Intra-abdominal candidiasis: Description of an under-appreciated disease and a case report of rapid diagnosis by whole blood T2Candida assay

1447

Cornelius J. Clancy, Paschalis Vergidis, Ryan K. Shields, M. Hong Nguyen
University of Pittsburgh Medical Center, Pittsburgh, PA, USA

Background

- Candidemia is generally accepted as the most common type of invasive candidiasis (IC), and it accounts for the overwhelming majority of cases included in clinical trials and other studies. Other types of IC are less well-characterized.
- A review at our center in 2010-2011 demonstrated that deep-seated candidiasis (DSC) accounted for 65% of IC, compared to only 35% for candidemia. Moreover, intra-abdominal candidiasis (IAC) represented 83% and 60% of DSC and IC, respectively.
- Our data and the limited published experience suggest that IAC is more common than recognized, and is associated with significant morbidity and mortality.
- The diagnosis of both IAC and candidemia is limited by the poor sensitivity of blood culture, the diagnostic gold standard.
  - Intra-abdominal cultures are also limited by poor sensitivity, and they are often delayed or contraindicated by patients' conditions
- The development of a rapid, blood-based diagnostic test that is sensitive for blood culture-negative candidiasis is a top priority
- T2Candida assay is a non-culture, whole blood Candida detection system with limit of detection = 1 CFU/mL (Neely, Sci Transl Med 2014; 5:182ra54)

Objectives

- To present a case that highlights important clinical features of IAC, and the difficulty in making timely diagnosis
- To describe the epidemiology, risk factors, treatment and outcome of patients with IAC

Methods

- Observational study of patients at our center with ≥1 sterile site culture positive for *Candida* spp. over 15 months (2011-12)
- Case report of a patient enrolled in a diagnostic trial of T2Candida assay

- T2Candida assay and T2Dx instrument makes diagnoses of candidiasis within ~ 3 hrs, testing whole blood directly in a one-step automated process (Beyda, Diagn Microbiol Infect Dis 2013; 77:324)

Definitions

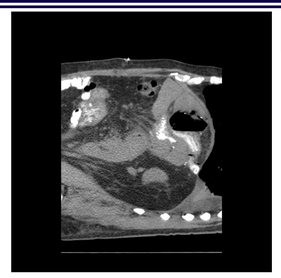
- *Intra-abdominal candidiasis (IAC)*: sterilely-collected abdominal fluid cultures that are positive for *Candida* spp., in the setting of signs and symptoms consistent with an active infection.

- *Intra-abdominal infection (IAI)* refers to intra-abdominal abscesses (IAA) and peritonitis, which can be due to bacteria or *Candida*. *Peritonitis* is defined as infected fluid in the peritoneal cavity with evidence of an inflammatory response. *IAA* is defined as a localized pocket of infection that is walled-off by the host inflammatory response

IAC was classified as: Primary (spontaneous or dialysis-associated), Secondary (seeded from GI tract during perforation or surgery), Tertiary (persistence/recurrence after seemingly adequate treatment).

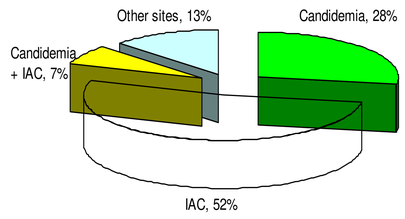
Case report

- A liver transplant recipient with negative blood cultures for Candida and bacteria was enrolled as a control in a multi-center diagnostic trial of the T2Candida assay
- He was treated with voriconazole targeted prophylaxis, per UPMC protocol (Eschenauer, Am J Transplant 2014; in press)
- He developed a perihepatic abscess, but was too unstable for drainage. He was treated with broad-spectrum antibiotics and voriconazole + caspofungin; 12 blood cultures were negative
- T2Candida assay on whole blood was positive for *C. albicans*. The diagnosis was confirmed 7 days later by culture of surgical drainage.
- He completed a course of caspofungin
- T2Candida shortened the time to diagnosis of blood culture-negative IAC



