

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

4

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50

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52 **Abstract**

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

61 **Introduction**

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

69
70 The reasons for the dramatic emergence of *C. auris* as a pathogen in healthcare settings are
71 not clear. We know that East Asia, South Asia, Africa and South America have unique *C.*
72 *auris* clades separated from other clades by tens of thousands of single nucleotide
73 polymorphisms (10). This is consistent with the hypothesis that *C. auris* emerged
74 independently and simultaneously on several continents. While *C. auris* is likely to have an
75 environmental reservoir outside the healthcare setting, this has yet to be established.
76 Several intrinsic properties of the pathogen probably facilitated its rapid spread in hospitals.
77 *C. auris* produces biofilms (11-13). While this fungus rarely colonises the hands of
78 healthcare workers, it can survive for prolonged periods in the immediate environment
79 around infected or colonised patients and in a recent outbreak investigation, was found to
80 contaminate re-useable patient equipment (13-15). *C. auris* is also relatively resistant to
81 some chemical disinfectants (16, 17). Transmission can thus occur from an infected or
82 colonised person, the patient care environment or re-useable equipment to a susceptible
83 person. In South Africa, *C. auris* has become a common healthcare-associated pathogen in
84 the same geographic region where azole-resistant *Candida parapsilosis* was first described
85 (18). It is likely that inadequate antifungal stewardship (AFS) and infection prevention and
86 control (IPC) programmes are the underlying drivers of the emergence and transmission of
87 these azole-resistant pathogens. IPC and AFS are two key areas covered in this guideline
88 document. *C. auris* causes healthcare-associated outbreaks and is a public health concern;

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

91

92 Without a clear laboratory algorithm, *C. auris* is often misidentified by routine methods (19).

93 Misidentification delays initiation of appropriate antifungal treatment and rapid institution of

94 IPC measures. *C. auris* causes a wide range of invasive and non-invasive infections and

95 colonises various body sites. Identification to species level is not routine for isolates from

96 non-sterile sites so *C. auris* would be missed unless this is specifically looked for (20). *C.*

97 *auris* is almost universally resistant to fluconazole and has variable susceptibility to other

98 classes of antifungals (5, 10, 21). The lack of clinically-relevant breakpoints currently limits

99 interpretation of minimum inhibitory concentrations (MICs) and hence guidance for individual

100 patient treatment (22). This guideline includes recommendations for identifying and

101 performing antifungal susceptibility testing for *C. auris*.

102

103 Owing to its relatively recent emergence, cases of *C. auris* were not included in pre-

104 registration clinical trials for currently-available antifungal agents. Recommendations for

105 antifungal treatment of *C. auris* disease are thus extrapolated from evidence for *Candida*

106 infections with other species and there are no published recommendations for low- and

107 middle-income countries (23). Based on South African surveillance data, the following

108 independent risk factors have been identified for *C. auris* candidaemia: older patients,

109 prolonged hospitalisation, admission to private-sector facilities and having a central venous

110 catheter in situ (9). These risk factors are not sufficiently specific and so healthcare workers

111 need to maintain a high index of suspicion for *C. auris* particularly in settings where this

112 pathogen is endemic.

113

114 The objective of this guideline is to provide updated, evidence-informed recommendations

115 outlining a best-practice approach to preventing, diagnosing and managing *C. auris* disease

116 in public- and private-sector healthcare settings in South Africa. The recommendations

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

128 **Methods**

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

141
142 An in-person meeting was convened in Johannesburg on 6 July 2017 to discuss and
143 propose recommendations. The 19-member panel comprised of 7 clinical microbiologists, 1
144 paediatric infectious diseases (ID) specialist, 1 adult ID specialist, 1 critical care physician, 5
145 IPC nurse practitioners, 1 general medical practitioner, 2 medical epidemiologists and 1
146 clinical pharmacist. The proceedings of the meeting were recorded and transcribed. At this
147 meeting, members were assigned to writing groups for each section. The writing groups
148 subsequently met in person or via teleconference or corresponded by email to draft each set
149 of recommendations. Compiled draft recommendations were presented by N.P.G for
150 discussion on 4 November 2017 at the 7th FIDSSA conference in Cape Town. The guideline
151 development group then re-convened by teleconference on 27 November 2017.

