 1                       | Oral                |
|                          | F-FLCZ      | 400 mg       | 1                       | IV                  |

3) Maintenance therapy (for 6 to 12 months)

| Regimen                  | Antifungals | Dose         | Number of doses per day | Administration route |
|--------------------------|-------------|--------------|-------------------------|---------------------|
| Drug of first choice     |             |              |                         |                     |
| FLCZ (A-III) monotherapy | FLCZ       | 200 mg       | 1                       | Oral                |
7. Cutaneous cryptococcosis

I. Characteristics of cutaneous cryptococcosis
- Cutaneous cryptococcosis can be divided to skin lesions due to localized cutaneous cryptococcosis and disseminated cryptococcosis.
- Localized cutaneous cryptococcosis has lesions limited to the skin regardless of infection route and shows no systemic dissemination.
- C. neoformans of serum type D that tends to cause cutaneous cryptococcosis without systemic dissemination.
- Skin lesions from disseminated cryptococcosis manifest at an incidence of 5 to 15% of all cryptococcal patients. During about a year from 2014, 12 patients (9.7%) among 123 patients presented with skin lesions in Japan.
- Skin lesions from disseminated cryptococcosis are usually accompanied by underlying diseases or therapies such as HIV infection, systemic administration of steroids, malignant tumor, CD4-positive lymphocytopenia, chemotherapy, the immunocompromised state after organ transplantation, sarcoidosis, diabetes, and cirrhosis. Complications with sarcoidosis untreated with steroids have also been reported.
- Localized cutaneous cryptococcosis is a rare disease type characterized by skin lesions without systemic dissemination, with 65 patients having been reported to contract the disease from 1968 to August 2018.

II. Diagnosis of cutaneous cryptococcosis
- Skin lesions have a high incidence on the head and neck and show various clinical features including subcutaneous swelling, cellulitis, abscess, tumor mass, ulcer, granuloma, molluscum-like papule, nodule, and erythema.
- Approximately 6% of HIV-infected patients develop disseminated cutaneous cryptococcosis and appear as umbilicated papules, nodules, and violaceous plaques, and such lesions frequently mimic molluscum contagiosum and Kaposi’s sarcoma.
- Cellulitis of the lower limbs are typical skin lesions of disseminated cryptococcosis developed by patients who underwent a solid organ transplantation.  
- Common sites of localized cutaneous cryptococcosis are the face and limbs, and clinical presentation includes isolated lesions with ulcer in 38% of patients; papules, nodules, and tumor masses in 26%; subcutaneous nodules, induration, and cellulitis in 20%; and localized infiltrated erythema in 16%.  
- Tzanck smear (Giemsa staining) and India ink method prepared from the base of the vesicles, pustules, acneiform lesions, or ulcers show the encapsulated yeast of Cryptococcus, leading to rapid diagnosis.

III. Treatment of cutaneous cryptococcosis  
- Treatment of cutaneous cryptococcosis is different from disseminated cryptococcosis to localized cutaneous cryptococcosis.  
- Selection of therapeutic medication and administration duration is determined according to severity, response to therapy, and immunological state of the host.  
- In the case of fungemia or disseminated lesions (with skip lesion areas appearing in several sites or a serum GXM antigen dilution titer of 512 times or more), antifungals that is usually administered for cryptococcal meningoencephalitis should be provided.  
- When the possibility of cryptococcal meningoencephalitis and fungemia is excluded, the lesion is a single lesion, and the host does not develop immune deficiency, FLCZ should be administered at a dose of 400 mg/day for 3 months (A-III).  
- ITCZ (at 100 to 400 mg/day for 3 to 6 months) may be an option for treatment. In principle, oral solution with higher absorption efficiency should be recommended (B-III).