Results

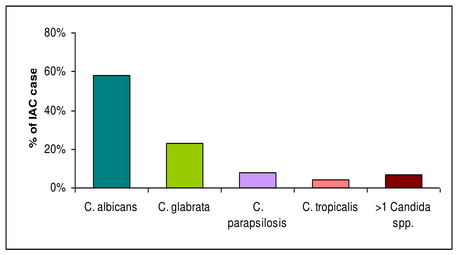
Fig. 1 - Types of IC among consented patients at UPMC (2010-2011)



Source of IAC

- Small bowel, 27%
- Colon, 27%
- Pancreas, 18%
- Liver, 9%
- Gastric, 8%
- Gall bladder, 3%

Microbiology



GRAM-POSITIVE ORGANISMS	
Enterococcus spp.	28% (25% vancomycin-R)
Viridans group Streptococci	13%
Group B Streptococcus	1%
Pediococcus	1%
Peptostreptococcus	1%
Lactobacillus	1%
Clostridium spp.	1%

Types of IAC

Abscess, 58%
Peritonitis, 39%
- ***Primary IAC*, 15%**
spontaneous ascites or peritoneal dialysis infections
- ***Secondary IAC*, 85%**
- post-abdominal surgery: 45%
- gut perforation: 30%
- transmural colitis, 16%
- others (pancreatitis, cholangitis, etc.), 9%

Types of abdominal surgery among patients with post-surgical IAC
- colon, 51%
- small bowel, 24%
- liver, 15%
- esophagus, 10%

GRAM-NEGATIVE ORGANISMS	
Klebsiella pneumoniae	20% (1% KPC-producing)
Escherichia coli	15% (3% ESBL-producing)
Pseudomonas aeruginosa	10%
Enterobacter cloacae	6%
Morganella morganii	3%
Enterobacter sakazakii	1%
Proteus vulgaris	1%
Serratia marcescens	1%
***Prevotella* spp.**	3%
Bacteroides fragilis	3%
Bacteroides caccae	1%
Bacteroides vulgatus	1%

- All pts had (+) IA cultures for *Candida*
- **Only 4% had (+) blood cultures**
- 65% of IAC were co-infected with bacteria (see above)

Treatment and Outcomes

- All patients were treated with percutaneous (59%) or surgical (41%) drainage
- 73% received an antifungal agent (Fluconazole, 68%; Caspofungin, 25%; Voriconazole , 5%)
- 100% received an antibacterial agent
- Mortality rate: 23%
  - IAC from GI perforation: 50%
  - IAC from other causes: 11% (p = 0.046)
- Among survivors, 27% developed tertiary IAC, requiring multiple surgeries and prolonged antifungal agents

Risk factors for FKS mutations among UPMC Candida isolates

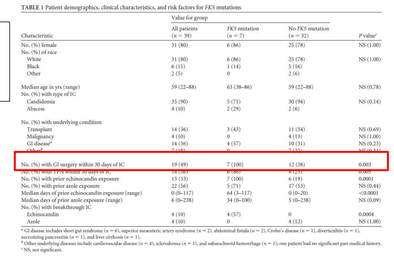


TABLE 1 Patient demographics, clinical characteristics, and risk factors for *FKS* mutations