152
153 Owing to the paucity of high-quality evidence specifically relevant to *C. auris*, systematic
154 reviews were not conducted for each focus area prior to developing this guideline. The
155 chairperson (N.P.G.) conducted a literature review prior to the July 2017 meeting and

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

168 **Section 1: Laboratory identification and antifungal susceptibility testing**

169

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

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

176

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

190

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

- 192 1. Perform species-level identification for all *Candida* isolates cultured from sterile body
193 sites. Ideally, species-level identification should also be obtained for *Candida*
194 isolates cultured from all non-sterile sites. However, in situations where this is not
195 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

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

226

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

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

252 7. Refer all strains with elevated amphotericin B ($\geq 2 \mu\text{g/ml}$) or anidulafungin/ micafungin
253 MICs ($\geq 4 \mu\text{g/ml}$) for testing at a reference laboratory

254

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

266

267 A standardised reference broth microdilution (BMD) test is the recommended antifungal
268 susceptibility testing method to resolve discrepancies and to confirm unusual phenotypes. A
269 direct comparison of the European Committee on Antifungal Susceptibility testing (EUCAST)
270 and US Clinical and Laboratory Standards Institute (CLSI) BMD methods for a *C. auris*
271 isolate collection yielded similar MICs for fluconazole, itraconazole, voriconazole,
272 isavuconazole, posaconazole, anidulafungin, micafungin and amphotericin B (22). When
273 CLSI-BMD and the commercial automated Vitek AST-YS07 were compared, there was
274 100% agreement of MIC₅₀ values for voriconazole, caspofungin and micafungin and
275 agreement for fluconazole and flucytosine within 2 dilutions. Of concern, Vitek AST-YS07
276 yielded falsely-elevated MICs (MIC₅₀ of $8 \mu\text{g/ml}$) for amphotericin B compared to the CLSI-
277 BMD MIC₅₀ of $1 \mu\text{g/ml}$ and an Etest MIC₅₀ of $0.5 \mu\text{g/ml}$ (29). The guideline development
278 group therefore recommends that all amphotericin B MIC results obtained with Vitek 2 AST-

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

288
289 There are currently no clinical breakpoints for *C. auris* and any antifungal agent. As limited
290 clinical and pharmacokinetic/ pharmacodynamic data currently preclude the development of
291 such breakpoints, ECOFFs may be helpful. ECOFFs distinguish organisms with and without
292 phenotypically-expressed resistance mechanisms for a species and an antifungal agent in a
293 defined test system; within a species, this is the highest MIC of organisms lacking
294 phenotypically-expressed resistance. ECOFFs may thus be used to identify isolates that are
295 less likely to respond to antimicrobial therapy due to acquired resistance mechanisms (Table
296 2). Surveillance data from the National Institute for Communicable Diseases (unpublished,
297 personal communication N.P. Govender) obtained from *C. auris* bloodstream isolates from
298 South African public and private-sector hospitals roughly align with tentative ECOFFs
299 determined for 123 *C. auris* isolates (22). The US CDC has applied tentative non-validated
300 clinical breakpoints developed for other *Candida* species to *C. auris* for epidemiological
301 purposes; however, these may not necessarily be clinically relevant at an individual patient
302 level (27). Susceptibility data for *C. auris* isolates published from multiple countries
303 demonstrate uniformly high fluconazole MICs, with variable susceptibility to the other azoles,
304 echinocandins and amphotericin B (10). Some isolates may demonstrate high MICs to ≥ 2
305 antifungal classes (i.e. multidrug resistant).

306 **Section 2: Surveillance and outbreaks**

307

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

310 1. There should be nationally-coordinated surveillance for *C. auris* integrated into
311 broader surveillance for antimicrobial resistance (AMR). The overarching goal is to
312 prevent *C. auris* from becoming endemic in hospitals across South Africa.

313 2. At a facility level, all public-sector hospitals and private hospital groups should
314 passively monitor the number of laboratory-confirmed cases of *C. auris* disease and
315 colonisation.

