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ORIGINAL ARTICLE

Evaluation of the impact of the Spanish Consensus Document on the approach to osteoarticular infections in Spain through the Paediatrics Osteoarticular Infections Network (RIOPED)*

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Osteoarticular infections;
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Diagnosis;
Treatment

Abstract
Introduction: In 2014 the Consensus Document produced by the Spanish Paediatric Societies (SEIP-SERPE-SEOP) was published to help in the diagnosis and treatment of osteoarticular infections (OAI). In 2015 the RIOPed was considered as a multidisciplinary national network for the investigation into OAI. The aim of this study was to assess the level of adaption to the recommendations established in the Consensus during one year of follow-up.
Material and methods: A prospective, national multicentre study was carried out in 37 hospitals between September 2015 and September 2016. The study included patients >16 years-old with a diagnosis of OAI, confirmed by microbiological isolation, or probable: septic arthritis (SA) with >40,000 white cells in synovial fluid, or osteomyelitis (OM)/spondylodiscitis (SD) with a compatible imaging test. The results were compared with those obtained in a retrospective study conducted between 2008 and 2012.
Results: A total of 235 cases were included, of which 131 were OM, 79 SA, 30 OA, and 15 SD. As regards the complementary tests that the Consensus considered mandatory to perform, radiography was carried out on 87.8% of the cases, a blood culture on 91.6%, and culture of the

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◊ Appendix A presents the members of the RIOPed Network.

synovial fluid in 99% of SA. A magnetic resonance (MR) was performed on 71% of the OM cases. The choice of intravenous empirical antibiotic treatment was adapted to the recommendations in 65.1% of cases, and in 62.3% for the oral treatment. Surgery was performed in 36.8% of SA cases (85.7% arthrotomy), with a significant decrease compared to the retrospective study ($P = .014$). Only 58.5% of cases followed the recommendations on the duration of the treatment; however, a lower duration of intravenous treatment was observed.
Conclusions: In general, the level of adaptation to the recommendations that were set by the Expert Group, is good for the complementary tests, and acceptable as regards the choice of antibiotic treatment, although inadequate in almost 40% of cases. A decrease in hospital stay was achieved.

PALABRAS CLAVE
Infecciones osteoarticulares;
Osteomielitis;
Artritis séptica;
Diagnóstico;
Tratamiento

Evaluación del impacto del Documento de Consenso español sobre el abordaje de las infecciones osteoarticulares en nuestro medio a través de la Red de Infecciones Osteoarticulares Pediátricas (RIOPed)

Resumen
Introducción: En 2014 se publicó el Documento de Consenso desarrollado por SEIP-SERPE-SEOP para el diagnóstico y el tratamiento de las infecciones osteoarticulares (IOA). En 2015 se constituyó RIOPed como red nacional multidisciplinar para la investigación en IOA. El objetivo del estudio ha sido valorar el grado de adecuación a las recomendaciones establecidas en el consenso durante un año de seguimiento.
Material y métodos: Estudio prospectivo multicéntrico nacional realizado entre septiembre de 2015 y septiembre de 2016 en 37 hospitales con inclusión de pacientes menores de 16 años diagnosticados de IOA, confirmada mediante aislamiento microbiológico, o probable: artritis séptica (AS) con >40.000 leucocitos en líquido sinovial u osteomielitis (OM)/osteoartritis (OA)/espondilodiscitis (ED) con prueba de imagen compatible. Los resultados se compararon con los obtenidos en el estudio retrospectivo realizado entre 2008 y 2012.
Resultados: Se incluyeron 255 casos: 131 OM, 79 AS, 30 OA y 15 ED. Respecto a las pruebas complementarias que el consenso consideró de obligada realización, la radiografía se llevó a cabo en el 87,8% de los casos, el hemocultivo en el 91,6% y el cultivo de líquido sinovial en el 99% de AS. Se realizó RM en el 71% de las OM. La elección del tratamiento antibiótico intravenoso empírico se adecuó a las recomendaciones en el 65,1% de los casos, y en el 62,3% para el tratamiento oral. Se llevó a cabo cirugía en el 36,8% de las AS (85,7% artrotomía), con un descenso significativo respecto al estudio retrospectivo ($P = ,014$). Solo el 58,5% de casos se ajustaron a las recomendaciones de duración del tratamiento; sin embargo, se comprobó una menor duración del tratamiento intravenoso.
Conclusiones: En general, el grado de adecuación a las recomendaciones que marcaron el grupo de expertos es bueno para las pruebas complementarias y aceptable respecto a la elección del tratamiento antibiótico, aun detectándose casi un 40% de inadecuación. Se ha conseguido un descenso de la estancia hospitalaria.

