Editorial introduction

Current Opinion in Rheumatology was launched in 1989. It is one of a successful series of review journals whose unique format is designed to provide a systematic and critical assessment of the literature as presented in the many primary journals. The field of Rheumatology is divided into 15 sections that are reviewed once a year. Each section is assigned a Section Editor, a leading authority in the area, who identifies the most important topics at that time. Here we are pleased to introduce the Journal's Section Editor for this issue.

SECTION EDITOR

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Novel imaging techniques for sacroiliac joint assessment

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Purpose of review
Imaging of the sacroiliac joints is one of the cornerstones in the diagnosis and monitoring of axial spondyloarthritis. We aim to present an overview of the emerging imaging techniques for sacroiliac joint assessment and provide an insight into their relevant benefits and pitfalls.

Recent findings
Evaluation of structural and active inflammatory lesions in sacroiliitis are both important for understanding the disease process. Dual-energy computed tomography (CT) can detect inflammatory bone marrow edema in the sacroiliac joints and provides an alternative for magnetic resonance imaging (MRI). Three-dimensional gradient echo sequences improve the visualization of erosions on MRI. Susceptibility weighted MRI and deep learning-based synthetic CT are innovative MRI techniques that allow for generating 'CT-like' images and better depict osseous structural lesions than routine MRI sequences.

Summary
New imaging innovations and developments result in significant improvements in the imaging of spondyloarthritis. Advanced MRI techniques enhance its potential for the accurate detection of structural and active inflammatory lesions of sacroiliitis in one single imaging session.

Keywords
dual-energy computed tomography, magnetic resonance imaging, sacroiliac joints, spondyloarthritis

INTRODUCTION

Axial spondyloarthritis (SpA) is a chronic multisystem inflammatory disorder involving primarily the axial skeleton with sacroiliitis playing a key role in the classification of the disease. Imaging features of sacroiliitis can be classified into active inflammatory lesions, of which bone marrow edema (BME) is the hallmark of disease activity, and structural changes including erosions, sclerosis and joint space changes, which are crucial for monitoring disease progression [1]. For detection of BME fat–suppressed magnetic resonance imaging (MRI) sequences such as short tau inversion recovery (STIR) sequences have become the state or art imaging modality. Although features such as backfill, fat metaplasia, and ankylosis constitute some of the structural changes visible on conventional MRI sequences, mainly on T1-weighted images [2], MRI is limited for erosion detection because it cannot depict cortical bone directly. Structural MRI scores exist, but radiography still serves as the reference for grading structural lesions [3].

Although the use of conventional MRI has been of great diagnostic utility, the last few years have resulted in the emergence of enhanced technological modalities focusing on improved imaging and evaluation of SpA. These recent imaging advances and their relevant pitfalls are discussed in this review.

ADVANCEMENTS IN THE IMAGING OF BONE MARROW EDEMA

For many years, fluid sensitive MRI sequences are the cutting-edge technique for the detection of BME in sacroiliitis, which is an important component of the ASAS classification criteria [4]. A relatively new MRI technique for BME detection is diffusion-weighted imaging (DWI), of which the value is still subject to debate. In a proportion of patients, MRI is contraindicated. For these patients, dual-energy computed

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Curr Opin Rheumatol 2022, 34:187–194

DOI:10.1097/BOR.0000000000000871

KEY POINTS

- Imaging of the sacroiliac joint is a cornerstone in axial spondyloarthritis, with bone marrow edema and erosions as main imaging features of sacroiliitis.
- Dual-energy CT provides an alternative to MRI for detection of inflammatory bone marrow edema of the sacroiliac joints.
- Three-dimensional gradient echo MRI sequences enhance the detection of sacroiliac joint erosions on MRI.
- Susceptibility weighted imaging and deep-learning based synthetic CT are innovative MRI sequences that generate CT-like images and create a potential 'one-stop' imaging modality for spondyloarthritis.

tomography (DECT) provides an innovative alternative for BME detection of the sacroiliac (SI) joints.

Fluid sensitive magnetic resonance imaging sequences

Fluid sensitive MRI sequences with fat suppression can be obtained by either T2-weighted sequence with fat saturation (T2-FS), short tau inversion-recovery (STIR) imaging (Fig. 1a), chemical shift (Dixon) method or hybrid techniques, such as spectral attenuated inversion recovery (SPAIR). Greese *et al.* [5] suggested that T2-FS may have a better image quality as well as better detection of BME compared to STIR sequence. The T2-weighted multipoint dixon sequence based on chemical shift [6] and the T2 SPAIR sequence, which combines an inversion recovery pulse with an adiabatic radiofrequency pulse [7,8▪], have shorter scan time or better image quality than STIR/T2-FS. They provide alternatives for BME detection in patients with SpA. Recently, Huang *et al.* [9▪] found that the single T2 Dixon sequence is slightly superior to the standard protocol (T1SE and T2-FS) in patients with suspected SpA. Therefore they proposed it may replace the standard protocol and shorten the acquisition time.

For diagnosis of the active phase of sacroiliac arthritis Du *et al.* [10▪] proposed the MRI Dixon-VIBE sequence as a relatively accurate quantitative imaging technology. They found that the water-fat ratio in the study group was positively correlated with BASDAI score, BASFI score, and SPARCC score, suggesting that it can be used as a reference index to evaluate the clinical inflammatory activities. It is expected to become a simple, accurate and effective efficacy observation index which will guide clinical treatment and monitor disease activities. However, its reliability needs further validation.

DWI is a method of signal contrast generation based on assessing the random Brownian motion of water molecules through the measurement of the ADC value. Several studies have shown that DWI is an effective tool in the early diagnosis of SpA [11,12,13,14]. Furthermore, the ADC value may serve as a quantitative biomarker of disease activity, allowing monitoring and guiding treatment [11,15]. However, the post processing time and the variability of ADC value measurements among different readers and magnetic resonance units remain a challenge preventing widespread technique application [16]. In addition, single-shot echo-planar imaging (ss-EPI), the current standard clinical DWI technique [17], is vulnerable to geometric distortion, signal intensity drop-out and T2$*$-induced blurring. These restrictions are more pronounced around tissue interfaces, which are characteristic of the SI joints, given the complex anatomic

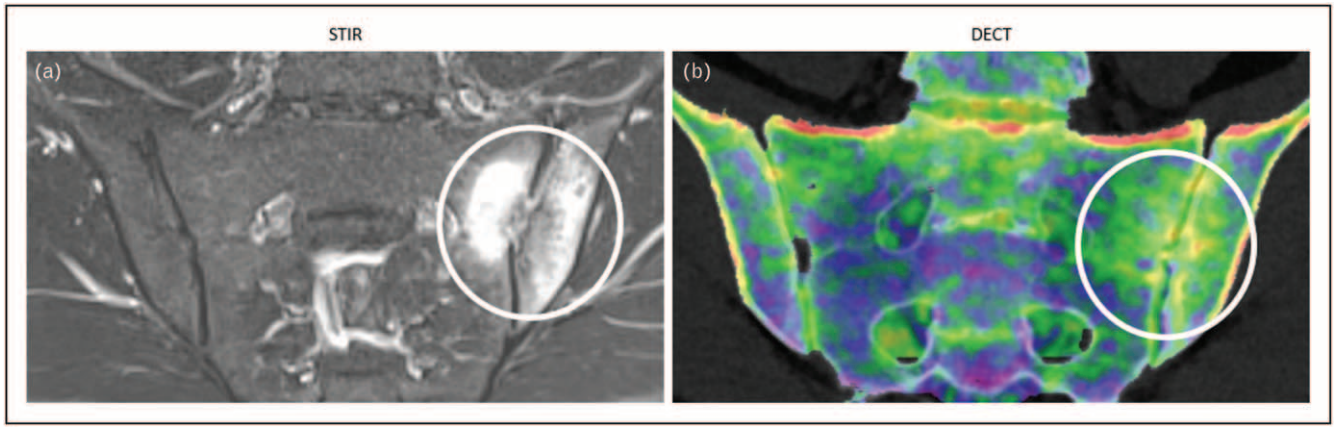

FIGURE 1. Bone marrow edema of the left sacroiliac joint in a 28-year-old male with sacroiliitis. The high signal (circle) on the short tau inversion-recovery (STIR) image (a) corresponds to the bright green areas (circle) with yellow and red spots on the dual-energy computed tomography (DECT) image (b).

structure and adjacent gas-containing bowel. As a result, DWI of the SI joints is considered of limited diagnostic value [14,18]. However, previous studies suggested DWI based on readout-segmented echo-planar imaging (rs-EPI) as an alternative approach to overcome the limitations of the ss-EPI technique [19]. Recently, Zhang *et al.* [20▪] showed that rs-EPI significantly improves the image quality of DWI in imaging of the SI joints and activity states are better differentiated by rs-EPI than ss-EPI. This study warrants further studies to investigate the added value of inclusion of rs-EPI in the routine clinical protocol for MRI of the SI joints.

