Southern African Journal of Infectious Diseases

FIDSSA Guideline: Recommendations for Detection, Management and Prevention of Healthcare-Associated *Candida auris* Colonisation and Disease in South Africa

Nelesh P. Govender[1, 2, 3], Theunis Avenant[4], Adrian Brink[3, 5], Vindana Chibabhai[2, 6, 7], Joy Cleghorn[8], Briette du Toit[9], Chetna Govind[10], Elsie Lewis[11], Warren Lowman[2, 12], Hleziphi Mahlangu[13], Caroline Maslo[14], Angeliki Messina[2, 14], Mervyn Mer[2, 7], Kim Pieton[15], Sharona Seetharam[10], Charlotte Sriruttan[1, 2], Karin Swart[14], Erika van Schalkwyk[1]

Affiliations

1. National Institute for Communicable Diseases [Centre for Healthcare-Associated Infections, Antimicrobial Resistance and Mycoses], a Division of the National Health Laboratory Service, Johannesburg, South Africa
2. Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa
3. Faculty of Health Sciences, University of Cape Town, Cape Town, South Africa
4. Kalafong Provincial Tertiary Hospital and Faculty of Health Sciences, University of Pretoria, Pretoria, South Africa
5. Ampath Laboratories
6. National Health Laboratory Service, Johannesburg
7. Charlotte Maxeke Johannesburg Academic Hospital, Johannesburg
8. Life Healthcare Group, Johannesburg
9. Mediclinic Southern Africa, Cape Town
10. Lancet Laboratories
11. Steve Biko Pretoria Academic Hospital, Pretoria
12. WITS Donald Gordon Medical Centre and Vermaak and Partners Pathologists, Johannesburg
13. Clinix, Johannesburg

14. Netcare Hospitals Limited, Johannesburg

15. Chris Hani Baragwanath Academic Hospital, Johannesburg

Corresponding author: Dr Nelesh P. Govender, National Institute for Communicable Diseases, 1 Modderfontein Road, Sandringham, 2131; telephone +27 11 555 0353; email neleshg@nicd.ac.za

Running head: *Candida auris* recommendations, South Africa

Conflicts of interest: All members of the guideline development group completed an International Committee of Medical Journal Editors (ICMJE) conflicts of interest form. Over the past 36 months, Adrian Brink served on speakers' bureaus for MSD South Africa and Pfizer. Warren Lowman received speaker fees from MSD South Africa, Pfizer and Astellas. Charlotte Sriruttan received a travel grant from MSD South Africa. For all other authors, no conflicts of interest were declared.

Funding: A face-to-face meeting of the guideline development group on 6 July 2017 was supported by MSD South Africa Pty (Ltd) through a grant provided to the South African Society for Clinical Microbiology. MSD also supported publication of this guideline through a grant to the Federation of Infectious Diseases Societies of Southern Africa. MSD had no role in developing these recommendations.

Word count (body): 8996

Abstract

Candida auris has been detected at almost 100 South African hospitals, causing large outbreaks at some facilities and this pathogen now accounts for approximately 1 in 10 cases of candidaemia. The objective of this guideline is to provide updated, evidence-informed recommendations outlining a best-practice approach to preventing, diagnosing and managing *C. auris* disease in public- and private-sector healthcare settings in South Africa. The 18 practical recommendations cover five focus areas: laboratory identification and antifungal susceptibility testing, surveillance and outbreak response, infection prevention and control, clinical management and antifungal stewardship.

Introduction

Cases of *C. auris* were first reported from East Asia in 2009, though earlier cases have since been detected in culture repositories from as early as 1996 (1-3). By 2018, cases of *C. auris* had been reported from all six inhabited continents (3, 4). Of particular concern, large outbreaks of *C. auris* have been reported from resource-limited settings in Asia, Africa and South and Central America (5-8). For instance, *C. auris* has been detected at almost 100 South African hospitals, causing large outbreaks at some facilities and this pathogen now accounts for approximately 1 in 10 cases of candidaemia (7, 9).

The reasons for the dramatic emergence of *C. auris* as a pathogen in healthcare settings are not clear. We know that East Asia, South Asia, Africa and South America have unique *C. auris* clades separated from other clades by tens of thousands of single nucleotide polymorphisms (10). This is consistent with the hypothesis that *C. auris* emerged independently and simultaneously on several continents. While *C. auris* is likely to have an environmental reservoir outside the healthcare setting, this has yet to be established. Several intrinsic properties of the pathogen probably facilitated its rapid spread in hospitals. *C. auris* produces biofilms (11-13). While this fungus rarely colonises the hands of healthcare workers, it can survive for prolonged periods in the immediate environment around infected or colonised patients and in a recent outbreak investigation, was found to contaminate re-useable patient equipment (13-15). *C. auris* is also relatively resistant to some chemical disinfectants (16, 17). Transmission can thus occur from an infected or colonised person, the patient care environment or re-useable equipment to a susceptible person. In South Africa, *C. auris* has become a common healthcare-associated pathogen in the same geographic region where azole-resistant *Candida parapsilosis* was first described (18). It is likely that inadequate antifungal stewardship (AFS) and infection prevention and control (IPC) programmes are the underlying drivers of the emergence and transmission of these azole-resistant pathogens. IPC and AFS are two key areas covered in this guideline document. *C. auris* causes healthcare-associated outbreaks and is a public health concern;

therefore, locally-relevant recommendations for appropriate surveillance and outbreak response activities are essential and covered herein.

Without a clear laboratory algorithm, *C. auris* is often misidentified by routine methods (19). Misidentification delays initiation of appropriate antifungal treatment and rapid institution of IPC measures. *C. auris* causes a wide range of invasive and non-invasive infections and colonises various body sites. Identification to species level is not routine for isolates from non-sterile sites so *C. auris* would be missed unless this is specifically looked for (20). *C. auris* is almost universally resistant to fluconazole and has variable susceptibility to other classes of antifungals (5, 10, 21). The lack of clinically-relevant breakpoints currently limits interpretation of minimum inhibitory concentrations (MICs) and hence guidance for individual patient treatment (22). This guideline includes recommendations for identifying and performing antifungal susceptibility testing for *C. auris*.

Owing to its relatively recent emergence, cases of *C. auris* were not included in pre-registration clinical trials for currently-available antifungal agents. Recommendations for antifungal treatment of *C. auris* disease are thus extrapolated from evidence for *Candida* infections with other species and there are no published recommendations for low- and middle-income countries (23). Based on South African surveillance data, the following independent risk factors have been identified for *C. auris* candidaemia: older patients, prolonged hospitalisation, admission to private-sector facilities and having a central venous catheter in situ (9). These risk factors are not sufficiently specific and so healthcare workers need to maintain a high index of suspicion for *C. auris* particularly in settings where this pathogen is endemic.

The objective of this guideline is to provide updated, evidence-informed recommendations outlining a best-practice approach to preventing, diagnosing and managing *C. auris* disease in public- and private-sector healthcare settings in South Africa. The recommendations

contained in this guideline are not all specific to *C. auris* and some sections (e.g. IPC, AFS, antifungal treatment) may be applied to healthcare-associated infections caused by other *Candida* species. This guideline is aimed at medical practitioners, nurses, IPC practitioners, clinical pharmacists, clinical microbiologists, laboratory technical personnel and members of interdisciplinary IPC/ antimicrobial stewardship hospital committees who are involved in diagnosis, prevention or management of *C. auris* in a healthcare setting. Although these recommendations were designed for acute-care settings, aspects of this guideline may also be applicable to chronic-care settings. Implementation of the recommendations should be informed by local context, including epidemiology of fungal infections and prevalence of other comorbidities, availability of resources, the organisation and capacity of the healthcare system and anticipated cost–effectiveness of the recommendations.

Methods

No previous South African guideline on candidiasis has been published. For this guideline, the Federation of Infectious Diseases Societies of Southern Africa convened a multidisciplinary panel. Nominations to the guideline development group were requested from the chairpersons of the following professional societies or groups: South African Society for Clinical Microbiology (including National Health Laboratory Service and private pathology practices), South African Paediatric Infectious Diseases Society, Infectious Diseases Society of Southern Africa, Infection Control Society of South Africa (including public- and private-sector IPC practitioners), South African Antibiotic Stewardship Programme and Critical Care Society of Southern Africa. In addition, members were nominated from the following institutions or private healthcare groups: National Institute for Communicable Diseases, Life Healthcare Group, Netcare, Clinix and Mediclinic Southern Africa.

An in-person meeting was convened in Johannesburg on 6 July 2017 to discuss and propose recommendations. The 19-member panel comprised of 7 clinical microbiologists, 1 paediatric infectious diseases (ID) specialist, 1 adult ID specialist, 1 critical care physician, 5 IPC nurse practitioners, 1 general medical practitioner, 2 medical epidemiologists and 1 clinical pharmacist. The proceedings of the meeting were recorded and transcribed. At this meeting, members were assigned to writing groups for each section. The writing groups subsequently met in person or via teleconference or corresponded by email to draft each set of recommendations. Compiled draft recommendations were presented by N.P.G for discussion on 4 November 2017 at the 7th FIDSSA conference in Cape Town. The guideline development group then re-convened by teleconference on 27 November 2017.

Owing to the paucity of high-quality evidence specifically relevant to *C. auris*, systematic reviews were not conducted for each focus area prior to developing this guideline. The chairperson (N.P.G.) conducted a literature review prior to the July 2017 meeting and

uploaded all relevant full-text articles or documents to a cloud-based file share service. Each writing group also conducted separate reviews of the literature. The quality of evidence was not specifically rated for each recommendation. The strength of each recommendation was also not quantified. These recommendations should thus be considered to be based on expert opinion. The guideline document was circulated to an external peer review group in May 2018. This group included 5 nominees from the professional societies listed above who had not been involved in developing the guideline (Sean Wasserman, Jeremy Nel, Colleen Bamford, Shaheen Mehtar, Lesley Devenish). The guideline was endorsed by the Federation of Infectious Diseases Societies of Southern Africa, South African Society for Clinical Microbiology, South African Paediatric Infectious Diseases Society, Infectious Diseases Society of Southern Africa, Infection Control Society of South Africa and the Critical Care Society of Southern Africa.

Section 1: Laboratory identification and antifungal susceptibility testing

Recommendation 1.1: When should the diagnostic laboratory suspect *C. auris*?

Current commercial automated or biochemical identification systems misidentify *C. auris*, often in a predictable manner. Yeasts identified as any of the organisms by the corresponding presumptive identification method (refer to Table 1) should be suspected to be *C. auris*, particularly if found to be fluconazole resistant, and tested further as per the recommended laboratory algorithm (refer to Figure 1).

Early identification of *C. auris* is important to guide appropriate antifungal treatment and to implement appropriate IPC measures. The laboratory should suspect *C. auris* when specimens are submitted from facilities or units known to be endemic for this pathogen. In a recent South African study, the odds of *C. auris* candidemia (versus fungaemia caused by any other *Candida* species) was three-fold higher among patients admitted to private-sector hospitals. Other risk factors included older age, longer hospitalisation before first positive culture and a central venous catheter in-situ (9). Current commercial identification systems often misidentify *C. auris* as the organisms listed in Table 1 (19, 20). *C. auris* is almost uniformly resistant to fluconazole (10); if a yeast is found to be resistant to fluconazole and the first-line automated or biochemical identification system also yields an unexpected identity (Table 1), consider *C. auris* and refer to a laboratory with Vitek 2 YST software version 8.01 or a matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) instrument or molecular testing platform.

Recommendation 1.2: How should *C. auris* be identified in the laboratory?