| Regimen                     | Antifungals | Dose         | Number of doses per day | Administration route          |
|-----------------------------|-------------|--------------|-------------------------|------------------------------|
| In the case where fungemia or disseminated lesions (when lesions exist in skip lesion areas and in several sites, or serum GXM antigen dilution titer is 512 times or more) concomitantly develop | Provide antifungal in a similar manner as treatment for cryptococcal meningoencephalitis (refer to the section describing treatment for cryptococcal meningoencephalitis in “Particular Theories”). | |
| In the case where the possibility of cryptococcal meningoencephalitis and fungemia is excluded, the lesion is a single lesion, and the host does not develop immune deficiency | Drug of first choice | Provide treatment for 3 months | |
| FLCZ (A-III) monotherapy    | FLCZ        | 400 mg       | 1                       | Oral                         |
| In the case where FLCZ cannot be used | ITCZ oral solution (B-III) monotherapy | ITCZ oral solution | 200 mg (20 mL) | 2 | Oral (Taken between meals) |
| ITCZ capsule (C-III) monotherapy | ITCZ capsule | 200 mg       | 2                       | Oral (Taken immediately after meals) |

8. FAQ
Q1. How reliable is the GXM antigen testing?
Answer
The GXM antigen is highly reliable, but various clinical issues still remain.

Description
The minimum detectable sensitivity for GXM antigen testing is reportedly 6.25 ng/mL with Cerodirect\(^1\) and 50 ng/mL with PASTOREX\(^2\), which means that a higher detectable sensitivity can be obtained with Cerodirect. While GXM antigen testing features high sensitivity and specificity and is highly useful for clinical diagnosis, its positive result duration is long and thus it cannot be used to judge therapeutic processes or as an index for completion of antifungal treatment\(^3\). If there are an excess number of specimens with GXM antigens that bind to the antibodies contained in the measurement kit, the precipitation reaction will be suppressed (zone phenomenon), possibly resulting in false-negative reactions\(^4,5\). If a cerebrospinal fluid specimen shows negative GXM antigen even though there was a positive reaction with the India ink stain method, the specimen should be diluted and the test should be repeated. It is known that reactivity against C. gattii is lower compared to that against C. neoformans. In particular, due caution should be exercised for PASTOREX using monoclonal antibodies\(^6\). It is also well known that the GXM antigen detection kit demonstrates cross reactivity with the Trichosporon \(^1,2\) and shows false positives. In addition, various additional false-positive factors \(^7-13\) have been con-
firmed.

References
1) Package insert of Cerodirect® ‘Eiken’ Cryptococcus. Revised in June 2009.
2) Package insert of PASTOREX™ CRYPTO PLUS. Revised in December 2011.
3) Kohno S, Kakeya H, Izumikawa K, Miyazaki T, Yamamoto Y, Yanagihara K, Mitsutake K, Miyazaki Y, Maesaki S, Yasuoka A, Tashiro T, Mine M, Uetani M, Ashizawa K: Clinical features of pulmonary cryptococcosis in non-HIV patients in Japan. J Infect Chemother 21:23-30, 2015.
4) Maziarz EK, Perfect JR: Cryptococcosis. Infect Dis Clin N Am 30:179-206, 2016.
5) Stamm AM, Pelt SS: False-negative cryptococcal antigen test. JAMA 244:1359, 1980.
6) Tintelnot K, Hagan F, Han CO, Seibold M, Rickerts V, Boekhout T: Pitfalls in serological diagnosis of Cryptococcus gattii infections. Med Mycol 53:874-879, 2015.
7) Westerink MAJ, Amsterdam D, Petell RJ, Stram MN, Apicella MA: Septicemia due to DF-2: Cause of false-positive cryptococcal latex agglutination test result. Am J Med 83:155-158, 1987.
8) Sachs MK, Huang CM, Ost D, Jungkind DL: Failure of dithiothreitol and pronase to reveal a false-positive cryptococcal antigen determination in cerebrospinal fluid. Am J Clin Pathol 96:381-384, 1991.
9) Millon L, Barale T, Julliot MC, Martinez J, Mantion G: Interference by hydroxyethyl starch used for vascular filling in latex agglutination test for cryptococcal antigen. J Clin Microbiol 33:1917-1919, 1995.
10) Blevins LB, Segal JFH, Newcomb-Gayman P, Carroll KC: False-positive cryptococcal antigen latex agglutination caused by disinfectants and soaps. J Clin Microbiol 33:1674-1675, 1995.
11) Wilson DA, Sholtis M, Parshould Should GS, Procop GW: False-positive cryptococcal antigen test associated with use of BBL Port-A Cul transport vials. J Clin Microbiol 49:702-703, 2011.
12) Isseh IN, Bourgi K, Nakhle A, Ali M, Zervos MJ: False-positive cerebrospinal fluid Cryptococcus antigen in Libman-Sacks endocarditis. Infection 44:803-805, 2016.
13) Tone K, Umeda Y, Makimura K: Cross-reactivity in Cryptococcus antigen latex agglutination test in two commercial kits. Med Mycol 54:439-443, 2016.

