



Clinical Characteristics, Epidemiology, and Evolution of Antifungal Use Over Fifteen Years in a Burn Intensive Care Unit



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Abstract

Introduction: Systemic antifungals (AF) and surgery are the cornerstone of therapy for burn-related fungal infections. Multiple AFs were introduced in the last decade with broader spectrum and improved safety profiles, but use in burn patients has yet to be thoroughly described. Here we evaluate 15 years of AF prescribing patterns in a burn intensive care unit (BICU).
Methods: We included all US Army Institute of Surgical Research BICU patients who received > 1 dose of AF from 2004-18. First we sought to describe overall AF prescribing. Clinical features, mortality and AF use (including in combination) from 2004-8 (T1), 2009-2013 (T2), 2014-18 (T3) were compared.
Results: From 2004-18, 361 patients with a median total body surface area (TBSA) of 45% (IQR: 25-60) received AF. Median duration of hospital stay prior to and duration of initial AF (AF1) were 13.5 (IQR: 7-22) and 4 days (IQR: 2-9), respectively. Patients prescribed AF had a median of 2 (IQR 1-3) different AFs. AF1 was most commonly fluconazole [FLC; n=141 (39%)], amphotericin [AMB; n=62 (17%)] and voriconazole [VRC; n=55 (15%)]. Of those who survived, (N=233) AF1 was AMB, 40 (17.2%); FLC, 102 (43.8%); itraconazole, 1 (0.4%); VRC, 35 (15%); posaconazole (POS), 6 (2.6%); isavuconazole (ISA), 4 (1.7%); caspofungin (CAS), 7 (3%); micafungin (MFG), 28 (12%), VRC/AMB, 8 (3.4%); FLC/AMB, 0; FLC/CSP, 1 (0.4%); and VCR/MFG 1 (0.4%). AF1 use differed across T1, T2, and T3 (Table). Notably, there was shift towards use of POS, ISA, and MFG. The use of AF1 combination therapy differed across T1, T2, and T3 (p = 0.002). 200 patients had a second AF (AF2) prescribed at a median of 4.15 days (IQR 1.1-12.5) after AF1 for a median duration of 5.3 days (IQR 2-9.7). AF2 were most commonly VRC (n=54, 27%), AMB (n =46, 23%) and FLC (n=44, 22%). There were no differences in AF2 over time.
Conclusions: AF use evolved to include echinocandins and broader spectrum triazoles and decreased use of AMB as part of AF1. However, AF2 remained most commonly VRC, AMB, and FLC.

Background

- Systemic antifungals (AF) along with surgical debridement are both critical aspects of treating burn-related fungal infections.
- Diagnosing invasive fungal infections (IFI) in patients in the burn intensive care unit (BICU) is challenging: risk factors are universally present, often the diagnosis is uncertain, differentiating wound colonization versus infection is difficult.
- Research gaps regarding diagnosis, duration of therapy, risk factors for death, and the effect of new antifungals continue to exist.
- We describe the general use of AF, epidemiology, management, risk factors for death, role of ID consultation, and evolution over time of antifungal use in a single-center BICU over a 15 year period.

Methods

- Inclusion criteria:** all patients admitted to the US Army Institute of Surgical Research BICU from 2004-2018 with orders for antifungal agents.
- Exclusion criteria:** patients in whom antifungals were cancelled without a treatment course and those that received topical therapy alone.
- Burn management:** early surgical debridement was standard. ID approval was required for all systemic antifungals except oral fluconazole.
- Clinical features, mortality and AF use,** including in combination, from 2004-2008 (T1), 2009-2013 (T2), and 2014-2018 (T3) were compared.
- Characteristics of those who survived versus those who died** were compared.
- Length of stay as well as duration of initial AF (AF1) and second AF (AF2)** were compared by ID consultation.