1. Perform species-level identification for all *Candida* isolates cultured from sterile body sites. Ideally, species-level identification should also be obtained for *Candida* isolates cultured from all non-sterile sites. However, in situations where this is not routinely possible, we recommend speciation from non-sterile sites:

196 a. If a patient is transferred from a facility known to be endemic for *C. auris*
197 b. During suspected or confirmed *C. auris* outbreaks
198 c. Among critically-ill patients
199 d. For severe infections
200 e. When a patient is being treated for a suspected invasive *Candida* infection
201 and is not responding to first-line antifungal therapy at appropriate doses
202 despite adequate source control
203 2. Confirm identification of *C. auris* on a MALDI-TOF instrument, the Vitek 2 YST ID
204 system or by sequencing the multi-copy fungal ribosomal gene (ITS or D1/D2
205 regions)
206
207 *C. auris* isolates are frequently misidentified in the clinical laboratory. They are germ tube-
208 negative yeasts and are able to grow at relatively high temperatures (42°C) (11). They
209 appear pink or purple on chromogenic *Candida* agar (CHROMagar, Paris, France).
210 Confirmation of species-level identification can be performed using either a MALDI-TOF
211 instrument (such as VITEK MS (Biomérieux, Marcy l'Étoile, France) or Bruker Biotyper
212 (Bruker, Billerica, Massachusetts, USA) using the corresponding research use only/
213 customised databases) or the Vitek 2 YST ID system (Biomérieux) updated with software
214 version 8.01 (19, 24). Molecular identification is the reference standard method (25, 26).
215 *Candida* should be routinely identified to species level if isolated from a sterile site such as
216 blood, cerebrospinal fluid, tissue, pus from deep abscesses, etc. Not all diagnostic
217 laboratories routinely identify *Candida* species other than *Candida albicans* from non-sterile
218 sites to species level. This may result in under-reporting during outbreaks. The guideline
219 development group believe that species-level identification is particularly important to detect
220 *C. auris* from all specimens for the following reasons: *C. auris* outbreaks may be prolonged
221 and difficult to control; patients who are colonised represent an important reservoir for
222 transmission. *C. auris* is potentially multidrug-resistant, with consistently high fluconazole
223 minimum inhibitory concentrations (MICs) and occasionally, high amphotericin B and

echinocandin MICs. Reported cases of therapeutic failure have been documented with azoles and amphotericin B (3, 16, 17).

Recommendation 1.3: When should antifungal susceptibility testing for *C. auris* be performed and how should results be interpreted?

1. Perform routine antifungal susceptibility testing if *C. auris* is isolated from
    a. Blood or any other sterile-site specimen
    b. Among all critically-ill patients
    c. From a non-sterile site if the patient is clinically unresponsive to appropriate antifungal therapy
    d. If there is persistent, recurrent or relapsed infection despite appropriate antifungal therapy and source control
2. If possible, perform antifungal susceptibility testing using a standardised broth microdilution method, Sensititre YeastOne or E-test. Confirm all Vitek 2 amphotericin B MICs by another method.
3. The following agents are recommended for antifungal susceptibility testing: fluconazole (also useful for identification), amphotericin B, anidulafungin/ micafungin. Caspofungin minimum inhibitory concentration (MIC) testing should be avoided to predict echinocandin resistance.
4. For each antifungal agent that is tested, laboratories should report an MIC.
5. Epidemiologic cut-off (ECOFF) values can be used to categorise isolates as wild type or non-wild type (i.e. mutants) for each antifungal agent. If the MIC ≥ ECOFF for that agent, report to the clinician using a standard clearly-worded comment.
6. Laboratories may consider use of cut-off values proposed by the US Centers for Disease Control and Prevention (US CDC) (27) but should be clear that these are not validated clinical breakpoints and if the MIC is higher than the proposed cut-off value, provide a report to the clinician using a clearly-worded comment including a recommendation that a clinical microbiologist or ID physician be consulted.

7. Refer all strains with elevated amphotericin B (≥2 μg/ml) or anidulafungin/ micafungin MICs (≥4 μg/ml) for testing at a reference laboratory

If carefully standardised and quality-controlled, antifungal susceptibility testing can yield reproducible MICs that facilitate selection of the optimal antifungal agent for use in a particular clinical scenario. Most laboratories perform routine testing on isolates from sterile sites. In certain circumstances, outlined in the recommendation above, antifungal susceptibility testing should be performed on non-sterile site isolates. Although very important, an MIC is not the only factor to be considered when selecting an antifungal agent. The ability of an antifungal agent to kill the pathogen may be important for early treatment success and to reduce the chance of persistent, recurrent or relapsed infection (28). Some infected body compartments or sites (e.g. the central nervous system, urinary tract, eye, intra-abdominal abscesses) are not easily penetrated by echinocandins and the pharmacokinetics/ pharmacodynamics of various agents should be compared.

A standardised reference broth microdilution (BMD) test is the recommended antifungal susceptibility testing method to resolve discrepancies and to confirm unusual phenotypes. A direct comparison of the European Committee on Antifungal Susceptibility testing (EUCAST) and US Clinical and Laboratory Standards Institute (CLSI) BMD methods for a *C. auris* isolate collection yielded similar MICs for fluconazole, itraconazole, voriconazole, isavuconazole, posaconazole, anidulafungin, micafungin and amphotericin B (22). When CLSI-BMD and the commercial automated Vitek AST-YS07 were compared, there was 100% agreement of MIC_{50} values for voriconazole, caspofungin and micafungin and agreement for fluconazole and flucytosine within 2 dilutions. Of concern, Vitek AST-YS07 yielded falsely-elevated MICs (MIC_{50} of 8 μg/ml) for amphotericin B compared to the CLSI-BMD MIC_{50} of 1 μg/ml and an Etest MIC_{50} of 0.5 μg/ml (29). The guideline development group therefore recommends that all amphotericin B MIC results obtained with Vitek 2 AST-

YS07 system should be confirmed with another method. There are no data comparing Sensititre YeastOne or Etest MICs to reference BMD MICs for *C. auris*; however, these methods provide MICs with close approximation to the reference methods for other *Candida* species. Laboratories should avoid testing or reporting caspofungin MICs for detection of echinocandin resistance because this method is subject to error (21); however, any echinocandin (including caspofungin) can be used for clinical treatment if the pathogen is shown to be echinocandin-susceptible. Mutations in the hotspot regions of the FKS gene are usually associated with echinocandin resistance in *C. auris*, though very few laboratories currently perform FKS gene sequencing.

There are currently no clinical breakpoints for *C. auris* and any antifungal agent. As limited clinical and pharmacokinetic/ pharmacodynamic data currently preclude the development of such breakpoints, ECOFFs may be helpful. ECOFFs distinguish organisms with and without phenotypically-expressed resistance mechanisms for a species and an antifungal agent in a defined test system; within a species, this is the highest MIC of organisms lacking phenotypically-expressed resistance. ECOFFs may thus be used to identify isolates that are less likely to respond to antimicrobial therapy due to acquired resistance mechanisms (Table 2). Surveillance data from the National Institute for Communicable Diseases (unpublished, personal communication N.P. Govender) obtained from *C. auris* bloodstream isolates from South African public and private-sector hospitals roughly align with tentative ECOFFs determined for 123 *C. auris* isolates (22). The US CDC has applied tentative non-validated clinical breakpoints developed for other *Candida* species to *C. auris* for epidemiological purposes; however, these may not necessarily be clinically relevant at an individual patient level (27). Susceptibility data for *C. auris* isolates published from multiple countries demonstrate uniformly high fluconazole MICs, with variable susceptibility to the other azoles, echinocandins and amphotericin B (10). Some isolates may demonstrate high MICs to ≥2 antifungal classes (i.e. multidrug resistant).

Section 2: Surveillance and outbreaks

Recommendation 2.1: Should laboratory-confirmed cases of *C. auris* infection and colonisation be routinely reported through surveillance?

1. There should be nationally-coordinated surveillance for *C. auris* integrated into broader surveillance for antimicrobial resistance (AMR). The overarching goal is to prevent *C. auris* from becoming endemic in hospitals across South Africa.
2. At a facility level, all public-sector hospitals and private hospital groups should passively monitor the number of laboratory-confirmed cases of *C. auris* disease and colonisation.
3. At a national level, the National Institute for Communicable Diseases (NICD) should conduct regular cross-sectional surveys in order to monitor epidemiological and geographical trends over time.

C. auris is an emerging and multi-drug resistant pathogen that spreads rapidly in healthcare settings. The overarching goal of national surveillance is to provide information to prevent *C. auris* from becoming endemic in healthcare facilities and communities across South Africa and facilitate preparedness in laboratories for accurate detection and in IPC programmes for prevention and control (30). The objectives of surveillance should be to:

- At a healthcare facility level, to monitor the prevalence of culture-confirmed *C. auris* disease and colonisation
- At a healthcare facility level, to detect outbreaks
- At a national level, to detect emergence of antifungal resistance in strains of *C. auris* and thus guide empiric treatment
- At a national level, to describe potentially-modifiable risk factors for invasive disease and death

At a healthcare facility level, all public-sector hospitals and private hospital groups should passively monitor the number of cases of *C. auris* disease and colonisation by maintaining a line-list of culture-confirmed cases. The facility IPC practitioner/s should be promptly notified of every *C. auris* case and should keep a record of the number of cases, by site of infection, wards where cases occurred and rates of infection, if possible, on a monthly basis. Facilities may be classified into three tiers (regular re-classification should be done by the facility IPC practitioner/s.)

- Tier 1 ("green status"): Facilities with no prior cases of *C. auris* disease or colonisation. Such facilities are requested to report their first cases to the National Institute for Communicable Diseases (NICD) and/or the relevant district communicable disease control (CDC) team
- Tier 2 ("orange status"): Facilities with sporadic cases of *C. auris* infection or colonisation (i.e. <12 cases in the past 6 months and/or <3 units affected). Facilities are requested to report any increase in the number of cases compared to a baseline; units affected for the first time; or apparent clustering within a facility to the NICD and/or relevant district CDC team
- Tier 3 ("red status"): Facilities with relative endemicity (>12 cases in the last 6 months and/or >3 units with *C. auris* cases in the last 6 months) are requested to report any increase in the number of cases compared to a baseline or apparent clustering within a facility to the NICD and relevant district CDC team

At a national level, NICD should conduct regular cross-sectional surveys as part of integrated AMR surveillance. These surveys could be scheduled at the same time every year and could be integrated with national point prevalence surveys for healthcare-associated infections (HAI) and AMR (23). NICD should coordinate nested epidemiologic studies through its existing surveillance platforms. *C. auris* is included in a list of alert organisms that SA healthcare facilities are encouraged to compile (31). Guidance has been

issued from several other public health agencies across the world. US facilities are currently requested to report all cases to the US CDC, by using a dedicated email address (32). Public Health England (PHE) currently requests facilities to report all new cases of colonisation or infection to their local PHE Centre Health Protection Team. The European Centre for Disease Prevention and Control (ECDC) recommends that Member States consider laboratory-based notification of *C. auris* invasive disease and prospective data collection at national level . Surveillance systems for HAIs should be updated to include *C. auris* in the list of reportable pathogens associated with HAIs.

Recommendation 2.2: How should an outbreak of *C. auris* be defined, reported and managed?

1. All suspected clusters/ outbreaks should be reported to the relevant district CDC team and to the NICD in high-priority scenarios (refer to text below).
2. In a resource-constrained setting, outbreak response efforts should be focused on high-priority scenarios, as recommended in the text below.

