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Evolution of the Antimicrobial Resistance of *Staphylococcus* spp. in Spain: Five Nationwide Prevalence Studies, 1986 to 2002

Oscar Cuevas, Emilia Cercenado,* Ana Vindel, Jesús Guinea, Matilde Sánchez-Conde, Mar Sánchez-Somolinos, Emilio Bouza, and the Spanish Group for the Study of *Staphylococcus*†

Department of Clinical Microbiology and Infectious Diseases, Hospital General Universitario "Gregorio Marañón," Madrid, Spain

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Data regarding the evolution of *Staphylococcus* resistance in a whole country have a definite influence on the design of empirical treatment regimens. Nevertheless, incidence studies over long periods of time are expensive and very difficult to carry out. In order to ascertain the present situation of the antimicrobial resistance of *Staphylococcus* in Spain and the change of this resistance over time, we performed five point prevalence studies (1986 to 2002) in a large group of Spanish hospitals (from 68 institutions in 1986 to 143 in 2002) collecting all *Staphylococcus* strains isolated on a single selected day. All microorganisms were identified in the five studies at the same laboratory, and antimicrobial susceptibility testing was performed against 17 antimicrobial agents by the agar dilution method and a microdilution method. During this period, there was an overall increase in resistance to most antimicrobials among *Staphylococcus aureus*/coagulase-negative staphylococci, mainly to oxacillin (1.5%/32.5% in 1986 versus 31.2%/61.3% in 2002) ($P < 0.001$), erythromycin (7%/41.1% in 1986 versus 31.7%/63% in 2002) ($P < 0.001$), gentamicin (5.2%/25.4% in 1986 versus 16.9%/27.8% in 2002) ($P < 0.001$; $P = 0.5$), and ciprofloxacin (0.6%/1.1% in 1986 versus 33.9%/44.9% in 2002) ($P < 0.001$). All of the isolates were uniformly susceptible to glycopeptides, linezolid, and quinupristin/dalfopristin. Resistance of *S. aureus* to trimethoprim/sulfamethoxazole was very low (from 0.5% to 2.1%) ($P = 0.152$). Periodic performance of prevalence studies is a useful, inexpensive, and easy tool to know the nationwide situation of a microorganism and its resistance to antimicrobials; it also helps us assess the emergence and spread of antimicrobial resistance.

Staphylococci are an important cause of both nosocomial and community-acquired infections (8, 33, 34). In the last decade, staphylococcal infection has reemerged as a cause for concern because of its numerical increase, the spread of methicillin-resistant *Staphylococcus aureus* (MRSA) isolates in the community, and the emergence of isolates not susceptible to vancomycin (4, 6, 7, 15, 19, 20, 23, 24, 26, 28, 37).

Most studies of staphylococcal resistance to antimicrobial agents rely on the situation in particular institutions or particular types of patients and clinical syndromes and thus provide biased information (2, 3, 10–12, 22, 31, 32, 36). Both the European Antimicrobial Resistance Surveillance System studies (14) and the SENTRY program (16) have demonstrated an increase in antimicrobial resistance in *S. aureus*, although they are based on a limited number of referral institutions per country, examine isolates of a particular origin, and have been carried out in recent years (16, 17). Similarly, uniformly high levels of methicillin resistance and resistance to other antimicrobial agents have been observed among coagulase-negative staphylococcus (CoNS) isolates in several surveillance studies (18, 21, 24). This situation underlines the need for wide surveillance studies in different geographical areas, including all types of institutions, all geographical areas, and unselected isolates.

Since 1986 we have undertaken four consecutive studies on the resistance of staphylococci to antimicrobials in more than 100 hospitals throughout Spain (5, 9, 13, 35). In this report, we present the data from the fifth national surveillance study and evaluate the present situation of resistance of *Staphylococcus* spp. to methicillin and other antimicrobial agents. In order to show the evolution of this situation, we report the results of the fifth national study in comparison with the four previous ones.