Introduction

Osteoarticular infections (OAIs) are relatively frequent in childhood. They are important due to the potential involvement of the growth plate or epiphyseal cartilage, which could affect growth and bone and/or joint development and result in sequelae at this level.[1]

The diagnosis, management and treatment of OAIs have changed significantly in recent years.[2–8] Early and accurate diagnosis and appropriate antibiotherapy are the keys to a quick recovery free of sequelae.[2] A definitive diagnosis requires the identification of the causative agent, but this is only accomplished in approximately 40% of cases,[9] which means that most patients received empiric treatment rather than treatment based on the results of antimicrobial susceptibility testing. The use of polymerase chain reaction (PCR) techniques for detection of unculturable or fastidious bacteria, such as *Kingella kingae*, has improved the diagnostic yield of microbiological testing.[10–13]

Addressing the need to standardise the management of OAIs, in 2014 the 3 societies in Spain representing the specialities involved in the management of these diseases—the Sociedad Española de Infectología Pediátrica (Spanish Society of Paediatric Infectious Diseases [SEIP]), the Sociedad Española de Reumatología Pediátrica (Spanish Society of Paediatric Rheumatology [SERPE]) and the Sociedad Española de Ortopedia Pediátrica (Spanish Society of Paediatric Orthopaedics [SEOP])— published a consensus document in *Anales de Pediatría* (available online since September-October 2014).[14,15] The document reviewed the evidence published to date on simple OAIs, that is, uncomplicated acute infections, usually haematogenous and acquired in the community.

On the other hand, despite the frequency and importance of these infections, no large-scale multicentre studies had been conducted to analyse the epidemiology, diagnosis and treatment of OAIs in Spain, and domestic data were needed to adapt existing recommendations to our particular epidemiological situation. In light of this, in an early phase of the project we conducted a retrospective study that included patients given a diagnosis of OAI in 23 hospitals in Spain between 2008 and 2012 followed up for at least 1 year. This study included 608 children,—299 (49%) with osteomyelitis (OM) (94 with microbiological confirmation), 232 (38%) with septic arthritis (SA) (111 confirmed) and 77 (13%) with osteoarthritis (OA)—and described the approach to diagnosis and treatment of OAIs in participating hospitals.[16]

In late 2014, a nationwide multidisciplinary network, the Red de Infecciones Osteoarticulares Pediátrica (Paediatric Osteoarticular Infection Network, RIOPed), was established to carry out research on OAIs. The main goal of the network was to determine the actual prevalence of OAIs, their epidemiological characteristics and the approach to their management in Spain, while promoting research studies at the domestic and international level. For this purpose, the network created a database through REDCap, a user-friendly research network platform that adheres to regulations on patient safety and confidentiality, and prospective data collection started in September 2015.

One of the first objectives established by this collaborative network was to assess the impact of the national consensus document on clinical practice, especially in relation to the diagnostic tests and the treatments used in the management of OAI by comparing the prospective data from the register with the findings of the previous retrospective study.[16] Thus, the main aim of this study was to assess the adherence to the consensus recommendations in order to develop new guidelines to optimise the future approach to the diagnosis and treatment of these infections, adapting it to local circumstances in Spain.

Patients and methods

We conducted a prospective, nationwide multicentre study between September 2015 and September 2016. The study was approved by the Ethics Committee of the Hospital Universitario Severo Ochoa and by participating centres. It included patients aged less than 16 years with a diagnosis of OAI (after obtaining signed informed consent) managed in 37 hospitals, applying the following criteria:

- Confirmed OAI: compatible clinical presentation and positive isolation in blood or joint fluid culture.
- Probable OAI: SA with a white blood cell count in joint fluid greater than 40,000; OM/spondylodiscitis (SD) in case of compatible imaging findings; OA in case criteria for both OM and SA were met.