Q2. When cryptococcosis is proven or suspected in sites other than the central nervous system, is cerebrospinal fluid testing necessary for all patients?

Answer
When the presence of meningoencephalitis is manifested such as by suspected meningeal irritation symptoms or decreasing cellular immunity, cerebrospinal fluid testing is basically recommended for all patients except for contraindicated patients. In other cases, physicians should determine whether to conduct cerebrospinal fluid testing according to the patient’s condition.

Description
Since the presence of cryptococcal meningoencephalitis influences the selection of therapeutic drugs, treatment period, necessity of monitoring cerebrospinal fluid pressure, hospitalization period, prognosis, and risk of sequelae, cerebrospinal fluid testing bears significant meaning. If a cryptococcal infection is proven or suspected regardless of infection site, the possibility of the cerebrospinal fluid testing should be considered. When the presence of meningoencephalitis is suspected due to a change in the state of consciousness or a symptom of meningeal irritation in particular, cerebrospinal fluid testing is basically recommended for all patients except for contraindicated patients. According to the practice guidelines for bacterial meningitis in Japan[1], lumbar puncture is contraindicated if patients present with signs of brain herniation (such as optic disc edema, fixed pupil or dilation of the pupil in one or both eyes, decerebration or decorticate posture, Cheyne-Stokes breathing, or fixed ocular displacement).

Decrease in cellular immunity is a risk factor for cryptococcal meningoencephalitis. HIV-infected patients frequently develop cryptococcal meningoencephalitis while pulmonary cryptococcal infection is not proven. While the precise incidence of asymptomatic cryptococcal meningoencephalitis is still unknown, cerebrospinal fluid testing is recommended for all patients with compromised cellular immunity except for contraindicated patients, even when no symptoms of suspected meningoencephalitis are observed.

Since the number of HIV-infected patients and C. gattii infections is low in Japan, the incidence of meningoencephalitis is lower among all cryptococcosis cases than in other countries. Among 151 non-HIV-infected patients with pulmonary cryptococcosis from 1977 to 2012, cerebrospinal fluid testing was conducted on 122 patients, and complications comprising central nervous system infections were identified in 14 of them (11.5%)[2]. No definite relationship has been demonstrated between findings from chest imaging and serum GXM antigen dilution titers, and the onset of cryptococcal meningoencephalitis.

Attention should be paid to complications associated with lumbar puncture. While lumbar punctures are conducted for different diseases, a study on 23 sites in Europe (3,868 patients) showed complications of some sort after lumbar
puncture in 1,065 patients (31%), with frequent complications including headache (19%) and back ache (17%). Although extremely rare (less than 0.01%), serious complications appeared as intraspinal infection, spinal subdural hematoma, and cerebral venous thrombosis. Retrospective studies in Europe and the US showed that the incidence of brain herniation due to lumbar puncture is approximately 1% for both adult and pediatric patients.

Therefore, indications for cerebrospinal fluid testing should be determined by taking the significance and frequency of cryptococcal meningococcalitis, and complications of lumbar puncture into consideration. Types and frequencies of complications and accidental symptoms associated with lumbar puncture depend on patient condition and surgeons’ skills. When lumbar puncture is to be conducted, the above-mentioned risks and benefits should be taken into account, and it is preferable that lumbar puncture should be conducted by doctors such as neurologists or doctors who are experienced in this type of testing or under the guidance of such doctors. Cerebrospinal fluid testing may be omitted for patients with asymptomatic localized pulmonary cryptococcosis without obvious immune deficiency.

References

1) Practical Guidelines for Bacterial Meningitis 2014, edited by the Committee of Practical Guidelines for Bacterial Meningitis, Japanese Society of Neurology, Japanese Society of Neurological Therapeutics, Japanese Society for Neuroinfectious Diseases: 55-57, Tokyo, 2014.