Dual-energy CT

DECT can be employed to assess tissues at both low and high high–energy levels, using polychromatic X–ray beams to differentiate between different elements. Computed tomography images equivalent to conventional 120 kV computed tomography (CT) can be derived from the original data sets. Meanwhile, the radiation dose of DECT is equal to standard CT (but higher than low-dose CT) as it is divided between the two energy levels [21]. DECT volume datasets are used to generate algorithms which are then used to construct virtual non calcium (VNCa) images [21]. The algorithms are based on the X–ray absorption of bone minerals and bone marrow, thus allowing for the detection of BME. Bone marrow can be visualized and displayed as grey-scaled or as color-coded maps (Fig. 1b). Color coding ranged from blue (fat/yellow bone marrow), green (water/BME) to yellow/red (increasing red marrow content). An increase of water content in bone marrow can be evaluated both visually and quantitatively through the measurements of CT numbers [22,23]. In addition, VNCa DECT images also provide the option of overlay, allowing for the concurrent evaluation of both bone marrow and bone density. Chen *et al.* [24▪] found that inflammatory sacroiliac BME can be detected by DECT VNCa images, with a good interobserver agreement, moderate sensitivity, and high specificity. Another recent study of Carotti *et al.* [25▪] also showed good diagnostic performance of DECT VNCa images in the evaluation of the extent of BME in patients with sacroiliitis associated with SpA. Limitations of DECT include the limited accuracy for the detection of BME in the subcortical area (within 2–3 mm from the cortical bone) and the possible misinterpretation by inexperienced readers as red bone marrow and sclerotic areas may mimic BME lesions on VNCa images [23].

Thus, DECT is useful for sacroiliac BME evaluation, especially in SpA patients with contraindications to MRI.

ADVANCEMENTS IN THE IMAGING OF STRUCTURAL LESIONS IN AXIAL SPONDYLOARTHRITIS

Structural lesions increasingly gain importance for diagnosis and follow-up of sacroiliitis in spondyloarthritis. Baraliakos *et al.* [26▪] recently showed that the MRI findings with the highest diagnostic value in patients in whom SpA is suspected, are structural changes in the SI joint, alone or in combination with BME. Plain film radiography is still used as the reference for the classification of structural lesions, of which erosion is the defining characteristic in SpA [27]. However, the limitations of plain radiography restrict the assessment of erosions resulting in diminished reliability and sensitivity.

Consequently, new advances in the imaging of erosions have been an area of important research. Both CT and MRI T1-weighted spin–echo (T1SE) sequences are utilized in the examination of erosions, with CT considered the gold standard [28]. CT shows higher sensitivity and specificity; however, due to its high radiation dose, it is not routinely used in clinical practice. The T1SE sequence has been shown to be more reliable and accurate than radiography [29]. A recent study [30▪] shows that the diagnostic accuracy of T1SE for erosion detection vs. a CT reference standard is affected by slice thickness. Thinner slices (2 or 3 mm) have significantly higher diagnostic accuracy than thicker slices (4 or 5 mm). The T1SE sequence still has several limitations. The partial volume effect, limited contrast between cortical bone and joint space, as well as the unclear boundaries between erosions and subcortical bone marrow decrease the accuracy of erosion detection. As a result, new techniques have been developed and studied to improve the detection of structural lesions in SpA.

Low-dose CT

The performance of CT to detect sacroiliitis has previously been shown to be better than radiography [31]. However, because of the additional radiation exposure typically involved, sacroiliitis on CT has not been incorporated into classification criteria. Technological advances have enabled the performance of SI joint CT with the relatively low radiation dose of 1.2 mSv [32▪], 0.5 mSv [29,33] using low-dose CT and even 0.11 mSv using tin-filtrated ultra-low-dose CT [34▪]. These studies have shown the potential of low-dose CT for detecting structural lesions in the SI joint [32▪,34▪] and spine [35▪]. Korcakova *et al.* showed that tin-filtrated ultra-low-dose CT has a better diagnostic performance in the detection of sacroiliitis than radiography. Ye *et al.* [32▪] found that low-dose CT is more sensitive for erosions or sclerosis in SpA than plain radiography

and MRI-structural lesions have similar sensitivity and lower specificity than low-dose CT. As low-dose CT is comparable to radiography in terms of radiation exposure, CT is preferred over radiography [36▪]. Further studies are warranted about the relative value of low-dose CT, and its place in diagnostic algorithms and classification criteria for SpA.

Three-dimensional gradient echo sequences

On gradient echo (GRE) sequences the bony margins stand out because of darkening related to susceptibility of trabeculae. As such, GRE sequences show high contrast between joint cavity, cartilage and cortical bone [37], thus can potentially better depict erosion of SI joints. Three-dimensional (3D) MRI sequences provide images in all three planes, as well as datasets that can be reformatted in freely selectable orientations, which is advantageous in the assessment of the SI joints. They also show higher spatial resolution and lower partial volume effects. One of the drawbacks of 3D GRE sequences is that fat–suppressed images do not gauge fat metaplastic structural lesions in the SI joints [37]. In the last decade, several 3D GRE sequences have been studied for the detection of erosions in axial SpA, including 3D fast low angle shot (FLASH), 3D double excitation in the steady-state sequence (DESS), 3D water suppressed balanced steady-state free precession sequence (b-WS-SSFP) and 3D volume-interpolated breath-hold examination (VIBE) sequences [38]. The 3D VIBE sequences (Fig. 2a,b) are at the forefront of a recent analysis and displayed a higher sensitivity and interrater reliability for detecting erosions than T1SE sequence [39,40]. This fat–saturated 3D GRE sequence with nearly isotropic resolution is completed with relatively short acquisition times and preserved image quality. Another recent study [41▪] showed that a VIBE sequence with 1.2 mm slice thickness and less than one-minute acquisition time was superior to T1SE for detection of SI joint space changes and erosions in patients with suspected SpA, whereas the utility of the 3 mm slice thickness VIBE remains questionable.

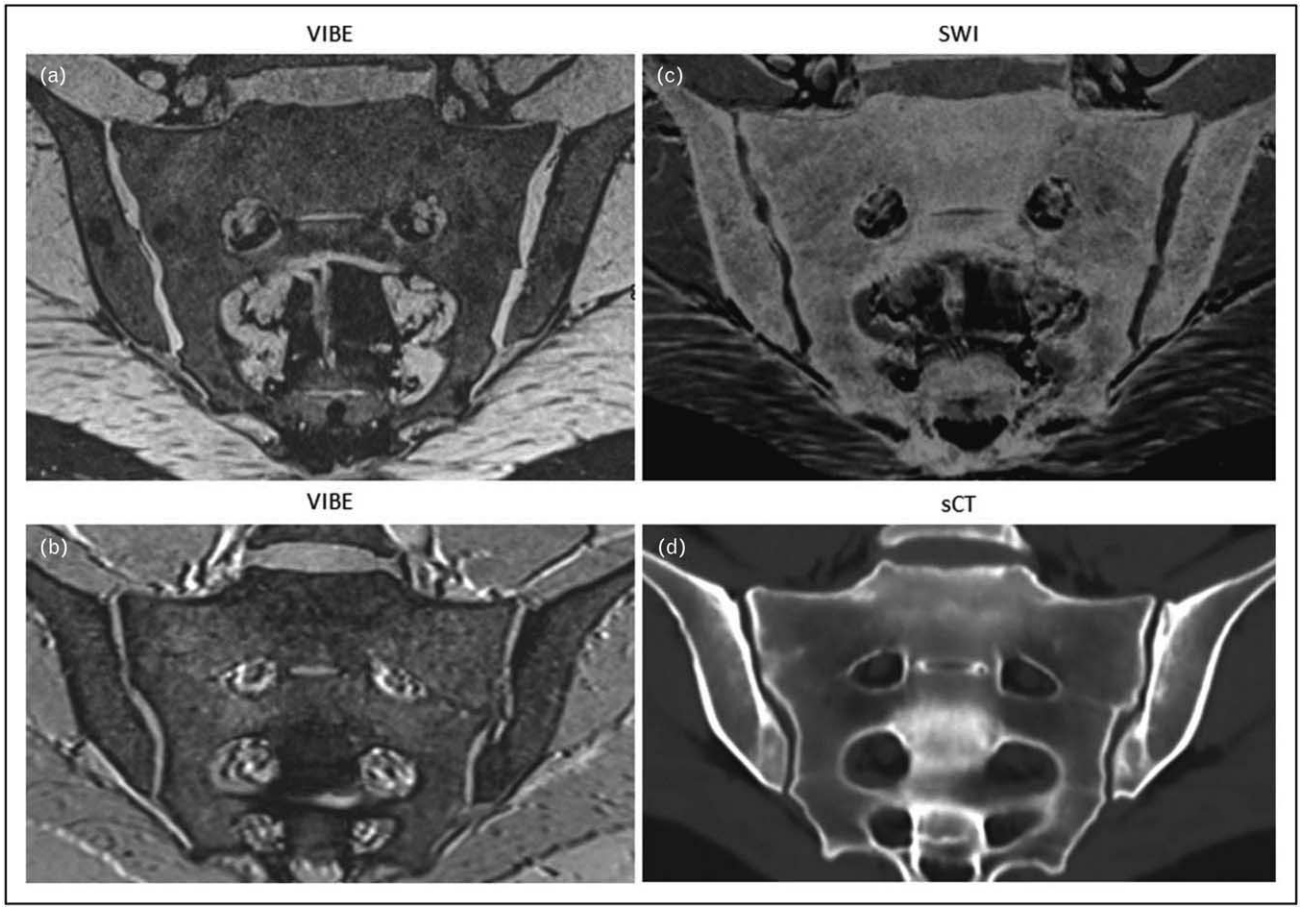

FIGURE 2. T1 volume-interpolated breath-hold examination (VIBE) images vs. computed tomography-like images in a healthy 34-year-old male (a, c) and 35-year-old female (b, d). (a, b) T1 VIBE images, (c) Magnitude image of susceptibility weighted imaging (SWI) with inverted grayscale to resemble conventional computed tomography, (d) MRI-based synthetic computed tomography (sCT) image.