We compared clinical manifestations, diagnostic tests, treatments and outcomes with the findings of the retrospective study carried out with data from the 2008–2012 period.[16] We evaluated the degree of adherence to the aforementioned consensus document and guidelines, and calculated the percentage of adherence to the recommendations that the group of experts considered absolutely essential, which were: obtention of a blood sample for culture in all cases, performance of arthrocentesis and joint fluid culture, and performance of a plain radiograph and magnetic resonance imaging (MRI) scan for evaluation of OM. When it came to treatment, we assessed the choice of antibiotic agent (for empiric and targeted therapy) and the duration of antibiotherapy based on the consensus recommendations (Table 1).

The defined complication as the development of pyomyositis, abscesses, nosocomial infections or deep venous thrombosis. We defined sequela as any condition resulting from the OAI that impaired the quality of life of the child (pain, limping, reduced mobility or limb length discrepancies).

Statistical analysis

We have expressed discrete variables as percentages and continuous variables as mean and standard deviation. We compared variables in the prospective and retrospective cohorts by means of the Student *t* test, the Mann–Whitney *U* test, the χ^2 test and the Fisher exact test as applicable. We defined statistical significance as a *P*-value of less than .05. The statistical analysis was made with the software Statistical Package for the Social Sciences (SPSS), version 21.0.

Results

The study included 255 cases of OAI diagnosed over a 1-year period in 37 Spanish hospitals: 131 of OM (50 [38.2%] confirmed), 79 of SA (45 [57%] confirmed), 30 of OA (19 [63.3%] confirmed), and 15 of SD, with significant differences in the percentage of confirmed cases depending on the disease (OM vs SA, $P = .01$; OM vs OA, $P = .015$). We did not find significant differences in the frequency distribution of the diagnoses between the prospective and retrospective cohorts (Table 2). We also did not find differences between cohorts in the clinical manifestations, save for a lower frequency of fever in the prospective cohort compared to the retrospective cohort (156/255 [61.4%] vs 446/641 [70%]; $P = .013$). Table 3 describes case characteristics in terms of the diagnostic tests performed, treatment and outcomes in both cohorts. The percentage of cases confirmed

Table 1 Recommendations for treatment of osteoarticular infections given in the National Consensus Document.

Intravenous treatment	<3 months: cloxacillin + cefotaxime/gentamicin
	3 months–5 years: cefuroxime or cloxacillin + cefotaxime
	>5 years: cefazoline or cloxacillin
Oral treatment	RN–3 months: cefuroxime
	3 months–5 years: cefuroxime or cefadroxil (especially if age >2 years)
	>5 years: cefadroxil
Targeted therapy	MSSA: cefadroxil
	MRSA: clindamycin/ciprofloxacin/TMP-SMX + rifampicin
	S. pyogenes, S. agalactiae and *S. pneumoniae*: amoxicillin
	Kingella kingae: amoxicillin for first-line treatment; cefuroxime or amoxicillin-clavulanic acid
Total duration of treatment	Septic arthritis: 14–21 days Osteoarthritis/osteomyelitis: 21–28 days

MRSA, community-acquired methicillin-resistant *S. aureus*; MSSA, methicillin-susceptible *S. aureus*; TMP-SMX, trimethoprim-sulfamethoxazole.

Table 2 Comparison of general characteristics in the 2 periods under study.

	Retrospective	Prospective
Participating hospitals, n	22	37
Study period	January 2008–December 2012	September 2015–September 2016
Sample size, n	641	255
Frequency distribution by disease, n (%), P = .485		
Acute osteomyelitis	299 (46.6%)	131 (51%)
Septic arthritis	232 (32%)	79 (31%)
Acute osteoarthritis	77 (12%)	30 (12%)
Spondylodiscitis	33 (5%)	15 (6%)

The differences between the 2 periods in the frequency distribution by type of osteoarticular infection were not statistically significant, nor were the differences in the proportions of confirmed cases.

by bacterial isolation increased from 38.8% (249/641) to 44% (113/255) in the prospective cohort, although the difference was not statistically significant ($P = .13$). An arthrocentesis had not been performed in 7 cases of SA without microbiological confirmation, so we did not consider that these cases meet the inclusion criteria. Once these cases were excluded from the analysis, the percentage of cases with bacterial isolation increased from 44.8% (104/232) to 61% (44/72) ($P = .016$). One salient finding in the second period was the increase in the incidence of community-associated methicillin-resistant *Staphylococcus aureus* (CA-MRSA) from 0.4% to 3.7% ($P < .001$), and the increase in the frequency of identification of *K. kingae*, particularly by means of PCR. We also ought to highlight that there was an increase in the delay in seeking care from the onset of symptoms, from 6.7 to 9.1 days on average. The frequency of complications also increased significantly, from 11.8 to 21% ($P < .001$), although there was no increase in the frequency of sequelae.

