Intra-abdominal candidiasis is associated with high mortality, repeated surgery and echinocandin resistance, and often not initially treated with antifungal agents

eP348

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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.

Objectives

• 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 (2010-11).

Definitions

- *Intra-abdominal candidiasis (IAC)* is defined by sterilely-collected abdominal fluid cultures that are positive for *Candida* spp., in the setting of signs and symptoms consistent with an active infection. IAC generally results from gastrointestinal perforation or surgical leak.
- *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:

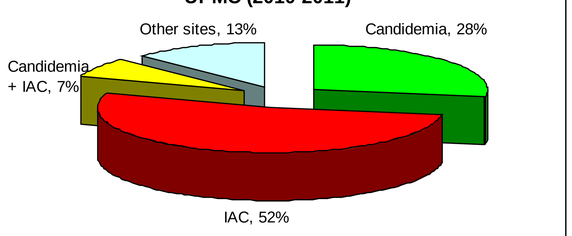
• Primary (spontaneous or dialysis-associated)

• Secondary (seeded from GI tract during perforation or surgery)

• Tertiary (persistence/recurrence after seemingly adequate treatment).

Results

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



IAC was more common than candidemia, accounting for 52% of 199 cases of IC

Types of IAC

Classification of IAC:
• ***Primary IAC* (15%):** spontaneous ascites or peritoneal dialysis infections

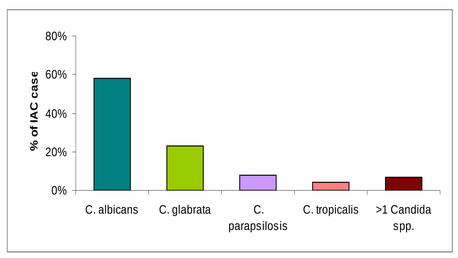
• ***Secondary IAC* (85%):**
- post-abdominal surgery: 45%
- gut perforation: 30%
- transmural colitis, 16%
- others (pancreatitis, cholangitis, etc.), 9%

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

Perforated organs leading to IAC

• Small bowel, 63%
• Gastric feeding tube displacement, 25%
• Colon, 11%

Microbiology



• All pts had (+) IA cultures for *Candida*
• Only 12% had (+) blood cultures
• 65% of IAC were co-infected with bacteria

Outcomes

• **Mortality rate: 23%**
  • IAC from GI peforation: 50%
  • IAC from other causes: 11%
    • p-value = 0.046

• **Among the survivors, 27% developed tertiary IAC**, requiring multiple surgeries and prolonged antifungal agents

• **38% were treated with surgical interventions without antifungal**:
  • 20% died
  • 50% developed persistent Candida infection requiring antifungal subsequently.

Risk factors for FKS mutations among UPMC Candida isolates

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

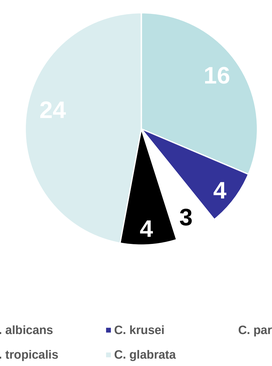
Characteristic	Value for group: All patients (n = 39)	*FKS* mutation (n = 7)	No *FKS* mutation (n = 32)	P value[c]
No. (%) female	31 (80)	6 (86)	25 (78)	NS (1.00)
No. (%) of race				
White	31 (80)	6 (86)	25 (78)	NS (1.00)
Black	6 (15)	1 (14)	5 (16)	
Other	2 (5)	0	2 (6)	
Median age in yrs (range)	59 (22–88)	63 (38–86)	59 (22–88)	NS (0.78)
No. (%) with type of IC				
Candidemia	35 (90)	5 (71)	30 (94)	NS (0.14)
Abscess	4 (10)	2 (29)	2 (6)	
No. (%) with underlying condition				
Transplant	14 (36)	3 (43)	11 (34)	NS (0.69)
Malignancy	4 (10)	0	4 (13)	NS (1.00)
GI disease[a]	14 (36)	4 (57)	10 (31)	NS (0.23)
Other[b]	7 (18)	0	7 (22)	NS (0.31)
No. (%) with GI surgery within 30 days of IC	19 (49)	7 (100)	12 (38)	0.003
No. (%) with TPN within 30 days of IC	14 (36)	6 (86)	8 (25)	0.005
No. (%) with prior echinocandin exposure	13 (33)	7 (100)	6 (19)	0.0001
No. (%) 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)
No. (%) 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 = 6), 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 echinocandin resistance
• All patients require antifungal therapy in addition to surgery, as clinicians cannot reliably identify patients who can be cured with surgical drainage alone
• Blood cultures have poor sensitivity, and IAC is under-recognized because of a dependence on IA cultures for diagnosis