BHIVA guidelines for the treatment of opportunistic infections: candidiasis

Public consultation comments

Compilation of all comments received via the BHIVA website. The writing group thanks everyone who replied to the consultation. All comments were considered by the writing group and amendments have been made where appropriate.
14 September 2018

Contents

	Name	Affiliation	Comments	Writing group response
1.	John Walsh	Imperial College Healthcare	Good, clear guideline	We appreciate the supportive comments
2.	Neal Marshall	Gilead Sciences UK	Thank you for the opportunity to review the candidiasis section of the BHIVA OI guidelines The following comments are provided by the Gilead UK HIV medical affairs team Within table 7.1 - Amphotericin + tenofovir: We would suggest specifying that it is tenofovir disoproxil fumarate (TDF) that should be used with caution with amphotericin. Note that this caution is listed within the TDF, but not TAF HIV portfolio SmPCs Truvada SmPC: https://www.medicines.org.uk/emc/product/3890 accessed 5/8/18 Descovy SmPC https://www.medicines.org.uk/emc/product/2108 accessed 5/8/18 This would also be consistent with the HIV-druginteractions.org website	The table has been further reviewed and amended as requested. Of note, the tables have not yet been reviewed by the guidelines pharmacist but will be as part of the last round of reviews

			Please note there are recommendations on use, monitoring and dosing with concomitant use of guideline advised antifungals within the following ARV SmPCs that the Writing Group may wish to review: Tybost (cobicistat) SmPC: https://www.medicines.org.uk/emc/product/1277 accessed 5/8/18 Stribild SmPC https://www.medicines.org.uk/emc/product/3154 accessed 5/8/18 Genvoya SmPC: https://www.medicines.org.uk/emc/product/5063 accessed 5/8/18 Descovy SmPC https://www.medicines.org.uk/emc/product/2108 accessed 5/8/18 Odefsey SmPC https://www.medicines.org.uk/emc/product/7262 accessed 5/8/18 Thank you again for the opportunity to comment on these guidelines. Kind regards Neal	
3.	David White	Umbrella sexual health service	I'm not sure that the guidelines are correct in certain details. Firstly they suggest vaginal candidiasis is clearly associated with HIV immune deficiency but this was not the experience in the pre HAART era except on those who were very immune compromised. I recall it being controversial as to whether it was an AIDS defining condition. This is in keeping with recent immunological findings e.g. those by Paul Fidel suggesting that IL-17 is less crucial in the vagina. Finally Boric acid is very poorly documented as a treatment for antifungal resistance vagian infection. It's major advantage is that resistance is unlikely to arise. There is a small series from Rachel Challenor in the Int Journal of STDS and AIDS for antifungal resistant c. albicans in immune competent women and other publications of the use of flucytosine either alone or	Vaginal candidiasis is more common in PLWH in some series while severity and recurrence do not appear different. There is also not an association between vaginal candidiasis and CD4 T cell count. So we agree the impact of HIV is less on the vagina. We did not suggest it was an AIDS-defining condition or comment on the role of Th17 in the vagina which we agree may be less important. We have rephrased for clarity to remove any ambiguity

