P 804

22nd ECCMID London, United Kingdom 31 March – 3 April 2012

SaludMadrid

Hospital General Universitario Gregorio Marañón
Comunidad de Madrid

C/ Dr. Esquerdo, 46
28007 Madrid, Spain
E-mail: pmunoz@micro.hggm.es

Invasive Aspergillosis Among Heart Transplant Recipients: A 24-year Perspective

P. Muñoz, I. Cerón, M. Valerio, J. Palomo, A. Villa, A. Eworo, J. Guinea, I.A. González, E. Bouza

Introduction and purpose

- Invasive aspergillosis (IA) is not uncommon in heart transplant (HT) recipients. The incidence rate in this population fluctuates between 3.3%-14% and is associated to high mortality.
- Despite the severity of IA in this setting, there are few series that analyze the problem.
- **The objective of this study was to determine the incidence, clinical characteristics, risk factors and outcome associated with IA in HT recipients.**

Methods

- **Design:** Prospective follow-up of all HT patient from Aug 1988 to Aug 2011 at the Gregorio Marañón General Hospital.
- **Setting:** Tertiary teaching hospital with 1,550 to 1,750-bed, serving a population between 650,000-715,000 inhabitants. HEPA filtered air was not universally provided in all areas used by the HT patients.
- Antifungal prophylaxis (AP): None before Oct 1994; From Oct 1994 and Dec 2002: universal oral itraconazole; From Jan 2003 targeted (candins or voriconazole) to patients with risk factors for IA (1).
- **Definitions:**
  - Proven o probable cases of IA were defined according to the EORTC/MSG recommendations(2)
  - IA that occurred in the first 3 months after HT was considered "Early IA"

Results

- **IA** was diagnosed in 31/479 consecutive HT recipients (**6.5%**): 25 **proven (80.6%)** and 6 probable and showed a **decreased incidence** in the last decade: 23/277 (**8.3%**) vs. 8/202 (**4%**) (p = 0.05) (Fig 1) despite an outbreak in the MHS from 2007-8 (3 cases)
- **Early IA** accounted for 23 cases **(74%)** and 8 cases were **late IA (26%)**
- **Main risk factors:** Other IA case near in the HT program (58%), CMV disease (54.8%), re-operation (38.7%) and post-Tx hemodialysis (19.4%)
- ***A. fumigatus*** was the most common isolated species **(74.2%)**

Figure 1: Annual Distribution of IA cases

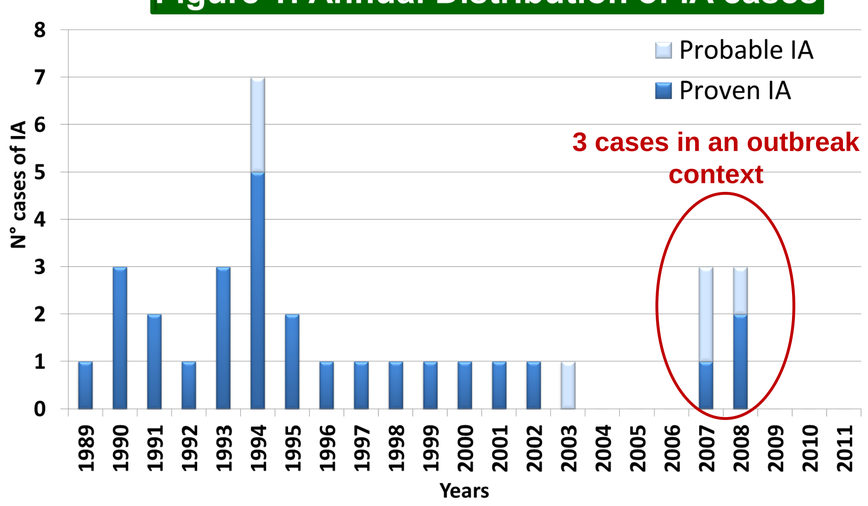


Table 1: Clinical characteristics for Early and Late IA

	Early IA n (%)	Late IA n (%)	p
Age, years, mean ± SD	56 ± 7.9	57.1± 5.7	0.3
Median time after HT (days [range])	34 [19-58]	125.5 [100-237]	< 0.01
Antifungal prophylaxis*	5 (21.7)	3 (37.5)	0.3
Extent of disease			
- Pulmonar	21 (91)	7 (87.5)	1
- CNS	1 (4.3)	**3 (37.5)**	**0.04**
- Myocardium	2 (8.7)	0 (0)	1
- Mediastinum	3 (13)	0 (0)	0.5
- Others sites**	0 (0)	**4 (50)**	**< 0.01**
Symtoms			
- Asymptomatic	5 (21.7)	1 (12.5)	1
- Fever	9 (39)	5 (62.5)	0.4
- Dyspnoea	6 (26)	5 (62.5)	0.09
- Cough	6 (26)	4 (50)	0.3
- Expectoration	4 (17)	1 (12.5)	1
- Chest pain	5 (21.7)	1 (12.5)	1
- Neurologic symtoms	0 (0)	**3 (37.5)**	**0.01**
- Others	3 (13)	3 (37.5)	0.1
Radiological findings			
- Nodules	5 (21.7)	1 (12.5)	1
- Cavitated nodules	7 (30.4)	**6 (75)**	**0.04**
- Alveolar infiltrate	5 (21.7)	1 (12.5)	0.09
- Pleural fluid	11 (47.8)	2 (25)	1