MATERIALS AND METHODS

Participating hospitals. From 1986 to 2002, we carried out five point-prevalence studies (1986, 1991, 1994, 1996, and 2002), analyzing all staphylococci identified on a single day in a large number of Spanish hospitals, with only one strain per patient and sample. In all of the studies, all isolates were sent to the same reference laboratory for reidentification and susceptibility testing. Seventy-four hospitals took part in the first study (1986), 68 took part in the second (1991), 113 took part in the third (1994), and 107 took part in the fourth. A total of 143 hospitals from all over Spain participated in the fifth study (2002), and the results obtained were compared with those from the previously published national studies (5, 9, 13, 35). The increase in the number of participating hospitals in the last three studies was due to the inclusion of new local institutions in order to achieve a progressively greater representation. The methodology for all studies was the same. All isolates identified on a single day were referred to the central laboratory accompanied by a uniform protocol which included the characteristics of the hospital of origin, the number of beds, ward, site of the isolate, acquisition (community, positive culture within the first 48 h after the admission; or nosocomial, positive culture after the first 48 h after the admission), local identification of the microorganism, and susceptibility to selected antimicrobial agents.

* Corresponding author. Mailing address: Servicio de Microbiología Clínica y E. Infecciosas, Hospital General Universitario "Gregorio Marañón," Dr. Esquerdo 46, 28007 Madrid, Spain. Phone: 34-91-586-8459. Fax: 34-91-504-4906. E-mail: ecercenado@teleline.es.

† Contributing members of the Spanish Group for the Study of *Staphylococcus* are listed in Acknowledgments.

TABLE 1. Isolates studied in the five nationwide studies in Spain

Yr (study)	No. (%) of isolates		Total no. of strains
	S. aureus	CoNS	
1986 (I)	195 (41.5)	275 (58.5)	470
1991 (II)	206 (49.2)	213 (50.8)	419
1994 (III)	248 (45.7)	295 (54.3)	543
1996 (IV)	256 (46.5)	294 (53.5)	550
2002 (V)	439 (54.3)	370 (45.7)	809

Identification of the isolates and susceptibility testing. All isolates were reidentified at the reference laboratory, following standard procedures (25). Antimicrobial susceptibility testing and determination of MIC breakpoints were performed following National Committee for Clinical Laboratory Standards recommendations (29, 30). The agar dilution method was used in the first, second, and third studies, and an automated broth microdilution method (MicroScan, Dade Behring, Sacramento, Calif.) was used in the fourth and fifth studies with Pos Combo 1S panels (except for linezolid and quinupristin/dalfopristin, which were handled by the manual broth microdilution method) following the manufacturer's guidelines. β-Lactamase production was detected with the nitrocefin test. The antimicrobials evaluated were penicillin, oxacillin, erythromycin, clindamycin, gentamicin, ciprofloxacin, chloramphenicol, cotrimoxazole, rifampin, vancomycin, teicoplanin, linezolid, and quinupristin/dalfopristin. *S. aureus* ATCC 29213 and *Enterococcus faecalis* ATCC 29212 were used as control strains in all studies. Further details on the materials and methods used are available in previous studies (5, 9, 13, 35).

Statistical analysis. Statistical analysis was performed with SPSS software version 11.5. We analyzed the changes in the resistance patterns over the period of time with the chi-square test.

RESULTS

Demographic and identification data. In this fifth study, carried out in 2002, a total of 812 isolates from a single day were received. Of these, 809 were suitable for study. Thirteen hospitals reported that, on the selected day, they had not isolated any staphylococci.

The number of strains received in the different studies ranged from 419 to 812. *S. aureus* was identified in 195 to 439 strains (41.5 to 45.3%), and the remainder were CoNS (Table 1).

Among the CoNS, the most frequently isolated species in the four studies was *Staphylococcus epidermidis*, which always represented more than 50% of the total number of CoNS isolated (Table 2).

The distribution of *S. aureus* and CoNS according to acquisition (community or nosocomial) is shown in Table 3. In the four previous studies, the percentage of nosocomially acquired isolates varied between 66 and 76% (62 to 72% of *S. aureus* and 64 to 81% of CoNS). In the fifth study, however, the distribution of nosocomial versus community-acquired isolates almost reached the proportion 1:1 (47% of *S. aureus* and 64% of CoNS isolates were nosocomially acquired). There were no significant changes during the five studies concerning the distribution of isolates of *S. aureus* and CoNS according to hospital size. In the fifth study, the distributions of *S. aureus* isolates were 32, 43, and 25% for hospitals of <500, between 500 and 1,000, and >1,000 beds, respectively. The corresponding percentages for CoNS were 39, 39, and 22%. No significant changes were observed concerning the ward of isolation of *S. aureus* and CoNS in comparison with previous studies. Both *S. aureus* and CoNS were recovered in all wards, as expected, although the medical and surgical wards provided numerically the greatest number of isolates (32 and 29%, respectively). Nevertheless, considering the smaller number of beds belonging to high-risk areas (intensive care units and units caring for transplant and deeply immunocompromised patients), the proportion of staphylococci isolated in these areas was greater. In this study, the distribution of staphylococci according to source showed that wounds (45%), lower respiratory tract (13.5%), soft tissues (16%), and blood (11%) represented the most frequent origins of *S. aureus*. In the case of CoNS, the most frequent sources of isolation were blood (32%), catheter tip (20%), wounds and abscesses (21%), and urine (12%).