Results

- 361 patients received AF with a median total body surface area (TBSA) burn of 45% (IQR: 25-60).
- Median duration of stay prior to, and duration of AF1 was 13.5 days (IQR: 7-22) and 4 days (IQR: 2-9) respectively.
- AF1 was most commonly fluconazole [FLC; n=141 (39%)], amphotericin [AMB; n=62 (17%)] and voriconazole [VRC; n=55 (15%)]. AF2 was most commonly VRC (n=54, 27%), AMB (n =46, 23%) and FLC (n=44, 22%) prescribed at a median of 4.15 days (IQR 1.1-12.5) after AF1.
- Overall 128 patients (35.4%) died.
- Hospital length of stay was longer in those patients with ID consult [median 59 days (IQR 30-501)] compared with those without [median 39 days (IQR 17-174)] (p = 0.002). Other variables including duration of AF1 and AF2 were not significant.

	2004 -2008 N= 122 (%)	2009-2013 N= 128 (%)	2014-2018 N= 111 (%)	p-value
Age, median (IQR)	33 (23-49)	49 (32-65)	43 (31-57)	<0.001
TBSA burn, median (IQR)	52 (33-70)	44 (26-58)	35 (22-51)	0.009
Male gender, no. (%)	104 (85.2)	92 (71.9)	79 (71.2)	0.011
Duration of hospitalization prior to AF, median (IQR)	14 (8-23)	13 (7-23)	13 (7-18)	0.226
ID consulted, no. (%)	93 (76.2)	108 (84.4)	87 (78.4)	0.311
Total length of stay, median (IQR)	64 (37-99)	32 (23-89)	49 (29-75)	0.025
Mortality, no. (%)	23 (18.9)	64 (50.0)	41 (36.9)	0.003
Use of initial combination antifungal therapy, no (%)	3 (2.4)	19 (14.8)	8 (7.2)	0.002

Table 1. Comparison of clinical characteristics in patients receiving AF by five year increments T1 (2004-2008), T2 (2009-2013), T3 (2014-2018).

