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Clinical science

Towards the definition of disease phenotypes in paediatric SAPHO syndrome: a national multicentric study

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Abstract

Objectives: The objective of this study was to confirm the presence of different disease phenotypes of paediatric SAPHO syndrome (pSAPHO) based on their skin manifestations in a large cohort of Italian patients.

Methods: Patients with pSAPHO were enrolled in the Eurofever Registry and the data retrospectively analysed. The patients were categorized according to their skin manifestations into an acne – hidradenitis suppurativa (Acne-HS) group and a palmoplantar pustulosis – psoriasis vulgaris (PPP-PV) group and were compared with patients without skin manifestations (chronic non-bacterial osteomyelitis, CNO). Comparisons of frequencies between groups were performed using the χ^2 test or the Fischer's exact test.

Results: A total of 54 pSAPHO patients with skin manifestations (35 Acne-HS, 19 PPP-PV) were enrolled and compared with 167 patients with chronic recurrent multifocal osteomyelitis (CRMO). In the Acne-HS group, 82.9% were males, in the PPP-PV, 84.2% were females, while in the chronic non-bacterial osteomyelitis (CNO) group, no gender differences were observed ($P < 0.0001$). The three groups differed significantly with respect to age at disease onset: Acne-HS median 13.3 years, PPP-PV median 10.2 years, CNO median 9.5 years ($P = 0.0001$). An axial pattern was more frequent in the Acne-HS (91.4%) group and the PPP-PV group (89.4%) compared with in the CNO group (46%) ($P < 0.0001$). Both the Acne-HS (82.9%) and the PPP-PV (63.2%) groups required a biologic therapy more frequently than the CNO group (36.8%), but patients with Acne-HS presented with a refractory skin disease requiring steroids and other lines of treatment, while PPP-PV responded well to biologics.

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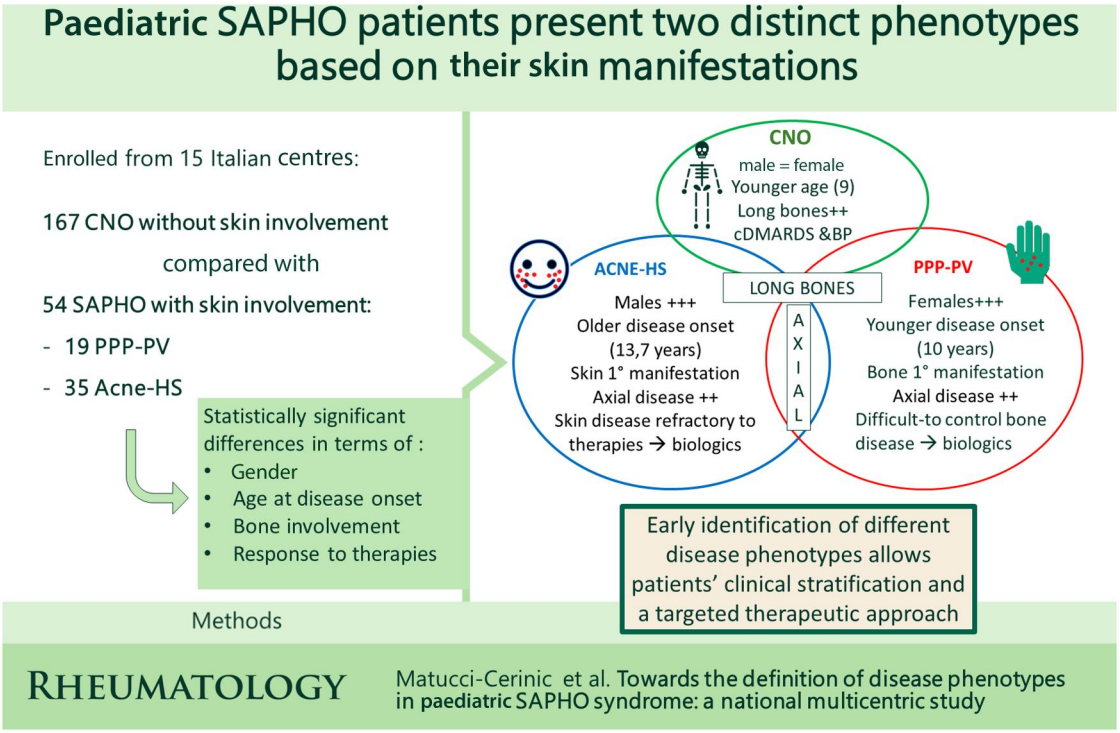
Conclusion: Our data have identified two different phenotypes of pSAPHO based on skin manifestations, with different age of onset, gender, and response to treatments. These two groups have peculiar clinical features that differ from those of the CNO group. A new classification encompassing these phenotypes is warranted.

Graphical abstract



Keywords: SAPHO, chronic recurrent multifocal osteomyelitis, CRMO, CNO, acne, hidradenitis suppurativa, pyoderma gangrenosum, palmo-plantar pustulosis, psoriasis.

Rheumatology key messages

- Two different skin phenotypes of SAPHO have been confirmed in a cohort of Italian patients.
- Acne-HS and PPP-PV define two phenotypes differing in age of onset, gender prevalences, and response to treatment.
- Early identification of the different disease phenotypes allows the clinical stratification of patients and a targeted therapeutic approach.

Introduction

SAPHO syndrome is a rare, chronic inflammatory disorder characterized by osteoarticular and skin involvement. The cutaneous manifestations are very heterogeneous, ranging from the more frequently reported palmoplantar pustulosis (PPP), psoriasis vulgaris (PV) and acne, to the rarer hidradenitis suppurativa (HS), pyoderma gangrenosum (PG) and Sweet syndrome [1]. Skin lesions may precede, follow, or occur simultaneously with the onset of the osteoarticular manifestations [2].

The hallmark of the osteoarticular involvement is a sterile bone osteitis, which in adults involves the anterior chest-wall (resulting in the scintigraphic 'bull's head sign') and the axial skeleton. In one-third of patients, peripheral arthritis and enthesitis can occur, and isolated sterile hyperostosis and osteitis have also been reported [3]. In children, the osteoarticular involvement takes the aspect of chronic recurrent multifocal osteomyelitis (CRMO), also known as chronic non-bacterial osteomyelitis (CNO). It typically involves the meta-epiphysis of the long bones, together with the axial skeleton and in some cases the anterior chest wall, especially the clavicle [4].