TABLE 2. Distribution of the different species of CoNS

Species	No. (%) of CoNS isolates in yr:				
	1986	1991	1994	1996	2002
S. epidermidis	184 (67)	121 (57)	194 (66)	196 (67)	208 (56)
S. hominis	21 (8)	22 (10)	15 (5)	35 (12)	66 (18)
S. haemolyticus	20 (7)	14 (7)	24 (8)	9 (3)	18 (5)
S. wameri	18 (6)	4 (2)	7 (2)	5 (2)	14 (4)
S. simulans	13 (5)	15 (7)	9 (3)	6 (2)	4 (1)
S. capitis	6 (2)	5 (2)	7 (2)	6 (2)	9 (3)
S. cohnii	5 (2)	0	5 (2)	1 (0)	1 (0)
S. xylosus	5 (2)	9 (4)	0	0	1 (0)
S. saprophyticus	0	0	3 (1)	7 (2)	19 (5)
Other	3 (1)	23 (11)	31 (11)	29 (10)	29 (8)

Evolution of resistance of *S. aureus* to different antimicrobials. Resistance of *S. aureus* to penicillin remained stable throughout the first four studies, with percentages of approximately 95%. In the last study, we observed a small decrease in resistance to this antimicrobial agent, with 89.3% of isolates resistant to penicillin ($P = 0.212$). In contrast, resistance to oxacillin increased progressively from 1.5% in 1986 to 31.2% in 2002 ($P < 0.001$) (Table 4). Resistance to erythromycin and clindamycin, which increased progressively throughout the first three studies and decreased during the fourth, presented similar percentages in this fifth study to those obtained in the third study: 31.7 and 20.1%, respectively. Resistance to gentamicin presented the same increasing evolution during the first three studies, but in the last two studies, this resistance stabilized. Vancomycin and teicoplanin were uniformly active against all *S. aureus* isolates (MIC at which 90% of isolates tested are inhibited [MIC_{90}], ≤1 mg/liter each for vancomycin and teicoplanin; linezolid MIC_{90} = 2 mg/liter; and quinupristin/dalfopristin MIC_{90} = 0.25 mg/liter).

During the 17-year period of the studies, a significant increase in resistance to ciprofloxacin was observed, from 0.6% in 1986 to 33.9% in 2002 ($P < 0.001$). Resistance to rifampin, which increased between 1986 and 1996, was only 1.8% in the 2002 study. It is important to note the low resistance of *S. aureus* to cotrimoxazole in all studies (from 0.5 to 2.1%) ($P = 0.152$). In the first two studies, susceptibility to this antimicrobial was not determined. In general, resistance to chloramphenicol was very low (below 6%), with the exception of the 1994 study (18.9%).

Evolution of resistance of CoNS to different antimicrobials. In general, resistance of CoNS to penicillin remained stable throughout the five studies (Table 5). Resistance to oxacillin, which remained stable in the first three studies, increased sig-

TABLE 3. Distribution of the isolates by acquisition (community/nosocomial)

Yr	No. (%) of isolates[a]								
	S. aureus			CoNS			Total		
	C	N	N/A	C	N	N/A	C	N	N/A
1986	54 (28)	137 (72)	4	78 (29)	191 (71)	6	132 (29)	328 (71)	10
1991	60 (30)	142 (70)	4	40 (19)	167 (81)	6	100 (24)	309 (76)	10
1994	91 (38)	149 (62)	8	86 (31)	193 (69)	16	177 (34)	342 (66)	24
1996	77 (31)	170 (69)	9	57 (20)	232 (80)	5	134 (25)	402 (75)	14
2002	230 (53)	206 (47)	3	134 (36)	235 (64)	1	364 (45)	441 (55)	4