*Low serum level of itraconazole (7) and 1 caspofungin low dose for body mass
** Skin, prostate, digestive tract, Paranasal sinuses

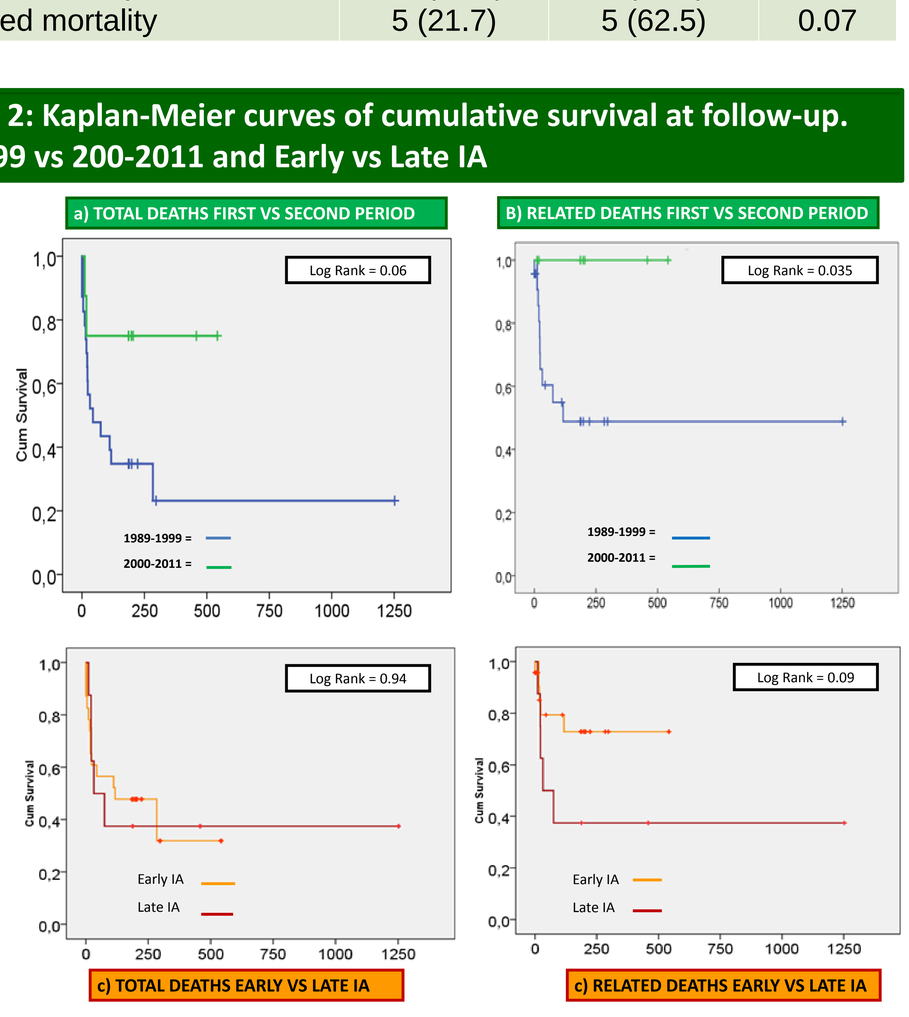
Table 2: Diagnosis, Treatment and Outcome

	Early IA n (%)	Late IA n (%)	p
Diagnostic methods			
- Culture	19 (82.6)	8 (100)	0.5
- Radiographic	16 (69.6)	8 (100)	0.1
- Histology	4 (17)	2 (25)	0.6
- Galactomannan	2 (8.7)	0 (0)	1
- PCR	3 (13)	1 (12.5)	1
- Autopsy	4 (17)	1 (12.5)	1
Treatment			
- Monotherapy	15 (625.)	6 (75)	1
- Initial combined therapy	4 (17)	1 (12.5)	0.81
- Rescue combined therapy	2 (8.7)	0 (0)	1
- Surgery	7 (30.4)	0 (0)	0.1
Outcome			
- Global mortality	13 (56.5)	5 (62.5)	1
- Related mortality	5 (21.7)	5 (62.5)	0.07

Risk factors for mortality

- **Univariate analysis**: long pre-Tx stay, pre-Tx mechanical ventilation (MV), emergent surgery, OKT3 induction, concomitant CMV disease, CNS involvement, alveolar infiltrate, need of MV and thrombocytopenia.
- **Multivariate analysis: CMV disease during the IA episode (OR 6.6, 95% CI 1.3-33.6; p=0.02)**
- Mortality rate was lower in the last decade (Figure 2)

Figure 2: Kaplan-Meier curves of cumulative survival at follow-up. 1988-99 vs 200-2011 and Early vs Late IA



Conclusions

- **The incidence of IA in HT recipients has decreased in recent years, probably due to the antifungal prophylaxis and this trend is accompanied by a significant reduction in related mortality.**
- **Most IA cases occur in the first 3 months after HT (74%). Late IA presents high frequency of disseminated disease (with CNS involvement) and a non-significant trend towards a higher related mortality.**
- **If we optimize environmental management, we should aim for zero incidence of IA in HT.**

References

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2) De Pauw, B., et al.,. Clin Infect Dis, 2008. 46(12): p. 1813-21
3) Pelaez, T., et al.,. Clinical Infectious Diseases, 2011. in press