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Mycology
F-C 2020

Participant Summary/Final Critique

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2020 F-C
PARTICIPANT SUMMARY/FINAL CRITIQUE

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Evaluation Criteria

To provide a timely evaluation of your results, statistics presented in this Participant Summary reflect participant data received by the due date.

The CAP is required to submit PT results to the Centers for Medicare and Medicaid Services (CMS) for all labs that have provided a CLIA identification number. If you do not notify the CAP that your lab has discontinued testing of a regulated analyte, **a score of zero will be given**. Your reporting preferences are outlined on the CMS Analyte Reporting Selections document. If new products are ordered and/or canceled, this may affect your reporting selections, so it is recommended that you periodically check this report on e-LAB Solutions Suite, which will always reflect the most up-to-date information. This information can also be obtained by calling the Customer Contact Center at 800-323-4040, Option 1 (domestic) or 001-847-832-7000, Option 1 (international).

In the event a result is not graded, a numeric code will appear next to your result. A definition of the code will appear on the first page of your evaluation. Please see "Actions Laboratories Should Take when a PT Result is Not Graded" on page 20.

Analyte	Evaluation Criteria
Dermatophyte	**80% Participant or Referee Consensus**
Mold	**80% Participant or Referee Consensus**
Yeast	**80% Participant or Referee Consensus**
Antifungal susceptibility and testing	80% Participant Consensus and CLSI guidelines*

* Only the qualitative interpretation (resistant, intermediate, susceptible, S-DD or No Interpretation) is formally evaluated. Grading is based on FDA and CLSI method interpretive tables.

The CAP wishes to thank Rosemary C. She, MD, FCAP; and Aida Mangahis, CLS, for providing these photographs. Unless permission is received from Dr. She and Ms. Mangahis, these photographs may not be used for any purpose except in connection with this Survey.

Specimen F-13

The F-13 challenge was a simulated blood culture specimen from a 25-year-old female receiving chemotherapy with fever and neutropenia. Participants were asked to determine the presence or absence of any yeast or aerobic Actinomycetes and identify any yeast or aerobic Actinomycetes present; and to perform antifungal susceptibility testing. The challenge contained *Candida guilliermondii.* A response of *Candida guilliermondii*, *Candida famata/guillermondii, Candida* sp. not *albicans*, *Candida* sp., or Yeast, sent to reference lab for identification was considered satisfactory. Referee and participant responses are summarized below.

Table 1. Summary of Participant Responses

	Identification	Referees (70) No.	%	Participants (1006) No.	%
F-13	*Candida guilliermondii*	52	74.3	722	71.8
	Candida famata/guillermondii	7	10.0	84	8.3
	Candida sp. not *albicans*	5	7.1	41	4.1
	Candida sp.	3	4.3	64	6.4
	Yeast, sent to reference lab for identification	2	2.9	67	6.7

Table 2. Results by Method.

		% of Laboratory Designation	
System	No. Labs	*Candida guilliermondii*	*Candida famata/ guilliermondii*
API	67	86.6	3.0
BD Phoenix	15	86.7	-
Mass spectrometry/Bruker MALDI	200	96.0	3.0
Mass spectrometry/Vitek MS MALDI	171	99.4	-
MicroScan	25	32.0	4.0
Morphology and Bruker MALDI	81	97.5	-
Morphology and Vitek MS MALDI	76	93.4	5.3
Morphologic exam/biochemical	41	9.8	-
Remel RapID Yeast Plus	40	62.5	-
Vitek 2	250	34.1	28.1
Other[a]	31	35.5	-

[a] Includes other commercial kits and methods with <10 users.

Discussion

Taxonomy

Candida guilliermondii was initially described by Castellani in 1912. Historically, it was identified using phenotypic methods including sugar assimilation and fermentation but over time, these methods were found to be inaccurate.[1] Subsequently, DNA sequencing techniques led to the formation of various complexes within the genus *Candida*. Based on DNA sequencing of the intergenic spacer region 2 of ribosomal DNA, the *Candida*

guilliermondii complex is now composed of several different species: *C. guilliermondii* sensu stricto*, C. fermentati,* and *C. carpophila.*[2]

Identification

Candida guilliermondii complex colonies are cream-colored, moist, and flat on Sabouraud dextrose agar. Colonies are glossy with a smooth edge and may turn tan or pink with age. Microscopically, *C. guilliermondii* complex forms clusters of ovoid to ellipsoidal cells (2-4 x 3-6 µm) with short chains of pseudohyphae. Clusters of small blastospores may be noted along the length of the pseudohyphae. Members of *C. guilliermondii* complex do not form germ tubes.[3]

Candida guilliermondii complex can be identified using many commercially available phenotypic systems but differentiation from *C. famata* can be challenging particularly when using biochemical methods.[4,5] By contrast, MALDI-TOF MS is highly accurate in the identification of *C. guilliermondii* sensu stricto. The FDA-cleared Bruker CA system and Vitek MS both identify *C. guilliermodii* but do not identify the other two members of the complex due to lack of representation in their respective databases.

Clinical Significance

Candida guilliermondii complex is a commensal of the skin and mucosal surfaces.[6] Various studies have reported an association between *C. guilliermondii* infections and hematologic malignancy, solid tumors, prior cardiovascular or intra-abdominal surgery, and solid organ transplant.[6] Factors that increase the risk of infections involving *C. guilliermondii* include neutropenia (ANC <500/mL), corticosteroid use, and indwelling catheters.[6-8] Reported mortality of patients with invasive infections involving this organism ranges from 14% to 59%.[6-8]

Key Points

- The *C. guilliermondii* complex is composed of *C. guilliermondii* sensu stricto*, C. fermentati,* and *C. carpophila.*
- *Candida guilliermondii* and *C. famata* are often misidentified by commercial identification systems that use biochemical methods. MALDI TOF MS provides accurate identification of *C. guilliermondii* sensu stricto but may not identify other members of the complex.
- Echinocandin are useful antifungal options for treatment of invasive *C. guilliermondii* infections.

Table 3. Antifungal Susceptibility Testing

Antifungal Susceptibility Testing - MIC*			
Antifungal Susceptibility Testing Intended	F/F1-13:	Antifungal agent	MIC Interpretation ♦
		Anidulafungin	S,NI
		Amphotericin B	U
		5-fluorocytosine	S,NI
		Fluconazole	S,NI
		Itraconazole	NI
		Caspofungin	S,NI
		Voriconazole	S,NI
		Micafungin	S,NI
		Posaconazole	U
		Isavuconazole	U

♦ S – Susceptible; I – Intermediate; R – Resistant; NC – Non-consensus; NI – No Interpretation; S-DD – Susceptible-Dose Dependent; NS – Non-Susceptible; U – Ungraded

Antifungal Susceptibility Testing - MIC*, cont'd

F/F1-13
Candida guilliermondii

MIC testing	Interpretation	Participants No.	Participants %
Anidulafungin	Susceptible	101	100.0
Amphotericin B**	Susceptible	47	27.3
	Resistant	1	0.6
	No Interpretation	124	72.1
5-fluorocytosine	Susceptible	47	37.9
	No Interpretation	77	62.1
Fluconazole	Susceptible	128	41.4
	Resistant	1	0.3
	S-DD	6	1.9
	No Interpretation	174	56.3
Itraconazole	Susceptible	2	2.0
	Intermediate	2	2.0
	Resistant	2	2.0
	S-DD	11	11.1
	No Interpretation	82	82.8
Caspofungin	Susceptible	351	98.0
	Resistant	2	0.6
	No Interpretation	6	1.7
Voriconazole	Susceptible	123	46.8
	No Interpretation	140	53.2
Micafungin	Susceptible	302	95.9
	Intermediate	3	0.9
	Resistant	1	0.3
	No Interpretation	9	2.9
Posaconazole***	Susceptible	1	33.3
	No Interpretation	2	66.7
Isavuconazole***	No Interpretation	6	100.0

* The data for antifungal susceptibility has been combined with the F1 Survey to provide sufficient data to grade this challenge.