[a] C, community; N, nosocomial; N/A, not available.

nificantly in the fourth (50.7%) ($P < 0.001$) and reached 61.3% in the last study ($P = 0.006$). CoNS also showed progressively higher percentages of resistance to erythromycin (63% in 2002). However, we have observed a decrease in the resistance to clindamycin (33.8%) ($P = 0.183$) and gentamicin (27.8%) ($P = 0.001$) in the fifth study. We did not detect resistance to linezolid (MIC_{90} = 1 mg/liter) or quinupristin/dalfopristin (MIC_{90} = 0.12 mg/liter). All isolates have remained uniformly susceptible to vancomycin and teicoplanin, with the exception of two isolates of CoNS detected in the 1996 study. In all cases, the MIC of teicoplanin for these isolates was 16 mg/liter.

Resistance of CoNS to ciprofloxacin also increased progressively from 1.1% in 1986 to 44.9% in 2002 ($P < 0.001$), and resistance to rifampin remained stable and below 10% in all five studies. Resistance to cotrimoxazole among CoNS increased from 22.4% in 1994 to 31.3% in 1996 ($P = 0.015$), but decreased in 2002 to 24.3% ($P = 0.046$). With regard to chloramphenicol, resistance in the last two studies has decreased in comparison with the previous ones, but in general, it has varied between approximately 10 and 20%.

MRSA. As indicated above, *S. aureus* isolates showed a progressive increase in resistance to oxacillin, from 1.5% in 1986 to 31.2% in 2002 ($P < 0.001$) (Table 4). One of the most striking aspects of the 2002 study is the higher number of methicillin-resistant isolates recovered from outpatients. While in the 1986, 1991, and 1994 studies fewer than 5% of community-acquired *S. aureus* isolates were resistant to methicillin, in 1996 the percentage was 11.7% ($P = 0.148$). In 2002, 17.8% of MRSA isolates were community acquired ($P = 0.207$). This study also shows that the percentages of isolates resistant to methicillin have increased in small and large hospitals. In those with fewer than 500 beds, the rate of MRSA isolation in 2002 was 28.8% (22.2% in 1996) ($P = 0.287$), in those with 500 to 1,000 beds it was 29.8% (17.1% in 1996) ($P = 0.013$), and the highest increase was observed in large hospitals in which the percentage of MRSA was 36.6% (13.8% in 1996) ($P = 0.002$). MRSA has also spread to high-risk (34.1%), surgical (34.6%), and medical (35.4%) wards. Low-risk wards presented lower rates of MRSA (11.1%). In all cases, these percentages were higher than those obtained in the 1996 study: 28.3% for high-risk ($P = 0.460$), 10.4% for surgical ($P < 0.001$), 20.7% for medical ($P = 0.018$), and 9.7% for low-risk ($P = 0.832$) wards.

Only 8.8% of MRSA isolates were susceptible to ciprofloxacin, although 32.8% were susceptible to erythromycin, 50.4% to clindamycin, 59.9% to gentamicin, and 94.9% to rifampin. It is important to note the low percentages of resistance to cotrimoxazole (5.1%) and chloramphenicol (6.8%). All isolates were uniformly susceptible to linezolid, quinupristin/dalfopristin, teicoplanin, and vancomycin.

TABLE 4. Changes in antimicrobial resistance patterns in *S. aureus* over time

Antimicrobial	% Resistant in yr:				
	1986	1991	1994	1996	2002
Penicillin	94.9	97.1	92.3	92.1	89.3
Oxacillin	1.5	11.2	16.6	17.9	31.2
Erythromycin	7	24.5	33.9	24.2	31.7
Clindamycin	0	6.4	20.6	18.7	20.1
Gentamicin	5.2	14.1	19.3	16.4	16.9
Rifampin	1.1	4.9	8.7	7	1.8
Cotrimoxazole	ND[a]	ND	0.5	1.1	2.1
Chloramphenicol	5.2	2	18.9	1.2	2.5
Ciprofloxacin	0.6	16.6	20.6	19.9	33.9
Vancomycin	0	0	0	0	0
Teicoplanin	0	0	0	0	0
Linezolid	ND	ND	ND	ND	0
Q/D[b]	ND	ND	ND	ND	0

[a] ND, not determined.
[b] Q/D, quinupristin/dalfopristin.