An outbreak is defined as a sudden temporal increase in the number of cases of *C. auris* colonisation or infection within a unit or facility compared to a baseline, with epidemiological links which suggest clustering. The definition of an outbreak will not necessarily be the same for all units or facilities; therefore, each facility should be aware of their own tier status and distribution of prior cases within the facility. All suspected clusters/ outbreaks should be reported by the facility IPC practitioner or laboratory to the relevant district CDC team and to the NICD in the following high-priority scenarios. Not all outbreaks will require the same type of response. As resources for outbreak detection and response are limited particularly in the public sector, urgent outbreak response efforts should be focused on:

- Clusters of cases in
    - Patient groups who have not been previously described to be affected

387 - Units where the risk of horizontal transmission is high or consequences of
388 disease are severe, e.g. neonatal or oncology units
389 - Facilities with no prior cases (i.e. Tier 1/ green-status hospitals)
390 - Geographic regions with no/ few prior cases
391 • Large outbreaks in facilities with or without relative endemicity (i.e. Tier 2 or 3
392 facilities)
393
394 Outbreak response activities may include (but are not limited to):
395 • Intensifying IPC measures (refer to section 3), including screening of other high-risk
396 patients, e.g. a patient who has been in a neighbouring bed to a case patient in an
397 open ward and who is not known to have *C. auris* disease. Screening of facility
398 personnel is not routinely recommended during an outbreak
399 • Environmental screening, where appropriate
400 • Emphasising AFS (Section 5)
401
402 Outbreak investigations reported from other countries describe response activities which
403 have been effective. Following a large outbreak in a cardiothoracic facility in the United
404 Kingdom, screening of all direct contacts was recommended. Screening of hospital
405 personnel had a very low yield and was not recommended (33). In the United States,
406 screening of close contacts of 77 case patients resulted in identification of an additional 45
407 patients with *C. auris* colonisation. Public health surveillance and ongoing investigations
408 were recommended (23).

Section 3: Infection prevention and control

Recommendation 3.1: Which IPC precautions are necessary for patients colonised or infected with *C. auris*?

Two sets of precautions are recommended:

1. Standard precautions: These apply to all patients and in all situations and are designed to reduce the risk of transmission of microorganisms from both recognised and unrecognised sources of infection in healthcare settings.
2. Contact transmission-based precautions for patients known to be colonised or infected with *C. auris*: These are designed to interrupt transmission of epidemiologically-important pathogens such as *C. auris* based on the contact route of transmission.

Standard precautions apply to all patients and in all situations, regardless of diagnosis or presumed infection/ colonisation status. Standard precautions apply to blood, all other body fluids, secretions, and excretions except sweat (regardless of whether they contain visible blood or not), non-intact skin and mucous membranes. As part of standard precautions, 70% alcohol-based hand rub is recommended for hand hygiene; a combination of chlorhexidine and alcohol may provide additional benefit (34). Personnel should perform hand hygiene before touching a patient, before a clean/aseptic procedure (e.g. inserting a peripheral line), after body fluid exposure, after touching a patient and after touching patient surroundings. Hand hygiene adherence should be measured with a standardised checklist and adherence should be monitored on a regular basis in all wards of a facility on a rotating basis. Routine hand sampling of staff to monitor adherence to hand hygiene is not recommended.

Contact transmission-based precautions (including isolation, cohorting and use of personal protective equipment such as disposable aprons and gloves) are not specific to *C. auris* and are recommended for several other multi-drug resistant organisms (35). Adherence to

contact precautions should be monitored on a regular basis in all wards with patients who have contact precautions implemented due to *C. auris* infection and/or colonisation. If this level of monitoring is not possible, consider monitoring adherence primarily in the isolation unit where patients with *C. auris* are cohorted.

Recommendation 3.2: For how long should the IPC precautions remain in place for a patient with infection or colonisation?

1. Contact precautions should be implemented for the length of stay in an acute-care healthcare facility owing to prolonged colonisation, probable shedding of *C. auris* into the environment and no known effective methods for decolonisation
2. Patients known to be colonised or infected with *C. auris* should ideally have contact precautions implemented when re-admitted to a healthcare facility.

The duration of colonisation is not clearly defined; in some cases, colonisation with *C. auris* may persist for many months, perhaps indefinitely (3, 36). The optimal approach to reducing the skin or mucosal microbial load (decolonisation) of infected or colonised patients with *C. auris* has not been determined (37). While daily topical application of chlorhexidine gluconate 0.5% (including body washes and mouth gargles) has been recommended by at least one public health agency, patients have been documented to remain colonised with *C. auris* in prolonged outbreak settings despite this intervention (33). Similarly, the use of chlorhexidine-impregnated central vascular catheter dressings or topical nystatin have not been evaluated and these interventions are not recommended. Therefore, the most conservative approach for patients who are known to be infected or colonised with *C. auris* is to maintain contact precautions for the duration of admission. Patients known to be colonised or infected with *C. auris* should also be isolated when re-admitted to a healthcare facility; we have not specified a recommended time limit since the last admission because colonisation may be prolonged.

<u>Recommendation 3.3</u>: When is it appropriate to assess whether a patient or healthcare worker is colonised with *C. auris* and how can colonisation status be ascertained?

1. Routine screening of all newly-admitted patients for *C. auris* colonisation is not recommended
2. Routine screening of healthcare personnel is not routinely recommended
3. Screening might be considered in an outbreak situation to establish the prevalence of colonisation among epidemiologically-linked patients, but not to establish colonisation of healthcare personnel
4. Screening for colonisation can be performed by submitting skin swabs from the axilla and groin for selective culture (direct molecular tests are not currently available in South Africa).

Routine screening of all newly-admitted patients is not feasible or recommended in a resource-constrained setting. However, screening may be considered in an outbreak situation to establish colonisation of epidemiologically-linked patients. Epidemiologically-linked contacts are defined as patients who are currently sharing a cubicle with a confirmed case. In areas that do not have cubicles, but are shared rooms with or without semi-permanent barriers, epidemiologically-linked contacts include all patients in a shared physical area. Given the likely rapid colonisation potential of *C. auris*, the IPC practitioner could also consider screening any roommates the case-patients may have had during the last month. Screening of healthcare personnel during an outbreak is not routinely recommended owing to the difficulty to evaluate the role of healthcare workers in the transmission of pathogens between patients and because the reported prevalence of carriage is relatively low (33).

In an outbreak situation to establish colonisation of epidemiologically-linked patients, specimens that could be submitted include the following: axillary skin swabs, groin skin

493 swabs, nose/ throat swabs, rectal swabs or stool samples, urine, wound fluid and respiratory
494 tract specimens. The axillae and groin areas appear to be the most common and consistent
495 sites of colonisation. We recommend that IPC practitioners wait at least 48 hours after
496 administration of topical antiseptics, e.g. chlorhexidine, before collecting specimens for *C.*
497 *auris* colonisation. An enrichment protocol has been described to optimise laboratory
498 isolation of *C. auris* from colonisation samples (14). If a patient screens positive for *C. auris*,
499 no further sampling is indicated. A negative colonisation screen should not be used as
500 evidence to discontinue contact transmission-based precautions in a person with prior
501 culture-confirmed invasive disease or colonisation; in such patients, it may be prudent to
502 isolate but not cohort with other infected or colonised patients.
503
504 **Recommendation 3.4: How should the immediate environment of patients infected or**
505 **colonised with *C. auris* be cleaned?**

506 1. All surfaces should be cleaned daily with a neutral detergent and water and then
507 wiped with a freshly-constituted sodium-hypochlorite (1000 parts per million) solution.
508 Other disinfectants such as quaternary ammonium compounds and ethyl alcohol are
509 less effective and should not be used.
510 2. There is insufficient evidence to recommend routine UV light disinfection though
511 hydrogen peroxide vapour or wipes may be considered
512 3. Rooms/ bathrooms or bed spaces should be terminally cleaned after the patient
513 vacates the space.
514
515 Environmental surfaces are a reservoir for *C. auris* (38). Like *C. parapsilosis*, *C. auris* has
516 been documented to persist on plastic surfaces for up to 28 days in a controlled environment
517 mimicking a healthcare setting (14). *C. auris* forms biofilms which may enhance its
518 persistence in the environment (11-13). Guidance for environmental cleaning is not
519 consistent, with variability across the recommendations from several public health agencies
520 (37).

Daily cleaning: All surfaces and equipment should be cleaned daily with a neutral detergent and water. Standard cleaning should be followed by wiping surfaces with an appropriate disinfectant. Chlorine-based disinfectants effectively kill *C. auris* in suspension and inoculated on surfaces (16, 17, 34, 39). Chlorine disinfectants also kill other multi-drug resistant pathogens such as methicillin-resistant *Staphylococcus aureus* and carbapenem-resistant Enterobacteriaceae. A sodium-hypochlorite solution (1000 parts per million) is recommended for daily cleaning. While some public health agencies recommend higher concentrations of sodium hypochlorite, there is limited evidence to support this and the guideline development group had concerns about corrosive damage to re-useable equipment and adverse (noxious) effects on personnel working with a concentrated solution (37). New chlorine-based solution should be prepared daily at a minimum and stored away from sunlight and heat to preserve potency. Cleaners should be given clear instructions how to prepare the chlorine solutions, including pictorial depictions of the dilution process. Cleaning should proceed from cleanest to dirtiest areas, e.g. cleaning patient's bedside table prior to cleaning the commode. Cleaning supplies, e.g. mop heads and buckets, should be decontaminated regularly. Adequate contact time should be allowed with the disinfectant (at least 3 minutes) (16). Frequently-touched areas should be cleaned and disinfected more often (at least twice a day). Quaternary ammonium compounds and ethyl alcohol appear to be less effective for environmental disinfection of *C. auris* and should not be used (17, 37, 39). Routine environmental sampling to culture *C. auris* from patient care areas as a proxy for efficacy of terminal cleaning is not recommended.

Equipment: Single-use equipment is preferred, but if not available, dedicated equipment should be used for the duration of the patient's stay. Equipment should be cleaned thoroughly and disinfected according to manufacturer's recommendations. Surfaces of equipment should be cleaned adequately to remove dirt and organic material prior to disinfection; sodium hypochlorite is less effective in the presence of organic material.

549

550 Terminal cleaning: Terminal cleaning protocols must be strictly adhered to using checklists
551 which are completed by the IPC team. Terminal cleaning should involve cleaning and
552 disinfection of all items and surfaces in the patient care area or room as well as laundering
553 or changing any difficult-to-clean items, e.g. curtains, movable partitions. Terminal cleaning/
554 disinfection should begin with removing all disposable items (e.g. suction canisters, glove
555 boxes, tubing, waste) and items intended to be removed and cleaned outside patient care
556 area (e.g. laundry items). All surfaces and equipment should be cleaned with a neutral
557 detergent and water and then wiped with a sodium-hypochlorite solution. Although higher
558 concentrations of this solution have been used for terminal disinfection in outbreaks (33), we
559 recommend 1000 parts per million. Hydrogen peroxide vapour or wipes appear to be
560 effective against *C. auris* and may be added as an additional measure after cleaning and
561 disinfection (16, 17, 39). There is limited evidence for the use of ultraviolet (UV) light
562 disinfection for *C. auris*. A recent study examining the efficacy of UV-C light (254 nm)
563 showed that an exposure time of 20 minutes was required to destroy *C. auris*; this was
564 substantially longer than the time required to kill MRSA (40). It is important to note that "non-
565 touch" environmental disinfection methods such as hydrogen peroxide vapour and UV light
566 cannot replace traditional methods and may only be considered an adjunct to traditional
567 cleaning and contact disinfection of the environment.

