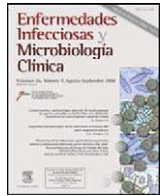


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Original article

Mortality risk factors in patients with zygomycosis: a retrospective and multicentre study of 25 cases

Andreu Llorente^{a,*}, Ignacio Perez-Valero^b, E. García^c, I. Heras^d, V. Fraile^e, P. García^f, J. López^g, M. Salavert^h, F. Bobilloⁱ

^a Servicio de Hematología, Hospital Joan XXIII, IISPV, Tarragona, Spain

^b Servicio Medicina Interna, Hospital Universitario La Paz, Madrid, Spain

^c Enfermedades Infecciosas, Clínica Universitaria de Navarra, Pamplona, Navarra, Spain

^d Servicio Hematología, Hospital General Universitario Morales Messeguer, Murcia, Spain

^e Servicio Hematología, Hospital Universitario "Río Hortega", Valladolid, Spain

^f Servicio Hematología, Hospital Clínico San Carlos, Madrid, Spain

^g Servicio Hematología, Hospital Universitario Ramón y Cajal, Madrid, Spain

^h Servicio Hematología, Hospital Universitario La Fe, Valencia, Spain

ⁱ Servicio Medicina Intensiva, Hospital Clínico Universitario de Valladolid, Valladolid, Spain

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ABSTRACT

Aim: To investigate mortality risk factors in patients with zygomycosis.

Patients and Methods: Retrospective case history review of patients diagnosed with proven zygomycosis in 17 centres in Spain. We compared demographics and risk factors in patients who survived, and in those who died.

Results: We identified twenty-five patients with proven zygomycosis. The primary site of infection was rhino-orbito-cerebral (28%) and disseminated (20%) or cutaneous/soft infections (20%) of the patients. Eleven patients (44%) received preemptive or empirical antifungal treatment; of these patients, 4 received liposomal amphotericin B, 1 received amphotericin B lipid complex, and 6 received other antifungals. The overall mortality rate was 72%. In the univariate analysis factors associated with an increased risk of death were the presence of a haematological malignancy ($P = .03$), neutropenia ($P = .03$) and monocytopenia ($P = .008$).

Conclusion: Our study supports previous research that has documented a high mortality rate among patients with invasive zygomycosis, especially among those with an underlying haematological malignancy, and the need for a rapid initiation of an effective antifungal treatment.

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Factores de riesgo de mortalidad en pacientes con zigomicosis: un estudio retrospectivo y multicéntrico de 25 casos

RESUMEN

Objetivo: Investigar los factores de riesgo de mortalidad en pacientes con zigomicosis.

Pacientes & Métodos: Revisión retrospectiva de pacientes diagnosticados de zigomicosis documentada en 17 centros en España, comparando los datos demográficos y los factores de riesgo entre los pacientes que sobrevivieron y aquellos que fallecieron.

Resultados: Se identificaron 25 pacientes con zigomicosis probada. El lugar primario de la infección fue rino-órbito-cerebral (28%) e infecciones diseminadas o cutáneas / de tejidos blandos en el 20% de los pacientes cada una. Once pacientes (44%) recibieron tratamiento antifúngico anticipado o empírico; de estos pacientes, cuatro de ellos recibieron anfotericina B liposomal, un paciente recibió anfotericina B complejo lipídico y 6 pacientes recibieron otros antifúngicos. La tasa de mortalidad global fue del 72%. En el análisis univariado, los factores asociados a un mayor riesgo de muerte fueron la presencia de enfermedad hematológica maligna ($p = 0,03$), neutropenia ($p = 0,03$) y monocitopenia ($p = 0,008$).

Palabras clave:

Zigomicosis

Mortalidad

Factores de riesgo

Anfotericina B

* Corresponding author.

E-mail address: allorete.hj23.ics@gencat.cat (A. Llorente).

Conclusión: Los datos de nuestro estudio concuerdan con los de trabajos previos que habían documentado una elevada tasa de mortalidad en pacientes con zigomicosis invasiva, especialmente en aquellos con enfermedad hematológica maligna subyacente, y la necesidad de instaurar rápidamente un tratamiento antifúngico eficaz.