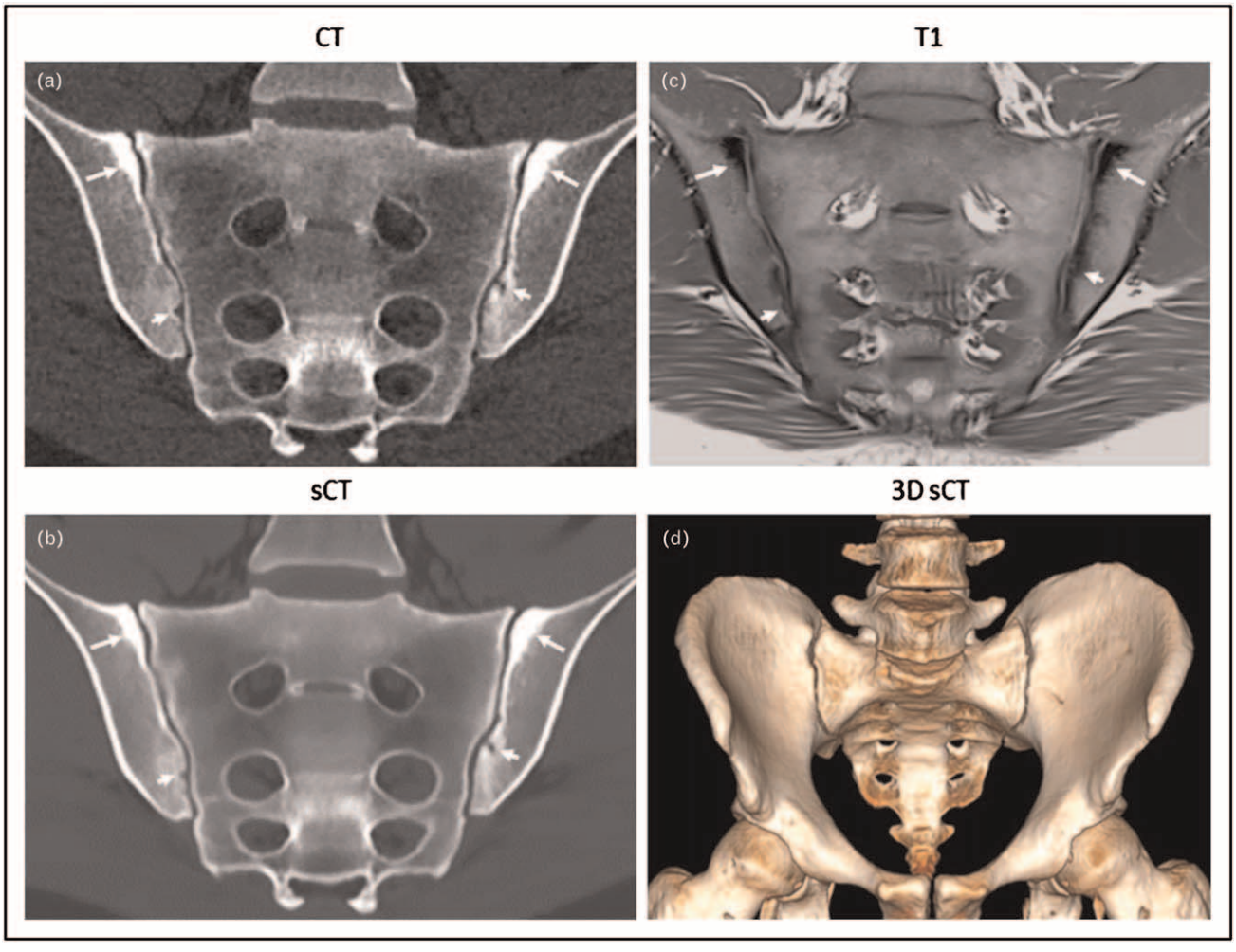

FIGURE 3. Structural changes of the sacroiliac joints in a 25-year-old male with axial spondyloarthritis. Subchondral sclerosis (long arrow) and erosions (short arrow) are more clearly identified and delineated on conventional computed tomography (a) and MRI-based synthetic computed tomography (sCT) (b) than on the T1-weighted image (c). (d) 3D rendering of MRI-based synthetic CT (3D sCT).

Despite the limited amount of studies, 3D MRI sequences have been shown to be advantageous in the detection of erosions in the SI joints and therefore justify further studies to validate their diagnostic value.

Susceptibility weighted imaging

Susceptibility weighted imaging (SWI) (Fig. 2c) can be considered a technical optimization of classical GRE sequences designed to increase the accuracy of MRI for detection of areas with high susceptibility variations in the local magnetic field. SWI depicts calcium structures directly by detecting and quantifying small magnetic field inhomogeneities surrounding calcium atoms. Inversion of these SWI images creates the impression of CT images in MRI [42]. This technique is not much applied in the musculoskeletal system, probably due to the lack of specific clinical applications and technical issues related to coil design and image interpretation [43]. Previous studies highlighted the diagnostic potential of SWI for the detection of erosions of the hand [44], but recently Deppe *et al.* [45▪▪] provided the first study using SWI to create CT-like magnetic resonance images for detection of structural SI joint lesions in SpA. They found that SWI depicts erosions and sclerosis more accurately than T1-weighted spin echo MRI at 1.5 T and may provide useful additional information for the diagnosis of SpA. A standard MRI protocol supplemented by SWI both provides diagnostic information on the presence of active bone marrow lesions and allows accurate detection of structural lesions in a single imaging session [46]. However, these results need to be verified in further studies, including larger patient populations, MRI at

Table 1. Novel imaging techniques for sacroiliac joint assessment

Feature	Modality	Technique	Advantages	Disadvantages
BME	CT	Dual-energy CT	Quantitative evaluation of disease activity	Ionizing radiation
			Alternative for BME detection, especially for patients not accessible to MRI	Limited in detecting BME close to cortical bone
				Low accuracy in sclerotic areas
	MRI	Fat-suppressed sequences *T2-SPAIR & T2-Weighted Multipoint Dixon Sequence*	Shorter scan time or better image quality (in comparison with STIR/T2-FS)	Reliability needs further validation
	MRI	DWI sequence with ADC maps	Quantitative evaluation of disease activity	Time consuming for quantitative analysis
			May improve specificity for spondyloarthritis	Reliability needs further validation
	MRI	Dixon sequences *Dixon-VIBE sequence water-fat ratio*	Quantitative evaluation of disease activity	Time consuming for quantitative analysis
			Objective basis for disease staging	Reliability needs further validation
Erosions	CT	(Ultra-)low-dose CT	Direct depiction of osseous structures	No simultaneous detection of active inflammation
			Higher sensitivity than radiography with comparable radiation dose	(Limited) radiation exposure
	MRI	3D GRE sequences *FLASH, DESS, b-WS-SSFP and VIBE*	High contrast between cartilage and cortical bone	More subject to artifacts
			High spatial resolution and lower partial volume effects than T1SE	Reliability needs further validation
	MRI	Synthetic CT/BoneMRI	''Radiograph-like'' and ''CT-like'' images	Limited availability
			Excellent depiction of osseous structures	Requires synthetic CT postprocessing software
			No manual post processing required to generate CT-like images	
			Hounsfield unit maps	
	MRI	SWI MRI sequence	Direct depiction of osseous structures	Limited experience in the musculoskeletal system
			Grey-scale image inversion creates ''CT-like'' images	No radiograph-like images (as BoneMRI)

3D, three-dimensional; ADC, apparent diffusion coefficient; BME, bone marrow edema; b-WS-SSFP, water suppressed balanced steady-state free precession sequence; DESS, double excitation in the steady-state sequence; DWI, diffusion-weighted imaging; FLASH, fast low angle shot; GRE, gradient echo; SPAIR, spectral attenuated inversion recovery; STIR, short tau inversion recovery; SWI, susceptibility weighted imaging; T2-FS, T2-weighted sequence with fat saturation; VIBE, volume-interpolated breath-hold examination.

3 T, comparison with other novel sequences and thinner slices. The diagnostic impact of SWI should also be examined [45▪▪].

MRI-based synthetic CT

Over the past few years, development and validation of models of artificial intelligence in medical imaging resulted in a rapidly increasing number of different applications. The algorithm developed by Shenkman *et al.* [47] for instance enables automatic detection and grading of sacroiliitis in CT scans of the abdomen or lower back as an incidental finding, with a sensitivity of 95% for diagnosis and 82% for grading. This can be helpful as structural damage of the SI joint may be missed when subtle.

Recently, artificial intelligence models have also been developed to compute new images. A novel technique, synthetic CT (Fig. 2d, Fig. 3b,d) or 'BoneMRI', refers to a deep learning-based multiparametric MRI technique that permits the creation of radiograph-like and CT-like images without ionizing radiation [48▪]. This technique has been clinically validated in the spine, SI joints and pelvis [49,50▪,51]. In the study of Jans *et al.* [50▪], these synthetic CT images outperformed T1-weighted MRI-images for detection of erosions, sclerosis and ankylosis in patients with SpA, and were found to be equally reliable to conventional CT images. Furthermore, this technique has the advantage of providing quantitative HU maps like conventional CT and a fully automatic postprocessing process that does not

require user input. Like SWI MRI, synthetic CT may facilitate MRI to become a one-stop modality for accurate detection of structural lesions, as well as diagnostic information on the presence of active bone marrow lesions. Although further studies are required with larger patient populations and comparison with other novel sequences, this synthetic CT technique may provide a whole new horizon for evaluation of osseous structural lesions in SpA, and not only for imaging of the SI joints, but also for spine imaging.