568 **Section 4: Treatment of invasive and non-invasive *C. auris* disease**

569

570 **<u>Recommendation 4.1</u>: What are the suggested treatment regimens for confirmed or**
571 **strongly-suspected invasive *C. auris* disease in adults and children?**

572 1. In the vast majority of adults, an echinocandin is recommended as first-line
573 treatment. Amphotericin B deoxycholate is an alternative agent in settings where
574 echinocandins are unavailable and is recommended for central nervous system,
575 urinary tract or eye infections
576 2. Among children aged <2 months, the initial treatment of choice is amphotericin B
577 deoxycholate 1 mg/kg daily
578 3. Among children aged >2 months, an echinocandin is recommended for the initial
579 treatment

580

581 Early aggressive treatment of invasive *Candida* disease is vital for improved outcomes in
582 critically-ill adults (41). In the vast majority of adults with invasive *Candida* disease (including
583 *C. auris*), an echinocandin is recommended as first-line treatment (42). Amphotericin B
584 deoxycholate is an alternative agent in settings where echinocandins are unavailable.
585 Amphotericin B is also preferred in invasive infections of the central nervous system, eye
586 and urinary tract (43). Although amphotericin B deoxycholate is known to exhibit
587 concentration-dependent killing activity, continuous infusion may be associated with better
588 tolerability and less renal toxicity and may therefore be desirable in those settings where this
589 is possible (44). Azole antifungal agents such as fluconazole and voriconazole are not
590 recommended as initial treatment for suspected or confirmed *C. auris* invasive disease. In
591 many centres, reduced susceptibility or high-level resistance has been demonstrated to
592 these agents (10). While posaconazole MICs for South African *C. auris* strains are relatively
593 low (MIC_{50} of 0.12 mg/L), first-line use of this agent should only be considered in
594 consultation with an ID specialist or specialist with a particular interest in this field.
595 Posaconazole is currently only available as an oral formulation in South Africa. Clinicians are

advised to check for potential drug-drug interactions and adverse effects when prescribing antifungals. A useful antifungal interactions smartphone application can be accessed at https://www.aspergillus.org.uk/content/antifungal-drug-interactions. Currently-available antifungal agents with efficacy against *C. auris* are shown in Table 5.

Neonates or infants aged <2 months: For neonates or infants less than 2 months old, amphotericin B deoxycholate should be used as first-line treatment of invasive infections (45). Amphotericin B is efficacious and well tolerated in neonates. Fluconazole should not be used for treatment of *C. auris*; fluconazole also has no activity against azole-resistant strains of *C. parapsilosis* which are endemic in some South African neonatal units (18). Echinocandin use should be limited and reserved for cases of salvage therapy or where severe toxicity precludes the use of amphotericin B. There is no evidence for combination antifungal therapy in this age group for the treatment of *C. auris*.

Children aged >2 months: Echinocandins are the preferred agents for most cases of candidaemia and invasive candidiasis. Exceptions are infections of the central nervous system, eye, and urinary tract where amphotericin B deoxycholate should be used. Patients should be closely monitored for treatment failure, as indicated by persistently positive clinical cultures. Switching to amphotericin B should be considered if the patient has persistent fungaemia for >5 days or is unresponsive to echinocandin treatment. Fluconazole should not be used for treatment of *C. auris*. No supporting evidence exists for combination antifungal therapy in children.

Recommendation 4.2: How should the source of infection be identified and controlled in adults and children?

C. auris bloodstream infections are usually associated with healthcare settings and occur among patients with intravascular catheters and prosthetic devices. While many of these bloodstream infections represent candidaemia alone, attempts to exclude deep-seated

infections such as infective endocarditis, osteomyelitis, meningitis, pyelonephritis and endophthalmitis (by dilated retinal examination) should be undertaken (23, 46). This will influence treatment duration and penetration of antifungal agents into the source area will need to be considered. In such cases, consultation with an ID specialist (or specialist with a particular interest in this condition) is recommended. *C. auris* fungaemia may be difficult to control. Without adequate and appropriate source control, antifungal treatment alone may be futile. All attempts should be made to remove or replace indwelling central venous and arterial devices, as well as urinary catheters. Infected prosthetic material such as heart valves, shunts and bone fixation devices should be surgically removed, where feasible. Any collections should be drained. In addition, risk factors for candidaemia should be modified where possible. A summary of recommended source control and risk factor modification measures is presented in Table 8. In neonates with blood and/or urine cultures positive for *C. auris*, a lumbar puncture and a dilated retinal examination are recommended. If cultures are persistently positive, imaging of the genitourinary tract, heart, liver, and spleen should be performed. Central venous catheter removal is strongly recommended. Surgical intervention should be considered for fungal balls in the kidneys and for endocarditis (42).

Recommendation 4.3: How should response to treatment be monitored following a confirmed episode of invasive disease?

Blood cultures and laboratory/biochemical markers (including peripheral white cell count (WCC), platelet count and C-reactive protein (CRP)) should be repeated at least three times a week to monitor clearance after candidaemia is confirmed by blood culture.

Blood cultures for initial diagnosis of candidaemia or monitoring clearance of bloodstream infection should be collected using strict aseptic technique. Among adults, each blood culture bottle should be inoculated with at least 10 ml of blood from a peripheral venepuncture site (total volume of a blood culture set: up to 40-60 ml) (47). Follow-up blood cultures can help to determine the appropriate duration of antifungal therapy. Blood cultures

should be repeated at least three times a week in order to document clearance of candidaemia (42). Many laboratories routinely perform MIC testing on all invasive *Candida* strains: MICs of subsequently-cultured strains should be closely monitored to identify antifungal resistance which may require treatment modification (23). In addition, we suggest that markers such as a peripheral WCC, platelet count and CRP be measured regularly to assist with treatment monitoring and clinical response. Kidney function and electrolytes (especially potassium and magnesium) should be monitored closely, particularly if the patient is being treated with amphotericin B deoxycholate (48). Serum procalcitonin levels usually remain between 2.0 ng/ml and 2.5 ng/ml among patients with invasive *Candida* infections; thus procalcitonin is not a useful marker for monitoring response to treatment (49). A negative serum (1,3) beta-D-glucan (BDG) level may be a useful adjunct to exclude a diagnosis of candidaemia in critically-ill adults (42, 50, 51). There are no published data on the utility of serum BDG for initial diagnosis of invasive *C. auris* infection. A decrease in serially-collected serum BDG levels during treatment for candidaemia is associated with clinical/ microbiological resolution (52, 53). However, no recommendation can be made on the use of serum BDG for monitoring response to *C. auris* infection because no data are currently available.

<u>Recommendation 4.4</u>: What is the recommended duration of treatment for an episode of invasive disease?

If no evidence of a deep-seated fungal infection is found (e.g. infective endocarditis, meningitis, osteomyelitis, pyelonephritis, endophthalmitis or prosthetic infection) and disease is thus considered uncomplicated, antifungals are recommended to be continued for a minimum period of 2 weeks from the date of clearance of the candidaemia, as documented by negative blood cultures, in conjunction with clinical resolution (42). Treatment of deep-seated or complicated infections is usually prolonged and should be in consultation with an ID specialist.

<u>Recommendation 4.5</u>: When may combination antifungal treatment be considered for invasive disease?

1. Combination therapy is not recommended among clinically-stable patients with invasive *C. auris* disease. There is no evidence for combination antifungal therapy in children for the treatment of *C. auris*.
2. Among a minority of critically-ill patients with septic shock, initial combination therapy with an echinocandin plus either amphotericin B or flucytosine may be considered for a short period until antifungal susceptibility results are available
3. In addition, combination therapy may be considered, following consultation with an ID specialist, in patients with persistent fungaemia, relapsing fungaemia, recurrent fungaemia where source control has been addressed
4. For infective endocarditis and meningitis, flucytosine (if available and the isolate is susceptible) may be added to the treatment regimen.
5. Combination therapy in the absence of adequate source control is futile.

Although there is currently no evidence for combination therapy in *any* patient population with invasive *C. auris* disease, crude (unadjusted) mortality is unacceptably high (54), especially among critically-ill and immunosuppressed patients. We therefore recommend initial combination therapy in the sub-groups mentioned above, along with prompt source control. Where initial combination antifungal therapy is commenced among patients in septic shock (defined as a mean arterial blood pressure (MABP) ≤65 mmHg or requiring vasopressor support and lactate >2 mmol/L (55)), daily evaluation for the ongoing requirement of combination therapy should be reviewed, pending antifungal susceptibility results and/or clinical stabilisation. Following susceptibility testing results, de-escalation to a single antifungal agent to which the pathogen is susceptible should be considered, provided that the patient has clinical and laboratory improvement and has undergone adequate, appropriate source control measures. This should happen within a 72-hour time frame. Combination therapy may be considered among patients who remain blood culture positive

after 5-7 days (defined as persistent fungaemia) despite attempts at suitable source control, appropriate antifungal dosing and optimised antifungal penetration to the site of infection; isolate MICs should be reviewed with a clinical microbiologist. Patients who become culture positive following completion of initial antifungal treatment and presumed clearance of infection (defined as recurrent fungaemia), as well as patients who become culture positive after a period of negative cultures while still receiving appropriate treatment (defined as relapsing fungaemia) may also be considered for combination therapy, as well as detailed further investigations. In all patients, appropriate antifungal dosing and source control is of paramount importance. Treatment of these complex patients is recommended to be continued in consultation with an ID specialist and clinical microbiologist.

Recommendation 4.6: How should a patient be managed if *C. auris* is isolated from a non-sterile body site?

Isolation of *C. auris* from a non-normally sterile body site (such as skin, rectum, upper or lower respiratory tract or urinary tract) in the absence of markers of inflammation or organ dysfunction and clinical signs of infection, is usually an indication of colonisation and not disease. In this setting, antifungal treatment should be avoided; however, colonisation may prompt removal of indwelling devices (such as urinary catheters) and institution of appropriate IPC measures (refer to Section 3). In the presence of clinical signs of infection, attempts to isolate *C. auris* from a sterile site (such as blood, CSF, tissue, central venous catheters, etc.) should be made. Ancillary markers of fungaemia such as a serum BDG assay may be useful to exclude cases of candidaemia (this assay has excellent negative predictive value among critically-ill adults) (42, 50).

Section 5: Antifungal stewardship

<u>Recommendation 5.1</u>: When is antifungal prophylaxis indicated for critically-ill patients and which agent should be used?

1. The approach to prophylaxis should not be universal but selective, in which the following high-risk patient groups are targeted:
    a. Surgical patients:
        i. Presenting with anastomotic leakage after abdominal surgery
        ii. Re-operation of the digestive tract during the same hospitalization
    b. Neonates:
        i. Extremely low birth weight (ELBW) infants (BW <1000 g) in neonatal ICUs with a baseline rate of invasive candidiasis of 5%-10%
2. Depending on local epidemiology and patient population, fluconazole, an echinocandin or amphotericin B may be considered. Fluconazole prophylaxis should be avoided in settings with *C. auris* or azole-resistant *C. parapsilosis*.
3. The optimal duration of prophylaxis is not known.