** Due to lack of participant consensus, this drug/interpretation was not graded.

*** Due to the limited number of participants (<10) reporting results, this drug/interpretation was not graded.

Antifungal Susceptibility Testing – Disk Agar*

Antifungal Susceptibility Testing Intended Interpretations	F/F1-13: Antifungal agent	Disk Agar Diffusion ♦
	Fluconazole**	U
	Capsofungin**	U
	Voriconazole**	U

♦ S – Susceptible; I – Intermediate; R – Resistant; S-DD – Susceptible-Dose Dependent; U - Ungraded

F/F1-13 *Candida guilliermondii*

Disk Agar Diffusion	Interpretation	Participants No.	%
Fluconazole**	Susceptible	3	75.0
	No Interpretation	1	25.0
Voriconazole**	Susceptible	1	100.0

* The data for antifungal susceptibility has been combined with the F1 Survey.

** Due to the limited number of participants (<10) reporting results, this drug/interpretation was not graded.

Table 4. Supplemental questions for antifungal susceptibility testing of *Candida guilliermondii* for F-13 2020.

	Participant response:
1. Test methods:	
Broth microdilution	18
Disk Diffusion	8
YeastOne colorimetric microdilution	184
Gradient diffusion strips (eg, Etest, MTS)	31
Vitek 2	179
Other	8
2. Test performed according to:	
CLSIM27-S4/CLSI M60	363
CLSI M27-S3 (obsolete)	14
FDA	18
Other	14
3. Does your laboratory use or plan on using/reporting Epidemiologic cutoff values (ECVs)?	
Yes	67
No	321

Table 5. Distribution of antifungal MIC results by method for F/F1-13*

Occurrences at MIC (µg/mL)

5 - FLUOROCYTOSINE	<	<=	<=	<=	<=	<=	<=
Method	**0.020**	**0.030**	**0.060**	**0.120**	**0.125**	**1.000**	**2.000**
Broth microdilution	-	1	-	1	1	-	1
Vitek 2	-	-	-	-	-	30	-
YeastOne	1	13	57	1	-	-	-

AMPHOTERICIN B	<=	=	=	<=	<=	=	<=	>=	<=	=	=
Method	**0.032**	**0.060**	**0.064**	**0.120**	**0.125**	**0.19**	**0.250**	**0.250**	**0.500**	**1.000**	**8.000**
Broth macrodilution	-	-	-	-	-	1	-	-	-	-	-
Broth microdilution	3	1	-	1	-	-	2	-	4	1	-
Gradient diffusion strips	2	-	1	-	3	1	-	-	-	-	-
Vitek 2	-	-	-	-	-	-	37	-	2	-	1
YeastOne	1	-	1	9	-	-	52	1	23	1	-

ANIDULAFUNGIN	=	<=	<=	>=	<=
Method	**0.250**	**0.500**	**1.000**	**1.000**	**2.000**
Broth macrodilution	-	-	-	-	1
Broth microdilution	1	-	5	-	4
Gradient diffusion strips	-	-	1	-	1
Vitek 2	-	-	1	-	-
YeastOne	1	8	43	1	22

CASPOFUNGIN	<=	>=	>=	<=	<=	=	<=	<=	<=	>=	>
Method	**0.030**	**0.060**	**0.120**	**0.190**	**0.250**	**0.380**	**0.500**	**1.000**	**2.000**	**8.000**	**32.000**
Broth macrodilution	-	-	1	-	-	-	-	-	-	-	-
Broth microdilution	-	-	2	1	3	-	4	1	-	-	-
Gradient diffusion strips	-	1	-	1	3	1	1	-	-	-	1
Vitek 2	-	-	-	-	125	-	41	4	2	1	-
YeastOne	1	2	23	-	59	-	26	1	1	-	-

FLUCONAZOLE	<=	<=	>=	=	<=	>=	<=	>	<=	>
Method	**1.000**	**2.000**	**2.000**	**3.000**	**4.000**	**4.000**	**8.000**	**8.000**	**16.000**	**256.000**
Broth macrodilution	-	1	-	-	-	-	-	-	-	-
Broth microdilution	2	7	-	-	6	-	-	-	-	-
Gradient diffusion strips	1	8	-	5	3	-	1	-	1	1
Vitek 2	1	67	-	-	26	-	2	1	-	-
YeastOne	3	15	2	-	97	2	8	-	-	-

* Some MIC values may have been combined due to space limitations

Occurrences at MIC (μg/mL)

ISAVUCONAZOLE	=	=
Method	**0.120**	**0.250**
Broth macrodilution	-	1
Broth microdilution	2	1

ITRACONAZOLE	=	<=	=	<=	=	=
Method	**0.120**	**0.125**	**0.25**	**0.500**	**1.000**	**4.000**
Broth macrodilution	-	-	1	-	-	-
Broth microdilution	-	1	4	4	-	-
Gradient diffusion strips	-	-	-	-	1	1
YeastOne	4	-	39	29	1	-

MICAFUNGIN	=	=	=	<=	>=	=	<=	<=	>=	<=
Method	**0.120**	**0.250**	**0.38**	**0.500**	**0.500**	**0.75**	**1.000**	**2.000**	**4.000**	**8.000**
Broth macrodilution	-	-	-	-	1	-	-	-	-	-
Broth microdilution	-	4	-	-	5	-	7	-	-	1
Gradient diffusion strips	-	-	1	-	1	1	-	3	-	-
Vitek 2	-	1	-	24	84	-	1	1	-	-
YeastOne	2	5	-	2	34	-	82	7	1	-

POSACONAZOLE	<=	=	=	<=
Method	**0.030**	**0.120**	**0.125**	**0.250**
Broth macrodilution	-	-	-	1
Broth microdilution	1	1	1	2
YeastOne	-	3	-	1

VORICONAZOLE	=	=	<=	<=	=	=	<=	>=	=	=
Method	**0.016**	**0.030**	**0.047**	**0.060**	**0.064**	**0.094**	**0.120**	**0.120**	**0.125**	**1.500**
Broth microdilution	-	1	-	12	-	-	-	-	-	-
Gradient diffusion strips	1	-	1	-	2	1	-	-	2	1
Vitek 2	-	-	-	-	-	-	96	-	-	-
YeastOne	-	1	-	62	-	-	38	1	2	-