When it came to the diagnostic tests that had to be performed according to the consensus document, we found that a plain radiograph was performed in 87.8% of cases (SA, 77.2%; OM, 91.6%; $P = .01$), blood culture in 91.6% (SA, 92.3%; OM, 88.5%; $P = .82$) and joint fluid culture in 100% of cases of SA in which a sample was obtained. In the group of patients with OM, an MRI scan was performed in 93 cases (71%), compared to a percentage of 58.8% for performance of a bone scan. Table 3 presents the changes in the approach to diagnosis and treatment after the publication of the Spanish consensus guidelines.

In opposition to the recommendations, 9.9% of patients were not admitted to hospital, reflecting a significant increase in the outpatient management of OAIs after the publication of the consensus document.

The selection of intravenous (IV) empiric therapy adhered to the recommendations in 65.1% of cases (SA, 72.9%; OM, 57.3%; $P = .03$), with a lower percentage of adherence when it came to oral therapy, whether empiric or targeted (total, 62.3%; SA, 60.8%; OM, 64.3%). In both periods, the most frequently used IV antibiotherapy regimen was cloxacillin + cefotaxime. In the prospective cohort, the second most frequently used agent was cefuroxime in patients aged up to 5 years and cloxacillin in patients aged more than 5 years (used in 17.5% of patients in each of those age groups).

As for oral therapy, in the prospective cohort cefadroxil was the antibiotic used the most (31%), followed by cefuroxime (28.2%). Amoxicillin-clavulanic acid, on the other hand, went from being the most frequently used oral antibiotic in the retrospective cohort (32%) to being the third most-used in the prospective cohort (25%), in adherence with the recommendations.

Surgery was performed in 36.8% of cases of SA (arthrotomy in 85.7%), a significant decrease relative to the retrospective cohort ($P = .014$).

When we analysed the degree of adherence to the consensus recommendations, according to which the appropriate total duration of treatment is 14–21 days for SA and 21–28 days for uncomplicated OM, we found that treatment duration had only adhered to recommendations in 58.5% of cases (SA, 58.3%; OM, 60.4%; $P = .73$). However, we found that the duration of IV therapy had decreased, and therefore the length of stay, compared to the retrospective cohort (Table 3).

Table 3 Comparison of diagnosis, treatment and outcomes of osteoarticular infections in the retrospective and prospective cohorts.

	Retrospective cohort $n = 641$ (SA, 232; OM, 299)	Prospective cohort $n = 255$ (SA, 79; OM, 131)	*P*
Diagnostic tests performed			
ESR at admission (%)	64.2%	68.7%	.38
CRP at admission (%)	98.1%	100	.028
Blood culture (%)	81.7%	91.6%	.001
Arthrocentesis for SA (%)	95.7%	84.8%	<.001
Joint fluid culture in cases of SA in which sample was collected (%)	95.5%	100	.364
PCR for bacterial detection in joint fluid in SA (%)	14.9%	42.3%	<.001
Plain radiograph (% of total cases of OAI)	74.8%	88.2%	<.001
Ultrasound scan in SA	69.8%	87.3%	<.001
MRI in OM (%)	58.2%	71.5%	<.001
Scintigraphy in OM (%)	53.8%	40.2%	<.001
Time elapsed from onset to visit (days)	6.7	9.1	.009
Bacterial isolation			
MSSA *(%)*	27%	24%	.35
K. kingae (%)	6.3%	11.1%	.02
CA-MRSA *(%)*	0.4%	3.7%	.001
Overall isolation (%)	38.8%	44	.13
Treatment			
Admission to hospital (%)	94.7%	90.4%	.02
Overall IV therapy, mean (days)	12.8 ± 7.5	10.4 ± 7.0	<.001
IV therapy in OM, mean (days)	13 ± 8	10 ± 6	<.001
IV therapy in SA, mean (days)	12.1 ± 7.1	9.12 ± 4.9	<.001
IV ABX	<.001		
Cloxacillin (%)	20.4%	17.5%	
Cefuroxime (%)	7.4%	17.5%	
Cloxacillin + cefotaxime (%)	44.6%	36.7%	
Cefazoline (%)	8.1%	11.8%	
Length of stay, mean (days)	13.5 ± 7.7	11.25 ± 7.4	<.001
Oral therapy, mean (days)	23.5 ± 24.5	22.19 ± 11.8	.42
Oral therapy for SA, mean (days)	29 ± 16	25 ± 8	.061
Oral ABX	0.035		
Cloxacillin (%)	9.2%	2.9%	
Cefuroxime (%)	24.1%	28.2%	
Amoxicillin-clavulanic acid (%)	32%	26.1%	
Cefadroxil	29%	31%	
Overall therapy, media (días)	34.9 ± 25.6	31.7 ± 16.1	.075
Surgery for SA (%)	53%	36.8%	.014
Complications and sequelae			
Complications (% of total OAIs)	11.8%	21.2%	<.001
Abscesses (% of complications)	25	38.2%	.02
Pyomyositis (% of complications)	35	41.8%	.07
Sequelae	4.2%	5.5%	.41