CONCLUSION

Evaluation of BME and structural lesions are both important for diagnosis, follow-up and treatment response evaluation in SpA. DECT shows potential in the assessment of sacroiliitis as it depicts sacroiliac BME, while structural lesion detection is further improved by new sophisticated MRI sequences. 3D GRE sequences generate images with greater tissue contrast, while SWI MRI and MRI-based synthetic CT create CT-like images of the SI joint without ionizing radiation. These emerging imaging techniques (summarized in Table 1) are promising in enhancing the diagnostic accuracy and confidence in SpA and facilitating a more efficient imaging work-up.

Acknowledgements

None.

Financial support and sponsorship

None.

Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ■ of special interest
- ■■ of outstanding interest

1. van der Linden S, Valkenburg HA, Cats A. Evaluation of diagnostic Criteria for ankylosing spondylitis. A proposal for modification of the New York criteria. Arthritis Rheum 1984; 27:361–368.
2. Rudwaleit M, Jurik AG, Hermann KGA, *et al.* Defining active sacroiliitis on magnetic resonance imaging (MRI) for classification of axial spondyloarthritis: a consensual approach by the ASAS/OMERACT MRI group. Ann Rheum Dis 2009; 68:1520–1527.
3. Mandl P, Navarro-Compán V, Terslev L, *et al.* EULAR recommendations for the use of imaging in the diagnosis and management of spondyloarthritis in clinical practice. Ann Rheum Dis 2015; 74:1327–1339.
4. Sieper J, Rudwaleit M, Baraliakos X, *et al.* The Assessment of SpondyloArthritis international Society (ASAS) handbook: a guide to assess spondyloarthritis. Ann Rheum Dis 2009; 68 Suppl 2:ii1–ii44.
5. Greese J, Diekhoff T, Sieper J, *et al.* Detection of sacroiliitis by short-tau inversion recovery and T2-weighted turbo spin echo sequences: results from the SIMACT Study. J Rheumatol 2019; 46:376–383.
6. Özgen A. The value of the T2-weighted multipoint dixon sequence in MRI of sacroiliac joints for the diagnosis of active and chronic sacroiliitis. AJR Am J Roentgenol 2017; 208:603–608.
7. Dalto VF, Assad RL, Crema MD, *et al.* MRI assessment of bone marrow oedema in the sacroiliac joints of patients with spondyloarthritis: is the SPAIR T2w technique comparable to STIR? Eur Radiol 2017; 27:3669–3676.
8. ■ Dalto VF, Assad RL, Lorenzato MM, *et al.* Comparison between STIR and T2-weighted SPAIR sequences in the evaluation of inflammatory sacroiliitis: diagnostic performance and signal-to-noise ratio. Radiol Bras 2020; 53:223–228.

This study compares two different fat-saturated MRI techniques, STIR and T2 SPAIR, in terms of image quality and diagnostic performance in detecting sacroiliac joint active inflammation.

9. ■ Huang H, Zhang Y, Zhang H, *et al.* Qualitative and quantitative assessment of sacroiliitis in axial spondyloarthropathy: can a single T2-weighted dixon sequence replace the standard protocol? Clin Radiol 2020; 75:321.e13–321.e20.

This study proposes to shorten the acquisition time by replacing the standard protocol by the single T2 Dixon sequence in patients with suspected SpA.

10. ■ Du M-S, Xiong X-Q, Liu H, *et al.* The evaluation of bone marrow edema in sacroiliac joint in patients with ankylosing spondylitis using magnetic resonance imaging Dixon sequence. BMC Musculoskelet Disord 2021; 22:919.

This study proposes the water-fat ratio of the Dixon sequence as a reference index to quantitatively evaluate the degree of bone marrow edema in the active stage of sacroiliitis.

11. Gezmis E, Donmez FY, Agildere M. Diagnosis of early sacroiliitis in seronegative spondyloarthropathies by DWI and correlation of clinical and laboratory findings with ADC values. Eur J Radiol 2013; 82:2316–2321.
12. Ren C, Zhu Q, Yuan H. Mono-exponential and bi-exponential model-based diffusion-weighted MR imaging and IDEAL-IQ sequence for quantitative evaluation of sacroiliitis in patients with ankylosing spondylitis. Clin Rheumatol 2018; 37:3069–3076.
13. Beltran LS, Samim M, Gyftopoulos S, *et al.* Does the addition of DWI to fluid-sensitive conventional MRI of the sacroiliac joints improve the diagnosis of sacroiliitis? AJR Am J Roentgenol 2018; 210:1309–1316.
14. Kucybała I, Ciuk S, Urbanik A, Wojciechowski W. The usefulness of diffusion-weighted imaging (DWI) and dynamic contrast-enhanced (DCE) sequences visual assessment in the early diagnosis of axial spondyloarthritis. Rheumatol Int 2019; 39:1559–1565.
15. Wang F, Chu C, Zhu L, *et al.* Whole-lesion ADC histogram analysis and the spondyloarthritis research consortium of canada (SPARCC) MRI index in evaluating the disease activity of ankylosing spondylitis. J Magn Reson Imaging 2019; 50:114–126.
16. Lambert RG, Maksymowych WP. Diffusion-weighted imaging in axial spondyloarthritis: a measure of effusion or does it elicit confusion? J Rheumatol 2018; 45:729–730.
17. Khoo MMY, Tyler PA, Saifuddin A, Padhani AR. Diffusion-weighted imaging (DWI) in musculoskeletal MRI: a critical review. Skeletal Radiol 2011; 40:665–681.
18. Sanal HT, Yilmaz S, Simsek I, *et al.* Apparent diffusion coefficients of sacroiliitis in patients with established ankylosing spondylitis. Clin Imaging 2013; 37:734–739.
19. Porter DA, Heidemann RM. High resolution diffusion-weighted imaging using readout-segmented echo-planar imaging, parallel imaging and a two-dimensional navigator-based reacquisition. Magn Reson Med 2009; 62:468–475.
20. ■ Zhang H, Huang H, Zhang Y, *et al.* Diffusion-weighted MRI to assess sacroiliitis: improved image quality and diagnostic performance of readout-segmented echo-planar imaging (EPI) over conventional single-shot EPI. AJR Am J Roentgenol 2021; 217:450–459.

This study proposes to include readout-segmented EPI, a more robust tool than ss-EPI for imaging of SpA, in routine clinical protocols for MRI of the sacroiliac joints.

21. Yu L, Christner JA, Leng S, *et al.* Virtual monochromatic imaging in dual-source dual-energy CT: radiation dose and image quality. Med Phys 2011; 38:6371–6379.
22. Foti G, Catania M, Caia S, *et al.* Identification of bone marrow edema of the ankle: diagnostic accuracy of dual-energy CT in comparison with MRI. Radiol Med 2019; 124:1028–1036.
23. Wu H, Zhang G, Shi L, *et al.* Axial spondyloarthritis: dual-energy virtual noncalcium CT in the detection of bone marrow edema in the sacroiliac joints. Radiology 2019; 290:157–164.
24. ■ Chen M, Herregods N, Jaremko JL, *et al.* Bone marrow edema in sacroiliitis: detection with dual-energy CT. Eur Radiol 2020; 30:3393–3400.

This study evaluates the feasibility and diagnostic accuracy of DECT for the detection of BME in patients suspected for sacroiliitis.

25. ■ Carotti M, Benfaremo D, Di Carlo M, *et al.* Dual-energy computed tomography for the detection of sacroiliac joints bone marrow oedema in patients with axial spondyloarthritis. Clin Exp Rheumatol 2021; 39:1316–1323.

This study investigates the diagnostic performance of DECT in detection of BME in patients with sacroiliitis associated with SpA.

26. ■ Baraliakos X, Ghadir A, Fruth M, *et al.* Which magnetic resonance imaging lesions in the sacroiliac joints are most relevant for diagnosing axial spondyloarthritis? A prospective study comparing rheumatologists' evaluations with radiologists' findings. Arthritis Rheumatol 2021; 73:800–805.

This study evaluates the impact of MRI sacroiliac joint findings on the identification of SpA by radiologists, in comparison to diagnosis by rheumatologists.

27. Weber U, Lambert RGW, Østergaard M, *et al.* The diagnostic utility of magnetic resonance imaging in spondylarthritis: an international multicenter evaluation of one hundred eighty-seven subjects. Arthritis Rheum 2010; 62:3048–3058.

28. Hu L, Huang Z, Zhang X, *et al.* The performance of MRI in detecting subarticular bone erosion of sacroiliac joint in patients with spondyloarthropathy: a comparison with X-ray and CT. Eur J Radiol 2014; 83:2058–2064.

29. Diekhoff T, Hermann K-GA, Greese J, *et al.* Comparison of MRI with radiography for detecting structural lesions of the sacroiliac joint using CT as standard of reference: results from the SIMACT study. Ann Rheum Dis 2017; 76:1502–1508.

30. ■ Chen M, Herregods N, Jaremko JL, *et al.* Diagnostic performance for erosion detection in sacroiliac joints on MR T1-weighted images: comparison between different slice thicknesses. Eur J Radiol 2020; 133:109352.

This study assesses the effect of slice thickness on the diagnostic accuracy of erosion detection at magnetic resonance T1-weighted images of the sacroiliac joints in adult patients suspected of sacroiliitis.