* Some MIC values may have been combined due to space limitations

Table 6. Interpretation by Method

F/F1-13

	Broth Microdilution					YeastOne Colorimetric					Gradient diffusion strips (eg, Etest, MTS)					Vitek 2					
Antimicrobial	**S**	**I**	**R**	**S-DD**	**NI**	**S**	**I**	**R**	**S-DD**	**NI**	**S**	**I**	**R**	**S-DD**	**NI**	**S**	**I**	**R**	**S-DD**	**NS**	**NI**
Anidulafungin	10	-	-	-	-	75	-	-	-	-	2	-	-	-	-	1	-	-	-	-	-
Amphotericin B	2	-	-	-	10	5	-	-	-	82	2	-	-	-	5	29	-	1	-	-	10
Caspofungin	11	-	-	-	-	110	-	-	-	4	8	-	1	-	-	172	-	1	-	-	1
Fluconazole	2	-	-	2	10	19	-	-	4	103	5	-	1	-	13	75	-	-	-	-	22
Micafungin	15	-	1	-	1	127	1	-	-	5	5	-	-	-	1	111	1	-	-	-	1
Itraconazole	-	-	-	-	8	1	1	2	8	59	-	-	-	-	2	-	-	-	-	-	-
Voriconazole	3	-	-	-	9	16	-	-	-	87	2	-	-	-	6	78	-	-	-	-	17
5-Fluorocytosine	1	-	-	-	3	12	-	-	-	59	-	-	-	-	-	24	-	-	-	-	-
Posaconazole	1	-	-	-	-	-	-	-	-	2	-	-	-	-	-	-	-	-	-	-	-
Isavuconazole	-	-	-	-	2	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

Antimicrobial Resistance and Susceptibility Testing

The Infectious Diseases Society of America (IDSA) recommends the use of an echinocandin (caspofungin, micafungin, or anidulafungin) for initial treatment of candidemia in both neutropenic and non-neutropenic patients.[9] *In vitro* studies of *C. guilliermondii* have reported higher fluconazole and echinocandin minimum inhibitory concentrations (MICs) compared to *C. albicans*.[10] However, clinical studies reporting outcomes of patients treated for invasive *C. guilliermondii* infections have generally shown good therapeutic response to caspofungin with MICs in the range of ≤ 2 µg/mL.[8] The Clinical and Laboratory Standards Institute (CLSI) currently recommends the following breakpoints for *C. guilliermondii* and caspofungin, anidulafungin, and micafungin: ≤2 µg/mL (susceptible); 4 µg/mL (intermediate); and ≥ 8 µg/mL (resistant).[11] Survey participants reached consensus for the echinocandins with >95% reporting susceptible status for all three drugs. Because some laboratories may follow EUCAST guidelines, which do not have interpretive breakpoints for *C. guilliermondii* and echinocandins, a response of “no interpretation” was also accepted.

Elevated fluconazole MICs have been widely reported in *C. guilliermondii*, with polymorphic mutations in the *ERG* 11 gene of the ergosterol biosynthesis pathway likely reducing affinity to fluconazole.[13] Neither CLSI nor EUCAST provide interpretive breakpoints for *C. guilliermondii* and any azole. CLSI has published epidemiological cutoff values (ECVs) for *C. guilliermondii* and fluconazole and posaconazole but ECVs only distinguish between wild-type and non-wild type isolates and do not predict therapeutic response.[14] In the absence of CLSI or EUCAST interpretive breakpoints for *C. guilliermondii* and fluconazole and voriconazole, the ideal response for these drugs was “no interpretation”. Some laboratories may be following the outdated M27-S3 breakpoints. The response of “susceptible” was therefore accepted for fluconazole and voriconazole. Laboratories that reported susceptibility status using outdated interpretive breakpoints should strongly consider updating their antifungal susceptibility policies to reflect current interpretive breakpoints. Further, neither CLSI nor EUCAST provide interpretive breakpoints for *C. guilliermondii* and itraconazole, isavuconazole, or posaconazole. Accordingly, the ideal response for these drugs was “no interpretation”.

Neither CLSI nor EUCAST have published interpretive breakpoints for 5-fluorocytosine, but the U.S. Food and Drug Administration (FDA) recognizes the M27-S3 breakpoints.[15] Responses of “no interpretation” and “susceptible” were therefore accepted.

Because neither CLSI nor EUCAST have published interpretive breakpoints for amphotericin B, the ideal response for these drugs was “no interpretation”. However, due to lack of consensus among participants, this drug was not graded.

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Specimen F-14

The F-14 challenge was a simulated blood culture specimen from a 20-year-old trauma patient receiving probiotics. Participants were asked to determine the presence or absence of any fungus or aerobic Actinomycetes and identify any fungus or aerobic Actinomycetes present. The challenge contained *Saccharomyces cerevisiae* and *Staphylococcus epidermidis* as a contaminant. A response of *Saccharomyces cerevisiae*, *Saccharomyces* sp., or Yeast, sent to reference lab for identification was considered satisfactory.

Table 1. Summary of Participant Responses

	Identification	Referees (70) No.	%	Participants (1005) No.	%
F-14	*Saccharomyces cerevisiae*	61	87.1	860	85.6
	Saccharomyces sp.	5	7.1	56	5.6
	Yeast, sent to reference lab for identification	5	7.1	73	7.3

Table 2. Results by Method

		% of Laboratory Designation	
System	No. Labs	*Saccharomyces cerevisiae*	*Saccharomyces sp.*
API	67	89.5	7.5
BD Phoenix	20	95.0	-
Mass spectrometry/Bruker MALDI	177	91.5	4.0
Mass spectrometry/Vitek MS MALDI	174	97.7	1.7
MicroScan	28	92.9	3.6
Morphology and Bruker MALDI	74	90.5	9.5
Morphology and Vitek MS MALDI	75	96.0	2.7
Morphologic exam/biochemical	52	28.9	7.7
Remel RapID Yeast Plus	40	65.0	12.5
Vitek 2	259	86.9	7.0
Other[a]	29	41.4	10.4

[a] Includes other commercial kits and methods with <10 users.

Discussion

Taxonomy and Identification

Saccharomyces cerevisiae belongs to the family Saccharomycetaceae, genus *Saccharomyce*s, that was formerly divided into two subgroups (sensu stricto and sensu lato) according to complex criteria of how closely related the *Saccharomyes* were related to *S. cervevisiae*.[6] Recently, changes in taxonomy have abandoned this subdivision and assigned some species to other genera such as *Naumovia* and *Lachancea*.[6]

The *Saccharomyces cerevisiae* grow well within two to three days, and produce dull, smooth, white, slightly raised, creamy colonies. They do not grow on media that contain cycloheximide. *Saccharomyces cerevisiae* is germ tube negative. The organism is urease negative, which differentiates it from the Cryptococci. This organism is differentiated from *Candida* species by its morphology on cornmeal agar and consist primarily of yeast cells, but rudimentary pseudohyphae can occasionally be seen.