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Introduction

Zygomycosis is a rare but devastating invasive fungal infection (IFI) caused by the agents of Zygomycetes, most commonly by those of the order Mucorales.¹ Zygomycosis is becoming increasingly important among certain populations, such as recipients of haematopoietic stem cell or solid-organ transplants and among patients with haematological malignancies.^{1,2} In these populations, reports of zygomycosis have been increasing since the 1990 s,^{2,3} and zygomycosis has become the third leading cause of IFI (following invasive aspergillosis and invasive candidiasis).^{1,4} Although it has been proposed that this increase in the frequency of zygomycosis might be due to the introduction of voriconazole, an antifungal not active against Zygomycetes, for the prophylaxis of opportunistic fungal infections,^{5,6} this association is not yet well-established.³

The clinical manifestations of invasive zygomycosis include tissue necrosis from invasion of blood vessels and subsequent thrombosis, and the most common clinical presentations are a rhinocerebral syndrome and pulmonary infection.¹ A definitive diagnosis of zygomycosis can be difficult to reach and requires histopathological confirmation.¹ The adequate management of zygomycosis requires a multifaceted approach that includes the control or reversal of the underlying risk factors (such as diabetic ketoacidosis or immunosuppression), surgical debridement, and the use of systemic antifungal therapy.^{1,7} Amphotericin B, particularly the liposomal formulation, is the mainstay for the treatment of this IFI.^{7–9} More recently, posaconazole has also been shown to be active against zygomycosis,¹⁰ with some evidence of its clinical efficacy as a salvage therapy^{11,12} but without the same spectrum of coverage as amphotericin B.

Zygomycosis has a poor prognosis. Despite the introduction of amphotericin B, mortality in patients with zygomycosis is high and has remained almost unchanged in the last four decades.² According to data from the largest series of patients with zygomycosis,² the current mortality rate is close to 40%, and it can be as high as 76% in cases of pulmonary zygomycosis.² However, a smaller study examined 16 cases of proven zygomycosis and found an overall mortality rate of only 25%.¹³ These different mortality rates may be due to differences in the clinical characteristics of the cases or in their management. To better manage this serious infection, it is important to know what factors are associated with a greater risk of mortality.

Our study was aimed at investigating risk factors for mortality in a retrospective case series of patients with proven zygomycosis.

Patients and methods

We performed a retrospective review of the clinical history of all patients with zygomycosis who were seen in seventeen health centres in Spain between January 1, 2007 and June 30, 2008. Patients were included in the study only if they had no previous history of zygomycosis and had been diagnosed with proven zygomycosis according to the EORTC/MSG criteria.¹⁴

A standardised case report form was used to extract information from the medical records. Demographic information, including age and sex, and clinical data were recorded. The clinical information collected included (1) clinical outcome and, in cases of death, the relationship between this outcome and the IFI; (2) site

of the infection (categorized as sinusitis, sinopulmonary, pneumonia, rhino-orbito-cerebral, disseminated, and cutaneous/soft-tissue infection); (3) underlying conditions and APACHE II at the time of diagnosis; (4) risk factors for zygomycosis within one month of the diagnosis (including type of bone marrow transplantation (BMT), graft-versus-host disease grade, use of immunosuppressive therapy, cytomegalovirus infection, diagnosis of diabetes mellitus, hyperglycaemia defined as a glucose level equal to or greater than 200 g/dL, neutropenia defined as a neutrophil count equal to or lower than 500 cells/mm³, lymphopenia, monocytopenia, acidosis defined as a pH value lower than 7.35, malnutrition defined as a serum albumin level equal to or lower than 3 g/dL, use of corticosteroids, use of tumour necrosis factor inhibitors, serum iron level, serum ferritin level, and use of deferoxamine therapy); (5) use of an antifungal agent within three months of the diagnosis as either prophylactic, pre-emptive, empirical, or targeted therapy; and (6) whether or not the patient underwent surgical debridement.

Demographic and clinical characteristics were described using the mean, median and standard deviation for continuous measures and the frequency and percentage for categorical variables. The demographic information and risk factors of patients who survived were compared with the information of those who died in a univariate analysis using the Student's *t*-test, Chi-squared test, or Fisher's exact test where appropriate. In addition, a stepwise logistic regression analysis was planned to explore variables independently associated with mortality. All statistical analyses were performed using SPSS version 15.0 (SPSS Inc, Chicago, Illinois). All analyses were two-tailed and were considered significant if *P* < .05.