31. Devauchelle-Pensec V, D'Agostino MA, Marion J, *et al.* Computed tomography scanning facilitates the diagnosis of sacroiliitis in patients with suspected spondylarthritis: results of a prospective multicenter French cohort study. Arthritis Rheum 2012; 64:1412–1419.

32. ■ Ye L, Liu Y, Xiao Q, *et al.* MRI compared with low-dose CT scanning in the diagnosis of axial spondyloarthritis. Clin Rheumatol 2020; 39:1295–1303.

This is the first study to have controlled data on whether low-dose computed tomography may have higher sensitivity to detect sacroiliac joint erosions compared with MRI.

33. Tan S, Ward MM. Computed tomography in axial spondyloarthritis. Curr Opin Rheumatol 2018; 30:334–339.

34. ■ Korcakova E, Stepankova J, Suchy D, *et al.* Is ultra low-dose CT with tin filtration useful for examination of SI joints? Can it replace X-ray in diagnostics of sacroiliitis? Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub 2022; 166:77–83.

This study compares the results of tin-filtrated ultra-low-dose computed tomography and radiography in the detection of sacroiliitis.

35. ■ Stal R, van Gaalen F, Sepriano A, *et al.* Facet joint ankylosis in r-axSpA: detection and 2-year progression on whole spine low-dose CT and comparison with syndesmophyte progression. Rheumatology (Oxford) 2020; 59:3776–3783.

This is the first study evaluating facet joints in the whole spine by low-dose computed tomography in radiographic SpA.

36. ■ Diekhoff T, Eshed I, Radny F, *et al.* Choose wisely: imaging for diagnosis of axial spondyloarthritis. Ann Rheum Dis 2021; 81:237–242.

This study assesses the diagnostic accuracy of radiography, computed tomography and MRI of the sacroiliac joints for diagnosis of SpA.

37. Krohn M, Braum LS, Sieper J, *et al.* Erosions and fatty lesions of sacroiliac joints in patients with axial spondyloarthritis: evaluation of different MRI techniques and two scoring methods. J Rheumatol 2014; 41:473–480.

38. Chen M, Bird P, Jans LBO. Emerging imaging techniques in spondyloarthritis: dual-energy computed tomography and new MRI sequences. Rheum Dis Clin North Am 2020; 46:287–296.

39. Baraliakos X, Hoffmann F, Deng X, *et al.* Detection of erosions in sacroiliac joints of patients with axial spondyloarthritis using the magnetic resonance imaging volumetric interpolated breath-hold examination. J Rheumatol 2019; 46:1445–1449.

40. Diekhoff T, Greese J, Sieper J, *et al.* Improved detection of erosions in the sacroiliac joints on MRI with volumetric interpolated breath-hold examination (VIBE): results from the SIMACT study. Ann Rheum Dis 2018; 77:1585–1589.

41. ■ Xie R, Sun D, Morelli JN, *et al.* Recognition of sacroiliac joint structural lesions: comparison of volumetric interpolated breath-hold examination (VIBE) sequences with different slice thicknesses to T1-weighted turbo-echo. Eur J Radiol 2020; 124:108849.

This study compares VIBE with different slice thicknesses to T1SE for identification of sacroiliac joint structural lesions in patients suspected of spondyloarthritis.

42. Diekhoff T, Hermann K-G, Proft F, *et al.* Fri0636 susceptibility weighted sequences in magnetic resonance imaging can create computed tomography-like images and improve the accuracy of structural lesion detection of the sacroiliac joint in axial spondyloarthritis. Annals of Rheumatic Diseases 2019; 78:1015.2–1016.2.

43. Berberat J, Grobholz R, Boxheimer L, *et al.* Differentiation between calcification and hemorrhage in brain tumors using susceptibility-weighted imaging: a pilot study. AJR Am J Roentgenol 2014; 202:847–850.

44. Ulas ST, Diekhoff T, Hermann KGA, *et al.* Susceptibility-weighted MR imaging to improve the specificity of erosion detection: a prospective feasibility study in hand arthritis. Skeletal Radiol 2019; 48:721–728.

45. ■■ Deppe D, Hermann K-G, Proft F, *et al.* CT-like images of the sacroiliac joint generated from MRI using susceptibility-weighted imaging (SWI) in patients with axial spondyloarthritis. RMD Open 2021; 7:.

This is the first study using SWI to create computed tomography-like magnetic resonance images for detection of structural sacroiliac joint lesions in SpA. They found that SWI depicts erosions and sclerosis more accurately than T1SE in patients with SpA.

46. Weber U, Lambert RGW, Pedersen SJ, *et al.* Assessment of structural lesions in sacroiliac joints enhances diagnostic utility of magnetic resonance imaging in early spondylarthritis. Arthritis Care Res (Hoboken) 2010; 62:1763–1771.

47. Shenkman Y, Qutteineh B, Joskowicz L, *et al.* Automatic detection and diagnosis of sacroiliitis in CT scans as incidental findings. Med Image Ana 2019; 57:165–175.

48. ■ Chea P, Mandell JC. Current applications and future directions of deep learning in musculoskeletal radiology. Skeletal Radiol 2020; 49:183–197.

This study presents the current and future developments of deep learning applications in musculoskeletal radiology.

49. Morbée L, Chen M, Herregods N, *et al.* MRI-based synthetic CT of the lumbar spine: Geometric measurements for surgery planning in comparison with CT. Eur J Radiol 2021; 144:109999.

50. ■ Jans LBO, Chen M, Elewaut D, *et al.* MRI-based synthetic CT in the detection of structural lesions in patients with suspected sacroiliitis: comparison with MRI. Radiology 2021; 298:343–349.

This is the first study using BoneMRI (a deep-learning based technique to create computed tomography-like magnetic resonance images) for detection of structural sacroiliac joint lesions in SpA.

51. Morbée L, Chen M, Van Den Berghe T, *et al.* MRI-based synthetic CT of the hip: can it be an alternative to conventional CT in the evaluation of osseous morphology? Eur Radiol 2021; 32:3112–3120.

Defining and managing flares in axial spondyloarthritis

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Purpose of review
Flares correspond to fluctuations in disease activity or symptoms. They should be avoided in chronic inflammatory diseases. In axial spondyloarthritis (axSpA), work is ongoing to better conceptualise and treat flares. This review highlights recent data on the definition and management of flares in axSpA.

Recent findings
Many definitions of flares have been used in clinical trials, limiting the interpretation and comparison of studies. The expert group Assessment of SpondyloArthritis International Society (ASAS) developed a data-driven definition of flares/disease worsening: an increase in Ankylosing Spondylitis Disease Activity Score-C-reactive protein (ASDAS-CRP) of at least 0.9 points, for use in axSpA clinical trials. Flares are more challenging to define in clinical practice because of their multifaceted nature. Qualitative studies have shown that flares from the patient's perspective are related not only to disease activity, but also to fatigue, mood, sleep and general well-being. The management of axSpA relies on a treat-to-target (T2T) strategy and aims at reaching clinical remission while monitoring closely disease activity to prevent and shorten flares.

Summary
The concept of flares has been clarified, and definitions have been developed for use in trials. The T2T approach aims at minimising flares in axSpA. The early recognition of flares and their severity may lead to better management.

Keywords
axial spondyloarthritis, definition, disease activity, flare, management

INTRODUCTION

Axial spondyloarthritis (axSpA) is a chronic inflammatory disease characterised by episodes of flares and remission. Flares were defined by the Outcome Measures in Rheumatology Clinical Trials (OMERACT) group in 2008 as 'a cluster of symptoms of sufficient duration and intensity that cannot be self-managed by the patient and require initiation, change or increase in therapy' [1]. A flare is a change in status, with a worsening of symptoms and/or disease activity [2]. Fluctuations in disease activity reflect systemic inflammation which may cause deleterious effects on long-term outcomes [3]. Furthermore, fluctuations in symptoms, even if not due to disease activity, impact patients' lives [4]. Flares should be controlled according to the recently updated treat-to-target (T2T) strategy for axSpA [5]. Therefore, better recognition and management of flares are important to improve disease prognosis and patient outcomes.

In recent years, many attempts have been made to define flares in different chronic rheumatic diseases like rheumatoid arthritis [6]. However, in a very heterogeneous disease such as axSpA, defining the concept of flare or remission is very challenging [7]. The perception of flares also differs from the patient's and physician's point of view, and this is an issue for a consensual definition in clinical practice [8,9]. Furthermore, a flare can be transient or persistent, mild or severe, can occur once or frequently during the disease course, and can prompt a patient to self-manage or to seek medical intervention.

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Curr Opin Rheumatol 2022, 34:195–202
DOI:10.1097/BOR.0000000000000883

KEY POINTS

- Flares correspond to a period of disease worsening and increased symptoms in axSpA.
- The ASAS expert group defined disease worsening as an increase in ASDAS-CRP of at least 0.9 points.
- Flares in axSpA are frequent, in particular minor flares which are reported by almost all patients several times a year or more, whereas major flares with high levels of symptoms, and prolonged flares, are less frequent.
- Flares have deleterious consequences on patients' lives and may lead to worse outcomes.
- Flares are related to increased inflammation should be managed according to T2T principles.

Overall, a better understanding of flares' characteristics and outcomes are key elements for adequate therapeutic decision-making and management of axSpA.

This review provides a comprehensive overview of the current definitions of flares in axSpA in trials and clinical practice, from the physician's and patient's perspective, as well as a highlight on the newest updates of the T2T management of flares.