SAPHO syndrome is considered a rare disease, with a prevalence of 1:10 000 in adults. Disease onset is commonly between the third and fifth decades [5], with a predilection for women when the disease onset is before 30 years of age [2]. In children, CNO has a reported prevalence of 0.4–1 per 100 000 [6, 7] and a peak age of onset between 9 and 11 years, with a slight predilection for females [8].

The pathogenesis of SAPHO and CNO still remains unknown. *Cutibacterium acnes* has been proposed as a contributor to skin and bone inflammation, suggesting its role in the activation of the NLRP3 inflammasome by suppressing FoxO1 [9]. This finding, alongside the elevation of pro-inflammatory

cytokines such as IL-8, IL-18, TNFα, and IL-17 [10, 11], and the similarity to monogenic autoinflammatory diseases characterized by IL-1 elevation and marked skin and bone involvement [Majeed syndrome [12, 13], deficiency of IL-1 receptor antagonist (DIRA) [14], or pyogenic arthritis, pyoderma gangrenosum, and acne (PAPA) syndrome [15]], have supported the classification of SAPHO and CNO within the spectrum of autoinflammatory diseases. Up till now, no genetic mutations have been identified for CNO/SAPHO, and while studies on PSTPIP2-mutated mice, which exhibit skin and bone abnormalities, showed initial promise [16, 17], these findings have not been corroborated in humans [18].

Despite the great clinical heterogeneity and pathogenic background of the skin manifestations, both acne, PPP and PV were incorporated into the entity 'SAPHO syndrome' in 1987, when it was first described by Chamot *et al.*, due to their common osteoarticular presentation [19]. Since its first description, several diagnostic criteria have been proposed, and the diagnosis of SAPHO is now based on the more recent criteria proposed by Kahn *et al.* in 2003 [20]. These criteria allow a diagnosis in the presence of an osteoarticular involvement associated with either acne or PPP and PV, or an isolated sterile hyperostosis/osteitis in adults or CNO in children, or an osteoarticular involvement associated with IBD. For children, CNO diagnostic criteria were proposed by Jansson *et al.* in 2007 [21] and, more recently, in 2016 by the Bristol group [22]. It is still debated whether SAPHO syndrome and CNO represent two different entities, or just two different aspects of the same disease, according to the different age at onset [23], seen that the Kahn's criteria consider the presence of CNO in children sufficient for the diagnosis of SAPHO [20], and given that CNO can be associated with the same skin manifestations reported in SAPHO [24, 25].

In our previous work on paediatric SAPHO, we highlighted two different SAPHO phenotypes according to their skin manifestations. One group, characterized by the presence of acne and HS, associated with male gender and disease onset at pubertal age, in whom skin manifestations were the first symptom and the main treatment issue. The other group characterized by female patients, with disease onset at a younger age with osteoarticular manifestations, and subsequent appearance of PPP and PV [26].

The aim of the present study was to confirm the existence of these two different disease phenotypes of SAPHO syndrome, in a large cohort of paediatric Italian patients, comparing them with patients with CNO without skin manifestations.

Methods

This is a retrospective–prospective multicentric observational study involving 13 Italian Centres of the Italian Pediatric Rheumatology Society (ReumaPed). The patients were recruited retrospectively and prospectively from December 2022 to December 2023.

The patients included in the study fulfilled Kahn's diagnostic criteria for SAPHO syndrome [20] and Jansson's criteria for CNO [21]. Only patients with disease onset before 18 years of age were considered. All patients were enrolled in the Eurofever Registry, for which the main characteristics have been previously described [27, 28]. The study was approved by the Ethical Review Board of Regione Liguria. All patients gave their written consent for inclusion in the registry and for publication.

The demographic, clinical, radiological and therapeutic characteristics of the enrolled SAPHO patients were retrospectively analysed. As described in our previous study [26], SAPHO patients with skin involvement were categorized into two groups according to their pattern of skin involvement: an Acne-HS group, and a PPP-PV group. A control cohort composed of SAPHO patients without skin involvement (therefore pure CNO patients), was provided by each centre (with a proportion of at least three CNO patients to every SAPHO patient). For the sake of clarity, in this work, we will use the term SAPHO in relation to those patients with skin involvement, and CNO in relation to those patients without skin involvement.

The skin manifestations were evaluated at the time of the visit by an experienced local dermatologist, or retrospectively by an experienced dermatologist of the Istituto Giannina Gaslini (GV), through the available photographic documentation.

Whenever available, data about genetic studies were collected.

Images of whole-body MRI at disease onset and during follow-up were evaluated by an expert local radiologist.

Responses to the various treatments, obtained during the patients' follow-up visits, were also assessed. As in previous studies [29, 30], response to treatment was classified as (i) complete: clinical remission in therapy and normalization of acute phase reactants; for bone response, a resolution of the bone marrow oedema compared with the previous MRI exam, (ii) partial: amelioration of the clinical and laboratory parameters or need of additional treatments to achieve a complete remission; for bone response, a reduction in the signal intensity and extension of the bone marrow oedema compared with the previous MRI exam, (iii) absent: lack of response and no changes or worsening of the signal intensity or extension of the bone marrow oedema compared with the previous MRI exam.

Statistical analysis

Descriptive statistics were performed, and categorical variables were reported in terms of absolute frequencies and percentages; quantitative variables were reported in terms of median values and first and third quartiles (1st–3rd q), as the data distribution was skewed. The analysis of the normality of the distribution was performed by means of the Shapiro–Wilk test. Comparison of frequencies was undertaken using the χ^2 test or the Fisher's exact test (in the case of expected frequencies of <5). Comparison of quantitative variables in three different categories of patients was undertaken using the non-parametric Analysis of Variance (Kruskal–Wallis test). Post-hoc comparisons were performed and the Bonferroni's correction was applied; whenever the Bonferroni's correction was present, the statistical significance was indicated as P_B. Comparison of quantitative variables in more than two (three or four) different categories of patients was made by the non-parametric Analysis of Variance (Kruskal–Wallis W test). All the statistical tests were two-sided, and a P-value of <0.05 was considered statistically significant. The software 'Stata' (release 17.0, College Station, TX, USA) was used for all the univariate and bivariate analyses.