TABLE 5. Changes in antimicrobial resistance patterns in CoNS over time

Antimicrobial	% Resistant in yr:				
	1986	1991	1994	1996	2002
Penicillin	85.8	91.5	77.3	82.3	78.9
Oxacillin	32.5	25.6	34.3	50.7	61.3
Erythromycin	41.1	45.5	58.4	57.4	63
Clindamycin	24.3	33.4	41.4	38.7	33.8
Gentamicin	25.4	39.9	49.5	39.8	27.8
Rifampin	4	8.1	9.2	8.8	6.8
Cotrimoxazole	ND[a]	ND	22.4	31.3	24.3
Chloramphenicol	1.1	20.9	23.4	12.6	8.9
Ciprofloxacin	1.1	20.9	23.7	32.6	44.9
Vancomycin	0	0	0	0	0
Teicoplanin	0	0	0	1	0
Linezolid	ND	ND	ND	ND	0
Q/D[b]	ND	ND	ND	ND	0

[a] ND, not determined.
[b] Q/D, quinupristin/dalfopristin.

DISCUSSION

Although point prevalence studies have limitations, they are a useful, inexpensive, quick and easy tool to determine the nationwide situation of a microorganism and its resistance to antimicrobials (5, 9, 13, 35). They allow us to obtain a representative sample in a large number of hospitals throughout a country and, when repeated periodically, show the main trends.

In the five studies performed, we have observed that the ratio of *S. aureus* to CoNS was around 1:1. In the 2002 study, we observed that the majority of nosocomial CoNS isolates were obtained from blood samples, catheters, and wounds, indicating that CoNS have become increasingly recognized as important agents of nosocomial infection (33). With regard to the resistance of *S. aureus* to antimicrobial agents, the most important aspect is the increase in resistance to methicillin in Spain, although in the several European countries the rates of MRSA are higher (1, 38). Resistance to methicillin among *S. aureus* increased from 1.5% in 1986 to 31.2% in 2002 ($P < 0.001$). This also implies an increase in resistance to other antimicrobials such as macrolides, lincosamides, aminoglycosides, and quinolones. On the other hand, resistance to cotrimoxazole, chloramphenicol, and rifampin is still exceptional (2.1, 2.5, and 1.8%, respectively) and all *S. aureus* isolates have remained uniformly susceptible to glycopeptides and novel antimicrobials (linezolid and quinupristin/dalfopristin).

In the fourth study, the spread of the MRSA epidemic to small hospitals and to the community was a cause for concern, since 11.7% of all community-acquired *S. aureus* isolates were resistant to methicillin. This problem continued in the 2002 study, where methicillin resistance stabilized in small institutions but reached 17.8% of the community-acquired *S. aureus* isolates. In our opinion, this is a serious problem which may have an important influence on the correct choice of antimicrobial therapy and probably represents the difficulty in implementing control measures in this environment.

In spite of these variations with respect to previous studies, MRSA isolates are still more frequent among hospitalized patients. This is particularly true of high-risk wards, where the presence of bloodstream infections and pneumonia confirms its role as an important nosocomial pathogen producing severe infections. There are few therapeutic alternatives against these pathogens given that they are usually resistant to many other antimicrobial drugs. Nevertheless, in this study, MRSA isolates presented high percentages of susceptibility to cotrimoxazole (94.9%), chloramphenicol (94.2%), linezolid (100%), quinupristin/dalfopristin (100%), vancomycin (100%), and teicoplanin (100%).

With regard to CoNS, the increase in resistance to methicillin was even greater, reaching 61.3%. In most cases, this was associated with resistance to multiple antimicrobials. The emergence of CoNS with decreased levels of susceptibility to teicoplanin (MIC = 16 mg/liter) observed in the fourth study was absent in the 2002 study, and none of the isolates were resistant to vancomycin in any of the studies. In previous studies, we also noticed the in vivo development of resistance to teicoplanin among CoNS strains isolated in our hospital (10). The emergence of vancomycin-resistant *S. aureus* isolates described recently in the United States (6, 7) and the diminished susceptibility to vancomycin described in the United States and in other countries (23, 27) were not encountered in our studies.

This study underlines the need for surveillance studies of this type, which are easy to perform, even in situations where resources are limited.