316 3. At a national level, the National Institute for Communicable Diseases (NICD) should
317 conduct regular cross-sectional surveys in order to monitor epidemiological and
318 geographical trends over time.

319

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

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

332

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

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

353
354 At a national level, NICD should conduct regular cross-sectional surveys as part of
355 integrated AMR surveillance. These surveys could be scheduled at the same time every
356 year and could be integrated with national point prevalence surveys for healthcare-
357 associated infections (HAI) and AMR (23). NICD should coordinate nested epidemiologic
358 studies through its existing surveillance platforms. *C. auris* is included in a list of alert
359 organisms that SA healthcare facilities are encouraged to compile (31). Guidance has been

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

368

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

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

375

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

- 385 • Clusters of cases in
386 ○ 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).

409 **Section 3: Infection prevention and control**

410

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

413 Two sets of precautions are recommended:

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

421

422 Standard precautions apply to all patients and in all situations, regardless of diagnosis or
423 presumed infection/ colonisation status. Standard precautions apply to blood, all other body
424 fluids, secretions, and excretions except sweat (regardless of whether they contain visible
425 blood or not), non-intact skin and mucous membranes. As part of standard precautions, 70%
426 alcohol-based hand rub is recommended for hand hygiene; a combination of chlorhexidine
427 and alcohol may provide additional benefit (34). Personnel should perform hand hygiene
428 before touching a patient, before a clean/aseptic procedure (e.g. inserting a peripheral line),
429 after body fluid exposure, after touching a patient and after touching patient surroundings.

430 Hand hygiene adherence should be measured with a standardised checklist and adherence
431 should be monitored on a regular basis in all wards of a facility on a rotating basis. Routine
432 hand sampling of staff to monitor adherence to hand hygiene is not recommended.

433

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

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

441

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

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

449

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

464

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

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

477

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

490

491 In an outbreak situation to establish colonisation of epidemiologically-linked patients,
492 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).

521

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

543

544 Equipment: Single-use equipment is preferred, but if not available, dedicated equipment
545 should be used for the duration of the patient's stay. Equipment should be cleaned
546 thoroughly and disinfected according to manufacturer's recommendations. Surfaces of
547 equipment should be cleaned adequately to remove dirt and organic material prior to
548 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 **Recommendation 4.1: 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 (MIC₅₀ 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

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

600

601 Neonates or infants aged <2 months: For neonates or infants less than 2 months old,
602 amphotericin B deoxycholate should be used as first-line treatment of invasive infections
603 (45). Amphotericin B is efficacious and well tolerated in neonates. Fluconazole should not be
604 used for treatment of *C. auris*; fluconazole also has no activity against azole-resistant strains
605 of *C. parapsilosis* which are endemic in some South African neonatal units (18).

606 Echinocandin use should be limited and reserved for cases of salvage therapy or where
607 severe toxicity precludes the use of amphotericin B. There is no evidence for combination
608 antifungal therapy in this age group for the treatment of *C. auris*.

609

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

618

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

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

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

640

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

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

646

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

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

669

670 **Recommendation 4.4: What is the recommended duration of treatment for an episode**
671 **of invasive disease?**

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

679

680 **Recommendation 4.5: When may combination antifungal treatment be considered for**
681 **invasive disease?**

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

694

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

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

718

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

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

731 **Section 5: Antifungal stewardship**

732

733 **Recommendation 5.1: When is antifungal prophylaxis indicated for critically-ill**

734 **patients and which agent should be used?**

735 1. The approach to prophylaxis should not be universal but selective, in which the
736 following high-risk patient groups are targeted:

737 a. Surgical patients:

738 i. Presenting with anastomotic leakage after abdominal surgery

739 ii. Re-operation of the digestive tract during the same hospitalization

740 b. Neonates:

741 i. Extremely low birth weight (ELBW) infants (BW <1000 g) in neonatal
742 ICUs with a baseline rate of invasive candidiasis of 5%-10%

743 2. Depending on local epidemiology and patient population, fluconazole, an
744 echinocandin or amphotericin B may be considered. Fluconazole prophylaxis should
745 be avoided in settings with *C. auris* or azole-resistant *C. parapsilosis*.

746 3. The optimal duration of prophylaxis is not known.