Results

A total of 54 patients with SAPHO with different skin manifestations (35 Acne-HS and 19 PPP-PV) were enrolled and compared with 167 CNO patients.

Table 1. Description of the study patients

	Acne-HS [*N* = 35] *n* (%)	PPP-PV [*N* = 19] *n* (%)	CNO [*N* = 167] *n* (%)	*P*
Male	29 (82.9%)	3 (15.8%)	69 (41.3%)	<0.0001[a]
Female	6 (17.1%)	16 (84.2%)	98 (58.7%)	
	Median (1st–3rd quartile)	**Median (1st–3rd quartile)**	**Median (1st–3rd quartile)**	
Age at onset (years)	13.3 (12.0–14.9)	10.2 (9.0–12.0)	9.5 [*n* = 166] (7.0–11.4)	0.0001[b]

% Percentages in parentheses represent column percentages.
[a] χ^2 test;
[b] Kruskal–Wallis test. Post-hoc analysis for the sex variable: Acne-HS *vs* PPP: $P_B = 0.0001$; Acne-HS *vs* CNO: $P_B = 0.0001$; PPP *vs* CNO: $P_B = 0.09$.
Acne-HS: acne – hidradenitis suppurativa; CNO: chronic non-bacterial osteomyelitis; PPP-PV: palmo plantar pustolosis – psoriasis vulgaris.

Table 2. Symptoms at onset in the two SAPHO groups

	Acne-HS [*N* = 35] *n* (%)	PPP-PV [*N* = 19] *n* (%)	*P*
Symptoms at onset:			
Skin involvement as first symptom	30 (85.7%)	3 (15.8%)	<0.0001[a]
Bone involvement as first symptom	2 (5.7%)	15 (78.9%)	
Both skin and bone involvement as first symptoms	3 (5.6%)	1 (5.3%)	
	Median (1st–3rd quartile)	**Median (1st–3rd quartile)**	
Age of onset of skin involvement (years)	13.3 (12.0–14.9)	11.0 (9.0–12.2)	0.0008[b]
Age of onset of bone involvement (years)	14.6 (13.5–15.5)	10.3 (9.0–12.0)	<0.0001[b]

[a] χ^2 test;
[b] Mann–Whitney *U* test. Acne-HS: acne – hidradenitis suppurativa; PPP-PV: palmo plantar pustolosis – psoriasis vulgaris.

Demographic features

The overall median age of the entire study group at disease onset was 10.1 years (interquartile range 7.9–17.7). The male:female ratio was 0.8. All patients were Caucasian.

Acne-HS group

In the Acne-HS group, 82.9% of patients ($n = 29/35$) were male. The disease onset was characterized by the appearance of skin manifestations in 85.7% of patients (median age of onset of Acne-HS = 13.3, 1st–3rd q = 12.0–14.9 years), followed by the onset of the osteoarticular manifestations in the following year (median age of onset of the osteoarticular manifestations = 14.6 years, 1st–3rd q = 13.5–15.5 years) (Table 1). The bone manifestations preceded the appearance of skin disease in 2 patients only, while in 3 patients the onset was simultaneous (Table 2). One patient presented an associated IBD (ulcerative colitis), 1 patient Hashimoto thyroiditis, and the 2 patients with HS had a BMI of >25. Ten patients underwent a genetic analysis with a next-generation sequencing (NGS) panel for autoinflammatory diseases: no causative mutations were detected.

PPP-PV group

In the PPP-PV group, 84.2% of patients ($n = 16/19$) were female, with a disease onset characterized by osteoarticular manifestations in 78.9% of patients (median age of onset of osteoarticular manifestations = 10.3 years, 1st–3rd q = 9.0–12 years), followed by the appearance of PPP-PV in the following months (median age of onset of PPP-PV = 11 years, 1st–3rd q = 9–12.2 years). The skin manifestations preceded the appearance of bone disease in only 3 patients, and were simultaneous in 1 patient (Tables 1 and 2). One patient presented with Hashimoto thyroiditis, but no IBD were reported. Five patients underwent a genetic analysis with an NGS panel for autoinflammatory diseases: no causative mutations were detected.

CNO group

In the CNO group, 58.7% of patients were female, and the median age at disease onset was 9.5 years (1st–3rd q = 7.0–11.4 years). One patient presented with a concomitant celiac disease. Four patients underwent genetic analysis with an NGS panel for autoinflammatory diseases: no causative mutations were detected.

When comparing the three groups, the non-parametric analysis of variance (Kruskal–Wallis test) demonstrated a significant difference in terms of age at disease onset ($P = 0.0001$) (Table 1). The post-hoc analysis demonstrated that the Acne-HS group had a disease onset at an older age, when compared with both the PPP-PV ($P_B = 0.0001$) and CNO groups ($P_B < 0.0001$). However, a similar age at disease onset was found between PPP-PV and CNO ($P_B = 0.08$) (Supplementary Fig. S1, available at *Rheumatology* online).

A statistically significant difference was found also in terms of sex distribution between the three groups ($P < 0.0001$) (Table 1): the post-hoc analysis showed a male predominance in the Acne-HS group when compared with both the PPP-PV and the CNO groups ($P_B = 0.0001$). On the contrary, no significant sex distribution was found between the PPP-PV and CNO groups ($P_B = 0.09$).