Antifungal prophylaxis among non-neutropenic critically-ill patients remains controversial including among surgical patients with severe acute pancreatitis (56, 57). While fluconazole prophylaxis may reduce the incidence of invasive candidiasis in critically-ill adults and neonates, emergence of resistance in *Candida* species other than *Candida albicans* is a concern with universal prophylaxis in this high-risk population. Previous exposure to antifungals is associated with a shift in *Candida* species distribution and an upwards antifungal MIC "creep" (58). In addition, the threat of emergence of cross-resistance to both triazoles and echinocandins exists, as described in *Candida glabrata*, a species which notoriously sequentially acquires and expresses multiple resistance genes (59). The dominance of triazole-resistant *C. parapsilosis* causing bloodstream infections in South Africa was recently confirmed, particularly in ICU patients in the private sector (18). Overuse

759 of triazoles for prophylaxis and treatment of candidaemia and other fungal infections may
760 have led to the emergence and subsequent nosocomial transmission of these triazole-
761 resistant strains. Similar factors may apply to *C. auris* in South Africa (9). The epidemiology
762 of IC in South Africa is unusual: *C. albicans* and *C. parapsilosis* dominate in the public and
763 private sectors respectively (18). Multi-disciplinary antifungal stewardship teams should
764 choose prophylactic agents based on local surveillance data. The recommended antifungal
765 options and doses for prophylaxis in adults and children are summarised in Table 9 (42, 60).
766 However, the optimal duration of prophylactic treatment is not known (61).
767
768 **Recommendation 5.2: How can patients be identified for early antifungal treatment?**
769 There is insufficient evidence to make a firm recommendation on the optimal strategy to
770 identify patients who may benefit from early antifungal treatment.
771
772 From a clinical point of view, early diagnosis and treatment of invasive candidiasis is the key
773 to reduction in mortality. To minimise the negative impact of this infection, several
774 management strategies had previously been described: antifungal prophylaxis, empirical
775 therapy, pre-emptive therapy, and directed culture-based treatment. However, both universal
776 antifungal prophylaxis and empirical therapy (based on the persistence of fever non-
777 responsive to antibacterial agents and a combination of risk factors) may overexpose the
778 patients to antifungal treatment, potentially increasing antifungal resistance (62). Notably, up
779 to 70% of critically ill patients receive systemic antifungal therapy although they have no
780 documented invasive fungal infection (63), suggesting an urgent need for alternative
781 strategies. With use of biomarkers such as the serum BDG assay and to simplify auditing of
782 AFS process measures, the concepts of pre-emptive or empiric therapy should be
783 substituted by ‘‘early’’ antifungal treatment. Identifying patients at-risk for invasive
784 candidiasis includes recognition of a combination of risk factors. The *Candida* score was
785 developed for critically-ill non-neutropenic adults in Spanish ICUs and is calculated by
786 adding the following scores for each risk factor that is present: 1 (total parenteral nutrition), 1

(surgery), 1 (multifocal *Candida* species colonisation), 2 (severe sepsis) (64). Such predictive scores can help distinguish *Candida* colonisation and invasive candidiasis in ICUs, permit selection of high-risk patients who may benefit from early antifungal therapy and can also be used by AFS teams (65). However, given the low positive predictive values of such scores, many prescribed antifungal regimens have been shown to be unnecessary (66). In contrast, predictive scores have far better negative predictive values (NPV) (67).

Studies using non-culture-based assays, particularly serum BDG, together with a *Candida* score, have aided in establishing whether initiation of antifungal therapy in at-risk patients followed by close follow-up and discontinuation of antifungal therapy when invasive candidiasis is excluded has an impact on the outcomes of ICU patients. Combining BDG and the *Candida* score improves the sensitivity and NPV compared with either serum BDG or the *Candida* score alone (63). Using this approach, antifungal therapy was safely avoided in 73% of treatment-eligible ICU patients and treatment duration was shortened in another 20% (68). In another cohort, early discontinuation of antifungal therapy (initiated in high-risk ICU patients following a positive *Candida* score ≥3) based on 2 consecutive negative serum BDG tests appeared to be a reasonable AFS strategy such that the combined assay is potentially usable and safe for the therapeutic decision-making process and discontinuing of early antifungal therapy (69). Similar outcomes were observed in a biomarker-based strategy using an algorithm involving serum BDG, mannan and anti-mannan assays (70). A recent study also aimed to assess the combined performance of serum BDG and procalcitonin to differentiate between invasive candidiasis and bacteraemia (71). When both markers indicated invasive candidiasis (BDG ≥80 pg/ml and procalcitonin <2 ng/ml), they had a higher positive predictive value (PPV) (96%) compared to 79% and 66% for BDG or procalcitonin alone, respectively. When both markers indicated bacteraemia (BDG <80 pg/ml and procalcitonin ≥2 ng/ml), the NPV for invasive candidiasis was similar to that of BDG used alone (95% vs. 93%). The combined use of PCT and BDG could therefore be helpful in the diagnostic workflow for critically-ill patients with suspected candidaemia. The data

suggests that the concurrent use of the *Candida* score, BDG and other biomarkers may improve diagnostic stewardship in ICU patients at risk for *Candida* sepsis, but additional investigations are needed and their use as AFS tools remains to be established. In addition, the negative BDG cut-off <80 pg/ml for *C. auris* and *Candida* species other than *C. albicans* in SA needs to be confirmed.

Recommendation 5.3: Which AFS interventions should be considered in acute healthcare settings and how should these be implemented?

1. Implementation of AFS is recommended for all South African acute-care hospitals.
2. Multidisciplinary teams involving the necessary expertise should develop, implement and monitor AFS interventions.
3. Prospective audit and feedback is the recommended choice for the approach to AFS in South Africa, although other options may be considered in settings with limited resources. Targeted antifungal process measures should be audited as an AFS bundle.
4. AFS programmes are safe, irrespective of whether restrictive, structural and persuasive interventions are implemented alone or in combination.

No specific AFS programmes focusing on *C. auris* have yet been designed but it is likely that an environment with high and inappropriate antifungal utilisation will favour the emergence of multidrug-resistant fungi. Changes in the distribution of *Candida* species may impact on treatment recommendations due to differences in susceptibility to antifungal agents among species but previous exposure to antifungal agents has likely contributed to this shift in species distribution (62). Inappropriate use, as opposed to over-use, also needs to be considered. This was highlighted in a bedside audit of antifungal use in patients admitted to a general hospital where 57% of the prescriptions were found to be sub-optimal (72). Reasons for inappropriate use included inappropriate choice, dosing, de-escalation and duration of treatment. While an overall reduction in antifungal consumption is necessary,

using the correct agent at the correct dose for the correct duration is also important. In support of this, a 3-year comprehensive AFS programme not only resulted in improved overall utilisation but also a significant decrease in fluconazole consumption [from 242 to 117 DDDs per 1000 patient-days] which was associated with a significant reduction in the incidence of *C. glabrata* and *C. krusei* (61, 73). Therefore, to reduce overall consumption, enhance appropriate use of antifungal therapy and improve patient outcomes whilst minimising the risk of emergence of resistance, the implementation of an AFS programme is recommended in all South African hospitals.

Multidisciplinary teams encompassing the necessary expertise (pharmacy, clinical microbiology, infectious diseases, internal medicine, surgery, paediatrics and anaesthetics) is an international recommendation for AFS (74, 75). Given the lack of ID human resources in most South African hospitals, utilising existing multi-disciplinary resources in a collaborative manner, may enable an AFS programme to be embedded in routine practice.

Depending on resources, circumstances and the health sector in SA, restrictive stewardship interventions (such as formulary restriction, prior authorisation, therapeutic substitutions and automatic stop orders), structural interventions (such as changing from paper to computerised records, rapid laboratory testing, therapeutic drug monitoring, computerised decision support systems and the introduction of quality monitoring mechanisms) and persuasive strategies (such as distribution of educational materials, educational meetings and outreach visits, local consensus processes, reminders provided verbally, on paper or on computer) and prospective audit, intervention and feedback should be considered (76). However, prospective audit, intervention and feedback has been shown to be a very effective and safe antibiotic stewardship strategy in South African hospitals, particularly in settings without ID specialists (74). Potential multi-component AFS process and outcome measures for clinician and/or pharmacist and/or ICU nurse audits are proposed in Table 10.

AFS process measures (Table 10) should preferably be audited as an "AFS bundle" which is defined as a small set of evidence-based interventions for a defined patient population and care setting. In contrast to check lists, compliance with bundle components is measured using an all-or-nothing measurement, with a goal of 95% or greater. As mentioned, the first step in the development and implementation of AFS is to build a multidisciplinary team (74, 75). Using AFS bundles and all-or-none measurement may change the way care is provided for at-risk patients in important ways because bundles not only facilitate, but promote awareness that the entire care team must work together in a system designed for reliability.

The beneficial impact of 'bundles' on clinical outcomes in patients with invasive candidiasis was confirmed for the first time recently (77). The composite adherence to 9 measures (all-or-nothing) was only 6.9% in a Japanese study but there was a significant difference in clinical success between patients with and without adherence [92.9% versus 75.8%). When step-down oral therapy was excluded from the measures, adherence to the bundles was shown to be an independent predictor of clinical success (OR 4.42, 95% CI 2.05–9.52) and mortality (OR 0.27, 95% CI 0.13–0.57). Notably in none of the studies in supplementary Table 1, where the impact of various AFS interventions for invasive candidiasis in a variety of settings including non-academic hospitals have been summarised, were patient outcome measures negatively affected. This included length of stay, re-admissions, length of hospitalisation, time until clearance of candidaemia, persistent candidaemia, recurrent candidaemia, triazole-resistant *Candida* species other than *C. albicans* and mortality compared to the pre-implementation phase (data not shown).

893 References

894 1. Satoh K, Makimura K, Hasumi Y, Nishiyama Y, Uchida K, Yamaguchi H.
895 Candida auris sp. nov., a novel ascomycetous yeast isolated from the external ear
896 canal of an inpatient in a Japanese hospital. Microbiol Immunol. 2009;53(1):41-4.
897 2. Lee WG, Shin JH, Uh Y, Kang MG, Kim SH, Park KH, et al. First three
898 reported cases of nosocomial fungemia caused by Candida auris. J Clin Microbiol.
899 2011;49(9):3139-42.
900 3. Jeffery-Smith A, Taori SK, Schelenz S, Jeffery K, Johnson EM, Borman A, et
901 al. Candida auris: a Review of the Literature. Clin Microbiol Rev. 2018;31(1).
902 4. Heath CH, Dyer JR, Pang S, Coombs GW, Gardam DJ. Candida auris Sternal
903 Osteomyelitis in a Man from Kenya Visiting Australia, 2015. Emerg Infect Dis.
904 2019;25(1):192-4.
905 5. Chowdhary A, Prakash A, Sharma C, Kordalewska M, Kumar A, Sarma S, et
906 al. A multicentre study of antifungal susceptibility patterns among 350 Candida auris
907 isolates (2009-17) in India: role of the ERG11 and FKS1 genes in azole and
908 echinocandin resistance. J Antimicrob Chemother. 2018;73(4):891-9.
909 6. Chowdhary A, Sharma C, Duggal S, Agarwal K, Prakash A, Singh PK, et al.
910 New clonal strain of Candida auris, Delhi, India. Emerg Infect Dis. 2013;19(10):1670-
911 3.
912 7. Govender NP, Magobo RE, Mpembe R, Mhlanga M, Matlapeng P, Corcoran
913 C, et al. Candida auris in South Africa, 2012-2016. Emerg Infect Dis.
914 2018;24(11):2036-40.
915 8. Escandon P, Chow NA, Caceres DH, Gade L, Berkow EL, Armstrong P, et al.
916 Molecular epidemiology of Candida auris in Colombia reveals a highly-related,
917 country-wide colonization with regional patterns in Amphotericin B resistance. Clin
918 Infect Dis. 2018.
919 9. van Schalkwyk E, Govender, N.P. Independent risk factors associated with
920 Candida auris candidaemia in South Africa – an analysis of national surveillance
921 data, 2016-2017. 7th Conference of the Federation of Infectious Disease Societies
922 of Southern Africa; Cape Town, South Africa2017.
923 10. Lockhart SR, Etienne KA, Vallabhaneni S, Farooqi J, Chowdhary A, Govender
924 NP, et al. Simultaneous Emergence of Multidrug-Resistant Candida auris on 3
925 Continents Confirmed by Whole-Genome Sequencing and Epidemiological
926 Analyses. Clin Infect Dis. 2017;64(2):134-40.
927 11. Larkin E, Hager C, Chandra J, Mukherjee PK, Retuerto M, Salem I, et al. The
928 Emerging Pathogen Candida auris: Growth Phenotype, Virulence Factors, Activity of
929 Antifungals, and Effect of SCY-078, a Novel Glucan Synthesis Inhibitor, on Growth
930 Morphology and Biofilm Formation. Antimicrob Agents Chemother. 2017;61(5).
931 12. Oh BJ, Shin JH, Kim MN, Sung H, Lee K, Joo MY, et al. Biofilm formation and
932 genotyping of Candida haemulonii, Candida pseudohaemulonii, and a proposed new
933 species (Candida auris) isolates from Korea. Med Mycol. 2011;49(1):98-102.
934 13. Sherry L, Ramage G, Kean R, Borman A, Johnson EM, Richardson MD, et al.
935 Biofilm-Forming Capability of Highly Virulent, Multidrug-Resistant Candida auris.
936 Emerg Infect Dis. 2017;23(2):328-31.
937 14. Welsh RM, Bentz ML, Shams A, Houston H, Lyons A, Rose LJ, et al. Survival,
938 Persistence, and Isolation of the Emerging Multidrug-Resistant Pathogenic Yeast
939 Candida auris on a Plastic Health Care Surface. J Clin Microbiol. 2017;55(10):2996-
940 3005.