747

748 Antifungal prophylaxis among non-neutropenic critically-ill patients remains controversial
749 including among surgical patients with severe acute pancreatitis (56, 57). While fluconazole
750 prophylaxis may reduce the incidence of invasive candidiasis in critically-ill adults and
751 neonates, emergence of resistance in *Candida* species other than *Candida albicans* is a
752 concern with universal prophylaxis in this high-risk population. Previous exposure to
753 antifungals is associated with a shift in *Candida* species distribution and an upwards
754 antifungal MIC “creep” (58). In addition, the threat of emergence of cross-resistance to both
755 triazoles and echinocandins exists, as described in *Candida glabrata*, a species which
756 notoriously sequentially acquires and expresses multiple resistance genes (59). The
757 dominance of triazole-resistant *C. parapsilosis* causing bloodstream infections in South
758 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

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

793
794 Studies using non-culture-based assays, particularly serum BDG, together with a *Candida*
795 score, have aided in establishing whether initiation of antifungal therapy in at-risk patients
796 followed by close follow-up and discontinuation of antifungal therapy when invasive
797 candidiasis is excluded has an impact on the outcomes of ICU patients. Combining BDG and
798 the *Candida* score improves the sensitivity and NPV compared with either serum BDG or the
799 *Candida* score alone (63). Using this approach, antifungal therapy was safely avoided in
800 73% of treatment-eligible ICU patients and treatment duration was shortened in another 20%
801 (68). In another cohort, early discontinuation of antifungal therapy (initiated in high-risk ICU
802 patients following a positive *Candida* score ≥ 3) based on 2 consecutive negative serum BDG
803 tests appeared to be a reasonable AFS strategy such that the combined assay is potentially
804 usable and safe for the therapeutic decision-making process and discontinuing of early
805 antifungal therapy (69). Similar outcomes were observed in a biomarker-based strategy
806 using an algorithm involving serum BDG, mannan and anti-mannan assays (70). A recent
807 study also aimed to assess the combined performance of serum BDG and procalcitonin to
808 differentiate between invasive candidiasis and bacteraemia (71). When both markers
809 indicated invasive candidiasis (BDG ≥ 80 pg/ml and procalcitonin < 2 ng/ml), they had a
810 higher positive predictive value (PPV) (96%) compared to 79% and 66% for BDG or
811 procalcitonin alone, respectively. When both markers indicated bacteraemia (BDG < 80 pg/ml
812 and procalcitonin ≥ 2 ng/ml), the NPV for invasive candidiasis was similar to that of BDG
813 used alone (95% vs. 93%). The combined use of PCT and BDG could therefore be helpful in
814 the diagnostic workflow for critically-ill patients with suspected candidaemia. The data

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

820

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

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

832

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

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

851
852 Multidisciplinary teams encompassing the necessary expertise (pharmacy, clinical
853 microbiology, infectious diseases, internal medicine, surgery, paediatrics and anaesthetics)
854 is an international recommendation for AFS (74, 75). Given the lack of ID human resources
855 in most South African hospitals, utilising existing multi-disciplinary resources in a
856 collaborative manner, may enable an AFS programme to be embedded in routine practice.

857
858 Depending on resources, circumstances and the health sector in SA, restrictive stewardship
859 interventions (such as formulary restriction, prior authorisation, therapeutic substitutions and
860 automatic stop orders), structural interventions (such as changing from paper to
861 computerised records, rapid laboratory testing, therapeutic drug monitoring, computerised
862 decision support systems and the introduction of quality monitoring mechanisms) and
863 persuasive strategies (such as distribution of educational materials, educational meetings
864 and outreach visits, local consensus processes, reminders provided verbally, on paper or on
865 computer) and prospective audit, intervention and feedback should be considered (76).

866 However, prospective audit, intervention and feedback has been shown to be a very
867 effective and safe antibiotic stewardship strategy in South African hospitals, particularly in
868 settings without ID specialists (74). Potential multi-component AFS process and outcome
869 measures for clinician and/or pharmacist and/or ICU nurse audits are proposed in Table 10.