Skin manifestations

In the Acne-HS group, 94.2% ($n = 33$) of the patients presented with acneiform eruptions (pustular, nodular, cystic,

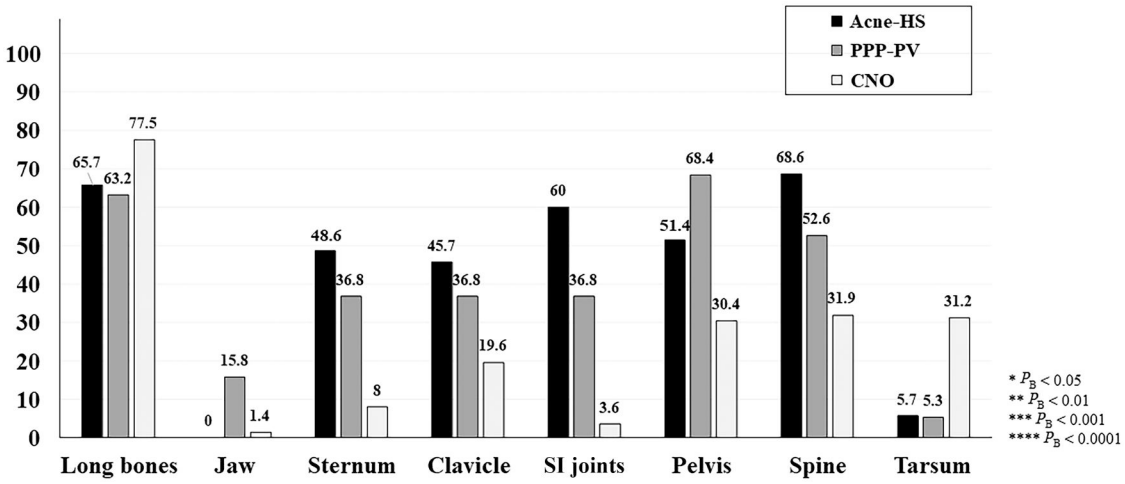


Figure 1. Bone involvement in the three groups of patients: Acne-HS: acne – hidradenitis suppurativa; PPP-PV: palmo plantar pustolosis – psoriasis vulgaris; CNO chronic non-bacterial osteomyelytis. [a] P_B: χ^2 test or Fisher's exact test (as appropriate) with Bonferroni's correction (three comparisons)

comedonic and ulcerative lesions), which in 3 cases were associated with HS, in 2 with HS and PG, while 2 patients presented isolated HS. In the PPP-PV group, 78.9% of the patients ($n = 15$) presented with PPP, associated with PV in 8 patients, while 4 presented with an isolated PV.

Osteoarticular manifestations

In Fig. 1, the frequency of the bone lesions in the three groups is reported, while in Supplementary Tables S1 and S2, available at *Rheumatology* online, the details of the statistical comparison between the groups, and the relative post-hoc analysis are reported.

All patients underwent a total body MRI at disease onset and follow-up, from which the bone response was evaluated. Six CNO patients and 1 patient with Acne-HS presented with a unifocal clavicle involvement, while all the other patients presented with a multifocal disease. Involvement of the metaepiphysis of the long bones was observed in the majority of patients in the three groups. Both Acne-HS and PPP-PV presented a more frequent axial involvement when compared with presentations in the CNO group (91.4%, 89.4% and 46%, respectively, $P < 0.0001$): sternum (48.6%), clavicle (45.7%), SI joints (60%) and spine (68.6%) were more frequently involved in the Acne-HS group, and the pelvis in the PPP-PV group (68.4%) (Fig. 1, Supplementary Table S1, available at *Rheumatology* online). Specifically, the post-hoc analysis comparing the three groups (Supplementary Table S2, available at *Rheumatology* online) showed a statistically significant sternal involvement in Acne-HS (48.6%) and PPP-PV (36.8%) compared with CNO (8%) (Acne-HS *vs* CNO, $P_B < 0.0001$; PPP-PV *vs* CNO, $P_B < 0.01$) (Fig. 1), and a statistically significant SI joint involvement in Acne-HS (60%) and PPP-PV (36.8%) compared with CNO (3.6%) (Acne-HS *vs* CNO and PPP-PV *vs* CNO, $P_B < 0.0001$). Also, a difference between Acne-HS and CNO was found for clavicle involvement (45.7 and 19.6%, respectively, $P_B < 0.01$) and spinal involvement (68.6% and 31.9%, respectively, $P_B < 0.0001$); a difference between PPP-PV and CNO was found for pelvic involvement (68.5% and 30.4%, respectively, $P_B < 0.01$). Of note, a more frequent mandible involvement was found in the PPP-PV group when compared with CNO (PPP-PV *vs* CNO $P_B = 0.038$).

Therapeutic approach

The various therapies are reported in Fig. 2 and Supplementary Tables S3–S6, available at *Rheumatology* online, and the responses to treatments are reported in detail in Supplementary Tables S7–S10, available at *Rheumatology* online. The response to the principal biologics are shown in Fig. 3.

Acne-HS group

In the Acne-HS group, NSAIDs were used in 51.4% of patients to initially control the osteoarticular manifestations, while 54.3% of patients were treated from the beginning with systemic steroids to control the skin disease. Among conventional DMARDs (cDMARDs), MTX and SSZ were initially used in 8.6% and 22.9% of patients, respectively, with a complete response in the bone manifestations in 33% and 25% of patients, respectively, but a poor response in skin manifestations (Supplementary Tables S7 and S9, available at *Rheumatology* online). Bisphosphonates were added in 34% ($n = 12$), because of spinal involvement, with a good response (66.7%). Skin manifestations were initially treated with antibiotics cycles (mainly tetracyclines), with a partial and short response, and with isotretinoin, which was efficacious in 8 of 19 treated patients (Supplementary Table S9, available at *Rheumatology* online). However, the skin manifestations proved to be steroid dependent and refractory to cDMARDs, requiring the addition of a biologic therapy in 82.9% of patients. Of note, dapsone was tried in 2 patients, with a complete cutaneous response in one, and a partial response in the other. All biologics proved able to control the osteoarticular manifestations. However, among these, adalimumab (ADA), alone or combined with MTX, and infliximab (IFX), resulted the more efficacious treatments also on the skin disease (complete response in 40%, 50% and 60%, respectively) (Fig. 3). One patient (out of 5) presented with a complete cutaneous response to anakinra. Secukinumab, ustekinumab, tofacitinib and apremilast were tried in a few patients with poor results. When considering all the biologics together, it is of note, however, that only 48.3% of these patients presented a complete response to the treatment, frequently needing the addition of steroids or a therapy cycling (Supplementary Table S10, available at *Rheumatology* online).