Clinical Significance

Saccharomyces cerevisiae is well known yeast in the baking and brewing industry and is also used a probiotic.[6] Like *Candida* species, it colonizes the respiratory, urinary, and gastrointestinal tract in humans.[5] *Saccharomyces cerevisiae* has been suggested as an uncommon cause of a variety of infections in humans from fungemia to vaginitis.[1,2,3,6] The fungemia has been linked to long term probiotic use and immunosuppression in some cases.[5,7] Definitive proof of causality is difficult to obtain, partially because colonization appears to be much more common than the rare symptomatic infection.[4] It is important to consider *S. cerevisiae* whenever probiotics are used on an immunocompromised patient.

Therapy Considerations

Isolates of *S. cerevisiae* are less susceptible to fluconazole than are isolates of *C. albicans,*[4] but it is difficult to assess the clinical significance of this observation. Adela Enache-Angoulvant et al. found that a combination of intravenous amphotericin B were effective treatment options in 92 cases of an invasive *Saccharomyces* infection.[8]

Key Points

- The *Saccharomyces cerevisiae* grow rapidly, usually within three days and produce dull, smooth, white, slightly raised, creamy colonies.
- *Saccharomyces cerevisiae* germ tube negative and is differentiated from *Candida* species by its morphology on cornmeal agar: primarily yeast with rudimentary pseudohyphae.
- The organism is urease negative, which differentiates it from the Cryptococci.
- *Saccharomyces cerevisiae* is used as a probiotic and is important to consider *S. cerevisiae* whenever probiotics are used on an immunocompromised patient with sepsis.

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Specimen F-15

The F-15 challenge was a simulated bronchoalveolar lavage specimen from a 36-year-old female with a history of systemic lupus erythematosus with respiratory failure and pulmonary infiltrates on chest x-ray. Participants were asked to determine the presence or absence of any fungus or aerobic Actinomycetes and identify any fungus or aerobic Actinomycetes present. The challenge contained *Aspergillus terreus* and *Staphylococcus epidermidis* as a contaminant. A response of *Aspergillus terreus*, *Aspergillus* sp. (not fumigatus), *Aspergillus* sp., *Aspergillus* sp. presumptive ID, and Mold recgonized sent to reference lab for identification was considered satisfactory.

Table 1. Summary of Participant Responses

F-15

Identification	Referees (69) No.	%	Participants (1006) No.	%
Aspergillus terreus	29	42.0	404	40.2
Aspergillus sp. (not *fumigatus*)	7	10.1	150	14.9
Aspergillus sp.	17	24.6	268	26.6
Aspergillus sp. presumptive ID	1	1.4	9	0.9
Mold recognized, sent to reference lab for identification	14	20.3	168	16.7

Table 2. Results by Method

		% of Laboratory Designation		
System	No. Labs	*Aspergillus terreus*	*Aspergillus* sp. (not fumigatus)	*Aspergillus* sp.
Biochemical method	13	30.8	23.1	23.1
Mass spectrometry/Vitek MS MALDI	10	80.0	-	-
Morphology and Bruker MALDI	30	86.7	6.7	6.7
Morphology and Vitek MS MALDI	39	84.6	7.7	7.7
Morphology and sequencing	20	100.0	-	-
Morphologic exam/biochemical	806	36.1	29.6	29.6
Other[a]	42	33.3	33.3	33.3

[a] Includes other commercial kits and methods with <10 users.

Discussion

Taxonomy

Aspergillus terreus complex is one of over 250 species described in the genus *Aspergillus*, in the family Trichocomaceae of the division Ascomycota. Using multigene phylogeny based on four genetic loci (β-tubulin, calmodulin, internal transcribed spacer and large subunit or the rDNA, and RNA polymerase II 2), members of genus *Aspergillus* have been subdivided into eight subgenera, and then further subdivided into 16 sections. *A. terreus* complex falls the section Terrei.[1]

Identification

Aspergillus terreus complex grows rapidly and produces mature colonies in about three days. Colonies have a characteristic cinnamon-brown color and a velvety texture (Figure 1). The reverse is yellow-to-tan. Microscopically, the organism produces smooth, relatively short conidiophores. At the end of conidiophores is a swollen, dome-shaped vesicle with biseriate phialides covering the upper half of the vesicle only. Metulae and phialides are equal in length. Conidia are round and smooth (Figure 2A). Solitary conidia are often produced along the side of hyphae that are submerged in medium.[2] MALDI-TOF MS can also be used for successful identification of *A. terreus* complex. Vitek MS is FDA-cleared for identification of *A. terreus* to the complex level although some members of the complex may fail to identify.

Clinical Significance

Aspergillus species are ubiquitous in nature and are commonly found in stored grains, dirt, and air. Despite frequent exposure to conidia from environmental sources, human infections are uncommon. Disease is reported primarily in patients with defective pulmonary clearance systems (eg, cystic fibrosis) and immune defects (eg. profound, protracted neutropenia; glucocorticoid or antineoplastic therapy; post-transplantation).[3]

The distinction between colonization of the respiratory tract and invasive disease can be challenging, especially in immunocompromised patients. Most *Aspergillus* culture isolates from non-sterile body sites do not represent disease and must be interpreted in context using clinical, radiologic and other laboratory findings.

When *Aspergillus* is responsible for disease, the term aspergillosis is used. Disease can manifest in various ways including airway or lung invasion, cutaneous infections, extrapulmonary dissemination, and allergic reactions. *Aspergillus terreus* complex is the fourth most common cause of invasive aspergillosis after *Aspergillus fumigatus, Aspergillus flavus,* and *Aspergillus niger* and occurs most often in immunocompromised hosts.[4] Allergic bronchopulmonary aspergillosis typically occurs in individuals with cystic fibrosis or asthma. The respiratory tree becomes colonized with *Aspergillus,* eliciting an allergic response and symptoms of reactive airway disease.[3]

Antimicrobial Resistance and Therapy Considerations

For invasive aspergillosis, voriconazole is the recommended as the first-line antifungal agent.[5] *Aspergillus terreus* complex isolates are intrinsically resistant to amphotericin B and providers should exercise caution when considering polyene drugs for treatment of invasive *A. terreus* complex infections.

For clinically significant *Aspergillus* isolates, the Clinical and Laboratory Standards Institute's M38-Ed3 document provides a standardized method for antifungal susceptibility testing of *Aspergillus* spp.[6] It should be noted, however, that MICs of azoles and echinocandins alone may not necessarily predict outcome of invasive aspergillosis. Host factors such as neutropenia and drug pharmacokinetics/ pharmacodynamics play an equally important role in determining patient outcome.

Despite appropriate therapy, patient mortality in invasive aspergillosis is high. In a prospective surveillance study describing 960 cases of invasive aspergillosis, Steinbach et al reported that more than one-third of cases died despite therapy.[4]

Key Points

- *Aspergillus terreus* complex isolates have a distinctive cinnamon color.
- Identification through MALDI-TOF MS is becoming more accessible.
- *Aspergillus* spp. are common in our environment.
- Invasive aspergillosis occurs predominantly in immunocompromised patients and is associated with high mortality.
- *Aspergillus terreus* complex is intrinsically resistant to amphotericin B.