DEFINITION OF FLARE IN CLINICAL TRIALS

Composite scores

Up to 2016, many definitions of flares were used in mainly two types of trials: 'flare design trials' and 'tapering/discontinuation trials' [10–22]. The main definitions used are summarised in Table 1. This lack of standardisation and variability in flare definition impaired comprehension and comparisons between different clinical trials and rendered translation for clinical practice difficult [2]. Therefore, in 2016, the Assessment of SpondyloArthritis international Society (ASAS), an international group of experts in the field of spondyloarthritis, developed a consensual definition of flare/disease worsening [2]. After a systematic literature review and a case vignette study, 12 preliminary definitions of flares were proposed, relying on validated composite scores (Ankylosing Spondylitis Disease Activity Score (ASDAS); Bath Ankylosing Spondylitis Disease Activity Index, BASDAI) and patient-reported outcomes (e.g. pain) [10]. Thereafter, a longitudinal study was conducted and the previously obtained definitions were tested, against the patient's perception of clinical worsening needing treatment intensification [8]. The consensus from the ASAS members in 2017 led to the selection of a single definition of flare based on the

Table 1. Examples of different definitions of flares used in axSpA trials

	Composite score	Objective elements	PROs / patient perspective
Breban *et al.* (2003) [21]			A loss of ≥50% of patient global assessment of pain improvement
Baraliakos *et al.* (2005) [12]	BASDAI ≥ 4		AND physician's global assessment ≥4
Brandt *et al.* (2005) [17]	BASDAI ≥ 4		AND pain ≥4 on a numerical rating scale
Song *et al.* (2012) (ESTHER trial) [15]	Increase of two points on BASDAI compared to a baseline		
Haibel *et al.* (2013) [14]	Loss of an established ASAS40 response as compared to baseline at any time point.		
Sebastian *et al.* (2017) [16]	BASDAI ≥ 4		
Landewe *et al.* (2018) (ABILITY-3) [13]	ASDAS ≥2.1 at two consecutive visits		
Lian *et al.* (2018) [18]	BASDAI ≥4 or an increase in BASDAI of ≥2 units		
Chen *et al.* (2018) [20]			Worsening in quality of life
Moreno *et al.* (2019) (REMINEA study) [11]	BASDAI ≥ 4	AND/OR CRP ≥ 0.8 mg/dl	
Landewe *et al.* (2019) (C-OPTIMISE) [19]	ASDAS ≥2.1 at two consecutive visits or ASDAS > 3.5 at any visit		
Bosch *et al.* (2020) [22]	ASDAS ESR ≥2.1		
ASAS Consensus, Molto *et al.* (2018) [8]	Increase in ASDAS ≥ 0.9 points		

ankylosing spondylitis disease activity score- C reactive protein (ASDAS-C-reactive protein [CRP]) score. 'Clinically important worsening' was determined as an increase in ASDAS-CRP of at least 0.9 points [8]. This definition of flares was proposed for clinical trials and observational studies.

A definition based on BASDAI was not proposed, because BASDAI performs less well than ASDAS-CRP in terms of psychometric properties [8]. However, recently an 'equivalence' was published between ASDAS-CRP and BASDAI: the cut-offs values of BASDAI 1.9, 3.5 and 4.9 corresponded respectively to the values of ASDAS-CRP 1.3, 2.1 and 3.5. These findings may be of use for clinicians when CRP is not available to calculate ASDAS-CRP [23▪,24▪]. However, a cut-off of the BASDAI corresponding to the ASAS-defined ASDAS worsening was not specifically obtained.

Other assessments of disease worsening

Disease activity scores, such as BASDAI or ASDAS-CRP, do not assess all the aspects of axSpA [7,25]. Although not included in composite scores, the new onset of extra-articular manifestations, such as uveitis, inflammatory bowel disease or psoriasis during the disease course may also be considered as a flare; this aspect has been little explored [7,26,27].

DEFINITION OF FLARE IN CLINICAL PRACTICE

Composite scores

Defining flares in axSpA in clinical practice is challenging [28]. In clinical care, flares are usually defined as worsened symptoms [25,29▪], primarily axial symptoms but also taking into account both peripheral involvement (arthritis, enthesitis and/or dactylitis) and extra-articular manifestations [7]. Published data focus, however, on axial flares.

In axSpA, Godfrin-Valnet *et al.* [9] proposed thresholds of disease activity variations associated with a flare from the patient's and the physician's point of view. Flares, corresponded to a worsening of disease activity composite scores by ≥ 1.3 units, ≥ 0.8 units and ≥ 2.1 units for ASDAS-CRP, ASDAS-ESR and BASDAI, respectively [9,30]. As expected, these thresholds were different from the ASAS consensus that was agreed on later for trials [8].

Overall, the optimal composite outcome measure and cut-off to use in clinical practice to detect flares is not yet fully established; we would propose to apply the ASAS cut-off for ASDAS-CRP when using a composite score.

Flares from the patient's perspective

For patients, flares correspond to the perception of a clinical worsening in their health status. Patients will consider many aspects of their health when reporting or not a flare, which is an argument for a holistic assessment of disease by health professionals. In this regard, trained nurses play an important role [31▪].

Patient-perceived flares do not only reflect inflammation. For example, in rheumatoid arthritis, flares reported by patients are linked not only to inflammation, but also to functional impairment, structural damage and higher cardiovascular risk [6]. Probably for this reason, both in axSpA and rheumatoid arthritis, physicians and patients may have different perceptions of flares [32]. This discordance between the patient's and physician's assessment in axSpA is mainly determined by spinal pain and fatigue reported by patients [32]. Overall, patients seem to report flares for lower thresholds of inflammation, compared to physicians [9,32]. They also seem to take into account non-inflammatory symptoms. Some qualitative studies have been performed in axSpA. A seminal qualitative study described two types of flares, both associated to pain, stiffness and fatigue: a minor/localised flare and a major/generalised flare (Table 2) [33]. Major

Table 2. Different types of flares in axSpA [33,34▪▪]

Type of flare	Musculoskeletal symptoms	General symptoms	Mental symptoms
Minor flare	• Pain in one area (localised) • Stiffness	• Fatigue	• Some emotional symptoms
Major flare	• Severe pain • Severe stiffness	• Increased widespread tenderness and sensitivity • Muscle spasms • Marked systemic features: - flu-like symptoms - sweats - fevers - loss of appetite - marked fatigue • Worsening of sleep quality	• Emotional symptoms: - Depression - Withdrawal - Anger - Worsening of mood • Stress

flares included generalised pain and stiffness affecting the whole body associated with 'flu-like' systemic illness, such as fever, sweats and marked fatigue (Table 2) [33]. A recent study using a smartphone app collected daily self-reported data on flares in patients with axSpA [34▪▪]. This study also identified two clusters of flares; important flares had greater changes in pain, fatigue and stress along with disturbances in mood and sleep[34▪▪].

Thus, flares are associated with symptoms but also with mental disease burden and consequences on social life, as has been shown in other inflammatory rheumatic diseases [6,35▪,36].

Frequency of flares in axial spondyloarthritis

Flare is a very frequent event in the disease course of patients with axSpA.

In qualitative studies, around 91–100% of patients with axSpA experience any flare [30,33, 37] and 40 to 58% a major flare [33,37] over a year and the duration varies from several days to several weeks [33,38]; over a week, up to 70% patients can flare with 12% reporting a major flare [30]. Around 72% experience a flare at the early stages of the disease before the diagnosis of axSpA [37]. The frequency and duration of flares vary according to the underlying treatment.

CONSEQUENCES OF FLARES

Flares lead to altered health-related quality of life and increased symptoms [39▪]. Indeed, time spent in flare is highly correlated to symptoms assessed by BASDAI, and severe flares are associated with impairment in physical function [30,38].

It seems that flares may also be associated with worse quality of life even during nonflare periods. Cooksey *et al.* [30] observed that patients who reported major flares had higher disease activity (on BASDAI and functional scores) even during flare-free periods compared to those who never experienced major flares.

Stone *et al.* reported two main disease activity patterns: patients with constant symptoms in between flares and patients with intermittent symptoms (Fig. 1) [40]. In the majority of patients (83%), a persistence of heightened disease activity was observed in between flares and led to worse health status and quality of life (Fig. 1.B). Only a minority