2) Kohno S, Kakeya H, Izumikawa K, Miyazaki T, Yamamoto Y, Yanagihara K, Mitsutake K, Miyazaki Y, Maesaki S, Yasuoka A, Tashiro T, Mine M, Uetani M, Ashizawa K: Clinical features of pulmonary cryptococcosis in non-HIV patients in Japan. J Infect Chemother 21: 23-30, 2015.

3) Duits FH, Martinez-Lage P, Paquet C, Engelborghs S, Lleo A, Hausner L, Molinuevo JL, Stomrud E, Farotti L, Ramakers IHGB, Tsolaki M, Skargasd C, Astrand R, Wallin A, Vyhralek M, Holmber-Clausen M, Forlenza OV, Ghezzi L, Ingelsson M, Hoff E, Roks G, de Mendonça A, Papma JM, Izagirre A, Tashiro T, Mine M, Uetani M, Ashizawa K: Clinical features of pulmonary cryptococcosis in non-HIV patients in Japan. J Infect Chemother 12: 154-163, 2016.

4) Engelborghs S, Niemantsverdriet E, Struys H, Blennow K, Brouns R, Comabella M, Dujmovic I, van der Flier W, Frölich L, Galimberti D, Gnanapavan S, Hemmer B, Hoff E, Hert J, Iacobaeus E, Ingelsson M, Jan de Jong F, Jonsson M, Khalil M, Kuhle J, Lleó A, de Mendonça A, Molinuevo JL, Nagels G, Paquet C, Parnetti L, Roks G, Rosa-Neto P, Scheltens P, Skårgard C, Stomrud E, Tumani H, Visser PJ, Wallin A, Winblad B, Zetterberg H, Duits F, Teunissen CE: Consensus guidelines for lumbar puncture in patients with neurological diseases. Alzheimer’s Dement (Amst) 8: 111-126, 2017.

5) Durand ML, Calderwood SB, Weber DJ, Miller SI, Southwick FS, Caviness VS Jr, Swartz MN: Acute bacterial meningitis in adults. A review of 493 episodes. N Engl J Med 328: 21-28, 1993.

6) Wylie PA, Stevens D, Drake W 3rd, Stuart J, Cartwright K: Epidemiology and clinical management of meningococcal disease in west Gloucestershire: retrospective, population based study. BMJ 315: 774-779, 1997.

Q3. How is cerebrospinal pressure managed?

Answer

Lumbar puncture should be repeated every day until the cerebrospinal fluid pressure and symptoms are resolving and stabilized. Alternative options of the cerebrospinal fluid pressure management include insertion of an intrathecal drain, ventriculostomy, and V-P shunt.

Description

In general, 50 to 70% of cryptococcal meningoencephalitis patients increase intracranial pressure. Increase of cerebrospinal fluid pressure is correlated with complications of the nervous system or mortality rate, and the risk of mortality can be reduced by controlling the cerebrospinal fluid pressure. Lumbar puncture should be repeated every day, and cerebrospinal fluid pressure should be proactively controlled until clinical improvement and proper and stabilized cerebrospinal fluid pressure are confirmed. For serious cases with uncontrollable cerebrospinal fluid pressure even after repeated lumbar puncture, the possibility of applying intraspinal drainage should be considered. If the initial cerebrospinal fluid pressure is extremely high at 25 cmH₂O or higher, cerebrospinal fluid should be drained until it lowers to under 20 cmH₂O or half of the initial pressure (for approximately 20 to 30 mL). If elevated cerebrospinal fluid pressure persists even with proper antifungals and cerebrospinal fluid drainage, the possibility of a VP shunt, ventriculostomy, or ventricular fenestration should be considered as a treatment option.

For cryptococcal meningoencephalitis in HIV-infected patients, use of steroids is not recommended to control cerebrospinal fluid pressure. As for non-HIV-infected patients, little evidence is available.