15. Eyre DW, Sheppard AE, Madder H, Moir I, Moroney R, Quan TP, et al. A Candida auris Outbreak and Its Control in an Intensive Care Setting. N Engl J Med. 2018;379(14):1322-31.
16. Abdolrasouli A, Armstrong-James D, Ryan L, Schelenz S. In vitro efficacy of disinfectants utilised for skin decolonisation and environmental decontamination during a hospital outbreak with Candida auris. Mycoses. 2017;60(11):758-63.
17. Cadnum JL, Shaikh AA, Piedrahita CT, Sankar T, Jencson AL, Larkin EL, et al. Effectiveness of Disinfectants Against Candida auris and Other Candida Species. Infect Control Hosp Epidemiol. 2017;38(10):1240-3.
18. Govender NP, Patel J, Magobo RE, Naicker S, Wadula J, Whitelaw A, et al. Emergence of azole-resistant Candida parapsilosis causing bloodstream infection: results from laboratory-based sentinel surveillance in South Africa. J Antimicrob Chemother.71(7):1994-2004.
19. Mizusawa M, Miller H, Green R, Lee R, Durante M, Perkins R, et al. Can Multidrug-Resistant Candida auris Be Reliably Identified in Clinical Microbiology Laboratories? J Clin Microbiol. 2017;55(2):638-40.
20. Lockhart SR, Jackson BR, Vallabhaneni S, Ostrosky-Zeichner L, Pappas PG, Chiller T. Thinking beyond the Common Candida Species: Need for Species-Level Identification of Candida Due to the Emergence of Multidrug-Resistant Candida auris. J Clin Microbiol. 2017;55(12):3324-7.
21. Kordalewska M, Lee A, Park S, Berrio I, Chowdhary A, Zhao Y, et al. Understanding Echinocandin Resistance in the Emerging Pathogen Candida auris. Antimicrob Agents Chemother. 2018;62(6).
22. Arendrup MC, Prakash A, Meletiadis J, Sharma C, Chowdhary A. Comparison of EUCAST and CLSI Reference Microdilution MICs of Eight Antifungal Compounds for Candida auris and Associated Tentative Epidemiological Cutoff Values. Antimicrob Agents Chemother. 2017;61(6).
23. Tsay S, Kallen A, Jackson BR, Chiller TM, Vallabhaneni S. Approach to the investigation and management of patients with Candida auris, an emerging multidrug-resistant yeast. Clin Infect Dis. 2017.
24. Spivak ES, Hanson KE. Candida auris: An Emerging Fungal Pathogen. J Clin Microbiol. 2017.
25. Chow NA, Gade L, Tsay SV, Forsberg K, Greenko JA, Southwick KL, et al. Multiple introductions and subsequent transmission of multidrug-resistant Candida auris in the USA: a molecular epidemiological survey. Lancet Infect Dis. 2018;18(12):1377-84.
26. Kordalewska M, Zhao Y, Lockhart SR, Chowdhary A, Berrio I, Perlin DS. Rapid and Accurate Molecular Identification of the Emerging Multidrug-Resistant Pathogen Candida auris. J Clin Microbiol. 2017;55(8):2445-52.
27. Prevention UCfDCa. Tracking Candida auris CDC 2018 [cited 2018 17 July 2018]. Available from: https://www.cdc.gov/fungal/candida-auris/tracking-c-auris.html.
28. Kumar A, Zarychanski R, Pisipati A, Kumar A, Kethireddy S, Bow E. Fungicidal versus fungistatic therapy of invasive Candida infection in non-neutropenic adults: a meta-analysis. Mycology. 2018;9:e.
29. Chowdhary A, Anil Kumar V, Sharma C, Prakash A, Agarwal K, Babu R, et al. Multidrug-resistant endemic clonal strain of Candida auris in India. Eur J Clin Microbiol Infect Dis. 2014;33(6):919-26.
30. Kohlenberg A, Struelens MJ, Monnet DL, Plachouras D, The Candida Auris Survey Collaborative G. Candida auris: epidemiological situation, laboratory capacity

and preparedness in European Union and European Economic Area countries, 2013 to 2017. Euro Surveill. 2018;23(13).
31. Department of Health N. Guidelines for the Prevention & Containment of Antimicrobial Resistance in South African Hospitals. In: Department of Health N, editor. Pretoria: Department of Health 2018.
32. Todd B. Clinical Alert: Candida Auris. Am J Nurs. 2017;117(4):53-5.
33. Schelenz S, Hagen F, Rhodes JL, Abdolrasouli A, Chowdhary A, Hall A, et al. First hospital outbreak of the globally emerging Candida auris in a European hospital. Antimicrob Resist Infect Control. 2016;5:35.
34. Moore G, Schelenz S, Borman AM, Johnson EM, Brown CS. Yeasticidal activity of chemical disinfectants and antiseptics against Candida auris. J Hosp Infect. 2017;97(4):371-5.
35. Health NDo. Antimicrobial Resistance National Strategy Framework 2014-2024. Pretoria2014.
36. Ruiz-Gaitan A, Moret AM, Tasias-Pitarch M, Aleixandre-Lopez AI, Martinez-Morel H, Calabuig E, et al. An outbreak due to Candida auris with prolonged colonization and candidemia in a tertiary care European hospital. Mycoses. 2018.
37. Ku TSN, Walraven CJ, Lee SA. Candida auris: Disinfectants and Implications for Infection Control. Front Microbiol. 2018;9:726.
38. Piedrahita CT, Cadnum JL, Jencson AL, Shaikh AA, Ghannoum MA, Donskey CJ. Environmental Surfaces in Healthcare Facilities are a Potential Source for Transmission of Candida auris and Other Candida Species. Infect Control Hosp Epidemiol. 2017;38(9):1107-9.
39. Biswal M, Rudramurthy SM, Jain N, Shamanth AS, Sharma D, Jain K, et al. Controlling a possible outbreak of Candida auris infection: lessons learnt from multiple interventions. J Hosp Infect. 2017;97(4):363-70.
40. Cadnum JL, Shaikh AA, Piedrahita CT, Jencson AL, Larkin EL, Ghannoum MA, et al. Relative Resistance of the Emerging Fungal Pathogen Candida auris and Other Candida Species to Killing by Ultraviolet Light. Infect Control Hosp Epidemiol. 2017:1-3.
41. Garey KW, Rege M, Pai MP, Mingo DE, Suda KJ, Turpin RS, et al. Time to initiation of fluconazole therapy impacts mortality in patients with candidemia: a multi-institutional study. Clin Infect Dis. 2006;43(1):25-31.
42. Pappas PG, Kauffman CA, Andes DR, Clancy CJ, Marr KA, Ostrosky-Zeichner L, et al. Clinical Practice Guideline for the Management of Candidiasis: 2016 Update by the Infectious Diseases Society of America. Clin Infect Dis. 2016;62(4):e1-50.
43. Cornely OA, Bassetti M, Calandra T, Garbino J, Kullberg BJ, Lortholary O, et al. ESCMID* guideline for the diagnosis and management of Candida diseases 2012: non-neutropenic adult patients. Clin Microbiol Infect. 2012;18 Suppl 7:19-37.
44. Falagas ME, Karageorgopoulos DE, Tansarli GS. continuous versus conventional infusion of amphotericin B deoxycholate: a meta-analysis. PLoS One. 2013;8(10):e77075.
45. Hope WW, Castagnola E, Groll AH, Roilides E, Akova M, Arendrup MC, et al. ESCMID* guideline for the diagnosis and management of Candida diseases 2012: prevention and management of invasive infections in neonates and children caused by Candida spp. Clin Microbiol Infect. 2012;18 Suppl 7:38-52.
46. Vallabhaneni S, Kallen A, Tsay S, Chow N, Welsh R, Kerins J, et al. Investigation of the First Seven Reported Cases of Candida auris, a Globally

Emerging Invasive, Multidrug-Resistant Fungus-United States, May 2013-August 2016. Am J Transplant. 2017;17(1):296-9.
47. Ntusi N, Aubin L, Oliver S, Whitelaw A, Mendelson M. Guideline for the optimal use of blood cultures. S Afr Med J. 2010;100(12):839-43.
48. Molloy SF, Kanyama C, Heyderman RS, Loyse A, Kouanfack C, Chanda D, et al. Antifungal Combinations for Treatment of Cryptococcal Meningitis in Africa. N Engl J Med. 2018;378(11):1004-17.
49. Raineri SM, Cortegiani A, Vitale F, Iozzo P, Giarratano A. Procalcitonin for the diagnosis of invasive candidiasis: what is the evidence? J Intensive Care. 2017;5:58.
50. Cuenca-Estrella M, Verweij PE, Arendrup MC, Arikan-Akdagli S, Bille J, Donnelly JP, et al. ESCMID* guideline for the diagnosis and management of Candida diseases 2012: diagnostic procedures. Clin Microbiol Infect. 2012;18 Suppl 7:9-18.
51. Clancy CJ, Nguyen MH. Finding the "missing 50%" of invasive candidiasis: how nonculture diagnostics will improve understanding of disease spectrum and transform patient care. Clin Infect Dis. 2013;56(9):1284-92.
52. Jaijakul S, Vazquez JA, Swanson RN, Ostrosky-Zeichner L. (1,3)-beta-D-glucan as a prognostic marker of treatment response in invasive candidiasis. Clin Infect Dis. 2012;55(4):521-6.
53. Sims CR, Jaijakul S, Mohr J, Rodriguez J, Finkelman M, Ostrosky-Zeichner L. Correlation of clinical outcomes with beta-glucan levels in patients with invasive candidiasis. J Clin Microbiol. 2012;50(6):2104-6.
54. Rudramurthy SM, Chakrabarti A, Paul RA, Sood P, Kaur H, Capoor MR, et al. Candida auris candidaemia in Indian ICUs: analysis of risk factors. J Antimicrob Chemother. 2017;72(6):1794-801.
55. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA. 2016;315(8):801-10.
56. Bailly S, Bouadma L, Azoulay E, Orgeas MG, Adrie C, Souweine B, et al. Failure of empirical systemic antifungal therapy in mechanically ventilated critically ill patients. Am J Respir Crit Care Med. 2015;191(10):1139-46.
57. Montravers P, Boudinet S, Houissa H. Candida and severe acute pancreatitis: we won't be fooled again. Crit Care. 2013;17(3):137.
58. Lortholary O, Desnos-Ollivier M, Sitbon K, Fontanet A, Bretagne S, Dromer F, et al. Recent exposure to caspofungin or fluconazole influences the epidemiology of candidemia: a prospective multicenter study involving 2,441 patients. Antimicrob Agents Chemother. 2011;55(2):532-8.
59. Pfaller MA, Castanheira M, Lockhart SR, Ahlquist AM, Messer SA, Jones RN. Frequency of decreased susceptibility and resistance to echinocandins among fluconazole-resistant bloodstream isolates of Candida glabrata. J Clin Microbiol. 2012;50(4):1199-203.
60. Leonart LP, Tonin FS, Ferreira VL, Tavares da Silva Penteado S, de Araujo Motta F, Pontarolo R. Fluconazole Doses Used for Prophylaxis of Invasive Fungal Infection in Neonatal Intensive Care Units: A Network Meta-Analysis. J Pediatr. 2017;185:129-35 e6.
61. Bassetti M, Peghin M, Timsit JF. The current treatment landscape: candidiasis. J Antimicrob Chemother. 2016;71(suppl 2):ii13-ii22.
62. Bassetti M, Leon C, Timsit JF. Are prophylactic antifungals in highly colonized patients safe and effective? Intensive Care Med. 2015;41(7):1336-9.