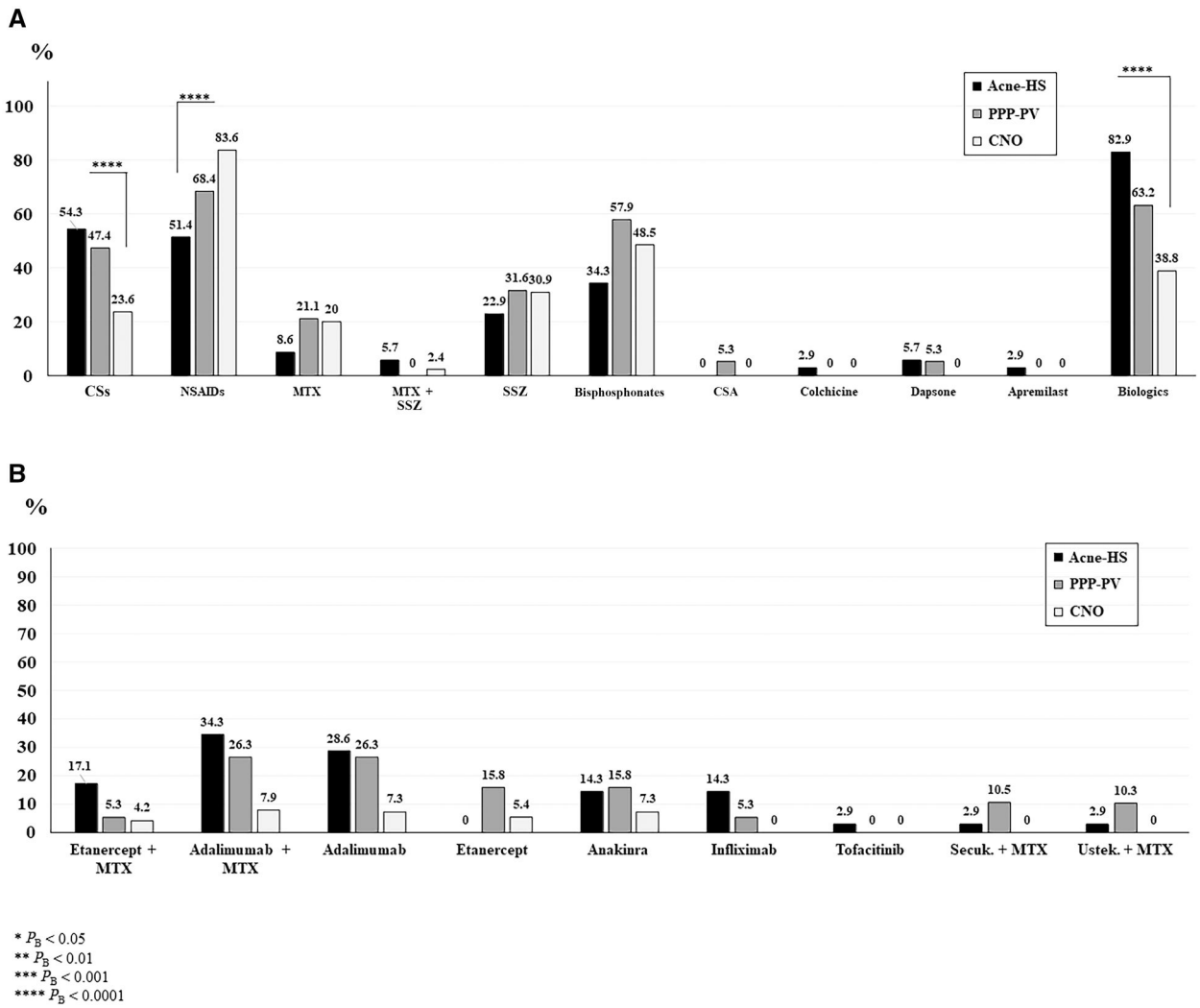


Figure 2. (A) Treatments in the three groups of patients and (B) biologic therapies in the three groups of patients: Acne-HS: acne – hidradenitis suppurativa; PPP-PV: palmo plantar pustolosis – psoriasis vulgaris; Secuk: secukinumab; Ustek: ustekinumab; CNO: chronic non-bacterial osteomyelytis

PPP-PV group

In the PPP-PV group, NSAIDs were used as a first-line treatment in 68.4% of patients, with a complete response in the bone manifestations in 30.8% of the patients. An initial steroid cycle was used in 47.4% when particularly inflamed. None of these patients developed a steroid dependence. MTX and SSZ were used in 21.1% and 31.6% of patients, respectively, with only partial efficacy in the osteoarticular manifestations treated with MTX, and a complete response in 33% of the patients treated with SSZ. Bisphosphonates were added in 57.9% of patients, with a complete response in 70%. However, biologics were needed in 63% of patients to completely control the disease. Among these, ADA and ADA + MTX were more efficacious in the bone manifestations (40% and 60% complete response, respectively) (Fig. 3). Skin involvement responded well to topical steroids in general and to cDMARDs; in the most difficult cases, a complete response was observed with the addition of biologic therapy (ADA 80% response, ADA + MTX 100% response, IFX 100% response) (Fig. 3).

CNO group

In the CNO group, NSAIDs represented the initial treatment in 83.6% of patients, and were able to control the disease in 33.3% of patients. The other patients were treated with MTX (20.0%) and SSZ (30.9%), with a complete response in 48.5% and 41.2% of patients, respectively. Also, bisphosphonates were used in 48.5% of patients, with disease remission being obtained in 73.1% of the treated patients (Supplementary Table S7, available at *Rheumatology* online). Of the patients who presented with a partial response to the above-mentioned therapies, 38.8% were treated with biologics. Among these, ADA, ADA + MTX, and etanercept + MTX were all efficacious in treating the bone manifestations (Supplementary Table S8, available at *Rheumatology* online).