			with nystatin or amphotericin in C. glabrata. Some of this was summarised by Sophia Davies, myself and Liz Johnson in a "How to" paper in STIs a few years ago. Again this is all in immune competent individuals. The last few years have seen a reduction in price of voriconazole and this may now be a more affordable possibility albeit with considerable side effects.	We appreciate the comments about BA and the option of 5Fc/nystatin and associated reference which we have added
4.	Mark Bower	BHIVA	Fungal prophylaxis during chemotherapy / radiotherapy remains part of the HIV malignancy guidelines so perhaps this needs to be cross-referenced in the prophylaxis section? BW Mark	We appreciate Mark's comments and have cross referenced
5.	Ed Wilkins	Medical Action Myanmar	Excellent section. Just one comment under section 7.5.1 2nd sentence. I'm uncertain if the authors meant that 'itraconazole may be used when fluconazole resistance has been demonstrated but cross resistance is common'. Presumably this is 'uncommon'	We appreciate the comment and have revised accordingly
6.	Anna Goodman		The consultation had limited response as during summer and the link to the consultation document sent from BHIVA erroneously linked to the comments proforma whilst the comments proforma erroneously linked to the consultation document. As such we hope further consultation (perhaps after review) will be arranged. Some readers of the email may have given up rather than email to request how to access the document. We feel the structure would benefit from further review and the text from further clarifications. Our main comments and some minor comments are below however even if addressed in full we feel that the text may still benefit from a subsequent round of review prior to publication, particularly in view of the failure of the consultation email to link to the consultation document correctly on the initial consultation. If it is circulated a second time (and for future similar consultations) please do include line numbers for ease of reviewer's comments. General points: All microbial Latin names would usually be italicised including non-albicans Candida also all species names need capital letters which occasionally appear to be missing. In addition, the US spelling has sometimes been used in the text e.g. candidemia, rather than UK spelling for a UK guideline.	We are grateful for these concerns which will be highlighted to the guidelines committee The guidelines will be returned to BIA for further review Genus and species names had been italicised and we have rechecked for any omissions and corrected these. We have italicised *albicans* in non-*albicans* but do not agree that species names should be capitalised, which is not the normal microbiological nomenclature.

				If this was intended to suggest genus names should be italicised, we have rechecked this. We have checked again and found one incident in the text. We have not changed the occasions when US spelling was used in publication titles (for example multiple references to esophageal), which by convention we do not believe should be changed
			As the GRADE system has been included please could some expanded methodology be included (perhaps in an appendix)- which of the 4 authors reviewed the papers? Were the conclusions those of all 4 or differing authors for each section? Is there a table of papers included and excluded and bias etc. grading given? This is particularly helpful when papers are excluded for the reader to understand why. And where low level of evidence is cited is this because none of the papers had looked into it or the evidence was weak?	We have added further detail to the methods but this is one of multiple sections and detailed methods would seem best placed online This will be further discussed with the BHIVA guidelines committee but we agree further methodological details should be included probably online
			The document could ideally guide the reader through for example monitoring of the medication and what to try once 14 days fluconazole has failed in a sensitive strain for example- with focus on the different syndromes. This could be a box with key points e.g. no prophylaxis, 14 days 100mg as first line (or whatever BHIVA feel it should be) in azole-susceptible strains, micro-guided in others, what to do if that fails and how often it might be expected to do so.	We have attempted to simplify the text and also restructured the treatment text which we hope will make this clearer
			Page 1 (lines counted from the top of each section) Keywords: Was esophagitis (US spelling) included in the search terms?	The text has been edited to address points except where highlighted below
			7.2 2nd line: Candida does not require selective media. Delete 'using selective media'. Should also include GI tract/faeces. 7.2 3rd line: makes no sense. Colonisation samples can be very helpful in choosing treatment as resistance does occur. Also, presence or absence of Candida can help to rule it in or out in patient's symptoms. Vulval itch has multiple possible causes. 7.2 lines 10-14: wordy - we suggest a summary statement e.g. 11-50% according to stage (with references). Also, oesophageal candidosis in HIV positives is still an AIDS-defining illness to our knowledge. 7.2 paragraph 2 final statement- Does this mean there is no increase in vulval/vaginal issues in HIV? If so please could the reference be	We have edited the text but do not feel we can recommend routine analysis of colonisation patterns. Instead we have re-emphasised the need for samples from episodes with clinical presentation