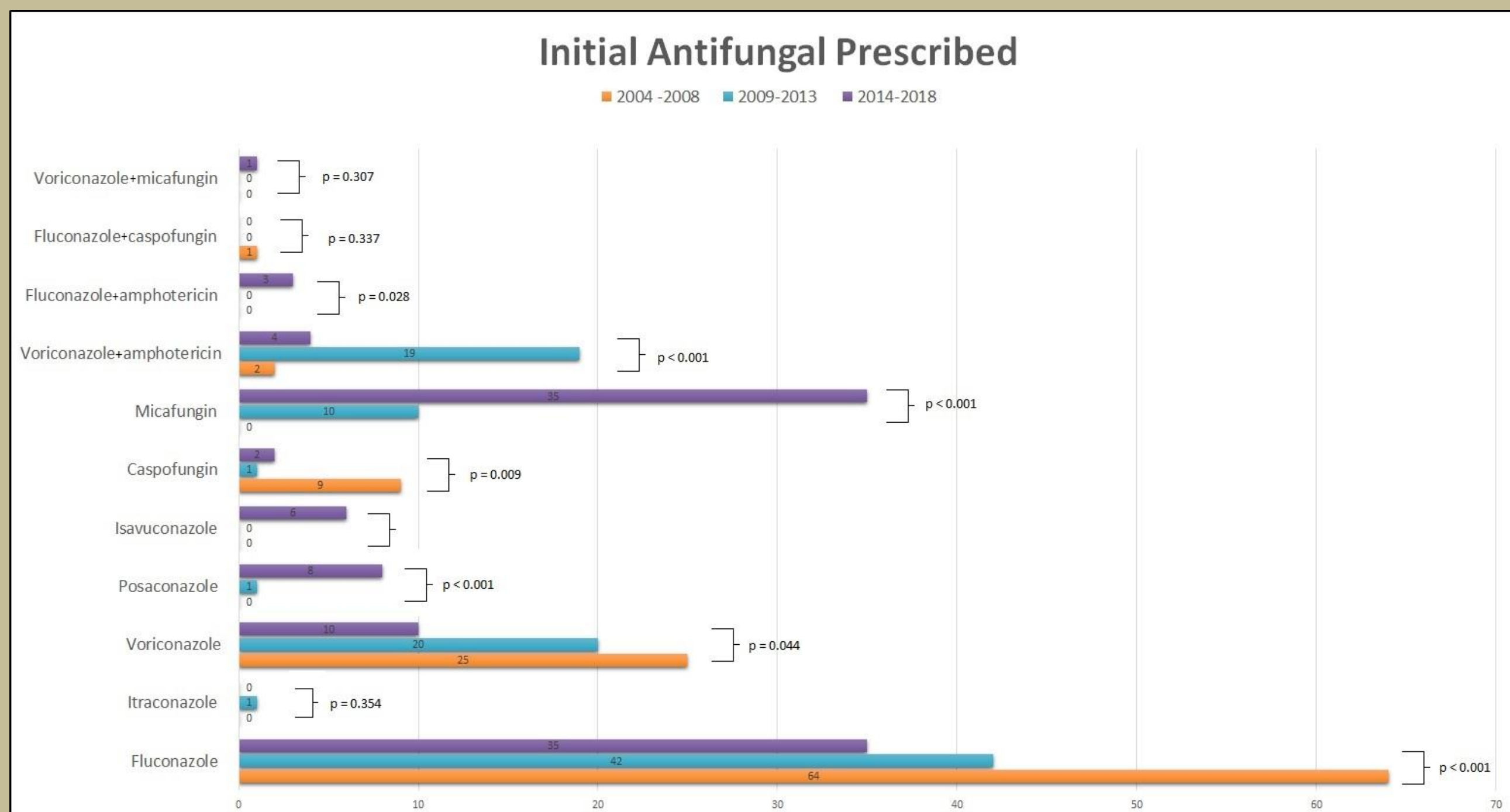


Figure 1. Initial antifungal prescribed compared by 5 year increments T1 (2004-2008), T2 (2009-2013), T3 (2014-2018).

Clinical characteristic	Survived n=233 (%)	Died n=128 (%)	p-value
Age in years, median (IQR)	35 (25-85)	52 (36-90)	<0.001
TBSA %, median (IQR)	45 (26-95)	44 (23-98)	0.931
Admit year, median (IQR)	2010 (2006-2018)	2011 (2009-2018)	0.004
Male sex, number (%)	184 (78.9)	91 (71.1)	0.061
Mechanism, number (%)			
Flame	91 (39)	74 (57.8)	<0.001
Scald	5 (2.1)	7 (5.4)	0.087
Blast	63 (27)	10 (7.8)	<0.001
Contact	1 (0.4)	1 (0.7)	1.00
Electrical	9 (3.8)	1 (0.7)	0.105
Skin disease	46 (19.7)	25 (19.5)	0.539
Unavailable	16 (7.8)	10 (7.8)	-
ID consult	181 (77.7)	107 (83.5)	0.114
Hospital LOS in days, median (IQR)	69 (42-501)	31 (17-151)	<0.001

Table 2. Comparison of those patients receiving systemic antifungals by survival versus death (univariate analysis)

- Multivariate analysis revealed that age [odds ratio (OR) 1.052; p < 0.001], and admission year (OR 1.125; p=0.002), were associated with death.

Conclusions

- Of the 361 patients treated with systemic antifungals in a single center BICU over 15 years, mortality was high (35.4%).
- Antifungal use evolved over time to include use of echinocandins and broader spectrum triazoles as they became available (eg. posaconazole, isavuconazole, micafungin). Median duration of stay prior to AF was similar across time periods. AF2 was commonly VRC, AMB, and FLC.
- Age was associated with mortality both on univariate and multivariate analysis.
- ID consultation did not appear to be associated with improved mortality, however this is likely confounded by the severity of illness and consultation requirements for most antifungals.

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