References

1) Chang CC, Perfect JR: Repeated therapeutic lumbar punctures in cryptococcal meningitis-necessity and/or
opportunity? Curr Opin Infect Dis 29: 539-545, 2016.
2) Bicanic T, Brouwer AE, Meintjes G, Rebe K, Limmuth-otsakul D, Chierakul W, Teparrakkul P, Loyse A, White NJ, Wood R, Jaffar S, Harrison T: Relationship of cerebrospinal fluid pressure, fungal burden and outcome in patients with cryptococcal meningitis undergoing serial lumbar punctures. AIDS 23: 701-706, 2009.
3) Kambugu A, Meya DB, Rhein J, O’Brien M, Janoff EN, Ronald AR, Kamya MR, Mayanja-Kizza H, Sande MA, Bohjanen PR, Boulware DR: Outcomes of cryptococcal meningitis in Uganda before and after the availability of highly active antiretroviral therapy. Clin Infect Dis 46: 1694-1701, 2008.
4) Day NJ, Chau TTH, Wolbers M, Mai PP, Dung NT, Mai NH, Phu NH, Nghia HD, Phong ND, Thai CQ, Thai LH, Chuong LV, Sinh DX, Duong VA, Hoang TN, Diep PT, Campbell JI, Sieu TPM, Baker SG, Chau NVV, Hien TT, Laloo DG, Farrar JJ: Combination antifungal therapy for cryptococcal meningitis. N Engl J Med 368: 1291-1302, 2013.
5) 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: e221-224, 2005.
6) Fessler RD, Sobel J, Guyot L, Crane L, Vazquez J, Szaba MJ, Diaz FG: Management of elevated intracranial pressure in patients with Cryptococcal meningitis. J Acquir Immune Defic Syndr Hum Retrovirol 17: 137-142, 1998.
7) Manosuthi W, Sungkanuparp S, Chottanapund S, Tansuphaswadikutik S, Chimsuntorn S, Limpanadusadee P, Pappas PG: Temporary external lumbar drainage for reducing elevated intracrani al pressure in HIV-infected patients with cryptococcal meningitis. Int J STD AIDS 19: 268-271, 2008.
8) Beardsley J, Wolbers M, Kiris AO, Ggayi AB, Kamali A, Cuc NT, Binh TQ, Chau NV, Farrar J, Merson L, Phuong L, Thwaites G, Van Kinh N, Thuy PT, Chierakul W, Siriboon S, Thiansukhon E, Onsanit S, Supphamongkolchaikul W, Chan AK, Feyderman R, Mwinjwa E, van Oosterhout JJ, Imran D, Basri H, Mayxay M, Dance D, Phimmasonse P, Rattanavong S, Laloo DG, Day JN; CryptoDex Investigators: Adjunctive Dexamethasone in HIV-Associated Cryptococcal Meningitis. N Engl J Med 374: 542-554, 2016.

Q4. Where are cryptococcosis infection sites other than the lung, central nervous system and skin?

Answer
Reports show that cryptococcosis infection focuses were observed in bones, joints, pharynx, prostate, thyroid gland, adrenal gland, peritoneal membrane, and pleura.

Description
1. Osseous cryptococcosis
Osseous cryptococcosis accounts for approximately 5 to 10% of disseminated cryptococcosis, with cases of single osseous lesions even rarer. In cases without systemic disseminated lesions, local pain and swelling is frequently observed for a week to a month, and systemic symptoms such as fever, diaphoresis, or weight loss may not be observed. Frequent sites for osseous lesions include the spine (32.5%), skull (14.6%), femoral bone (9.8%), rib bone (8.1%), upper forelimb bone (6.5%), and tibial bone (5.7%), while those for joint lesions include the knee joint (37.5%), elbow joint (16.7%), hip joint (12.5%), hand joint (8.3%), and ankle joint (8.3%). However, they have been identified in every bone site in the body.

The underlying immune deficiencies such as the use of steroids, HIV infection, IL-2 deficiency and T-cell dysfunction were found in 28.4% of the patients. While 35.2% of the hosts presented with relative immune depression such as diabetes, tuberculosis, and connective tissue disorder, 36.7% of the hosts showed no specific problem in their immune system. Another report showed that 60% of hosts presented with no obvious risk factor.