When comparing the response to treatments with the various drugs between the three groups, no statistically significant difference was found in the bone manifestations between cDMARDs and biologics. Regarding the cutaneous manifestations, steroids were more frequently used in the Acne-HS group, but with better results in patients with PPP-PV, in

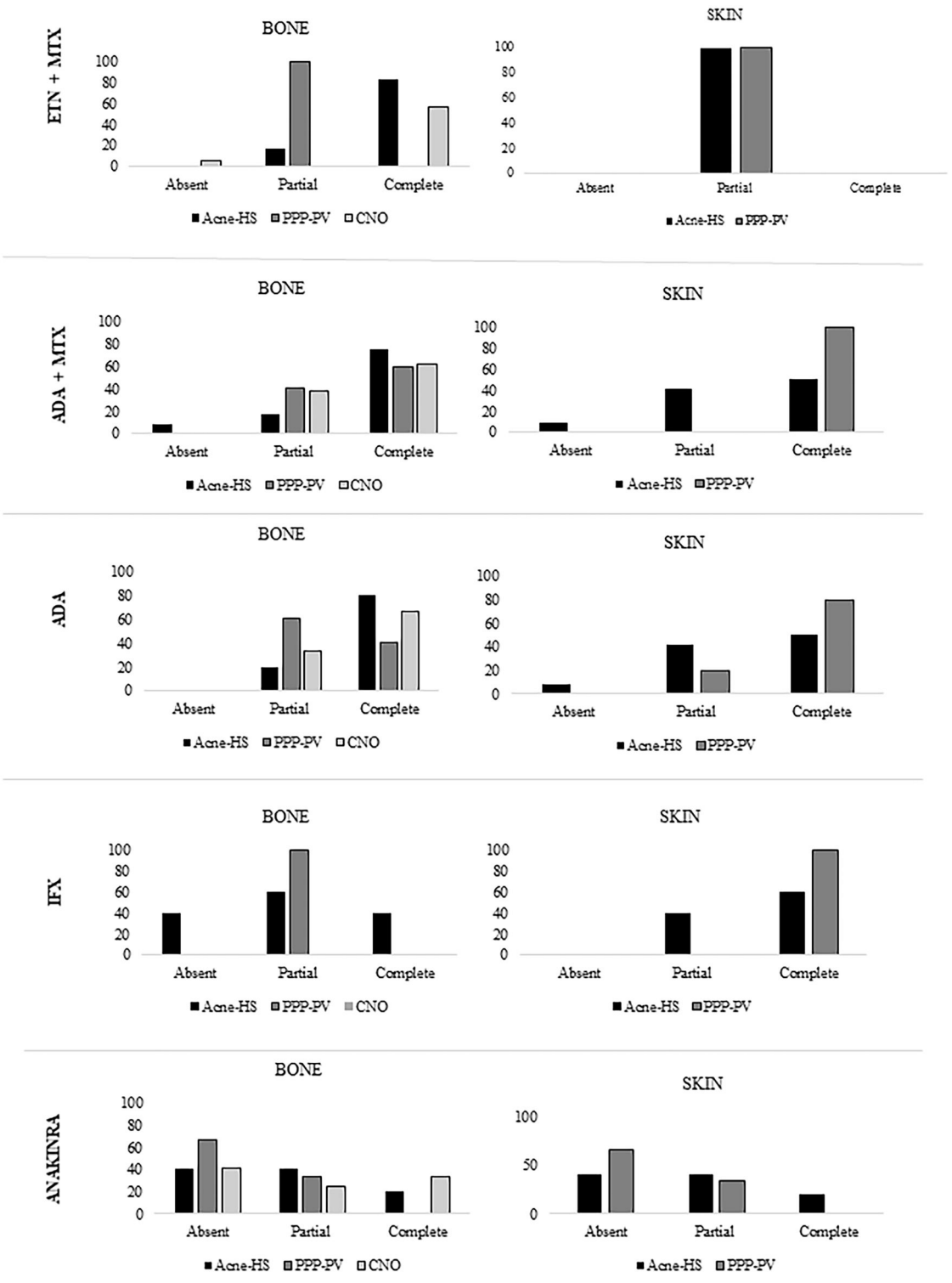


Figure 3. Bone and skin response to the principal biologic treatments in the three study groups. Acne-HS: acne – hidradenitis suppurativa; ADA: Adalimumab; CNO: chronic non-bacterial osteomyelytis; ETN: etanercept; IFX: infliximab; PPP-PV: palmo plantar pustolosis – psoriasis vulgaris

whom a complete response was seen in 77.7% of patients; in patients with Acne-HS, the response was mainly partial. Also, while no significant differences were found between patients with Acne-HS and those with PPP-PV in terms of cutaneous response to the single drugs, a significant difference was found between the two groups in terms of response to biologics: PPP-PV presented with a skin remission in 91.7% of patients, while only 48.3% of patients with Acne-HS ($P = 0.013$) responded to a biologic (Supplementary Table S10, available at *Rheumatology* online).

Discussion

In this paper, we describe a large cohort of paediatric SAPHO patients, comparing patients with and without skin manifestations (CNO). The analysis of the clinical features has confirmed

the presence of two different disease phenotypes among the SAPHO patients with skin manifestations. Patients with Acne-HS were typically male, with a disease onset in pubertal age characterized by refractory skin manifestations needing the addition of steroids and biologic therapies. Conversely, patients with PPP-PV were typically females, with an earlier onset characterized by osteoarticular manifestations. This latter group had a similar age of onset to the CNO cohort. Some distinctive features of the groups with skin manifestations emerged. In fact, long bones involvement was found in the majority of patients; however, more prevalent axial involvement was present in both Acne-HS and PPP-PV patients, when compared with CNO patients. In addition, patients with skin manifestations had a much greater need for biologics, when compared with CNO patients. In the Acne-HS group, skin involvement was particularly difficult to treat, with only a partial response to biologics; for this reason, frequent steroid cycles were required. On the other hand, all the PPP-PV patients who needed the addition of a biologic drug presented with complete osteoarticular and cutaneous remission.

These features highlight the heterogeneity of the clinical spectrum of SAPHO and also the difficulty in classifying patients with this syndrome. In fact, the two reported skin phenotypes showed evident differences in terms of clinical manifestations, sex predilection and age of onset, sharing the same osteoarticular manifestations as CNO, but with a prevalent axial involvement.

Therefore, our data indicate that CNO and the two SAPHO phenotypes are part of the same spectrum of disorders. In fact, all patients share a common clinical feature, osteitis, but the presence and the type of skin manifestations may create different subsets with significantly different disease progression and response to treatments.

The prevalent axial involvement and the common presence of osteitis, independent of skin manifestations, initially led Chamot and Benhamou to group these conditions together under the term SAPHO [19]. Moreover, the axial involvement has, since the beginning, highlighted a possible link between these conditions and the SpA group [31]. In fact, both diseases are characterized by arthritis, enthesitis, axial involvement, and association with psoriasis and IBD. Since then, whether to categorize SAPHO as belonging to the SpA-related diseases or as a single entity has remained unsolved. Interestingly, in a recent survey by the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA), SAPHO was classified as belonging to SpA by 48.7% of experts, as a subtype of PsA by 19.2%, as a separate entity by 25.6%, and as a type of reactive arthritis by 6.4% [32].