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Specimen F-16

The F-16 challenge was a simulated cerebrospinal fluid specimen from a 42-year-old male with history of renal transplant, on immunosuppresive therapy, and presenting with severe headaches. Participants were asked to determine the presence or absence of any fungus or aerobic Actinomycetes and identify any fungus or aerobic Actinomycetes present. The challenge contained *Trichoderma* sp. and *Staphylococcus epidermidis* as a contaminant. A response of *Trichoderma* sp., or Mold recognized, sent to reference lab for identification was considered satisfactory.

Table 1. Summary of Participant Responses

F-16

Identification	Referees (69) No.	%	Participants (1006) No.	%
Trichoderma sp.	35	50.7	589	58.5
Mold recognized, sent to reference lab for identification	31	44.9	349	34.7

Table 2. Results by Method

System	No. Labs	% of Laboratory Designation *Trichoderma* sp.
Biochemical method	12	41.7
Morphology and Bruker MALDI	16	75.0
Morphology and Vitek MS MALDI	10	60.0
Morphologic exam/biochemical	845	60.5
Morphology and sequencing	28	89.3
Other[a]	44	43.2

[a] Includes other commercial kits and methods with <10 users.

Discussion

Taxonomy

Trichoderma is a genus of Hyphomycete that traditionally was divided into five sections. Based solely on phenotypic characteristics, its scale of genetic diversity has been underrecognized. With modern application of molecular analysis, the genus now includes at least 260 distinct species.[1] *Trichoderma harzianum* complex itself includes at least 14 different species.[2] The medically important *Trichoderma* species include *T. citrinoviride*, *T. harzianum*, *T. koningii*, *T. longibrachiatum*, *T. pseudokoningii*, and *T. viride* with *T. longibranchium* being the most commonly reported species.[3]

Identification

Trichoderma species grow relatively rapidly, producing mature growth within 5 days. Colonies are initially white and fluffy, later becoming woolly. With age, blue-green to yellow-green conidia develop in tufted areas (Figure 3). The reverse appears white, yellow to tan-orange.[4-6]

Trichoderma spp. feature septate, hyaline hyphae and short conidiophores with right angle or wide-angle branching. Flask-shaped phialides are inflated at the base, form at wide angles to conidiophores, and produce round to oval conidia 2-5 µm in diameter. Conidia cluster at the end of phialides and are easily disrupted unless

handled very carefully. Some species demonstrate chlamydoconidia.[5-7] It is difficult to accurately identify the species based solely on morphology of the conidia and phialides.[1,2] *Trichoderma harzianum* has hyaline hyphae that are 1.5-2.0 µm wide. Conidiophores branch in pyramidal arrangement, usually at right angles. Phialides appear in groups of 3-5 and conidia are (sub)pherical and smooth-walled (Figure 4).[6]

Clinical Significance

Trichoderma spp. are widely distributed on decaying plant matter, on wood and in the soil.[1,2,5] *Trichoderma harzianum* is commonly found on wood.[2,4]

Trichoderma spp. are commonly considered clinically insignificant isolates. However, *Trichoderma* spp. have been increasingly recognized as the cause of invasive infections in immunocompromised individuals, particularly organ transplant recipients, patients with hematologic disorders, and patients who undergo peritoneal dialysis. Reported infections include sinusitis, peritonitis, pneumonia, and brain abscesses. Invasive infections are fatal in a substantial proportion of cases, which may be in part due to antifungal resistance found in *Trichoderma* spp.[3,7-11]

Antimicrobial Resistance and Therapy Considerations

Studies of clinical *Trichoderma* spp. isolates have found them to be potentially resistant to a number of antifungal agents, with no particular patterns associated with any one species.[7,11] The MIC of amphotericin is generally elevated. Itraconazole and posaconazole have poor *in vitro* activity against *Trichoderma* spp. while voriconazole appears to be the most active azole agent. Echinocandins generally demonstrate strong *in vitro* activity. Terbinafine has variable activity against organisms of this genus.

In spite of *in vitro* data, the *in vivo* response to antifungal agents has been reported to be unpredictable.[7,11,12] There are no CLSI interpretive breakpoints for antifungal MICs and the optimal antifungal treatment regimen is unknown due to the infrequency of infections with this fungal genus. In addition to antifungal therapy, control of infection source, e.g., discontinuation of lines, surgical debridement of infected site, etc., should be considered.[11,12]

Key Points

- *Trichoderma* is a genetically diverse genus that can be accurately identified to species level only with DNA sequence-based methods.
- In culture, *Trichoderma* spp. have characteristically green colonies and on microscopy show hyaline hyphae, short branching conidiophores, and flask-shaped phialides with rounded conidia clustered at the tip.
- Invasive infections are infrequently reported and occur in immunocompromised patients. The optimal treatment is unclear at this time, considering the infrequency of infections and that MICs to various antifungal agents are commonly elevated but do not clearly correlate with clinical outcomes.

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Specimen F-17

The F-17 challenge was a simulated finger wound specimen from a 32-year-old avid eco camper. Participants were asked to determine the presence or absence of any fungus or aerobic Actinomycetes and identify any fungus or aerobic Actinomycetes present. The challenge contained *Sporothrix schenkii* complex and *viridans* streptococcus as a contaminant. A response of *Sporothrix schenckii* complex, *Sporothrix* sp., Dematiaceous mold, Mold recognized, sent to reference lab for identification, Yeast, sent to reference lab for identification and Yeast was considered satisfactory.

Table 1. Summary of Participant Responses

F-17

Identification	Referees (69) No.	%	Participants (1009) No.	%
Sporothrix schenckii complex	24	34.8	439	43.5
Sporothrix sp.	15	21.7	219	21.7
Dematiaceous mold	-	-	3	0.3
Mold recognized, sent to reference lab for identification	29	42.0	278	27.6
Yeast, sent to reference lab for identificaion	-	-	19	1.9
Yeast	-	-	2	0.2

Table 2. Results by Method

System	No. Labs	% of Laboratory Designation *Sporothrix schenckii complex*	*Sporothrix* sp.
Biochemical method	12	33.3	8.3
Mass spectrometry/Bruker MALDI	10	80.0	10.0
Mass spectrometry/Vitek MS MALDI	30	100.0	-
Morphology and Bruker MALDI	38	79.0	15.8
Morphology and Vitek MS MALDI	53	94.3	5.7
Morphologic exam/biochemical	739	37.5	26.3
Morphology and sequencing	26	88.5	7.7
Other[a]	53	18.9	13.2

[a] Includes other commercial kits and methods with <10 users.