ABX, antibiotherapy; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; MRI, magnetic resonance imaging; CA-MRSA, community-associated methicillin-resistant *S. aureus*; MSSA, methicillin-susceptible *S. aureus*; PCR, polymerase chain reaction; OAI, osteoarticular infection; OM, osteomyelitis; SA, septic arthritis.

Discussion

Correct management of OAIs is crucial to prevent the development of complications and sequelae, and these diseases, while not infrequent, require a high level of suspicion for early diagnosis and treatment in order to guarantee a favourable outcome. The development of guidelines and consensus documents based on the best available evi-

dence is considered a useful strategy for improving clinical practice by reducing the unwarranted variability in their management between clinicians.[16] The establishment of the nationwide RIOPed network allowed us to assess the actual impact of the national consensus document on OAIs in clinical practice.[6,7] It would be reasonable to state that the adherence to the consensus recommendations is adequate and that the diagnostic approach has improved significantly, and we also found a trend toward improvement in the adherence to recommendations regarding treatment compared to the preceding period.

The retrospective and prospective cohorts were similar in terms of the distribution of OAI diagnoses. The clinical variables were also similar, with a few exceptions that we address below.

In terms of diagnostic tests, we found that compared to the retrospective study there was an increase in the performance of blood culture and of joint fluid culture for investigation of SA, with the proportion of the latter reaching 100% of patients that underwent arthrocentesis with collection of a fluid sample, which is the gold standard for isolation of the causative agent. In addition, the use of PCR for detection of bacteria in joint fluid samples has grown, with a relative frequency that exceeded 40% in the prospective study, which achieved isolation of the pathogen in a greater proportion of patients, mainly on account of *K. kingae*, which is difficult to culture.[10–12] All of this resulted in a higher proportion of cases with microbiological confirmation, which contributes significantly to delivering the most appropriate treatment for these infections. We ought to underscore the increase in the frequency of infections by MRSA, which could have been associated with an increase in the incidence of complications, as we observed an increased incidence of abscesses and pyomyositis. This is a relevant finding that ought to be re-evaluated in studies performed in upcoming years, as a change in the recommendations for empiric treatment may be necessary if the incidence of these infections continues to increase in Spain, and it also highlights the importance of making a correct microbiological diagnosis. An unexpected finding was the increased delay in seeking care after onset in patients in the prospective cohort (2 days longer compared to the previous period), which may have had an impact on the incidence of complications. We do not know the reasons for this change, although the lower frequency of fever in the prospective cohort may have contributed to it; however, it is also possible that fever was not documented reliably in the retrospective cohort. Either way, we think that it is important to improve the knowledge on OAIs and heighten the level of suspicion of these diseases in clinicians to prevent delays in diagnosis. As concerns imaging tests, and as recommended in the consensus document, there has been an increase in the performance of ultrasound examinations for diagnosis of SA and of MRI scans for diagnosis of OM, with a decrease in the use of scintigraphy, in what could be considered a very good adherence to recommendations. Paradoxically, there was a decrease in the performance of arthrocentesis for investigation of SA compared to the previous period if we take into account that we did not include cases in which arthrocentesis was not performed in this particular analysis. In any case, this trend should be evaluated in the future, and emphasis should be placed on the importance of draining the joint and obtaining fluid samples for analysis and culture in cases of SA, as this is the gold standard for the aetiological diagnosis of monoarthritis (with or without fever).