1089 63. Posteraro B, De Pascale G, Tumbarello M, Torelli R, Pennisi MA, Bello G, et
1090 al. Early diagnosis of candidemia in intensive care unit patients with sepsis: a
1091 prospective comparison of (1-->3)-beta-D-glucan assay, Candida score, and
1092 colonization index. Crit Care. 2011;15(5):R249.
1093 64. Leon C, Ruiz-Santana S, Saavedra P, Almirante B, Nolla-Salas J, Alvarez-
1094 Lerma F, et al. A bedside scoring system ("Candida score") for early antifungal
1095 treatment in nonneutropenic critically ill patients with Candida colonization. Crit Care
1096 Med. 2006;34(3):730-7.
1097 65. Leon C, Ruiz-Santana S, Saavedra P, Galvan B, Blanco A, Castro C, et al.
1098 Usefulness of the "Candida score" for discriminating between Candida colonization
1099 and invasive candidiasis in non-neutropenic critically ill patients: a prospective
1100 multicenter study. Crit Care Med. 2009;37(5):1624-33.
1101 66. Ferreira D, Grenouillet F, Blasco G, Samain E, Henon T, Dussaucy A, et al.
1102 Outcomes associated with routine systemic antifungal therapy in critically ill patients
1103 with Candida colonization. Intensive Care Med. 2015;41(6):1077-88.
1104 67. Leon C, Ostrosky-Zeichner L, Schuster M. What's new in the clinical and
1105 diagnostic management of invasive candidiasis in critically ill patients. Intensive Care
1106 Med. 2014;40(6):808-19.
1107 68. Posteraro B, Tumbarello M, De Pascale G, Liberto E, Vallecoccia MS, De
1108 Carolis E, et al. (1,3)-beta-d-Glucan-based antifungal treatment in critically ill adults
1109 at high risk of candidaemia: an observational study. J Antimicrob Chemother.
1110 2016;71(8):2262-9.
1111 69. Nucci M, Nouer SA, Esteves P, Guimaraes T, Breda G, de Miranda BG, et al.
1112 Discontinuation of empirical antifungal therapy in ICU patients using 1,3-beta-d-
1113 glucan. J Antimicrob Chemother. 2016;71(9):2628-33.
1114 70. Rouze A, Loridant S, Poissy J, Dervaux B, Sendid B, Cornu M, et al.
1115 Biomarker-based strategy for early discontinuation of empirical antifungal treatment
1116 in critically ill patients: a randomized controlled trial. Intensive Care Med.
1117 2017;43(11):1668-77.
1118 71. Giacobbe DR, Mikulska M, Tumbarello M, Furfaro E, Spadaro M, Losito AR,
1119 et al. Combined use of serum (1,3)-beta-D-glucan and procalcitonin for the early
1120 differential diagnosis between candidaemia and bacteraemia in intensive care units.
1121 Crit Care. 2017;21(1):176.
1122 72. Valerio M, Rodriguez-Gonzalez CG, Munoz P, Caliz B, Sanjurjo M, Bouza E,
1123 et al. Evaluation of antifungal use in a tertiary care institution: antifungal stewardship
1124 urgently needed. J Antimicrob Chemother. 2014;69(7):1993-9.
1125 73. Apisarnthanarak A, Yatrasert A, Mundy LM, Thammasat University
1126 Antimicrobial Stewardship T. Impact of education and an antifungal stewardship
1127 program for candidiasis at a Thai tertiary care center. Infect Control Hosp Epidemiol.
1128 2010;31(7):722-7.
1129 74. Richardson MD. An introduction to antifungal stewardship. J Antimicrob
1130 Chemother. 2016;71(suppl 2):ii3.
1131 75. Agrawal S, Barnes R, Bruggemann RJ, Rautemaa-Richardson R, Warris A.
1132 The role of the multidisciplinary team in antifungal stewardship. J Antimicrob
1133 Chemother. 2016;71(suppl 2):ii37-ii42.
1134 76. Davey P, Marwick CA, Scott CL, Charani E, McNeil K, Brown E, et al.
1135 Interventions to improve antibiotic prescribing practices for hospital inpatients.
1136 Cochrane Database Syst Rev. 2017;2:CD003543.

77. Takesue Y, Ueda T, Mikamo H, Oda S, Takakura S, Kitagawa Y, et al. Management bundles for candidaemia: the impact of compliance on clinical outcomes. J Antimicrob Chemother. 2015;70(2):587-93.
78. Eyre D, al e. Epidemiology and successful control of a Candida auris outbreak in a UK intensive care unit driven by multi-use patient monitoring equipment. 28th European Congress of Clinical Microbiology and Infectious Diseases; Madrid, Spain: ECCMID; 2018.
79. Cook PP, Catrou PG, Christie JD, Young PD, Polk RE. Reduction in broad-spectrum antimicrobial use associated with no improvement in hospital antibiogram. J Antimicrob Chemother. 2004;53(5):853-9.
80. Swoboda S, Lichtenstern C, Ober MC, Taylor LA, Storzinger D, Michel A, et al. Implementation of practice guidelines for antifungal therapy in a surgical intensive care unit and its impact on use and costs. Chemotherapy. 2009;55(6):418-24.
81. Standiford HC, Chan S, Tripoli M, Weekes E, Forrest GN. Antimicrobial stewardship at a large tertiary care academic medical center: cost analysis before, during, and after a 7-year program. Infect Control Hosp Epidemiol. 2012;33(4):338-45.
82. Lopez-Medrano F, Juan RS, Lizasoain M, Catalan M, Ferrari JM, Chaves F, et al. A non-compulsory stewardship programme for the management of antifungals in a university-affiliated hospital. Clin Microbiol Infect. 2013;19(1):56-61.
83. Antworth A, Collins CD, Kunapuli A, Klein K, Carver P, Gandhi T, et al. Impact of an antimicrobial stewardship program comprehensive care bundle on management of candidemia. Pharmacotherapy. 2013;33(2):137-43.
84. Guarascio AJ, Slain D, McKnight R, Petros K, Parker J, Wilson A, et al. A matched-control evaluation of an antifungal bundle in the intensive care unit at a university teaching hospital. Int J Clin Pharm. 2013;35(1):145-8.
85. Mondain V, Lieutier F, Hasseine L, Gari-Toussaint M, Poiree M, Lions C, et al. A 6-year antifungal stewardship programme in a teaching hospital. Infection. 2013;41(3):621-8.
86. Alfandari S, Berthon C, Coiteux V. Antifungal stewardship: implementation in a French teaching hospital. Med Mal Infect. 2014;44(4):154-8.
87. Micallef C, Aliyu SH, Santos R, Brown NM, Rosembert D, Enoch DA. Introduction of an antifungal stewardship programme targeting high-cost antifungals at a tertiary hospital in Cambridge, England. J Antimicrob Chemother. 2015;70(6):1908-11.

Tables

Table 1: When to suspect *C. auris* in the clinical laboratory

Instrument/ biochemical kit	Identification obtained	What to do next?
API 20C AUX or ID32C	*Rhodotorula glutinis*	If colonies are not pink or yeast is urease-negative, refer*
Auxacolor	*Saccharomyces*	Consider *C. auris* and refer*
Microscan	*Candida famata*	Consider *C. auris* and refer*
Microscan	*Candida lusitaniae, Candida guilliermondii, Candida parapsilosis, Candida catenulata*	Not possible to detect *C. auris* unless the yeast ID is confirmed with another method and/or fluconazole resistance is documented
Vitek 2 YST	*Candida haemulonii* if software update is not loaded	If fluconazole-resistant, treat as *C. auris* and refer*
Vitek 2 YST	*Candida auris* if software version 8.01 is loaded	Report as *Candida auris*
Vitek MS MALDI	*Candida auris* if research use only (RUO) library is used	Report as *Candida auris*
Bruker BioTyper MALDI	*Candida auris* if full/ partial extraction method and RUO library is used	Report as *Candida auris*

*Refer to a laboratory with Vitek 2 YST software version 8.01 or MALDI-TOF or molecular testing platform

1178 Table 2: Proposed cut-off values for *C. auris* for 10 antifungal agents and corresponding

1179 South African surveillance MIC_{90} data

Antifungal agent	**Minimum inhibitory concentration (MIC) (µg/ml):**			**Comment**
	NICD surveillance data (MIC_{90})	**Tentative ECOFF value**	**US CDC proposed cut-off value**	
Fluconazole	256	≥128	≥32	Resistant
Voriconazole	2	≥1	-	A high MIC has
Itraconazole	0.25	≥0.25	-	been obtained and
Isavuconazole	-	≥0.5	-	the isolate has been
Posaconazole	0.12	≥0.125	-	referred to a
Caspofungin	-	-	-	reference laboratory.
Anidulafungin	0.25	≥0.25	≥4	This MIC indicates
Micafungin	0.12	≥0.25	≥4	that use of this
Flucytosine	0.25	-	-	antifungal agent may
Amphotericin B	1	≥2	≥2	be ineffective.
				Please discuss with
				a clinical
				microbiologist or
				infectious diseases
				physician.

1180 MIC_{90}, lowest concentration of the antifungal at which 90% of the isolates are inhibited. MIC_{90} data obtained from
1181 National Institute for Communicable Diseases/ GERMS-SA surveillance for 344 bloodstream *C. auris* isolates.
1182 ECOFF, epidemiological cut-off value obtained via a derivatisation method using broth microdilution MICs
1183 obtained by Clinical and Laboratory Standards Institute M27-A3 and European Committee on Antimicrobial
1184 Susceptibility Testing E,Def 7.3 methods. US CDC, US Centers for Disease Control and Prevention

1185 **Table 3:** Suggested activities following detection of an outbreak of *C. auris* in a healthcare
1186 facility

Activity	Purpose
Notify relevant authorities	Obtain resources for prevention and control
Intensify infection prevention and control (IPC) measures, specifically contact precautions and environmental cleaning	Control outbreak, prevent further transmission
Isolate/ cohort case patients	Limit transmission within a unit or facility
Contact screening	Inform further IPC measures, possibly limit transmission
Emphasise antifungal stewardship (AFS)	Possibly prevent further cases

1187

1188 Table 4: Summary of recommendations for the prevention of transmission of *C. auris*

Measure	Description
Standard precautions	– Strictly adhere to the 5 moments of hand hygiene[a] including bare below the elbows and no jewellery (including rings, watches, bracelets) – Wash hands when visibly soiled or after contact with blood and body fluids. – Use a 70% alcohol-based hand rub on dry hands in all other instances – Monitor adherence to hand hygiene by visual inspection and auditing of adherence versus the number of opportunities
Contact transmission-based precautions	– Make gloves and disposable impervious aprons available – Wear disposable (impervious) gowns when there is close contact with a patient, e.g. turning a large patient where the healthcare worker's uniform might be contaminated, or a high risk of blood and body fluid exposure