			included. The term commonly used is Vulvovaginal candidosis(Br)/candidiasis(US), VVC. 7.2 paragraph 3 'Candidemia'- candidaemia- British guideline, no need to capitalise in this context. 7.2 paragraph 3 line 1: The risk factors for candidaemia do not include healthcare experience (we are unsure of the meaning of this). The main risk factors are broad spectrum antibiotics, multiple & longstanding lines, ICU stay, TPN etc. If the paragraph is referring to risk factors solely within HIV which we think it is then this needs repeated clarification in the text. 7.2 paragraph 3 Line 2: 'patients living with HIV'- people rather than patients more usually and in other parts of the text 7.2 paragraph 3: 'numerous updated guideline documents' -reference 12-15 are not all guidelines- perhaps refer to reference 14 as main updated guideline together with the European (ESCMID) guideline (ref #5) 7.2 paragraph 3 Final line: why particular risk in HIV of non-albicans? They are risk in all with compromised immunity. Candida albicans is generally thought to be the most pathogenic and virulent of the Candida species. The only reason for becoming colonised with non-albicans Candida species is their natural resistance to fluconazole and overuse of fluconazole. Please note, the term is non-albicans Candida species (not non-albicans species which can refer to any genus of life) Page 2 7.2.2 L9- no capital in candidiasis- this paragraph is the microbiome fully reversed? As the subsequent sentences suggest this may be partial perhaps? The last sentence seems to not flow and lists some risk factors which would impair immunity such as diabetes. 7.3.1 L5- pseudomembranes it may be rather than membranous - should say 'other oral presentations' rather than other presentations- vaginal candidiasis is common but also in those without HIV - is it more common? This is not explained. Also, as stated in the BASHH VVC guidelines the symptoms are non-specific and colonisation is common whereby diagnosis can be very tricky. There are other causes for itch and discharge beyond thrush. In particular, poor clinical response (in the absence of evidence of microbiological resistance) should alert the reader to consider other infections, dermatological conditions, eczema etc. The section on VVC should be expanded if it is considered to differ	

			in HIV. Or alternatively the authors could state it is not a problem in HIV any more than in general population and should be managed as usual (if this is what is believed). Are the cases with oesophageal not oral a minority? The authors subsequently state 55% which would be a majority 7.4 Bullet points are nice but only included for diagnosis and treatment and may be helpful in other sections. In case of poor/partial response to given treatment, culture and sensitivity testing is very helpful in clarifying if there is resistance or a second/alternative cause for the symptoms. This should be clarified (i.e. why?) 7.4.1 What exactly do you mean by scrutinising azole use? OTC? How do you suggest this is done? The evidence is there for the detrimental impact of low dose long term azole use on sensitivity. Once weekly 150mg fluconazole less so. This needs to be clarified. Also, with HAART, this should be less of a problem. Also, it seems liberally used in vets and environment and empiric azoles for oral/oesophageal first line still seems reasonable. If 'Candida' (with a capital C) then should be in italics too 7.4.2. Do we want this in a clinical guidance? Laboratory methods are very clearly defined by the UK standards (SMIs – see .gov) and laboratories have to follow these to be accredited. On the other hand, the document would benefit from inclusion of information about sampling – what is the best method to take a sample and from where (cheeks/ tongue/ teeth/ throat, vulva/ vagina/ HVS, swab/ scraping/ biopsy) and what is the role of self-sampling. These issues would be of greater relevance to the readers of this guideline. 7.4.3 'endoscopy should reveal white patches'- it usually would be but what if not? Perhaps 'should reveal typical appearances' is more accurate- also can malignancy be under the 'white patch'? Need to remind the need for microbiological samples to be sent for ID and sens. And clarify how to do so. 7.5 Treatment- azoles may be preferred option but surely only if	Bullets not included for other sections as not associated with GRADE recommendations. Thus adding for areas such as risk factors or background microbiology do not seem warranted. This reflects formatting across all sections Information has been added Information has been added

