



DREAMMM

Driving Reduced AIDS-associated Meningo-encephalitis Mortality



Safe Administration of Flucytosine & Fluconazole

Treating Cryptococcal Meningitis





Workshop Learning Objectives

- To demonstrate the safe administration of flucytosine (5-FC) and fluconazole.
- To describe the management of meningo-encephalitis treatment toxicity.
- For more information see online Cryptococcal Meningitis module sections : *Treating HIV-associated Cryptococcal Meningitis*



Recommended CM induction regimens for LMICs as a result of ACTA – WHO Guidance 2018

- In order of recommendation (depending on possibility of safe AmB administration and availability of 5-FC):
 - **1 week AmB (1mg/kg/day) + 5-FC (100mg/kg/day)**
-gold standard for LMICs
 - **2 weeks Fluconazole (1200mg daily) + 5-FC (100mg/kg/day)**
-alternative
 - 3rd line = 2 weeks AmB 1mg/kg/day + Fluconazole 1200mg daily



How to administer 5-FC?

- Dosing for the induction stage is 100mg/kg/day in 4 divided doses. 5-FC is administered over a 6 hour period.
- Nausea and vomiting may occur; this can be prevented by giving capsules individually during a 15 minute window.
- Please note that 5-FC level monitoring for HIV-associated CCM is not routinely required.
- Flucytosine can cause bone marrow depression leading to neutropaenia and thrombocytopenia. Monitor FBC & U&Es.
- FDA pregnancy Category C: Species specific teratogenicity in animal models.



5-FC dosing

Weight of Patient	Quarterly 6 Hour 5-FC Dosing (mg)	500mg Tablets
30 - 39 kg	500-1000-500-1000	1-2-1-2
40 - 49 kg	1000	2-2-2-2
50 - 59 kg	1000-1500-1000-1500	2-3-2-3
60 - 69 kg	1500	3-3-3-3
70 - 79 kg	1500-1200-1500-2000	3-4-3-4

The majority of patients will be over the 40- 49kg weight band



Renal Toxicity Management – 5-FC

Please refer to the CCM poster and safe 5-FC administration poster

- Ensure adequate hydration.
- If creatinine remains high or climbs despite increased hydration then switch to second line induction regimen: 2 weeks fluconazole + 5FC. Adjust 5FC dose as needed.
- Avoid nephrotoxic drugs such as NSAIDs (Non steroidal anti-inflammatory drugs) including ibuprofen and aminoglycosides.
- Monitor electrolytes closely – acute renal failure can lead to life threatening hyperkalaemia.



5-FC dose interval adjustment for renal impairment

- 5-FC may accumulate in renally impaired patients due to poor levels of excretion.
- The half life of 5-FC is prolonged in patients with renal insufficiency; the average half-life being 85 hours (compared to 2.4-4.8 in normal patients).
- 5-FC blood concentrations should be observed closely in these patients to monitor excretion.
- If creatinine clearance reduces to $< 50\text{mL}/\text{min}$, give the same initial $25\text{mg}/\text{kg}$ dose but increase the interval between 5-FC doses as per the adjacent table.

5-FC dose interval adjustment in renal impairment

Creatinine Clearance	Individual dose (mg/kg)	Dose Interval (hours)
>40	25	6
20-40	25	12
10-20	25	24
<10	25	>24

Est. Creatinine Clearance = $(140 - \text{age}) * (\text{weight in kg})$

$/ (72 * \text{serum Cr in mg/dL})$ [Multiply result by 0.85 for women]



5-FC dosing in case of neutropaenia

- Always repeat neutrophil count the next day if a grade 3 (500-749 $10^6/L$) or 4 (<500 $10^6/L$) case of neutropaenia has been recorded.
- If a patient has a sustained Grade 3 neutropenia (confirmed the following day), monitor carefully and if trend worsens halve the dose of 5-FC.
- If Grade 4 neutropaenia, or neutropenia-related complications develop, stop 5-FC immediately.
- Consider re-introduction of 5-FC if the neutrophil count the following day is grade 3 or better. If grade 3, re-introduce at half dose.

Platelets < 50,000 cells/mm ³ or Neutrophils < 750 cells/mm ³	If grade III range* monitor closely + if worsens then halve the dose of flucytosine (50%).
Platelets < 25,000 cells/mm ³ or Neutrophils < 500 cells/mm ³	Monitor closely and halve dose of flucytosine (50%).