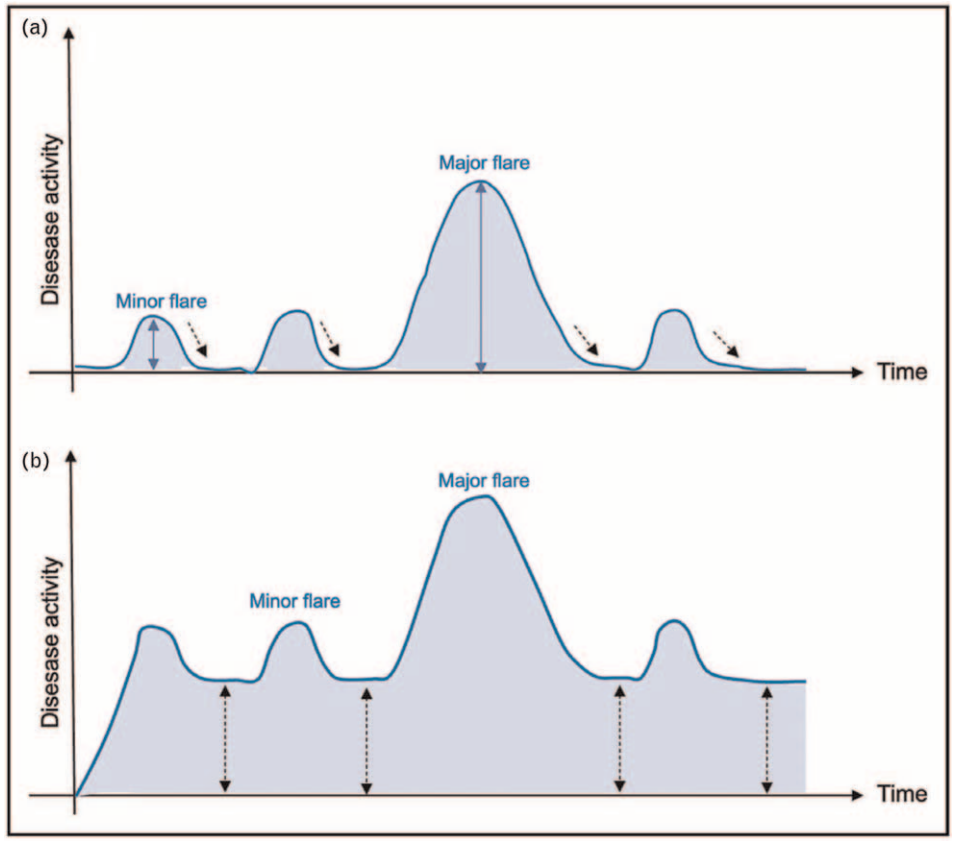

FIGURE 1. Different types of flares and disease patterns in axSpA patients, adapted from Stone *et al.* [40]. Part A shows major and minor types of flares with a return to an asymptomatic state in between flares. Part B shows major and minor types of flares with persisting disease activity in between flares.

of patients had an intermittent disease activity pattern with a return to a symptom-free baseline in between flares (Fig. 1.A).

The second potential consequence of flares is related to structural damage [41]. It is well acknowledged today that a strong correlation exists between disease activity and structural progression [42]. This strong link has been shown for long periods of increased disease activity, assessed by ASDAS-CRP [42]. Thus, patients with frequently heightened disease activity may have not only worse clinical outcomes but also more structural damage [5,42]. In rheumatoid arthritis, fluctuations in disease activity were associated with increased structural damage [3]. In axSpA, the link between flares and structural progression has not to date been fully confirmed.

The timing of flares in the disease course is also of interest: it seems a worse prognosis of axSpA can be expected when flares occur at the earlier stages of the disease [37].

PREDICTING FLARES: ARE WE THERE YET?

The identification of patients at risk of flares may help to better understand axSpA patterns.

Some flares are expected in case of discontinuation or tapering of bDMARDs. A recent meta-analysis including patients with axSpA and rheumatoid arthritis found an increased risk of flare and persistent flare, after tumour necrosis factor (TNF) inhibitors withdrawal; whereas an increased risk of flare but not persistent flare was reported with bDMARD/tsDMARD tapering [43▪▪].

Among patients continuing their treatment, some elements are associated with flares. A recent prospective study on 251 patients with axSpA achieving low disease activity showed that active sacroiliitis on magnetic resonance imaging (MRI) and absence of TNF inhibitor treatment were significantly associated with disease flares [44▪]. Inflammation on MRI of the sacroiliac joints at baseline was an independent risk factor of flares, whereas TNF inhibitor intake was a protective factor against flares. Even though MRI is not currently recommended for the monitoring and management of axSpA, several studies have shown that it could give valuable insights about disease activity status [45]. Another study reported that normal CRP at baseline, HLA-B27 negativity, higher spinal ankylosis scores, higher fatty degeneration scores at baseline MRI but lower ankylosis scores in the sacroiliac joint were associated with a higher risk for flares [46].

Finally, triggers of flares may be interesting to identify. In rheumatoid arthritis, recent data suggest that flares may be triggered by environmental factors like pollution [47]. Such data are not yet available in axSpA.

MANAGEMENT OF FLARES

Recent recommendations for the management of axSpA rely on the 'treat-to-target' (T2T) concept [5,48▪]. This strategy defines a treatment target to reach which is, in axSpA, clinical remission or alternatively low disease activity [5]. The recommended outcome measure to define remission in axSpA is a threshold of ASDAS-CRP corresponding to inactive disease < 1.3 or low disease activity < 2.1 [5]. The T2T strategy requires tight monitoring of disease activity and if the target is not achieved, treatment escalation is proposed.

Recently, the first T2T trial in axSpA published to date, the TICOSPA study, did not confirm the superiority of the T2T strategy compared to usual care for the primary outcome selected: the ASAS-Health Index (ASAS-HI) [49▪▪]. However, some secondary outcomes were significantly superior in the T2T arm compared to usual care: ASDAS-low disease activity and ASAS40 response [49▪▪]. Overall, despite this recent inconclusive clinical trial, the T2T strategy appears a promising approach and is recommended in the management of axSpA [5,48▪]. The T2T strategy considers flares as periods of disease activity which should be minimised.

The management of axSpA flares relies on pharmacological and nonpharmacological interventions (Fig. 2).

Physical exercise and patient education are an integral part of nonpharmacological flare management [48▪,50,51]. The recent French recommendations, for example, highlighted the value of patient education programs, patient associations and digital educational tools [48▪]. Furthermore, a recent study showed the benefits of a program centred on self-management and self-assessment of disease activity in patients with axSpA [52▪].

When considering pharmacological treatments, an important question is whether any type of clinical worsening (or flare) requires treatment intensification. The ASAS experts defined that a flare needed a treatment change if it was present at least for 2 weeks or reported at two consecutive visits [10].

Thus, a flare, if confirmed and durable, will necessitate a change in treatment and/or disease-modifying antirheumatic drugs (DMARDs). Here, two main management scenarios are possible, depending on the current DMARD status of the patient: a patient may experience a flare (1) while on treatment or (2) after treatment discontinuation or tapering (Fig. 2).

Non-steroidal anti-inflammatory drugs (NSAIDs) are recommended in axSpA as the first-line treatment

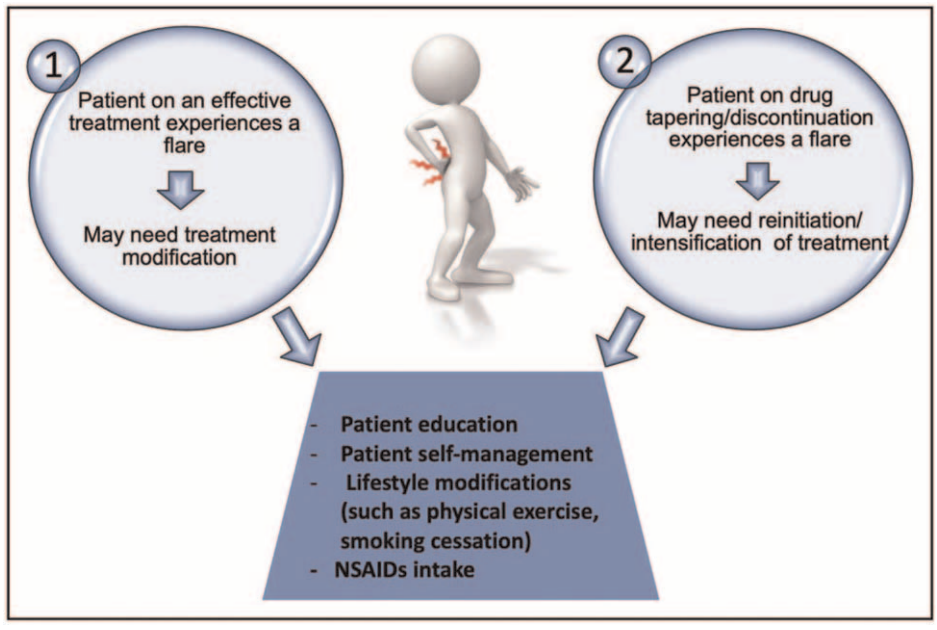

FIGURE 2. Main scenarios of flare management in patients with axSpA.

with at least two different classes of NSAIDs used at the highest dose for at least 2 weeks each [39▪,49▪▪]. In case of highly active disease failing to respond to NSAIDs, a biologic DMARD (bDMARD) can be started, generally a TNF inhibitor as first line [48▪,50]. In case of flares with a bDMARD, an NSAID course is possible in combination with the bDMARD [48▪].

We propose an algorithm for the management of flares based on the T2T strategy (Fig. 3).