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The members of the Spanish Group for the Study of *Staphylococcus* and the staff of the microbiology services of all participating hospitals are as follows: F. Lueiro and R. Villanueva, Hospital Juan Canalejo, La Coruña; M. Rodríguez-Jove and A. Álvarez, Hospital General Juan Cardona, El Ferrol-La Coruña; J. A. Agulla, A. Rodríguez-Mayo, and D. Domínguez, Complejo Hospitalario Arquitecto Marcide-Novoa Santos, El Ferrol-La Coruña; B. Regueiro and F. Pardo, Hospital de Conxo, Santiago de Compostela-La Coruña; P. Alonso and A. Rguez, Complejo Hospitalario Xeral-Calde, Lugo; A. Tinajas, I. Paz, B. Fernández, and G. Esteban, Complejo Hospitalario Cristal Piñor, Orense; M. A. Pascual and M. García-Campello, Hospital Montecelo, Pontevedra; V. Pulian and M. Hernández, Complejo Hospitalario, Pontevedra; T. González-Blanco, I. Otero, M. Alvarez, and I. Iglesias, Complejo Hospitalario Xeral-Cies, Vigo-Pontevedra; J. Torres and F. J. Vasallo, Hospital do Meixoeiro, Vigo-Pontevedra; J. Sevillano, I. Rodríguez-Conde, and A. González-Escalada, Policlínico POVISA, Vigo-Pontevedra; F. Vázquez, Hospital Monte Naranco, Oviedo-Asturias; F. Méndez and F. Pérez, Hospital Central de Asturias, Oviedo-Asturias; E. Hidalgo, Hospital de Jove, Gijón-Asturias; J. J. Palacios and M. D. Miguel, Hospital de Cabueñes, Gijón-Asturias; P. Prendes and J. Rodríguez-Álvarez, Hospital San Agustín, Avilés-Asturias; R. Cimadevilla, Hospital Comarcal de Jarrio, Asturias; A. Torreblanca and P. Iglesia, Hospital Carmen y Severo Ochoa, Cangas de Narcea-Asturias; C. Fernández-Mazarrasa, J. Calvo, and C. Martínez-Bernal, Hospital Marqués de Valdecilla, Santander; I. De Benito and P. Mellado, Hospital Comarcal de Laredo, Cantabria; R. Cisterna and C. Ezpeleta, Hospital de Basurto, Bilbao-Vizcaya; F. Calvo and J. López-Gracia, Hospital de Santa Marina, Bilbao-Vizcaya; I. Marzana, P. Liendo, I. Corral, and P. Martín-Saco, Hospital San Eloy, Baracaldo-Vizcaya; M. Alkorta and J. Barrón, Hospital de Cruces, Baracaldo-Vizcaya; M. J. López-Goikoetxea and J. Echeverría, Hospital de Galdakao, Vizcaya; L. Michaus, M. J. Lezaun, and A. Pablos, Hospital Txagorritxu, Vitoria; A. Labora and A. Canut, Hospital Santiago Apóstol, Vitoria; E. Pérez-Trallero and J. M. García-Arenzana, Hospital de Donostia, Guipúzcoa; J. A. Jiménez-Alfaro, Policlínica Guipúzcoa, San Sebastián-Guipúzcoa; J. L. Fernández-Calvo and L. Torroba, Hospital Virgen del Camino, Pamplona; C. Pina, Hospital San Juan de Dios, Pamplona; I. Dorronsoro and J. J. García-Irure, Hospital de Navarra, Pamplona; R. Díaz-García, S. Hernáez, and J. Leyva, Clínica Universitaria de Navarra, Pamplona; M. J. Gastañares, Complejo Hospitalario San Millan-San Pedro, Logroño; M. T. Jiménez-Anta and F. Marco, Hospital Clinic i Provincial, Barcelona; P. Coll and B. Mirelis, Hospital de la Santa Creu i Sant Pau, Barcelona; R. Martín, Hospital Princeps d'Espanya, Hospitalet Llobregat-Barcelona; M. Salvadó and C. Segura, Hospital del Mar, Hospitalet Llobregat-Barcelona; D. Fontanals and D. Mariscal, Consorcio Hospitalario del Parc Tauli, Sabadell-Barcelona; J. Lite, Mutua de Tarrasa, Barcelona; V. Ausina and L. Matas, Hospital Universitari Germans Trias i Pujol, Badalona-Barcelona; F. Corcoy and R. Angrill, Residencia Sant Camil, Sant Pere de Ribes-Barcelona; M. Morta, Hospital General de Manresa, Barcelona; J. M. Santamaría, Hospital Joan XXIII, Tarragona; A. Nogues and M. García, Hospital Universitari Arnau de Vilanova, Lérida; M. L. Urcula, Hospital Provincial de Santa Caterina, Gerona; J. Batlle, Hospital Universitario Doctor Josep Trueta, Gerona; A. García-Busto and R. Moreno, Hospital General, Castellón; M. Canós, Hospital La Plana, Villareal-Castellón; M. Gobernado and J. L. López-Ontangas, Hospital Universitario La Fe, Valencia; J. García-Lomas, Hospital Clínico, Valencia; A. Lloret, Hospital Arnau Vilanova, Valencia; J. Maiquez, Instituto Valenciano de Oncología, Valencia; J. M. Nogueira, Hospital Dr. Peset, Valencia; M. R. Llucián, Hospital General Universitario, Valencia; J. M. García-Aguayo, Hospital General de Requena, Valen-