Changes in osteolysis are frequently seen in imaging examinations and are sometimes accompanied by changes in periosteum. Most diagnoses are made mycologically and histopathologically with biopsies or fine-needle aspiration of lesions. Serum GXM antigens were confirmed positive in 82% of patients.

Diversified therapies are employed, with no therapies demonstrating highly-reliable evidence. In the review article by Zhou et al., concomitant therapies consisting of surgical procedures and antifungals were conducted with 45 out of 80 patients. While many cases were seen using amphotericin B product alone or amphotericin B product with 5-FC, 5 out of the 45 patients died. Three patients underwent surgical treatment alone, of which one patient died, and two patients showed improvement. Antifungal medication alone was provided for 32 patients, of which 6 patients died.

While many cases of localized osseous cryptococcosis are considered treatable with FLAZC alone, some opinions favor treatment with concomitant therapy consisting of AMPH-B lipid complex and 5-FC in the case of the possibility of disseminated lesions. In such a case, medication may be stepped down to oral FLAZC for patients who show clinical improvement or have no findings indicating dissemination. While antifungal medication was continued for 1 to 12 months or more in some cases, the median of the treatment period was 28 weeks.
2. Laryngeal cryptococcosis

According to a case report review of approximately 20 patients, hoarse voice observed as a symptom of this disease in a subacute to chronic clinical course is unavoidable. In addition, cough, difficulty in breathing, or acute airway obstruction is observed, and frequent findings from laryngoscopy include airway edema, tumor mass formation at the vocal cord section, and erythema of the airway.

The most significant risk factor for laryngeal cryptococcosis is the use of inhaled corticosteroid. Other risk factors include HIV infection, diabetes, systemic administration of steroids, smoking, and a history of contact with bird droppings.

While diagnoses are usually made mycologically and histopathologically with biopsy tissues, histologic diagnosis is also necessary to differentiate the disease from other fungal infections such as candidiasis, histoplasma, blastomyces, coccidioidomycosis, and paracoccidioidomycosis or other malignant diseases. Serum GXM antigens are confirmed negative in many cases. Cerebrospinal fluid testing was conducted on 7 out of 18 patients, but meningoencephalitis was not identified in all patients. If systemic immune deficiency is observed, however, presence or absence of a disseminated lesion should be closely examined.

Reliable evidence for various therapies has not been established. Antifungals including FLCZ are utilized in many cases. Surgical resection or laser therapy has been applied in established. Antifungals including FLCZ are utilized in many cases. However, dose reduction should be individually determined for each case.

References
1) Wood L, Miedzinski L: Skeletal cryptococcosis: Case report and review of the literature. Can J Infect Dis 7: 125-132, 1996.
2) Medaris LA, Ponce B, Hyde Z, Delgado D, Ennis D, Lapidus W, Larrison M, Pappas PG: Cryptococcal osteomyelitis: a report of 5 cases and review of the recent literature. Mycoses 59: 334-342, 2016.
3) Zhou HX, Lu L, Chu T, Wang T, Cao D, Li F, Ning G, Feng S: Skeletal cryptococcosis from 1977 to 2013. Frontiers in microbial 5, article 740: 1-18, 2015.

3. Prostate cryptococcosis

According to a review of 70 cases, many had developed in hosts in an immunosuppressive state such as patients administered steroids, HIV-infected patients, or patients with hematologic malignancy or diabetes, but in some of the cases, no specific risk factors were identified. While 44 patients showed scarce clinical findings indicating the presence of prostate lesions, 25 patients among them also suffered from cryptococcal meningoencephalitis. On the other hand, many cases showed no lesions on other organs and were diagnosed based on symptoms associated with prostatic hypertrophy or prostate nodules. Specimens used for diagnosis were taken from the urine or semen in many cases. Ten cases (14%) were diagnosed from biopsy of the prostate, and 16 cases (23%) from autopsy. No established evidence for therapies is currently available.

Reference
1) Shah SI, Bui H, Velasco N, Rungta S: Incidental finding of Cryptococcus on prostate biopsy for prostate adenocarcinoma following cardiac transplant: Case report and review of the literature. Am J Case Rep 18: 1171-1180, 2017.