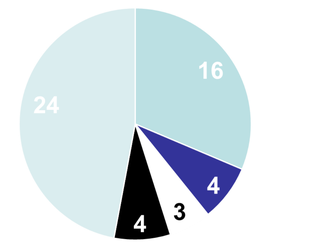
Characteristic	Value for group: All patients (n = 89)	*FKS* mutation (n = 9)	No *FKS* mutation (n = 32)	*P* value[a]
Nos. (%) female	31 (80)	6 (86)	25 (78)	NS (1.00)
Nos. (%) of race				
White	31 (80)	6 (86)	25 (78)	NS (1.00)
Black	6 (15)	1 (14)	5 (16)	
Other	2 (5)	0	2 (6)	
Median age in yrs (range)	59 (22–88)	63 (38–86)	59 (22–88)	NS (0.78)
Nos. (%) with type of IC				
Candidemia	35 (90)	5 (71)	30 (94)	NS (0.14)
Abscess	4 (10)	2 (29)	2 (6)	
Nos. (%) with underlying condition				
Transplant	14 (36)	3 (43)	11 (34)	NS (0.69)
Malignancy	4 (10)	0	4 (13)	NS (1.00)
GI disease[b]	14 (36)	4 (57)	10 (31)	NS (0.23)
Other[c]	9 (23)	0	9 (28)	NS (0.31)
Nos. (%) with GI surgery within 30 days of IC	19 (49)	7 (100)	12 (38)	0.003
Nos. (%) with TPN within 30 days of IC	19 (49)	7 (100)	12 (38)	0.003
Nos. (%) with prior echinocandin exposure	13 (35)	7 (100)	6 (19)	0.0001
Nos. (%) with prior azole exposure	22 (56)	5 (71)	17 (53)	NS (0.44)
Median days of prior echinocandin exposure (range)	0 (0–117)	64 (3–117)	0 (0–20)	<0.0001
Median days of prior azole exposure (range)	6 (0–238)	34 (0–100)	5 (0–238)	NS (0.09)
Nos. (%) with breakthrough IC				
Echinocandin	4 (10)	4 (57)	0	0.0004
Azole	4 (10)	0	4 (12)	NS (1.00)

[a] GI disease includes short gut syndrome (n = 4), superior mesenteric artery syndrome (n = 2), abdominal fistula (n = 2), Crohn's disease (n = 1), diverticulitis (n = 1), necrotizing pancreatitis (n = 1), and liver cirrhosis (n = 1).
[b] Other underlying diseases include cardiovascular disease (n = 4), scleroderma (n = 1), and subarachnoid hemorrhage (n = 1); one patient had no significant past medical history.
[c] NS, not significant.

Characteristics of patients infected with FKS mutants

Isolate	Underlying Disease	Days of Prior EC	*FKS* Mutation	Caspofungin MIC	Outcome
***Ca* 674**	DM, Obesity	8	FKS1 – R674I	0.12	**Failure**
***Ca* 1010**	Multivisceral txp	68	FKS1 – S645P	16	**Failure**
Cg 102	Short gut syndrome	46	FKS2 – F659del	8	**Success**
Cg 35	Multivisceral Txp	102	FKS2 – F659L	1	**Failure**
Cg 129	Crohn's Disease	9	FKS2 – F659L	1	**Failure**
Cg 187	Crohn's disease	117	FKS2 – F659L	2	**Failure**
Cg 309	Liver txp	64	FKS1 – D632H	2	**Failure**
Cg 999	Multivisceral Txp	122	FKS2 – S663P	16	**Failure**
Cg 755	Esophageal CA, GI Perf	7	FKS2 – F659S	0.5	Not treated

Sterile site cultures were obtained from patients with intra-abdominal candidiasis (n=51)
- All abscesses were drained prior to inclusion



59% (30/51) of isolates were collected from patients with prior echinocandin exposure

20% (6/30) of isolates from patients with prior echinocandin exposure harbored *FKS* mutations
5 *C. glabrata* (3 *FKS1,* 2 *FKS2*), 1 *C. albicans*

FKS mutations occurred more commonly among patients with abdominal candidiasis (20%, 6/30) than candidemia (10%, 9/89), $p = 0.20$

Breakthrough candidiasis was more common 27% (14/51) versus 8% (18/251), $p = 0.0006$

Conclusions

- IAC was the most common cause of IC at our center, and was associated with high mortality (especially following perforation), need for repeated surgeries, and emergence of antifungal resistance
- All patients require antifungal therapy in addition to drainage, as clinicians cannot reliably identify patients who can be cured with drainage alone
- Blood cultures have poor sensitivity, and IAC is under-recognized because of a dependence on intra-abdominal cultures for diagnosis
- T2Candida assay can rapidly identify patients with IAC in whom blood cultures are negative, using whole blood and not requiring an intra-abdominal sample
- Since collection of intra-abdominal samples is often delayed or contra-indicated, T2Candida assay can shorten time to diagnosis of IAC in addition to improving the sensitivity of diagnosis