cia; M. C. Alonso and R. Igual, Hospital Francesc Borja, Gandía-Valencia; D. González-Granda and R. M. Ferreruela, Hospital Lluis Alcanyis, Játiva-Valencia; M. Castelo and J. M. García, Hospital Militar Vázquez Bernabeu, Quart Poblet-Valencia; J. Prat, Hospital Sagunto, Valencia; S. Giner, Hospital Dr. Moliner, Serra-Valencia; J. Plazas, Hospital General Universitario, Alicante; V. Ortiz and C. Martín-González, Hospital de San Juan, Alicante; A. Yagüe and N. Gonzalo, Hospital de la Vega Baja, San Bartolomé-Alicante; G. Royo and E. Cascales, Hospital General Universitario, Elche-Alicante; A. Antúnez and G. Yagüe, Hospital General Universitario, Murcia; M. Segovia and A. Menasalvas, Hospital Morales Meseguer, Murcia; J. Piqueras and M. L. Núñez, Hospital General Santa María del Rosell, Cartagena-Murcia; J. Ruiz, Hospital Universitario Virgen de la Arrixaca, El Palmar-Murcia; J. L. Pérez, A. Borrell, and A. Oliver, Hospital Son Dureta, Palma de Mallorca; J. Sánchez-Gómez, Hospital Can Misses, Ibiza; A. Gutiérrez and A. García-Perea, Hospital La Paz, Madrid; J. J. Rodríguez-Otero and F. Chaves, Hospital Universitario Doce de Octubre, Madrid; M. Menéndez-Rivas, Hospital del Niño Jesús, Madrid; F. Hervas and F. Gutiérrez, Hospital Militar Gómez Ulla, Madrid; J. J. Picazo, P. Merino, and F. Torre, Hospital Clínico San Carlos, Madrid; F. Baquero, I. Morosini, R. Cantón, and J. Martínez-Beltrán, Hospital Ramón y Cajal, Madrid; M. A. Blanco and C. Pazos, Hospital Santa Cristina, Madrid; M. Baquero and A. M. Enríquez, Hospital Carlos III, Madrid; D. Dámaso, Hospital Puerta de Hierro, Madrid; M. López-Brea and T. Alarcón, Hospital Universitario de la Princesa, Madrid; R. Cortés and M. V. Portús, Hospital de la Cruz Roja-San José y Santa Adela, Madrid; A. Urmeneta and C. Martín-Scapa, Hospital de Cantoblanco, Madrid; M. Beltrán, J. Cuadros, J. Peña, and R. González-Palacios, Hospital Príncipe de Asturias, Alcalá de Henares-Madrid; J. L. Gómez and A. Pérez-Revilla, Hospital General, Móstoles-Madrid; I. Wilhelmi-Cal and M. Páez, Hospital Severo Ochoa, Leganés-Madrid; J. R. Domínguez, P. García, P. Díez, and M. Sánchez, Hospital Universitario, Getafe-Madrid; M. Rollán, Hospital Militar, Zaragoza; C. Miñiana, Hospital N. Señora de Gracia, Zaragoza; M. J. Revillo, Hospital Miguel Servet, Zaragoza; C. Rubio, Hospital Clínico Universitario Lozano Blesa, Zaragoza; M. Ferrero and P. Mairal, Hospital General San Jorge, Huesca; P. Chocarro, Hospital General Obispo Polanco, Teruel; C. Navarro and T. Nebreda, Hospital de Alcañiz, Teruel; L. Díaz, Hospital Virgen De La Salud, Toledo; A. M. Leturia, Hospital Nacional de Parapléjicos, Toledo; J. C. González-Rodríguez, Hospital Nuestra Señora del Carmen, Ciudad Real; M. D. Romero, Hospitales Alarcos y Carmen, Ciudad Real; J. Bisquert, Hospital