			sensitive/albicans - so some proviso of that in the bullet point and reminder of the need of diagnostics. 7.5.1 no question mark needed after line 1 As treatment of oral, oesophageal and vaginal candida infections are very different we suggest this be divided into three sections. The main differences are: Oral thrush is a biofilm disease giving rise from dental plaque and it requires mechanical removal of the biofilms using a toothbrush and floss. Disinfecting mouth rinses can help controlling the plaque and topical/systemic antifungals are adjunctive. A useful reference to this could be Oral candidosis--clinical challenges of a biofilm disease. Rautemaa R, Ramage G. Crit Rev Microbiol. 2011 Nov;37(4):328-36. With oesophageal disease, good oral care is an important part of source control as well but the treatment itself requires systemic antifungals, normally significantly higher doses compared to oral thrush. Also, GORD favours Candida growth in the oesophagus and has to be manged properly for optimal good long-term results. VVC on the other hand, is less of a biofilm disease and often problem is made worse by increasing hygiene measures disrupting the normal flora. Instead, good skin care with emollient creams is important. There is detailed info re this in the updated BASHH guideline. L3 'is prescribed for 7-14 days' should be prescribed? Is usually prescribed? L4 itraconazole- 'may also be effective' or some other wording- it reads like you could just use it rather than fluconazole routinely otherwise. Note, that most other azole antifungals (including itraconazole) have significant drug-drug interactions with HIV drugs and a link to the Liverpool database in addition to the helpful table would be of use. Itraconazole is not an easy option in HIV patients and requires TDM to avoid resistance (low levels) and toxicity. Mention of TDM would be helpful. L8 would be nice to have figures e.g. 95% response both groups but this is in setting of high albicans L9 - reads oddly to the reader L13 doesn't make sense and needs mention that gastric acid still important with oral solution preparation - and withholding (spelled incorrectly) PPI- Is there in vivo evidence too? We agree it is important to mention that PPIs interact with azoles	We mostly agree with these comments, but not completely with regard to GORD; there is much evidence for PPI promoting Candida although also some studies that do not confirm this. So we do not feel we can routinely recommend this Links to BASSH Candida guidelines to be clarified

			(particularly with itraconazole and voriconazole) and can increase the levels to toxic levels. Is the evidence listed sufficient to clearly conclude withholding this treatment given the impact of GORD on maintaining the Candida? If so please could this be clarified with suggestion of e.g. ranitidine switch. 7.5.2 L6- 'where this is not possible' does this mean not possible to swallow? Or where azoles are contraindicated e.g. due to heart failure- and also some mention of heart failure would be helpful in general- it is BHIVA guidance so if clotrimazole troches are really never available in UK perhaps some explanation of UK access or appendix mention. For all these alternatives some efficacy data would be helpful if available. 7.5.3 L8 'altered susceptibility' in some cases inherent resistance – we suggest 'reduced susceptibility' as perhaps alternative appropriate terminology. If 100mg every other day or 150mg twice weekly or 100mg once daily is the favoured regime please clarify. Perhaps worth mention of concerns of resistance with 50mg od as the current document reads (at first read at least) as though 50-100mg is the preferred dosing. Monitoring? Nil on this- LFTs? How often? Levels of itraconazole (if available?)? 7.5.4 if invasive disease is treated as in non-HIV then perhaps so should auris? 7.6.1 random) typo L2 L10- odds ratio of what? L11-12 but this is not mucosal - why mentioned here in this section? A conclusion of sorts may be helpful even if a single line though perhaps this will be less relevant in the full document of all OIs.	
7.	Andy Ustianowski		I think this is a well written and useful update to the BHIVA OI guidelines. I have just a few minor points: Section 7.3.1: It is commented that 'oesophageal candidiasis without oral evidence of plaques is infrequent', and then 2 lines later that 'in a minority of cases oesophageal candidiasis may occur without oral involvement' [a repetition] but then the data supporting it states that' 55% had no oral candida' - the phrasing needs considering to remove repetition but also 55% is neither infrequent nor a minority -	We appreciate these comments and have addressed each point raised