Results

Throughout the 18-months study period, we identified twenty-five patients with proven zygomycosis. Patients were predominantly male (80%) with a median age of 46 years. The most common underlying conditions were haematological malignancies (52%) and diabetes mellitus (32%). At the time of diagnosis, nearly one third of the patients presented with rhino-orbito-cerebral infections; 20% of the patients presented with disseminated infections and 20% presented with cutaneous/soft-tissue infections. The median of the follow-up duration was 2 months (interquartile range 0.9 to 5.5) and the mean (SD) was 5.2 (7.1) months. Mean time between the beginning of the symptoms and the diagnosis, independently of patient outcome, was 8 days. In all cases, targeted antifungal treatment was started in the first 24 h after a confirmatory diagnosis. Patient demographics, underlying conditions, infection locations and case history are presented in Table 1.

Eleven patients (44%) received pre-emptive or empirical antifungal treatment; of these, 4 (16%) received liposomal amphotericin B (in one case, this treatment was combined with caspofungin), 1 (4%) received amphotericin B lipid complex, and 6 (24%) received other antifungals (Table 2). These other antifungals were not effective against zygomycosis. The rationale to start empirical or pre-emptive antifungal treatment was based on clinical suspicion by the clinician in charge of the patient. One patient did not receive any antifungal treatment, and the remaining thirteen patients (52%) commenced antifungal treatment after they were diagnosed with zygomycosis. The most common antifungals, used either alone or in combination as targeted treatment, were

Table 1
Demographic and clinical characteristics.

Characteristic	N = 25
Age, years	
Mean (SD)	47.4 (14.1)
Median (Range)	46 (21–76)
Sex, n (%)	
Male	20 (80)
Female	5 (20)
Underlying condition at the time of the infection, n (%)	
Hematological malignancy	13 (52)
Allogeneic transplant	5 (2)
Autologous transplant	1 (4)
Diabetes	8 (32)
Solid organ transplantation	3 (12)
Trauma	2 (8)
Solid tumor	2 (8)
Rheumatological	1 (4)
None	1 (4)
Location of the infection, n (%)	
Rhinoorbitocerebral	7 (28)
Disseminated	5 (20)
Cutaneous/soft tissue	5 (20)
Gastrointestinal	3 (12)
Sinusitis + Rhinoorbitocerebral	2 (8)
Other	3 (12)
Case documentation	
Histopathological assessment	11 (44)
Culture	7 (28)
Histopathological assessment and culture	7 (28)

SD: standard deviation.

liposomal amphotericin B (n = 19, 76%), posaconazole (n = 7, 28%), caspofungin (n = 6, 24%), voriconazole (n = 3, 12%), and amphotericin B lipid complex (n = 1, 4%). Table 2 shows the antifungals received by each patient during the entire follow-up period. Seventeen patients (68%) underwent surgical debridement.

The overall mortality rate in our cohort was 72% (18 of 25 patients). Mortality was high between patients treated empirically with an ineffective drug (80%). The only case treated empirically with an active antifungal against zygomycosis survived. The mortality rate was similar between patients treated empirically (67%) and patients who received a targeted treatment (70%). Zygomycosis was the cause of death in 13 of the 18 patients who died (52%) and contributed to the death of four other patients (16%). In the univariate analysis (Table 3) the factors associated with an increased risk of death were the presence of an underlying haematological malignancy ($P = .03$), neutropenia ($P = .03$) and monocytopenia ($P = .008$). We did not run a multivariate analysis since the same patients had both haematological malignancies and neutropenia, and the monocytopenia variable had a zero cell count.

Discussion

In our cohort of 25 patients with proven zygomycosis the overall mortality rate was 72%. This rate is much higher than the 40% mortality rate found by Roden et al.² in the largest review of reported zygomycosis cases over the last several decades. However, the primary sites of infection among patients in our cohort differed from those in the cases reported by Roden et al. In their review, Roden et al. found that 58% of 929 patients presented with either sinus (39%) or cutaneous (19%) infections; these locations were associated with the lowest mortality rates (46% and 31%, respectively).² In our sample, two-thirds of the patients had rhino-orbito-cerebral, disseminated, or gastrointestinal infection; Rhoden et al. found that infections in these locations were associated with higher mortality rates (from 62% in the case of rhinocerebral infection to 85% in the case of gastrointestinal infection).² The most common underlying