General Universitario, Guadalajara; D. Crespo, A. Martín, and P. Robles, Complejo Hospitalario, Albacete; F. Cachón, I. Fernández-Natal, and I. Antolín, Hospital de León, León; C. Fuster and C. Raya, Hospital del Bierzo, Ponferrada-León; M. F. Brezmes, Hospital Virgen de La Concha, Zamora; J. A. García-Rodríguez and J. E. García-Sánchez, Hospital Virgen de La Vega, Salamanca; S. García-Carbajosa and P. Carrero, Hospital General, Segovia; I. Pozas and E. Ojeda, Hospital General Yagüe, Burgos; M. D. Badía, Hospital Provincial Divino Vallés, Burgos; C. Gimeno, Hospital Comarcal Santiago Apóstol, Miranda de Ebro-Burgos; R. Ibáñez, Hospital Ntra. Sra. de Sonsoles, Ávila; A. Campos and F. Merino, Hospital General, Soria; M. A. García-Castro and E. Álvarez, Hospital General Río Carrión, Palencia; R. Torío and P. Pérez-Pascual, Hospital del Río Hortega, Valladolid; A. Rodríguez-Torres and M. A. Bratos, Hospital Universitario, Valladolid; R. Iñiguez, Hospital Nuestra Señora de La Montaña, Cáceres; P. Teno, Complejo Hospitalario San Pedro de Alcántara, Cáceres; J. Blanco and E. Garduño, Hospital Universitario Infanta Cristina, Badajoz; J. García-Herruzo, Hospital Universitario Puerta Del Mar, Cádiz; I. Ruiz, Hospital Punta de Europa, Algeciras-Cádiz; C. Miguel-Sastre, Hospital de Jerez de La Frontera, Cádiz; A. Sánchez-Porto, Hospital La Línea de La Concepción, Cádiz; M. Casal, Hospital Universitario Reina Sofía, Córdoba; C. Plata, Hospital Infanta Margarita, Cabra-Córdoba; M. Rosa-Fraile and A. Martínez-Brocal, Hospital Virgen de Las Nieves, Granada; G. Piédrola, M. C. Maroto, and T. Escobar, Hospital Universitario San Cecilio, Granada; P. Manchado, Hospital Carlos Haya, Málaga; A. Pinedo, C. Arana, and M. A. Sánchez, Hospital Virgen de La Victoria, Málaga; A. Reyes, Hospital Torrecárdenas, Almería; I. Cuesta, Hospital Universitario, Jaén; J. M. Saavedra and L. Pascual, Hospital Juan Ramón Jiménez, Huelva; C. García-Iglesias, Hospital San Lázaro, Sevilla; A. Petit, Hospital San Juan de Dios, Sevilla; E. Perea and M. Cueto, Hospital Virgen Macarena, Sevilla; J. Pachón, J. Aznar, and M. Ruiz, Hospital Virgen del Rocío, Sevilla; E. Martín, Hospital Nuestra Señora de Valme, Dos Hermanas-Sevilla; A. Muñoz, Hospital Militar O'Donell, Ceuta; J. López-Barba, Hospital Cruz Roja, Ceuta; M. Galán, Hospital Comarcal, Melilla; J. A. Tur, Hospital Militar Pages, Melilla; N. Batista, Hospital Nuestra Señora de La Candelaria, Santa Cruz de Tenerife; A. Sierra, Hospital Universitario de Canarias, La Laguna-Santa Cruz de Tenerife; R. M. Gallardo and L. Martín, Hospital General de La Palma, Santa Cruz de La Palma-Santa Cruz de Tenerife; and A. M. Martín and F. Cañas, Hospital Insular de Gran Canaria, Las Palmas de Gran Canaria.

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