			alternatively reference other papers. Section 7.4 - Diagnosis: does not significantly comment on candidaemia/blood cultures Section 7.5 - the only dosing and length of therapy data is provided for fluconazole - people refer to guidelines often to establish dose and duration - perhaps a table for all the agents mentioned? Section 7.5.1 - The sentence commencing 'Therefore patients with low CD4...' in para 2 does not make sense - is there some phrasing missing? Section 7.5.2 - is this guidance for UK physicians or aimed as an international resource? - this affects whether there is discussion (as there is) about products only available in the US. Section 7.5.3: With a comment such as 'Caspofungin, micafungin and anidulafungin have shown efficacy comparable to fluconazole....' it would be useful to define what you mean by efficacy - as in some parameters there seems to be comparable data but not others (as you comment in following sentence). There is a need for further editorial review: There are a few typos that should be addressed - including: variable use of capitals in Candida, candida, Candidiasis, candidiasis etc.; occasional missing word such as section 7.2.1 should read 'C. auris, an inherently multi-drug resistant species....'; there are '?' at the end of some of the headings and the word 'recommended' needs removing at end of heading for 7.6.2; first 2 lines of section 6 need formatting as for other recommendations; missing odds ratio for reference 78 in 7.6.1 I congratulate the authors on a good review.	
8.	Roy Trevelion		Many thanks for this revised section on candida. It is very comprehensive. As it says, "Overall prevalence has been substantially reduced by virtue of cART availability." It also says that, "The most successful strategy for managing patients with candidiasis is to commence cART."	Thank you for these comments

			And even though drug-drug interactions should be considered with ARVs and antifungals, "meta-analysis . . . confirms cART dramatically reduces the incidence of mucosal candida with oral candida being one of the opportunistic infections showing greatest impact." It's serious of course if you can't swallow because of oral candida. But is this only the case with very late HIV diagnosis? In this instance the details of drug interactions are helpful. It's good to know that once started, "effective cART prevents relapses of symptomatic candidiasis." Thanks again, Roy	
9.	Sebastian Lucas	GSTT	I note that no mention is made of biopsy or histology in the diagnosis of candidiasis [I word checked the text] - which is a bit odd in that a) quite a number of cases - this is purely anecdotal - are diagnosed by histopathologists for the first time; b) the text mentions endoscopy - as a last resort for diagnosis - without continuing with the fact that in many/most such procedures, biopsies are taken. And all such biopsies end up in Cellular Pathology labs. Do you want me to compose a sentence or two, or can you just distil this information yourselves. I know of no data that give the sensitivity/specificity of histopathologists observing ?candida infections, but presumably neither is 100%.	Some further discussion on the role of histopathology has been included
10.	Liz Hart	Nottingham University Hospitals	Thank you for asking me to read this, Regards Liz 1. In a prospective endoscopy study people living with HIV reported higher symptom scores for a range of upper gastrointestinal symptoms, and neither odynophagia or dysphagia were predictive of candida oesophagitis [40]. Does this mean that people had lots of OGD performed? Would it be simpler to miss out the 'In a prospective endoscopy study' or to clarify	These comments have been addressed

			what the study was about because this sounds a little odd. 2. Therefore patients with low CD4 T-cell counts are thus best treated those requiring systemic antacid preparations are unsuitable for itraconazole. From 7.5.1; the language used here does not make sense, there are a number of instances in the document where the sentence structure could be simplified and reduced to make the sentences clearer to understand. These may be ironed out at the final editing stage of course. 3. 7.5.2, I had to look up what troches were – would it be possible to use lozenges? 4. 7.5.4: is there any merit in adding in treatment lengths for invasive candidiasis or something along the line of 'treatment length may depend on patient factors and presence of deep seated source of infections'? 5. 7.6.1 A case control study in a high income setting examining the risk of oesophageal candidiasis shows cART is associated with a reduced odds ratio of [78]. Of what? 6. Is it worth mentioning that levels of some anti-fungals can be monitored if felt to be necessary and there are concerns regarding drug interactions and possible low/high antifungal levels? Eg itraconazole/voriconazole	