In our Acne-HS group, skin manifestations represented the first symptom, with the appearance of osteoarticular manifestations in the following year, thus recalling the behaviour of reactive arthritis. In the context of patients with severe acne or HS or PG with signs of systemic inflammation and complaints of bone pain, we suggest, therefore, to perform a whole-body MRI to rule out the development of SAPHO.

The presence of osteitis, axial involvement and skin manifestations is also shared by another group of recently described autoinflammatory multifactorial conditions, characterized by the presence of acne, PG, and HS, variably associated with musculoskeletal or gut involvement. These patients are grouped under the term 'PAPA spectrum disorders', recalling their similarity with the monogenic PAPA syndrome [33]. This group includes several dermatological syndromes, named according to their cutaneous and osteoarticular manifestations: PAPASH (Pyogenic Arthritis, PG, acne, HS), PsAPASH (PsA, PG, acne, HS), PASS (PG, acne, HS, AS) and PASH (PG, acne, HS) [33–35]. Thus, the Acne-HS SAPHO subgroup could be assimilated into this group of autoinflammatory conditions, in which, the appearance of the osteoarticular involvement after the cutaneous manifestations recalls effectively the behaviour of reactive arthritis.

In our work, patients with acne and HS were grouped together, because these two conditions are frequently seen in association as part of the follicular occlusion syndrome, sharing a common pathogenic mechanism related to the inflammatory involvement of the pilo-sebaceous unit [36].

Interestingly, patients with skin involvement showed a particular sex distribution, Acne-HS patients being male and PPP-PV mostly female, while in CNO no particular sex differences were found. These differences have been shown in previous research in children by Wu *et al.* and by our group, and in adults by Li *et al.* [26, 37, 38]. In the adult population, Li *et al.* highlighted in females a PPP predominance with prevalent sternal involvement, and in males an acne predominance with a major clavicular and lumbar involvement [37]. While the different sex distribution was confirmed in our study, no statistically significant differences in terms of osteoarticular involvement were found between the Acne-HS and PPP-PV groups, in whom the axial involvement was preponderant when compared with the CNO group.

The main limit of our study was the small sample of involved patients (35 Acne-HS and 19 PPP-PV), even if these diseases are rather rare in paediatric age. Also, the Acne-HS group was more numerous than the PPP-PV group. This differs from what is generally reported in the adult literature, in which PPP-PV is considered the more frequent presentation [2, 39], though a major incidence of Acne-HS was also reported by Wu *et al.* in their paediatric series [38]. This could be due to the fact that, while PV and PPP often respond well to the treatments, acne patients present a particularly severe and refractory clinical picture, being thus easier to recall, causing a selection retrospective bias.

Another limit, especially concerning the skin manifestations data, was due to the retrospective nature of the study: not all patients were initially evaluated by a dermatologist, and a grading with adequate tools was not always available.

In conclusion, we have described two different phenotypes of pSAPHO, based on their skin manifestations, with different gender prevalences, age of onset, and response to treatments, and identified the differences with paediatric CNO. However, further biological and serological analyses are warranted to confirm these differences. This could lead to a new classification of the SAPHO syndrome in childhood, suggesting that inflammatory osteitis is the common denominator of a broad spectrum of diseases, with a continuum ranging from pure CNO to the different skin disease phenotypes, with the Acne-HS group being more similar to patients with PAPA spectrum disorders than to the groups with PPP and PV.

Supplementary material

Supplementary material is available at *Rheumatology* online.

Data availability

The data that support the findings of this study are available in the supplementary material and from the corresponding author upon reasonable request.