Discussion

Taxonomy

The genus *Sporothrix* is found in the order Ophiostomatales, the core genus of which is *Opiostoma*, fungi that that live in association with bark beetles. Thirty-two accepted species of *Sporothrix* have been identified, including those that caused human disease (sporotrichosis) and saprophytic species. Molecular testing and the use of internal transcribed spacer (ITS) region sequence analysis of chitin synthase, β-tubulin, and calmodulin (CAL) genes have demonstrated that *Sporothrix schenckii* is a species complex comprised of five distinct pathogenic species: *Sporothrix schenckii* senso stricto, *S. brasiliensis*, *S. globosa*, *S. luriei*, and *S. mexicana*.[1] Each species of the S. *schenckii* complex is prevalent in a different geographic region. *Sporothrix schenckii* s. str. is common in Australia, southern Africa, western South America, Central and North America, whereas *S. globosa* causes

disease in Asia and *S. brasiliensis* in south-eastern South America.[1] *Sporothrix mexicana* is relatively uncommon causes of sporotrichosis. In rare cases, environmental species, including *S. stenoceras* and *S. pallida,* have caused human disease, but limited to patients with immunocompromising conditions.[1]

Identification

Sporothrix schenckii complex are thermally dimorphic and some species (including *Sporothrix schenckii* senso stricto) are dematiaceous, growing as a white-to-brown or black mold at room temperature (Figure 5), but as a yeast at 37ºC.[2] The key to identification of this organism is to demonstrate the typical microscopic morphology on tape preps or on slide culture. A thin septate mycelium is produced. Fine conidiophores bear round to oval conidia in small flowerettes or in clavate, sympodial orientation (Figure 6A). These structures are often disrupted on tape preparations and so review of slide cultures may be necessary. The morphology observed was the production of large numbers of dark and non-pigmented conidia arising directly from the hyphae in “sleeve-like formations”. This same morphology has been noted by previous authors.[3,4] Perithecia with crescent-shaped ascospores may be produced on potato dextrose agar with prolonged incubation. Thermal conversion to the yeast phase at 37ºC is required for definitive morphologic identification. The yeast are typically round, oval to cigar-shaped and measure 1-3 × 3-10 µm in diameter (Figure 6B). The yeast form is the morphology that may be detected in direct tissue specimens histologically. Exoantigen testing, mating studies and growth enhancement in the presence of thiamine may also be used to assist in definitive identification of *S. schenckii* complex, but these tests are not commonly available.[3] Unlike the other thermally dimorphic molds, there is no commercially available probe. Although PCR has been used for the detection of the organism in direct specimens, this is not commercially available.[5]

Clinical Significance

Sporothrix schenckii complex is not a particularly common isolate in most clinical laboratories. Cases are generally sporadic, but some very interesting outbreaks have been identified. Outbreaks are due to sapronosis (infection from plants) or zoonosis (infection from infected cats). In North America, most outbreaks have focused around contaminated sphagnum moss originating from bogs in Wisconsin and Michigan. Florists, nursery workers, gardeners and individuals working in forestry were at greatest risk for infection where contaminated sphagnum moss was used in plant preparation.[6-11] The largest outbreak described involved 84 documented cases in 15 states where infected sphagnum moss had been distributed.[11] The majority of cases of sporotrichosis present as cutaneous lesions at the site of a penetrating trauma with or without ascending lymphangitis. The association between infection with *S. schenckii* and traumatic injury with a rose thorn has given the disease the name “Rose Handler’s Disease”. In Brazil, cat scratches are the most common source of infection, and due to *S. brasiliensis*.[1,12] In the setting of immunocompromise, rare patients have developed meningitis.[11] Cases of pulmonary disease with sporotrichosis have also been seen.[4]

Antimicrobial Resistance and Therapy Considerations

Most cases of sporotrichosis are localized to the skin and subcutaneous tissues. Sponteneous resolution of is rare and treatment is required for most patients. Itraconazole, given orally for 2-4 weeks after lesions have resolved (typically a total duration of 3-6 months) is the primary treatment for sporotrichosis. Terbinafine or a saturation solution of potassium iodide applied topically are alternative treatment options for patients who do not respond with itraconazole. Cryotherapy may also be used, if disease is fixed cutaneous in nature. For disease outside the skin and soft tissues, amphotericin B is generally administered, alone or in combination with other agents.[13]

Antifungal susceptibility testing is not generally performed on isolates of *Sporothrix schenkii*. However, the Clinical and Laboratory Standards Institute (CLSI) has described testing conditions for members of the filamentous phase of the *Sporothrix schenckii* complex.[14] Clinical breakpoints have not been established for any *Sporothrix schenckii* species complex, but epidemiological cutoff values (ECVs) have been proposed.[15] Very limited data have been documented to evaluate the correlation between MICs and outcomes of therapy for sporotrichosis. In one study, four of five patients who responded to oral itraconazole for treatment of lymphagitic and fixed cutaneous sporotrichosis were infected with isolates that had itraconzole MICs below the CLSI proposed ECV (i.e., <4 ug/ml,

wild-type), whereas one had an MIC above this cut-off.[16] Until such time clinical breakpoints can be established for *S. schenckii* species complex, laboratories should not perform routine susceptibility testing.

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Actions Laboratories Should Take when a PT Result is Not Graded

The CAP uses exception reason codes that signify the proficiency testing (PT) for an analyte has not been graded. The exception reason code is located on the evaluation report in brackets to the right of the result. Your laboratory must identify all analytes with an exception reason code, review, and document the acceptability of performance as outlined below and retain documentation of review for at least 2 years. The actions laboratories should take include, but are not limited to:

Code	***Exception Reason Code Description***	***Action Required***
11	Unable to analyze	Document why the specimens were not analyzed (eg, instrument not functioning or reagents not available). Perform and document alternative assessment (ie, split samples) for the period that commercial PT was not tested to the same level and extent that would have been tested.
20	Response was not formally graded due to insufficient peer group data. Please see the participant summary for additional information.	Applies to a response that is not formally evaluated when a peer group is not established due to fewer than 10 laboratories reporting. Document that the laboratory performed a self-evaluation using the data presented in the participant summary and compared its results to a similar method, all method, all participant statistics, or data tables for groups of 3-9 laboratories, if provided. Perform and document the corrective action of any unacceptable results. If self-evaluation is not possible, it is up to the laboratory director/designee to determine an alternative performance assessment.
21	Specimen problem	Document that the laboratory has reviewed the proper statistics supplied in the participant summary. Perform and document alternative assessment for the period that commercial PT was not tested to the same level and extent that would have been tested. Credit is not awarded in these cases.
22	Result is outside the method/ instrument reportable range	Document the comparison of results to the proper statistics supplied in the participant summary. Verify detection limits. Perform and document the corrective action of any unacceptable results.
24	Incorrect response due to failure to provide a valid response code	Document the laboratory's self-evaluation against the proper statistics and evaluation criteria supplied in the participant summary. Perform and document the corrective action of any unacceptable results. Document corrective action to prevent future failures.
25	Inappropriate use of antimicrobial	Document the investigation of the results as if they were unacceptable and review the proper reference documents to gain knowledge of the reason your response is not appropriate.
26	Educational challenge	Review participant summary for comparative results and document performance accordingly. Evaluation criteria are not established for educational challenges. Laboratories should determine their own evaluation criteria approved by their laboratory director for self-evaluation. Response to the CAP is not required.
27,31	Lack of participant or referee consensus	Document that the laboratory performed a self-evaluation and compared its results to the intended response when provided in the participant summary. If comparison is not available, perform and document alternative assessment (ie, split samples) for the period that commercial PT reached non-consensus to the same level and extent that would have been tested.
28	Response qualified with a greater than or less than sign; unable to quantitate	Applies to a response that is not formally evaluated when a less than or greater than sign is reported. Document that the laboratory performed a self-evaluation and compared its results to the proper statistics supplied in the participant summary. Verify detection limits. Perform and document the corrective action of any unacceptable results.
30	Scientific committee decision	Applies to a response that is not penalized based on scientific committee decision. Document that the laboratory has reviewed the proper statistics supplied in the participant summary.