disease in our study was haematological malignancy, which was present in over half of the patients. Mortality rates reported in the literature in patients with zygomycosis and underlying haematological malignancies are similar to those seen in our study.^{15,16} In a retrospective study of 59 patients with haematological malignancies and proven or probable zygomycosis, the overall mortality rate was 79.7%; in 41 of the cases (69.5%) the death was attributed to the IFI.¹⁵ In another review of 120 cases of zygomycosis with an underlying haematological or oncological disorder, the overall mortality rate was 61.6%; 68 of the patients (56.7%) died from either zygomycosis or a combination of zygomycosis and an additional factor.¹⁶ However, the presence of a haematological malignancy as underlying disease cannot entirely explain the high mortality observed in our study. In a recently reported survey which included 60 cases of zygomycosis, 37 (60%) of them having a haematological malignancy, Pagano et al. reported an attributable mortality rate of 32%, a rate that is substantially lower than the 52% we have found in our study.¹⁷

We identified several mortality risk factors in the univariate analysis: the presence of an underlying haematological malignancy, neutropenia, and monocytopenia. These risk factors for mortality are consistent with those reported in previous studies of patients with zygomycosis and other IFIs. As mentioned earlier, zygomycosis in patients with haematological malignancies is associated with a high mortality rate.^{15,16} Moreover, in a multivariate analysis of 70 patients with zygomycosis and haematological malignancies, Chamilos et al. reported that the presence of an active haematological malignancy was an independent predictor of a poorer outcome.¹⁸ Neutropenia has been associated with a higher risk of mortality in patients with haematological malignancies and other IFIs such as *Fusarium* sp.¹⁹ or invasive aspergillosis.²⁰ However, in two different series of patients with haematological malignancies and zygomycosis, neutropenia was not associated with a higher risk of mortality in either univariate or multivariate analysis.^{15,18} One of those studies, however, found that monocytopenia was an independent risk factor for a poorer outcome¹⁸ and both studies found that neutrophil recovery was associated with a protective effect.^{15,18} Like Chamilos,¹⁸ we think that it is likely that monocytopenia reflects the immunosuppression state of those patients, and the neutrophil recovery reflects the reversal of the predisposing underlying condition.

In our analysis the use of amphotericin B was not identified as a protective factor; this may be due to the small study sample size. However, the use of amphotericin B has been associated with a positive outcome in patients who have zygomycosis and several underlying conditions, such as patients with underlying haematological malignancies,^{15,18} patients with haematological or oncological disorders¹⁶ and solid organ transplant recipients.²¹ In the multivariate analysis by Chamilos et al., a delay in treatment with an amphotericin-based regimen was an independent predictor of mortality (OR 8.1, 95% CI 1.7–38.2).¹⁴ Similarly, a multivariate analysis of 59 patients with zygomycosis and underlying haematological malignancies found that treatment with liposomal amphotericin B was the only factor that predicted recovery from the IFI (Relative risk 0.5, 95% CI 0.3–0.8).¹² It is noteworthy that only 5 patients (20%) in our study received an amphotericin B-based treatment as a pre-emptive or empirical treatment. This fact alone could explain the high mortality rate observed in our study, and it illustrates the need for a rapid initiation of an effective antifungal treatment. Early diagnosis and treatment, including surgical debridement, reversal of underlying risk factors, and rapid initiation of an amphotericin B-based treatment, are the mainstays of management of zygomycosis.^{1,7} Moreover, since zygomycosis is difficult to diagnose, some authors have proposed the use of pre-emptive amphotericin B-based regimens in patients who are at high risk for zygomycosis and who are receiving other antifungal

Table 2

Use of antifungals in 25 cases of definite or probable zygomycosis.