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References

1. Rukavina I. SAPHO syndrome: a review. J Child Orthop 2015; 9:19–27.
2. Hayem G, Bouchaud-Chabot A, Benali K *et al.* SAPHO syndrome: a long-term follow-up study of 120 cases. Semin Arthritis Rheum 1999;29:159–71.
3. Nguyen MT, Borchers A, Selmi C *et al.* The SAPHO Syndrome. Semin Arthritis Rheum 2012;42:254–65.
4. Hoffmann T, Finger D. Chronic recurrent multifocal osteomyelitis. J Rheumatol 2007;34:2499–500.
5. Van Doornum S, Barraclough D, McColl G, Wicks I. SAPHO: rare or just not recognized? Semin Arthritis Rheum 2000;30:70–7.
6. Jansson AF, Grote V; ESPED Study Group. Nonbacterial osteitis in children: data of a German Incidence Surveillance Study. Acta Paediatr 2011;100:1150–7.
7. Walsh P, Manners PJ, Vercoe J, Burgner D, Murray KJ. Chronic recurrent multifocal osteomyelitis in children: nine years' experience at a statewide tertiary paediatric rheumatology referral centre. Rheumatology (Oxford) 2015;54:1688–91.
8. Singhal S, Landes C, Shukla R, McCann LJ, Hedrich CM. Classification and management strategies for paediatric chronic nonbacterial osteomyelitis and chronic recurrent multifocal osteomyelitis. Expert Rev Clin Immunol 2023;19:1101–16.
9. Berthelot JM, Corvec S, Hayem G. SAPHO, autophagy, IL-1, FoxO1, and Propionibacterium (Cutibacterium) acnes. Joint Bone Spine 2018;85:171–6.
10. Hurtado-Nedelec M, Chollet-Martin S, Nicaise-Roland P *et al.* Characterization of the immune response in the synovitis, acne, pustulosis, hyperostosis, osteitis (SAPHO) syndrome. Rheumatology (Oxford) 2008;47:1160–7.
11. Firinu D, Barca MP, Lorrai MM *et al.* TH17 cells are increased in the peripheral blood of patients with SAPHO syndrome. Autoimmunity 2014;47:389–94.
12. Ferguson PJ, Chen S, Tayeh MK *et al.* Homozygous mutations in LPIN2 are responsible for the syndrome of chronic recurrent multifocal osteomyelitis and congenital dyserythropoietic anaemia (Majeed syndrome). J Med Genet 2005;42:551–7.
13. Majeed HA, Kalaawi M, Mohanty D *et al.* Congenital dyserythropoietic anemia and chronic recurrent multifocal osteomyelitis in three related children and the association with Sweet syndrome in two siblings. J Pediatr 1989;115:730–4.
14. Aksentijevich I, Masters SL, Ferguson PJ *et al.* An autoinflammatory disease with deficiency of the interleukin-1-receptor antagonist. N Engl J Med 2009;360:2426–37.
15. Lindor NM, Arsenault TM, Solomon H, Seidman CE, McEvoy MT. A new autosomal dominant disorder of pyogenic sterile arthritis, pyoderma gangrenosum, and acne: PAPA syndrome. Mayo Clin Proc 1997;72:611–5.
16. Ferguson PJ, Bing X, Vasef MA *et al.* A missense mutation in pstpip2 is associated with the murine autoinflammatory disorder chronic multifocal osteomyelitis. Bone 2006;38:41–7.
17. Grosse J, Chitu V, Marquardt A *et al.* Mutation of mouse Mayp/Pstpip2 causes a macrophage autoinflammatory disease. Blood 2006;107:3350–8.
18. Hurtado-Nedelec M, Chollet-Martin S, Chapeton D *et al.* Genetic susceptibility factors in a cohort of 38 patients with SAPHO syndrome: a study of PSTPIP2, NOD2, and LPIN2 genes. J Rheumatol 2010;37:401–9.
19. Chamot AM, Benhamou CL, Kahn MF *et al.* [Acne-pustulosis-hyperostosis-osteitis syndrome. Results of a national survey. 85 cases]. Rev Rhum Mal Osteoartic 1987;54:187–96.
20. Kahn ME. Abstracts of the American College of Rheumatology 67th annual meeting and the Association of Rheumatology Health Professionals 38th annual meeting. October 23-28, 2003. Orlando, Florida, USA. Arthritis Rheum 2003;48:S35–750.
21. Jansson A, Renner ED, Ramser J *et al.* Classification of non-bacterial osteitis: retrospective study of clinical, immunological and genetic aspects in 89 patients. Rheumatology (Oxford) 2007; 46:154–60.
22. Roderick MR, Shah R, Rogers V, Finn A, Ramanan AV. Chronic recurrent multifocal osteomyelitis (CRMO) - advancing the diagnosis. Pediatr Rheumatol Online J 2016;14:47.
23. Sharma M, Ferguson PJ. Autoinflammatory bone disorders: update on immunologic abnormalities and clues about possible triggers. Curr Opin Rheumatol 2013;25:658–64.
24. Hofmann SR, Kapplusch F, Girschick HJ *et al.* Chronic Recurrent Multifocal Osteomyelitis (CRMO): presentation, pathogenesis, and treatment. Curr Osteoporos Rep 2017;15:542–54.
25. Girschick H, Finetti M, Orlando F *et al.*; Paediatric Rheumatology International Trials Organisation (PRINTO) and the Eurofever Registry. The multifaceted presentation of chronic recurrent multifocal osteomyelitis: a series of 486 cases from the Eurofever international registry. Rheumatology (Oxford) 2018;57:1203–11.
26. Matucci-Cerinic C, Malattia C, Pistorio A *et al.* Skin manifestations help identifying different phenotypes of paediatric SAPHO syndrome. Semin Arthritis Rheum 2023;63:152277.
27. Ter Haar N, Lachmann H, Özen S *et al.*; Paediatric Rheumatology International Trials Organisation (PRINTO) and the Eurofever/Eurotraps Projects. Treatment of autoinflammatory diseases: results from the Eurofever Registry and a literature review. Ann Rheum Dis 2013;72:678–85.
28. Toplak N, Frenkel J, Ozen S *et al.*; Paediatric Rheumatology International Trials Organisation (PRINTO), Eurotraps and Eurofever Projects. An international registry on autoinflammatory diseases: the Eurofever experience. Ann Rheum Dis 2012; 71:1177–82.
29. Gattorno M, Obici L, Cattalini M *et al.* Canakinumab treatment for patients with active recurrent or chronic TNF receptor-associated periodic syndrome (TRAPS): an open-label, phase II study. Ann Rheum Dis 2017;76:173–8.
30. Papa R, Rusmini M, Volpi S *et al.* Next generation sequencing panel in undifferentiated autoinflammatory diseases identifies patients with colchicine-responder recurrent fevers. Rheumatology (Oxford) 2020;59:344–60.
31. Kahn MF. Ankylosing-spondylitis with exuberant sclerosis or SAPHO syndrome—reply. J Rheumatol 1993;20:203.
32. Furer V, Kishimoto M, Tsuji S *et al.* The Diagnosis and Treatment of Adult Patients with SAPHO Syndrome: controversies Revealed in a Multidisciplinary International Survey of Physicians. Rheumatol Ther 2020;7:883–91.
33. Maitrepierre F, Marzano AV, Lipsker D. A unified concept of acne in the PAPA spectrum disorders. Dermatology 2021;237:827–34.

34. Garcovich S, Genovese G, Moltrasio C, Malvaso D, Marzano AV. PASH, PAPASH, PsAPASH, and PASS: the autoinflammatory syndromes of hidradenitis suppurativa. Clin Dermatol 2021;39:240–7.
35. Marzano AV, Borghi A, Meroni PL, Cugno M. Pyoderma gangrenosum and its syndromic forms: evidence for a link with autoinflammation. Br J Dermatol 2016;175:882–91.
36. Pink A, Anzengruber F, Navarini AA. Acne and hidradenitis suppurativa. Br J Dermatol 2018;178:619–31.
37. Li Y, Li C, Wu N *et al.* Demographic, clinical, and scintigraphic comparison of patients affected by palmoplantar pustulosis and severe acne: a retrospective study. Clin Rheumatol 2020; 39:1989–96.
38. Wu N, Shao Y, Huo J *et al.* Clinical characteristics of pediatric synovitis, acne, pustulosis, hyperostosis, and osteitis (SAPHO) syndrome: the first Chinese case series from a single center. Clin Rheumatol 2021;40:1487–95.
39. Colina M, Govoni M, Orzincolo C, Trotta F. Clinical and radiologic evolution of synovitis, acne, pustulosis, hyperostosis, and osteitis syndrome: a single center study of a cohort of 71 subjects. Arthritis Rheum 2009;61:813–21.

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