870

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

879

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

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1172

1173 **Tables**

1174 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	<i>Rhodotorula glutinis</i>	If colonies are not pink or yeast is urease-negative, refer*
Auxacolor	<i>Saccharomyces</i>	Consider <i>C. auris</i> and refer*
Microscan	<i>Candida famata</i>	Consider <i>C. auris</i> and refer*
Microscan	<i>Candida lusitanae</i> , <i>Candida guilliermondii</i> , <i>Candida parapsilosis</i> , <i>Candida catenulata</i>	Not possible to detect <i>C. auris</i> unless the yeast ID is confirmed with another method and/or fluconazole resistance is documented
Vitek 2 YST	<i>Candida haemulonii</i> if software update is not loaded	If fluconazole-resistant, treat as <i>C. auris</i> and refer*
Vitek 2 YST	<i>Candida auris</i> if software version 8.01 is loaded	Report as <i>Candida auris</i>
Vitek MS MALDI	<i>Candida auris</i> if research use only (RUO) library is used	Report as <i>Candida auris</i>
Bruker BioTyper MALDI	<i>Candida auris</i> if full/ partial extraction method and RUO library is used	Report as <i>Candida auris</i>

1175 *Refer to a laboratory with Vitek 2 YST software version 8.01 or MALDI-TOF or molecular testing

1176 platform

1177

1178 Table 2: Proposed cut-off values for *C. auris* for 10 antifungal agents and corresponding
 1179 South African surveillance MIC₉₀ 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 MIC₉₀, lowest concentration of the antifungal at which 90% of the isolates are inhibited. MIC₉₀ 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	<ul style="list-style-type: none"> - 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	<ul style="list-style-type: none"> - 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
-

	<ul style="list-style-type: none">- 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	<ul style="list-style-type: none">- 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	<ul style="list-style-type: none">- 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	<ul style="list-style-type: none">- 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

- 1189 a) The “five moments of hand hygiene” is a term used by the World Health Organization to define the points at
1190 which hand hygiene should be performed in healthcare settings. These include the following “moments”:
1191 before patient contact, before an aseptic technique, after blood and body fluid exposure, after patient
1192 contact, after contact with the patient’s environment (24).
- 1193 b) A “care bundle” is a structured way of improving the processes of care and patient outcomes. A care bundle
1194 is a group of evidence-based practices, which when performed collectively and consistently, has proved to
1195 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	Loading dose 70 mg IV, then	Dose as in normal renal function	Fever, thrombophlebitis, headache, raised transaminases
Micafungin	50 mg IV daily 100 mg IV daily		
Anidulafungin	Loading dose 200 mg IV, then 100 mg IV daily		
Amphotericin B deoxycholate	1 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
Liposomal amphotericin B	5 mg/kg IV daily		
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

Candida auris recommendations, South Africa

1198 IV: intravenous infusion; bd: twice daily; po: per os; CrCl: creatinine clearance = (140 – age) * (weight in kg) / (72

1199 * serum creatinine in mg/dL) [Multiply result by 0.85 for women]

1200 *5-FC is available through Section 21 application through the South African Health Products Regulatory Authority

1201 (SAHPRA), formerly the SA Medicines Control Council. 5-FC should not be used as monotherapy but always in

1202 combination with another antifungal agent. The laboratory should determine 5-FC minimum inhibitory

1203 concentrations if this agent is being considered for use.

1204 ***C. auris* is usually not susceptible to fluconazole and voriconazole

1205

1206 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

1207

1208 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

1209

1210 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

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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

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

1218 BDG: (1,3)- β -D-glucan; PCT: Procalcitonin; CVC: central venous catheter; ICU: intensive care unit; MDR: Multi-
1219 drug resistant

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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 ^a	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)
Apisarnthanara k 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)

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

1221 [▫] Unless otherwise stated overall consumption was expressed as defined daily doses/1000 patient days

1222 [♦] 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)

1223 ^{*}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)