Patients ¹	Type of therapy ^a	Antifungal	Treatment Duration (Days)	Outcome	Surgery
CASE 1	Empirical	Voriconazole	4	Death	No
	Preemptive	Ambisome + Caspofungin	10		
	Targeted (1st)	Ambisome + Posaconazole	7		
	Targeted (2nd)	Posaconazole	4		
CASE 2	Targeted (1st)	Ambisome	30	Alive	Yes
	Targeted (2nd)	Posaconazole	28		
CASE 3	Empirical	Fluconazole	31	Alive	Yes
	Preemptive	Ambisome	4		
	Targeted (1st)	Ambisome	112		
	Targeted (2nd)	Posaconazole	40		
CASE 4	Prophylaxis	Fluconazole	2	Death	Yes
	Preemptive	Caspofungin	13		
	Targeted (1st)	Ambisome	16		
CASE 5	Empirical	Voriconazole	2	Death	No
	Empirical	Voriconazole + Caspofungin	6		
CASE 6	Prophylaxis	Fluconazole	4	Death	No
	Preemptive (without symptoms)	Caspofungin	6		
	Pre-emptive	Caspofungin + Voriconazole	3		
CASE 7	Prophylaxis	Fluconazole	12	Death	No
	Empirical	Caspofungin	17		
	Targeted	Caspofungin + Voriconazole	3		
CASE 8	Targeted	Ambisome	32	Alive	Yes
CASE 9	Prophylaxis	Fluconazole	70	Death	Yes
	Targeted (1st)	Abelcet	5		
	Targeted (2nd)	Posaconazole + Ambisome	19		
	Targeted (3rd)	Ambisome	35		
	Targeted (4th)	Posaconazole	47		
CASE 10	Targeted	Ambisome	31	Alive	Yes
CASE 11	Prophylaxis	Itraconazole	18	Death	No
	Empirical	Caspofungin	6		
	Targeted	Caspofungin + Voriconazole	2		
CASE 12	Targeted (1st)	Ambisome	43	Death	Yes
	Targeted (2nd)	Posaconazole	16		
CASE 13	Targeted	Ambisome	101	Alive	Yes
CASE 14	Targeted	Ambisome	17	Alive	Yes
CASE 15	Pre-emptive	Fluconazole	3	Death	No
	Targeted	Ambisome	1		
CASE 16	Prophylaxis	Fluconazole	14	Death	Yes
	Pre-emptive	Abelcet	1		
	Pre-emptive	Abelcet + Caspofungin	2		
	Targeted (1st)	Caspofungin + Ambisome	19		
	Targeted (2nd)	Ambisome + Posaconazole	66		
	Targeted (3rd)	Ambisome	10		
CASE 17	Targeted	Ambisome	5	Death	Yes
CASE 18	Pre-emptive	Ambisome	4	Death	No
	Targeted	Ambisome + Posaconazole	24		
CASE 19	Prophylaxis	Fluconazole	15	Death	Yes
	Targeted (1st)	Ambisome + Caspofungin	34		
	Targeted (2nd)	Caspofungin	79		
CASE 20	Prophylaxis	Itraconazole	13	Death	No
	Targeted (1st)	Caspofungin	2		
	Targeted (2nd)	Ambisome + Caspofungin	3		
CASE 21	Prophylaxis	Fluconazole	94	Death	Yes
	Targeted (1st)	Ambisome	2		
	Targeted (2nd)	Caspofungin + Ambisome	11		
CASE 22	Targeted (1st)	Ambisome	59	Death	Yes
CASE 23	Empirical	Ambisome	12	Alive	Yes
	Targeted	Ambisome + Voriconazole	12		
CASE 24	Prophylaxis	Itraconazole	41	Death	Yes
	Targeted	Ambisome	45		

NOTE. One patient did not receive any antifungal agent.

^a Except otherwise indicated pre-emptive treatment was initiated in the presence of symptoms.

Table 3

Univariate analysis of risk factors for mortality among 25 patients with proven or probable zygomycosis.