Actions Laboratories Should Take when a PT Result is Not Graded

The CAP uses exception reason codes that signify the proficiency testing (PT) for an analyte has not been graded. The exception reason code is located on the evaluation report in brackets to the right of the result. Your laboratory must identify all analytes with an exception reason code, review and document the acceptability of performance as outlined below and retain documentation of review for at least 2 years. The actions laboratories should take include but are not limited to:

Code	***Exception Reason Code Description***	***Action Required***
33	Specimen determined to be unsatisfactory after contacting the CAP	Document that the laboratory has contacted the CAP and no replacements specimens were available. Perform and document alternative assessment (ie, split samples) for the period that commercial PT was not tested to the same level and extent that would have been tested.
40 41	Results for this kit were not received. Results for this kit were received past the evaluation cut-off date.	Document why results were not received, corrective action to prevent recurrence and the laboratory's self-evaluation of the results by comparing results to the proper statistics and evaluation criteria supplied in the participant summary. If PT specimens were not analyzed, perform and document alternative assessment (ie, split samples) for the period that commercial PT was not tested to the same level and extent that would have been tested.
42	No credit assigned due to absence of response	The participant summary indicates which tests are graded (see evaluation criteria) and which tests are not evaluated/educational. Updates to grading will also be noted. If a test is educational, the laboratory is not penalized for leaving a result(s) blank. If a test is graded (regulated and non-regulated analytes) and your laboratory performs that test, results cannot be left blank. The laboratory is required to submit results for **all** challenges within that test or use an appropriate exception code or indicate test not performed/not applicable/not indicated. Exceptions may be noted in the kit instructions and/or the result form. Document corrective actions to prevent future failures.
44	This drug is not included in our test menu. Use of this code counts as a correct response.	Verify that the drug is not tested on patient samples and document to ensure proper future reporting.
45	Antimicrobial agent is likely ineffective for this organism or site of infection	Document that the laboratory performed a self-evaluation of written protocols and practices for routine reporting of antimicrobial susceptibility reports to patient medical records. Document that routine reporting of this result to clinicians for patient care is compliant with specific recommendations of relevant medical staff and committees (eg, infectious diseases, pharmacy and therapeutics, infection control). Response to the CAP is not required.
77	Improper use of the exception code for this mailing	Document the identification of the correct code to use for future mailings.
91	There was an insufficient number of contributing challenges to establish a composite grade.	Document the investigation of the result as if it were an unacceptable result. Perform and document the corrective action if required.
35, 43, 46, 88, 92	Various codes	No action required.

COLLEGE of AMERICAN PATHOLOGISTS

Attestation of Participation of Self-Reported Training*

We the participants below have completed the review of the F-C, 2020 CAP Survey

Product Mailing, Year

Participant Summary/Final Critique report and can self-report this activity towards fulfilling education and certification of maintenance requirements.

Participant	Date	Participant	Date
_____	_____	_____	_____
_____	_____	_____	_____
_____	_____	_____	_____
_____	_____	_____	_____

_____ _____

Director (or Designee) Signature - I have verified that the individuals listed above have successfully participated in this activity. Date

Retain this page for record-keeping and auditing purposes.

1. Go to www.cap.org
2. Click **Login** and enter your User ID and Password.
   - If you are unsure whether you have an *individual* web account with the CAP, or do not remember your user ID and password, click on **PASSWORD HINT**.
   - If you do not have an *individual* web account, click **CREATE AN ACCOUNT**. Complete and submit the account request form. You will be notified within one business day that your individual account has been activated.
3. Click **Learning** from the top menu bar
4. Click **Transcript** from the menu bar
5. Click **+ My Activity**
6. Follow prompts to enter 'Self-Reported Training Activities' including upload of this supporting documentation*.

For assistance, call our Customer Contact Center at 800-323-4040 or 847-832-7000 option 1.

**** CAP Self-Reported Training activities do not offer CE credit but can be used towards fulfilling requirements for certification of maintenance by agencies such as the American Society of Clinical Pathology (ASCP). Please verify with your certifying agency to determine your education requirements.***

NOTES

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This concludes the report.

COLLEGE of AMERICAN PATHOLOGISTS

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The CAP wishes to thank Rosemary C. She, MD, FCAP; and Aida Mangahis, CLS, for providing these photographs. Unless permission is received from Dr. She and Ms. Mangahis, these photographs may not be used for any purpose except in connection with this Survey.

Figure 1

Growth on Sabouraud Dextrose agar showing the tan-to-cinnamon brown color characteristic of *Aspergillus terreus.*

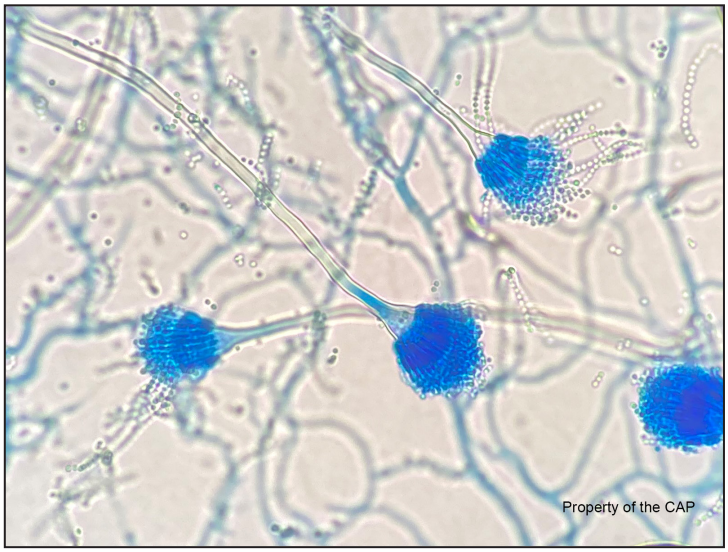

Figure 2A

Aspergillus terreus isolates have biserate phialides that only form on the upper half of the vesicle. Conidiophores are smooth and relatively short.