The current recommendations on the management of OAI contemplate 2 phases of treatment: an initial phase of short courses of IV therapy (3–5 days) in uncomplicated cases, followed by early initiation of a second phase of oral therapy. The evidence shows that in general, short antibiotherapy regimens are effective and safe for treatment of OAIs.[3,5,7,8] The selection of empiric therapy is based on the known epidemiology of causative agents, with a predominance of *S. aureus* in every age group and *K. kingae* in infants and young children.[13,16] We considered that the adjustments made in the prescription of antibiotherapy were adequate in the second period under study, with an increased use of cefuroxime (both oral and IV) and oral cefadroxil, as recommended in the consensus document. When it came to the admission of patients for delivery of IV therapy, we found that 10% of patients were not admitted to hospital and only received oral therapy. All of these patients were managed in the same hospital (Hospital La Paz), which applies an in-house protocol that includes serial arthrocentesis and oral antibiotherapy in uncomplicated cases with close outpatient monitoring, and has published data showing good outcomes.[17,18] This strategy should be evaluated in the future and is particularly interesting for the management of infections by *K. kingae*, which are usually less severe,[13] and for health care facilities with staff specifically trained and with the necessary resources to closely follow-up patients.

The duration of treatment is one of the aspects that has changed most in recent years based on well-documented clinical trials,[3,19–21] although there has been resistance to generalised shortening of antibiotherapy courses by paediatricians as a whole. It is clear that unnecessarily lengthy hospital stays and courses of IV treatment may facilitate development of complications and nosocomial infections, and therefore their duration must be reduced to the minimum possible. In this sense, the decrease observed in the duration of IV antibiotherapy and the length of stay by a mean of 3 days was a very positive outcome, although there is still considerable room for improvement, given that the mean duration remains at 10 days, and especially considering that early switch to oral therapy has been proven safe and efficacious.[20] The duration of oral therapy and the total duration of antibiotherapy did not change compared to the retrospective cohort (although there was a 3-day decrease in the latter that neared statistical significance), so these outcomes should be emphasised as opportunities for improvement. Needlessly prolonged antibiotherapy is also associated with an increase in the incidence of adverse events: decreased tolerability, risk of superinfection by pathogens such as *Clostridium difficile*[22] and selection of drug-resistant bacteria. The latter is currently one of the greatest problems in public health, with an alarmingly large number of difficult to treat bacterial infections associated with a high mortality.[23–25]

There are limitations to our study. First, the follow-up period was of only 1 year, which may be insufficient to assess the impact of the consensus recommendations. The aim of

the network is to collect data for every patient admitted to each participating hospital, but we have no way of knowing whether reporting to the register was exhaustive, so there is potential for bias in this regard. Nevertheless, the prospective collection of data and the uninterrupted collection to date are strengths that will continue to contribute information on OAIs and improve the reliability of the data as the sample size increases, and we intend to perform a new analysis at the 5-year timepoint.

In brief, we may conclude that the degree of adherence to the recommendations established in the national guideline is optimal when it comes to the use of diagnostic tests and acceptable when it comes to the selection of antibiotherapy regimen (with a high percentage of non-adherence remaining), so emphasis must be placed in the latter aspect to achieve implementation of more appropriate antibiotherapy regimens. Although the duration of treatment is still prolonged, a decrease in both the duration of IV therapy and the length of stay has been observed after the publication of the consensus document. However, there is a considerable reduction still needs to occur in the total duration of treatment. We consider that it is important that we continue evaluating and disseminating the findings of the prospective register managed by the RIOPed to improve our knowledge and optimise the management of these infections based on the best evidence as reflected in clinical guidelines. This network is also essential to be able to monitor epidemiological trends in these infections, including the prevalence of causative agents, with particular emphasis on surveillance of infections by CA-MRSA.

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Appendix A. Members of the RIOPed network

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