	- Wear eye protection and a mask during procedures where there might be a risk of splashes - Don all personal protective equipment (PPE) prior to entering the room and before touching a patient or the immediate environment (bed, linen, equipment, invasive devices and personal items). Remove and discard PPE and clean hands before leaving the patient's room or, in semi-private room or multi-bed bay situation, before leaving the patient's immediate vicinity. - Visitors need not use PPE unless performing a nursing duty. - Dedicate equipment to individual patients if possible, e.g. blood pressure cuffs, thermometers (78). If equipment is shared, disinfect these according to the manufacturer's guidelines between patient use.
Isolation or cohorting	- Accommodate each infected and/or colonised patient in a single room with en-suite facilities. Affix a "contact precautions" sign to the door. - If single rooms are not available, "cohort" patients who are infected or colonised with the same pathogen (i.e. same species, similar susceptibility profile) in the same room. Ensure that the space between beds is adequate when patients are cohorted, i.e. at least 2 metres between the sides of the beds to allow adequate movement and use of mobile equipment without touching the other patient - Restrict the number of visitors at a single time
Environmental cleaning	- Clean rooms at least daily. Clean the room to reduce the bioburden and then disinfect with a sodium hypochlorite solution (1000 parts per million) - Clean and disinfect equipment (according to manufacturer's guidelines) after use if single-use items are not available

	– Handle all linen from infected or colonised patients as infectious linen, immediately place in a yellow plastic bag and wash separately at 65˚C for 10 minutes – All linen including bed curtains should be removed and laundered after discharge – Consider hydrogen peroxide fogging or wipes as an adjunctive measure when the patient vacates the room – There is insufficient evidence to currently recommend UV light disinfection
Care bundles[2]	– Adherence to the relevant care bundles should be monitored and measured – The following care bundles apply, where relevant: tracheostomy, central line-associated bloodstream infection (CLABSI), catheter-associated urinary tract infection (CAUTI), ventilator-associated pneumonia (VAP) – All devices should be removed as soon as possible
Patient movement	– Notify receiving departments if patient is to be transported between departments – Notify the receiving hospital if the patient is transferred to another hospital or long-term care facility
Training	– Train cleaning personnel to correctly make sodium hypochlorite solutions and how to clean – Educate patients, visitors and families on hand hygiene – Train multi-disciplinary team members on IPC recommendations

a) The "five moments of hand hygiene" is a term used by the World Health Organization to define the points at which hand hygiene should be performed in healthcare settings. These include the following "moments": before patient contact, before an aseptic technique, after blood and body fluid exposure, after patient contact, after contact with the patient's environment (24).

b) A "care bundle" is a structured way of improving the processes of care and patient outcomes. A care bundle is a group of evidence-based practices, which when performed collectively and consistently, has proved to improve patient outcomes.

1196

1197 Table 5: Antifungal agents for adults with invasive disease

Agent	Dose	Dose adjustments with renal dysfunction	Common adverse effects
Caspofungin Micafungin Anidulafungin	Loading dose 70 mg IV, then 50 mg IV daily 100 mg IV daily Loading dose 200 mg IV, then 100 mg IV daily	Dose as in normal renal function	Fever, thrombophlebitis, headache, raised transaminases
Amphotericin B deoxycholate Liposomal amphotericin B	1 mg/kg IV daily 5 mg/kg IV daily	Avoid deoxycholate formulation if baseline CrCl <50 ml/min. If baseline CrCl ≥50 ml/min, can use deoxycholate but must ensure adequate hydration and avoid using other nephrotoxic agents.	Deoxycholate >lipid formulations: nephrotoxicity, hypokalaemia, hypomagnesaemia, fever, pain at injection site
Flucytosine*	25 mg/kg 6 hourly PO (total daily dose: 100 mg/kg)	If CrCl reduces to below 40 ml/min, give the same 25 mg/kg dose but increase the interval between doses: 20-40 ml/min, 12 hourly; 10-20 ml/min, every 24 hours; <10 ml/min, >24 hours	Photosensitivity, gastrointestinal, hepatotoxicity, haematological
Posaconazole**	400 mg BD PO with meals	Dose as in normal renal function	Gastrointestinal, raised transaminases, rash, hypokalaemia

IV: intravenous infusion; bd: twice daily; po: per os; CrCl: creatinine clearance = (140 – age) * (weight in kg) / (72 * serum creatinine in mg/dL) [Multiply result by 0.85 for women]

*5-FC is available through Section 21 application through the South African Health Products Regulatory Authority (SAHPRA), formerly the SA Medicines Control Council. 5-FC should not be used as monotherapy but always in combination with another antifungal agent. The laboratory should determine 5-FC minimum inhibitory concentrations if this agent is being considered for use.

**_C. auris_ is usually not susceptible to fluconazole and voriconazole

Table 6: Antifungal agents for children <2 months of age with invasive disease

Agent	**Dose**
Amphotericin B deoxycholate	1 mg/kg IV daily
Caspofungin	25 mg/m^2 IV daily
Micafungin	10 mg/kg IV daily

Table 7: Antifungal agents for children ≥2 months of age with invasive disease

Agent	**Dose**
Caspofungin	Loading dose: 70 mg/m^2 IV daily, then 50 mg/m^2 IV daily
Micafungin	2 mg/kg IV daily, with option to increase to 4 mg/kg IV daily in children >40 kg
Anidulafungin	Not approved for use in children
Amphotericin B deoxycholate	1 mg/kg IV daily

Table 8: Source control and risk factor modification measures

Source/ risk factor	**Suggested intervention**
Indwelling venous/ arterial catheters	Remove or replace
Urinary catheter	Remove or replace
Infected prosthetic material	Remove or replace
Collections/ abscesses	Drain surgically or insert pigtail

Antibiotics	Stop/de-escalate/use only if deemed absolutely necessary
Corticosteroids	Stop/ wean
Immunosuppressants	Stop/ wean/ modify
Total parenteral nutrition	Change to enteral nutrition, if possible

1211

1212 Table 9. Recommended antifungal agents and doses for prophylaxis among adults and
1213 children

Patient group	Antifungal agent	Loading dose	Daily maintenance dose
Adults	Fluconazole	800 mg (12 mg/kg)	400 mg (6 mg/kg)
	Amphotericin B	-	0.5 – 1 mg/kg
	Caspofungin	70 mg	50 mg
	Micafungin	-	100 mg
	Anidulafungin	200 mg	100 mg
Neonates	Fluconazole		
	GA<30 weeks or <1000 g	-	3-6 mg/kg/dose twice a week
	GA 30-40 weeks	-	6 mg/kg/dose 48 hourly
Infants and children > 1 month	Fluconazole	-	6 mg/kg/day
	Amphotericin B*	-	1 mg/kg/24 hours D1-7 1 mg/kg/48 hours after D7

1214 *Amphotericin B is recommended only in very rare instances; GA: gestational age

1215

1216 Table 10: Multi-component antifungal stewardship targets and corresponding recommended
1217 process/ outcome measures

Target	Recommended process measures
Accountable justification	Did the clinician provide free-text justification for prescribing an antifungal agent (i.e. prophylaxis vs. "early" AF therapy)?

	If for prophylaxis, was the antifungal agent prescribed according to consensus evidence-based indications?
Diagnostic stewardship	Was "early" antifungal therapy based on risk factors? If based on risk factors, was a predictive score calculated? Were blood specimens for BDG and PCT levels obtained? Were blood cultures submitted?
"Early" initial antifungal choice and dose	Was the chosen antifungal agent consistent with guidelines? Was the dose prescribed compliant with guidelines? Where applicable, was a loading dose prescribed? Was the dose adjusted according to body weight, liver and renal function?
Time from prescription to administration ("hang-time")	Was the antifungal agent administered within one hour?
Post-prescription review (48-72 hours)	Was antifungal therapy discontinued in patients pending clinical condition and biomarker results (e.g. serum BDG, PCT)? If blood cultures became positive, was antifungal therapy de-escalated to a narrow-spectrum agent, pending susceptibility results?
Source control	In case of a positive blood culture, were existing CVCs removed within 24 h of diagnosis?
Duration of therapy for sepsis	Was an antifungal agent prescribed for a total duration of 14 days after first negative blood culture?

Target	**Recommended outcome measures (per unit)**
Length of stay	ICU stay Candidaemia-related stay
Mortality	30-day crude mortality Candidaemia-related mortality
Longitudinal ecological impact	Antifungal susceptibility profile Species distribution

Antifungal consumption	Overall antifungal consumption
	Echinocandin consumption
	Triazole consumption
	Amphotericin B consumption

BDG: (1,3)-β-D-glucan; PCT: Procalcitonin; CVC: central venous catheter; ICU: intensive care unit: MDR: Multi-drug resistant

1220 Supplementary Table 1: Impact of antifungal stewardship programmes on non-patient related outcome measures

Reference	Study design and duration	Strategy: Restrictive (R), Persuasive (P), Structural (S)	Outcome measures	
			Overall AF reduction ¤	AF cost reduction (%/saving)
Cook et al. 2004 (79)	Pre-Post quasi-experimental, 4y	Formulary restrictions (R) Post–prescription review and feedback (n=2 measures) (P)	28% (P=0.02)	20%
Swoboda et al. 2009 (80)	Pre-Post quasi-experimental, 3y	Institutional practice guidelines (P) Post–prescription review (P)	ND	50% (298 304 **€**) (pre-post)
Apisarnthanarak et al 2012♦ (73)	Pre-Post quasi-experimental, 3y	Formulary restrictions (R) Post-prescription review and feedback (n=5 measures) (P) Institutional treatment guidelines (P) Dedicated AF prescription chart and AFS ward rounds (P) Scheduled educational programmes (P) Dose-adjustment tool (S)	59% (p<0.001)	31615 U$ (pre-post)

Standiford et al. 2012 (81)	3-phase interventional, 7y	Preauthorization (R) Post-prescription review and feedback (n=4 measures) (P) Institutional treatment guidelines (P) Computer decision support (S)	ND	45.8% (130000U$) (pre-post)
Lopez-Medrano et al. 2013 (82)	Pre-post non-randomized, 1y	Post-prescription review and feedback (n=4 measures) (P)	Overall no difference but V -31.4% and C -20.2%	11.8% (370680U$) (pre-post)
Antworth et al. 2013* (83)	Pre-Post quasi-experimental, 6m	Post-prescription review and feedback (n=6 measures) (P) (Bundle) -	ND	ND
Guarascio et al. 2013 (84)	Matched-controlled, 6m	Post-prescription bundle review and feedback (n=4 measures) (P) Caspofungin only	50% (DOT) (p=.001)	1,013 U$ (per patient)
Mondain et al. 2013• (85)	Prospective observational, 6y	Post-prescription review and feedback (n=4 measures) (P) Institutional treatment guidelines (P) Scheduled educational programmes (P)	38%	56% (682 409 **€**)

		AF order forms (S) TDM voriconazole and posaconazole (S) Diagnostic tools for IC (S)		
Alfandari et al. 2014 (86)	Retrospective observational, 9y	Post-prescription ID consultation (P) Institutional treatment guidelines (P) Scheduled educational programmes (P) AF order forms (S)	40%	ND
Micallef et al. 2015 (87)	Prospective observational, 1y	Post-prescription review and feedback(n=4 measures)(P) -High cost AFs only TDM voriconazole (S)	ND	178 708 £ (annum)
Takesue et al. 2015 (77)	Cluster non-randomized, 1y	Post-prescription review and feedback (n=9 measures) (P) (Bundle)	ND	ND

▫ Unless otherwise stated overall consumption was expressed as defined daily doses/1000 patient days

♦ A significant reduction in inappropriate antifungal drug use was documented from 71% during the pre-intervention period to 24% during the post- intervention period (P<.001)

*A significant increase in composite compliance to all bundle measures in the AFSP group versus the control group was demonstrated (78.0% versus 40.5%, *P*=0.0016)

• Improved compliance was achieved for the timing of antifungal treatment (*P*=0.0025), recommended first-line therapy (*P*=0.0025), duration of therapy (*P*=0.46) and the removal of central venous catheters (*P*=0.27), compared with pre-AFS implementation

AF: Antifungal; y: year; m: month: ND: Not determined; V: Voriconazole; C: Caspofungin; DOT: days of therapy

Figures

Figure 1: Laboratory testing algorithm for identification of *C. auris*