*Grade III Platelets: $25,000 \leq 50,000$ cells/mm³

*Grade III Neutrophils: 400—599 cells/mm³

DAIDS AE Grading Table V2.1 July 17



5-FC monitoring

Schedule for minimum laboratory monitoring for 1 week AmB + 5-FC

	Week 1 AmB Administration				
Day of Treatment	1	3	4	5	7
Minimum laboratory monitoring	Potassium (K) Creatinine (Creat) Haemoglobin (HB)		K Creat HB		K Creat HB

If results are abnormal on day 7, repeat on day 10

Please refer to the CCM poster on safe AmB administration

Refer to Safe Administration of Amphotericin B Workshop



5-FC monitoring

Minimum 5-FC laboratory monitoring **two weeks fluconazole + 5FC regimen**

	2 Weeks oral regimen administration				
Day of Treatment	1	3	7	10	14
Minimum Laboratory Monitoring	Haemoglobin (HB) Neutrophils (N) Platelets (P)		HB N P		

If results abnormal on day 7, repeat on day 10



How to administer Fluconazole?

- Oral antifungal medication available in 50, 100, 150, or 200 mg tablets.
- The 200mg tablet formulation is preferred for CCM treatment.
- Fluconazole dosage for 2nd and 3rd line induction treatment of CCM: 1200mg daily in combination with either 5-FC or AmB for 2 weeks.
- Fluconazole is also used for the maintenance and consolidation phases of CCM treatment (different dosage to induction phase).



Safe Administration of Fluconazole



- Can also be taken as an oral suspension.
- Taken with or without food and taken at any time of day.
- If concomitant use of sulfonylurea derivatives there is a risk of hypoglycaemia, so check glucose levels more often.
- Fluconazole may increase level of phenytoin, warfarin and sulfonylurea derivatives. If concomitant use of warfarin: check INR (International normalised ratio).
- Category D risk in pregnancy-
FDA: Chronic, high doses fluconazole(400-800mg/day) may be associated with rare and distinct set of birth defects in infants whose mothers were treated with fluconazole during 1st trimester.
- Also used to treat vaginal candidiasis (thrush) and oropharyngeal candidiasis.



Side effects and drug interactions

Side effects - rare

- Abdominal pain
- Headache, dizziness
- Rash
- Liver toxicity
- Monitor patients closely for signs of liver toxicity (rare).
- TB medications – rifampicin. Concomitant use of rifampicin and fluconazole decreases levels of fluconazole in the blood. In practice, fluconazole dose increased by 50% in induction phase. Consider increase 50% fluconazole dose during consolidation and maintenance phases of treatment.



Summary

- 5-FC level monitoring for HIV-associated CCM is not routinely required.
- Monitor FBC and U&Es whilst on 5-FC.
- Adjust the dose of 5-FC in cases of renal impairment (creatinine clearance <50 mL/min) and neutropaenia.
- FDA Category D for fluconazole in 1st trimester pregnancy.
FDA Category C for flucytosine in pregnancy.



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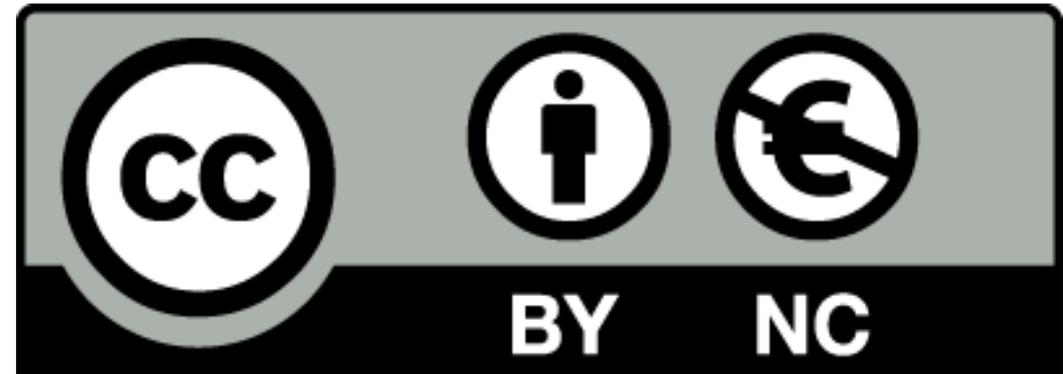
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