4. Thyroid cryptococcosis

Thyroid cryptococcosis is extremely rare, and only several cases have been reported so far. All these cases are considered as partial symptoms of disseminated cryptococcosis developed in immune deficient hosts. Swelling or tenderness of the thyroid gland was only seen in some cases. While positive findings were observed in gallium scintigraphy or image diagnosis using radioactive iodine or technetium, definite diagnoses were made from histopathological examinations such as aspiration biopsy cytology or autopsy.

While combination of AMPH-B and 5-FC were first used and FLCZ was then administered for the long term in improved cases, no established evidence regarding therapies is currently available.

Reference
1) Avram AM, Sturm CA, Michael CW, Sisson JC, Jaffe CA: Cryptococcal thyroiditis and Hyperthyroidism. Thyroid 14: 471-474, 2004.

5. Adrenal cryptococcosis

Adrenal cryptococcosis, developed as a partial symptom of disseminated cryptococcosis, is sometimes reported, but sporadic adrenal cryptococcosis is extremely rare, with only 5 cases reported thus far. Relatively many cases of adrenal cryptococcosis were identified only after adrenal insufficiency.
was detected. Some reports indicate lesions in bilateral adrenal glands, while others report negative GXM antigen. Many adrenal cryptococcosis cases were diagnosed from cytodiagnosis of specimens extracted by fine-needle aspiration. While no established evidence for therapies is currently available, some case reports indicate improvement in sporadic cases by treatment with FLCZ.

References
1) Ito M, Hinata T, Tamura K, Koga A, Ito T, Fujii H, Hirata F, Sakuta H: Disseminated cryptococcosis with adrenal insufficiency and meningitis in an immunocompetent individual. Int Med 56: 1259-1264, 2017.
2) Cocker R, McNair SA, Kahn L, Kwon S, Sung C: Isolated adrenal cryptococcosis, diagnosed by fine-needle aspiration. Diagnostic Cytopathology 42: 899-901, 2014.

6. Cryptococcal peritonitis
During the period between 1951 and 2012, 61 cases of cryptococcal peritonitis were reported. In many cases, the condition developed among patients with cirrhosis (45.9%), under CAPD (24.6%) and with AIDS (19.7%). It frequently develops as non-specific symptoms including abdominal pain, fever, and an increase in abdominal circumference, with many cases being difficult to diagnose. Diagnoses are made mycologically and cytologically by using ascites fluid extracted by abdominal paracentesis. Cryptococcal peritonitis may be regarded as a part of disseminated lesions since cryptococcus is frequently detected in blood, cerebrospinal fluid, and urine. While no established evidence for treatment is currently available, AMPH-B agents and FLCZ are selected in many cases. Peritoneal catheters should be removed. With death observed in 41% of patients and recovery in slightly more than 30%, the prognosis is not favorable.

References
1) El-Kersh K, Rawasia WF, Chaddha U, Guardiola J: Rarity revisited: cryptococcal peritonitis. BML Case Rep 2013. doi: 10.1136/bcr-2013-009099.

7. Cryptococcal pleuritis
Cryptococcosis with pleural effusion is rare, with only 30 cases reported so far. It is developed as a partial symptom of disseminated cryptococcosis or localized to the chest. If pleural effusion alone is observed as a clinical finding, it is difficult to make a diagnosis. While cryptococcal fungi were identified by PAS staining or methenamine silver staining of the pleura in some cases, the positive culture rate for pleural effusion is low, with one report claiming 42%. Detection of GXM antigens in serum or pleural effusion is useful for diagnosis. In unexplained pleural effusion of patients with immune deficiency, cryptococcal infections may have to be included in a differential diagnosis. No established evidence for therapies is currently available.

References
1) Young EJ, Hirsh DD, Fainstein V, Williams TW: Pleural effusion due to Cryptococcus neoformans: A review of the literature and report of two cases with cryptococcal antigen determinations. Am rev Resp Dis 121: 743-747, 1980.
2) Chen M, Wang X, Yu X, Dai C, Chen D, Yu C, Xu X, Yao D, Yang L, Li Y, Wang L, Huang X: Pleural effusion as the initial clinical presentation in disseminated cryptococcosis and fungemia: An unusual manifestation and a literature review. BMC 15: 385 doi: 10.1186/s12879-015-1132-4.