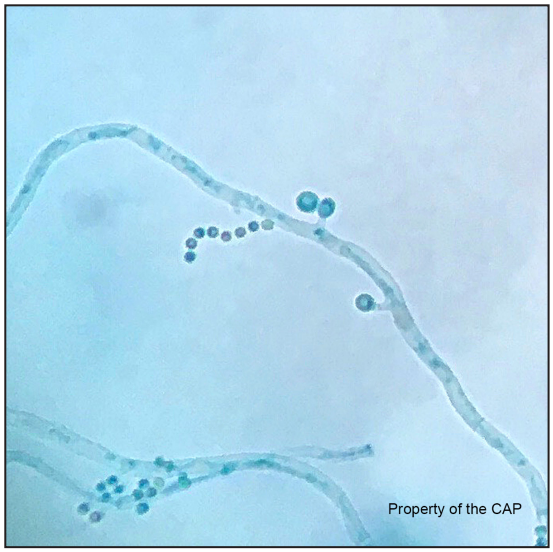

Figure 2B

Micrograph of aleuroconidia, or asexual spores produced directly on the hyphae, which are characteristic of *Aspergillus terreus.*

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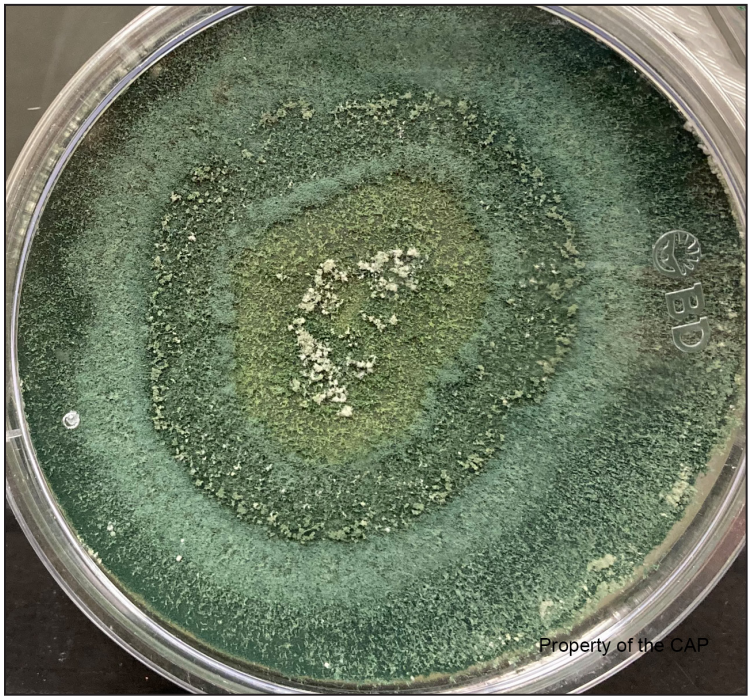

Figure 3

Mature colony of *Trichoderma* sp. on Saboraud Dextrose agar demonstrating a variegated green surface with tufted areas.

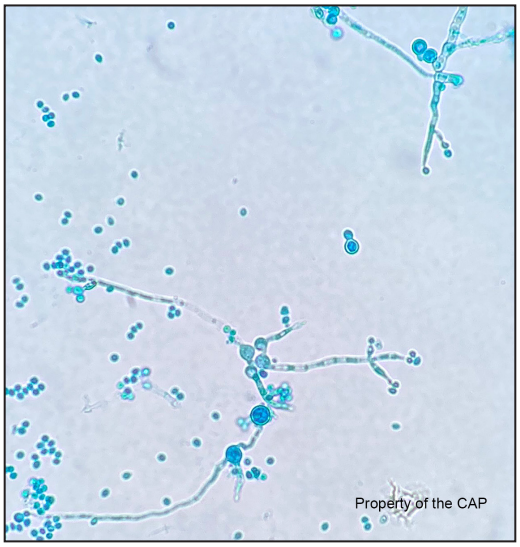

Figure 4

Trichoderma sp. conidiophores branch pyramidally into flask-shaped phialides that end in clusters of conidia. Intercalary chlamydoconidia are also evident in this field (slide culture on Potato Dextrose agar).

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Figure 5

Macroscopic features of *Sporothrix schenckii.* Grown at 25°C, colonies grow moderately rapid. They are moist, leathery-to-velvety and have a finely wrinkled surface. Both front and reverse are initially white and become cream-to-dark brown in time.

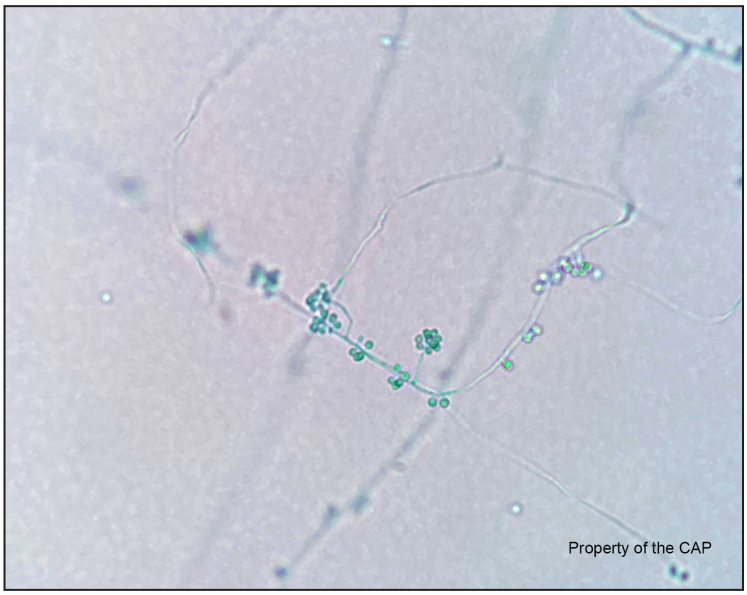

Figure 6A

At 25°C, septate hyaline hyphae, conidiophores and conidia are observed. Conidiophores are sympodial and often have an inflated base and arise at right angles from hyphae. Conidia have two types. The first are unicellular, hyaline-to-brown, oval, thin walled and arranged in rosette-like clusters at the tips of the conidiophores. The second type are brown, oval or triangular, thick-walled and sessile, and attach directly to the sides of the hyphae.

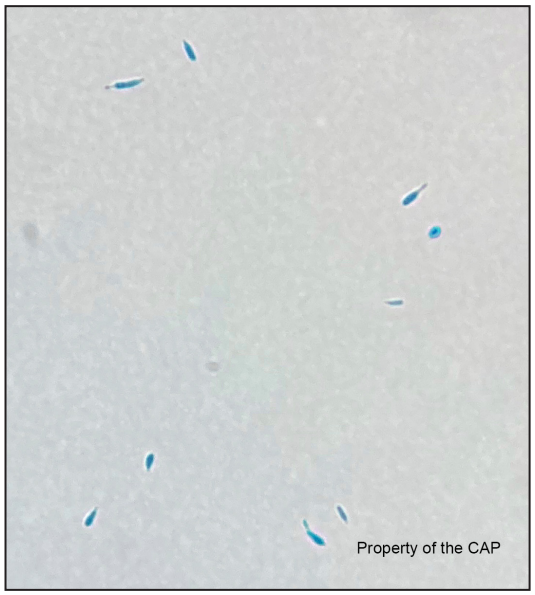

Figure 6B

At 37°C, *Sporothrix schenckii* produces oval to cigar-shaped yeast cells. Single or multiple buds may be produced by a single yeast cell.