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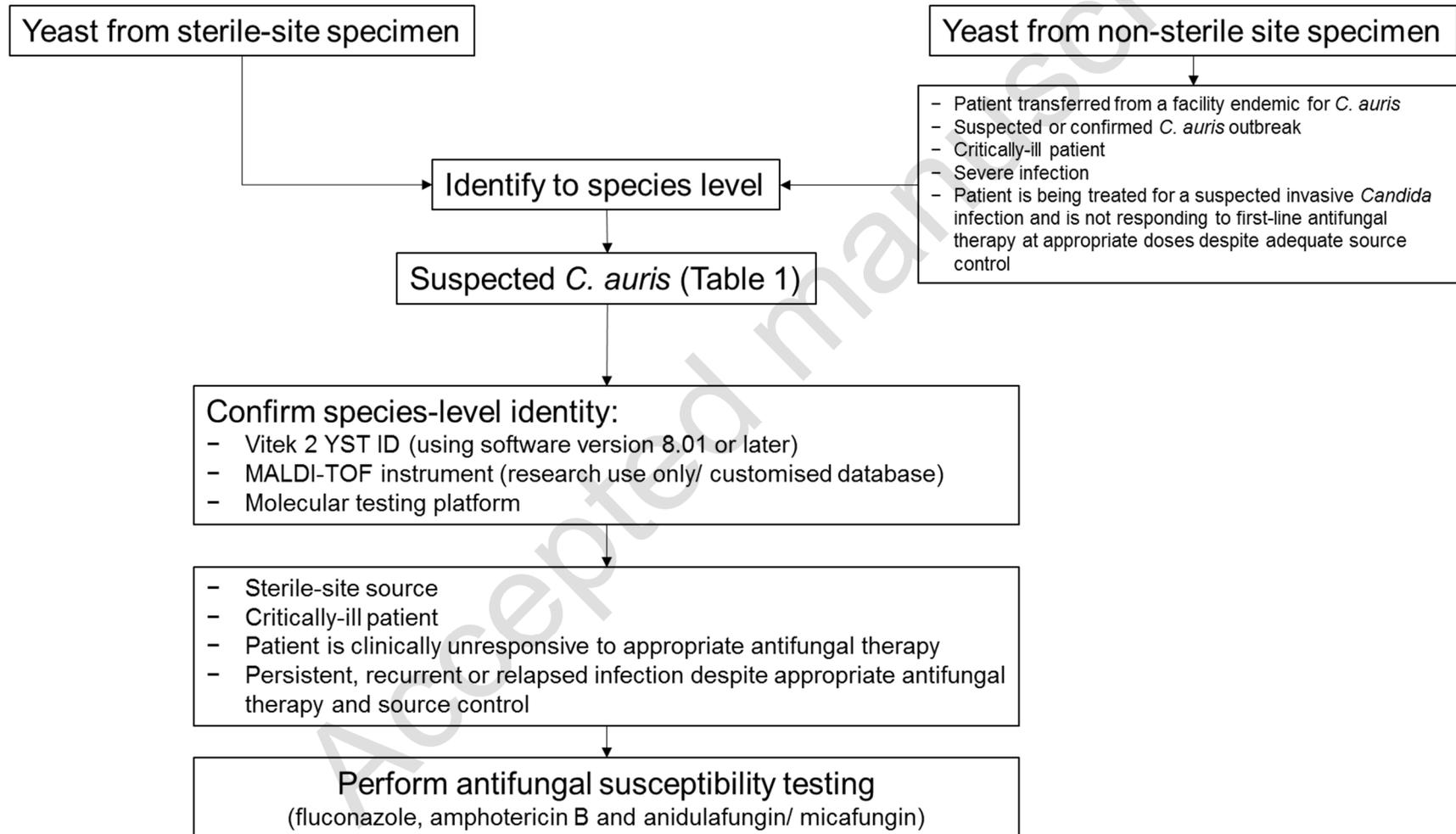
- 1224 • Improved compliance was achieved for the timing of antifungal treatment ($P=0.0025$), recommended first-line therapy ($P=0.0025$), duration of therapy ($P=0.46$) and the
1225 removal of central venous catheters ($P=0.27$), compared with pre-AFS implementation
1226 AF: Antifungal; y: year; m: month; ND: Not determined; V: Voriconazole; C: Caspofungin; DOT: days of therapy

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1227 **Figures**

1228 Figure 1: Laboratory testing algorithm for identification of *C. auris*

1229



1230