Characteristic ^a	Survival N = 7	Death N = 18	P-value
Age, mean (SD)	48.2 (14.2)	45.3 (14.8)	.657
Sex			.274
Male	7 (100)	13 (72.2)	
Female	0 (0)	5 (27.8)	
Underlying disease			
Haematological malignancy	1 (14.3)	12 (66.7)	.030
Solid tumor	1 (14.3)	1 (5.6)	.490
Solid organ transplantation	1 (14.3)	3 (16.7)	<.999
Other	5 (71.4)	7 (38.9)	.202
Active haematological malignancy ^b	1 (100)	10 (83.3)	>.999
APACHE II $\geq 16^b$	3 (75)	7 (50)	.588
Currently admitted at the ICU	2 (28.6)	3 (16.7)	.597
Previously admitted at the ICU	1 (14.3)	0 (0)	.280
Bone marrow transplantation			
None	7 (100)	12 (66.7)	
Autologous	0 (0)	1 (5.6)	.215
Allogeneic	0 (0)	5 (27.8)	
GvHD grade ^b			
I-II	0 (0)	1 (20)	-
III-IV	0 (0)	1 (20)	-
Immunosuppressive therapy	2 (28.6)	11 (61.1)	.202
Cytomegalovirus infection	1 (14.3)	2 (11.1)	>.999
Diabetes mellitus	2 (28.6)	6 (33.3)	>.999
Hyperglycaemia ≥ 200 g/dL	3 (42.9)	8 (44.4)	>.999
Neutropenia ($WBC \leq 500$ cells/mm ³)	1 (14.3)	12 (66.7)	.030
Neutropenia (≥ 10 days) ^b	1 (100)	10 (83.3)	>.999
Lymphopenia	3 (42.9)	12 (66.7)	.378
Monocytopenia	0 (0)	11 (61.1)	.008
Acidosis ($pH \leq 7.35$)	3 (42.9)	3 (17.6)	.307
Malnutrition (Albumin ≤ 3 g/dL)	3 (42.9)	9 (50)	>.999
Use of corticosteroids therapy	3 (42.9)	10 (55.6)	.673
Use of anti-tumour necrosis factor therapy	0 (0)	1 (5.6)	>.999
Use of deferoxamine therapy	0 (0)	0 (0)	-
Sinusitis	1 (14.3)	1 (5.6)	.490
Surgical procedures	1 (100)	10 (58.8)	.057
Treatment with liposomal amphotericin B ^b			
Early treatment (≤ 1 day)	6 (85.7)	9 (69.2)	.613
Delayed treatment (>1 day)	1 (14.3)	4 (30.8)	
Type of infection			
Hospital-acquired	2 (28.6)	10 (55.6)	.378
Community-acquired	5 (71.4)	8 (44.4)	
Breakthrough zygomycosis	0 (0)	3 (17.6)	.530
Prophylactic, pre-emptive or empirical treatment with liposomal amphotericin B	1 (14.3)	3 (16.7)	>.999

GvHD: graft-versus-host-disease; ICU: intensive care unit; SD: standard deviation.

^a All data are presented as number (%) of patients except otherwise indicated.^b Percentage of patients calculated over valid or available cases.

agents that have little or no activity against Zygomycetes.¹⁸ With the data obtained and according to the published literature, when a zygomycosis infection is suspected, treatment with effective *in vitro* antifungal drugs should be started as soon as possible.

Despite the limitations of our retrospective design and the small sample size, our study supports previous research that has documented a high mortality rate among patients with invasive zygomycosis, especially among those with an underlying haematological malignancy, and the need for a rapid initiation of an effective antifungal treatment and the correction of underlying predisposing factors.

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Conflict of interest

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Llorente A, Hospital Joan XXIII, Tarragona.

García E, Clínica Universitaria de Navarra, Navarra.

Heras I, Hospital General Universitario Morales Messeguer, Murcia.

Fraile V, Hospital Universitario "Río Hortega", Valladolid.

García P, Hospital Clínico San Carlos, Madrid.

López J, Hospital Universitario Ramón y Cajal, Spain

Salavert M, Hospital Universitario La Fe, Valencia.
 Pérez I, Hospital Universitario La Paz, Madrid.
 Bobillo F, Hospital Clínico Universitario de Valladolid, Valladolid.
 Cantalapiedra A, Hospital Universitario “Río Hortega”, Valladolid.
 Gómez J, Hospital Central de Asturias, Oviedo.
 Andreu MAJ, Hospital de Mostoles, Madrid.
 Fortún J, Hospital Ramón y Cajal, Madrid.
 Díaz MA, Hospital de Mérida, Badajoz.
 Heredia M, Hospital Clínico Universitario de Valladolid, Valladolid.
 Martín P, Complejo Hospitalario Carlos Haya, Málaga.
 Martínez P, Hospital Universitario Puerto Real, Cádiz.
 Sanduende Y, Hospital Montecelo, Pontevedra.
 Sarriá C, Hospital Universitario La Princesa, Madrid.
 Bermúdez A, Hospital Universitario Marqués de Valdecilla, Cantabria.

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