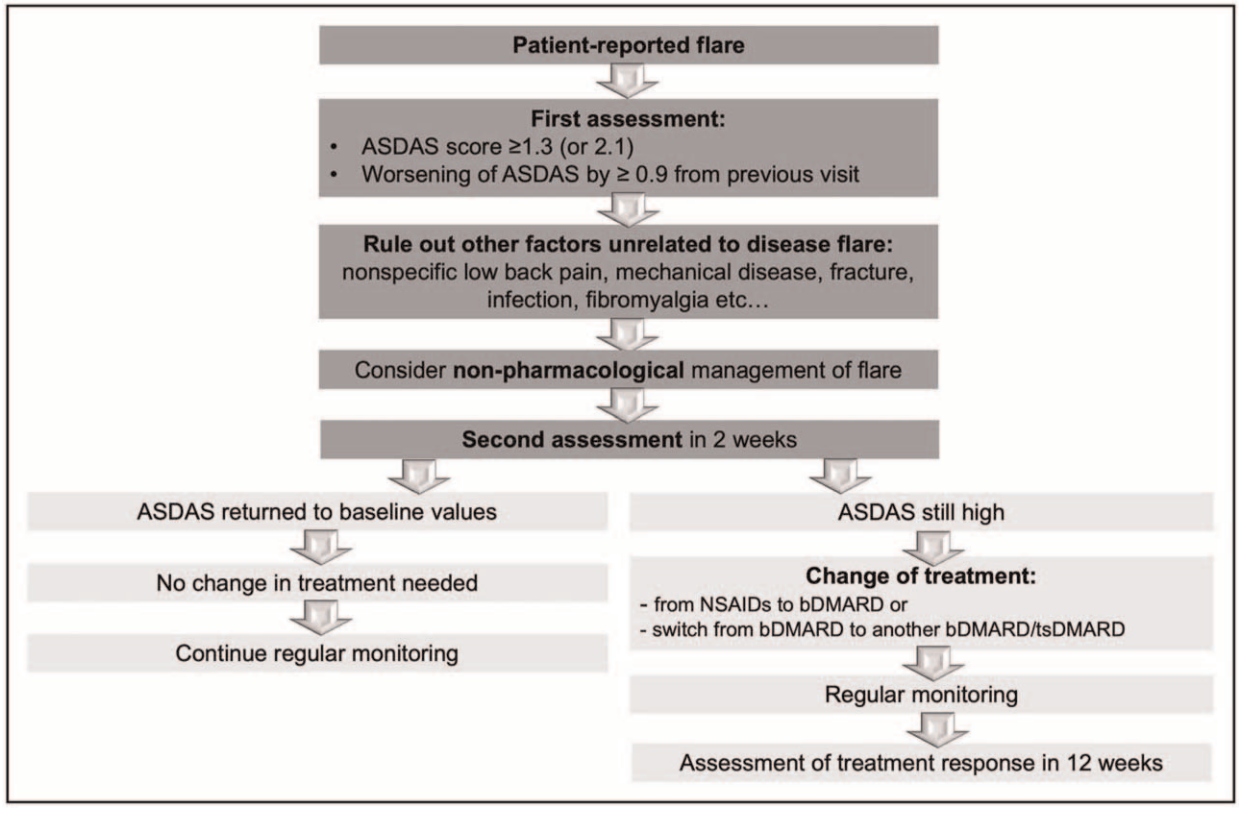

FIGURE 3. A proposal for flare management based on the Treat to target strategy in axSpA [5]. ASDAS, Ankylosing Spondylitis Disease Activity Score; bDMARD, biologic disease-modifying antirheumatic drug; tsDMARD, targeted synthetic disease-modifying antirheumatic drug.

CONCLUSION

Identifying a flare (or clinical worsening) is a crucial step in the management of a chronic illness with fluctuations in disease activity like axSpA. Although a standardised definition of flare based on the ASDAS score was proposed for trials by the ASAS group, defining flares in clinical practice remains challenging. Many aspects of the disease need to be taken into account in the clinical setting. Flares from the patient's perspective are also important to consider.

A better understanding of predictors of flares is needed to personalise the choice of an optimal treatment. The early recognition of flares and their severity may lead to better management, by applying a T2T strategy and taking into account nonpharmacological and pharmacological management.

Acknowledgements

None.

Financial support and sponsorship

None.

Conflicts of interest

Krystel Aouad: research grant: UCB, consulting fees: Novartis.
Laure Gossec: research grants: Amgen, Galapagos, Lilly, Pfizer, Sandoz, Sanofi; consulting fees: AbbVie, Amgen, BMS, Celltrion, Galapagos, Gilead, Janssen, Lilly, Novartis, Pfizer, Samsung Bioepis, Sanofi-Aventis, UCB.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:
- ■ of special interest
- ■■ of outstanding interest

1. Bingham CO, Pohl C, Woodworth TG, *et al.* Developing a standardized definition for disease 'flare' in rheumatoid arthritis (OMERACT 9 Special Interest Group). J Rheumatol 2009; 36:2335–2341.
2. Wendling D, Prati C. Flare in axial spondyloarthritis. The dark side of the outcome. Ann Rheum Dis 2016; 75:950–951.
3. Welsing PMJ, Landewé RBM, van Riel PLCM, *et al.* The relationship between disease activity and radiologic progression in patients with rheumatoid arthritis: a longitudinal analysis. Arthritis Rheum 2004; 50:2082–2093.
4. Dougados M, Wood E, Gossec L, *et al.* Flare in axial spondyloarthritis: investigation of meaningful changes in symptomatic outcome measures. Clin Exp Rheumatol 2017; 35:209–213.
5. Smolen JS, Schöls M, Braun J, *et al.* Treating axial spondyloarthritis and peripheral spondyloarthritis, especially psoriatic arthritis, to target: 2017 update of recommendations by an international task force. Ann Rheum Dis 2018; 77:3–17.
6. Aouad K, Gaudin P, Vittecoq O, *et al.* Cut-off value to identify a flare using the Flare Assessment in Rheumatoid Arthritis (FLARE-RA) questionnaire: analysis of the TOSCA study. Rheumatology (Oxford) 2021; 61:337–344.
7. Aouad K, Wendling D, Breban M, *et al.* Exploring remission concept in axial spondyloarthritis through the perception of rheumatologists using vignettes and priority ratings. Rheumatology (Oxford) 2021; keab711. doi: 10.1093/rheumatology/keab711.
8. Molto A, Gossec L, Meghnathi B, *et al.* An Assessment in SpondyloArthritis International Society (ASAS)-endorsed definition of clinically important worsening in axial spondyloarthritis based on ASDAS. Ann Rheum Dis 2018; 77:124–127.
9. Godfrin-Valnet M, Puyraveau M, Prati C, Wendling D. Flare in spondyloarthritis: thresholds of disease activity variations. Joint Bone Spine 2015; 82:192–195.
10. Gossec L, Portier A, Landewé R, *et al.* Preliminary definitions of 'flare' in axial spondyloarthritis, based on pain, BASDAI and ASDAS-CRP: an ASAS initiative. Ann Rheum Dis 2016; 75:991–996.
11. Moreno M, Gratacós J, Torrente-Segarra V, *et al.* Withdrawal of infliximab therapy in ankylosing spondylitis in persistent clinical remission, results from the REMINEA study. Arthritis Res Ther 2019; 21:88.
12. Baraliakos X, Listing J, Brandt J, *et al.* Clinical response to discontinuation of anti-TNF therapy in patients with ankylosing spondylitis after 3 years of continuous treatment with infliximab. Arthritis Res Ther 2005; 7:R439–R444.
13. Landewé R, Sieper J, Mease P, *et al.* Efficacy and safety of continuing versus withdrawing adalimumab therapy in maintaining remission in patients with nonradiographic axial spondyloarthritis (ABILITY-3): a multicentre, randomised, double-blind study. Lancet 2018; 392:134–144.
14. Haibel H, Heldmann F, Braun J, *et al.* Long-term efficacy of adalimumab after drug withdrawal and retreatment in patients with active nonradiographically evident axial spondyloarthritis who experience a flare. Arthritis Rheum 2013; 65:2211–2213.
15. Song I-H, Althoff CE, Haibel H, *et al.* Frequency and duration of drug-free remission after 1 year of treatment with etanercept versus sulfasalazine in early axial spondyloarthritis: 2 year data of the ESTHER trial. Ann Rheum Dis 2012; 71:1212–1215.
16. Sebastian A, Wojtala P, Lubiński Ł, *et al.* Disease activity in axial spondyloarthritis after discontinuation of TNF inhibitors therapy. Reumatologia 2017; 55:157–162.
17. Brandt J, Listing J, Haibel H, *et al.* Long-term efficacy and safety of etanercept after readministration in patients with active ankylosing spondylitis. Rheumatology (Oxford) 2005; 44:342–348.
18. Lian F, Zhou J, Wang Y, *et al.* Efficiency of dose reduction strategy of etanercept in patients with axial spondyloarthritis. Clin Exp Rheumatol 2018; 36:884–890.
19. Landewé RB, van der Heijde D, Dougados M, *et al.* Maintenance of clinical remission in early axial spondyloarthritis following certolizumab pegol dose reduction. Ann Rheum Dis 2020; 79:920–928.
20. Chen M-H, Lee M-H, Liao H-T, *et al.* Health-related quality of life outcomes in patients with rheumatoid arthritis and ankylosing spondylitis after tapering biologic treatment. Clin Rheumatol 2018; 37:429–438.
21. Breban M, Vignon E, Claudepierre P, *et al.* Efficacy of infliximab in refractory ankylosing spondylitis: results of a six-month open-label study. Rheumatology (Oxford) 2002; 41:1280–1285.
22. den Bosch FV, Wei JCC, Nash P, *et al.* Op0107 etanercept withdrawal and re-treatment in patients with inactive non-radiographic axial spondyloarthritis at 24 weeks: results of re-embark, an open-label, phase IV trial. Ann Rheum Dis 2020; 79:70–170.
23. ■ Chan Kwon O, Park M-C. BASDAI cut-off values corresponding to ASDAS cut-off values. Rheumatology (Oxford) 2021; keab494. doi: 10.1093/rheumatology/keab494.
This study highlights an 'equivalence' between ASDAS-CRP and BASDAI: the cut-offs values of BASDAI 1.9, 3.5 and 4.9 corresponded respectively to the values of ASDAS-CRP 1.3, 2.1 and 3.5.
24. ■ Aranda-Valera IC, Garrido-Castro JL, Ladehesa-Pineda L, *et al.* How to calculate the ASDAS based on C-reactive protein without individual questions from the BASDAI: the BASDAI-based ASDAS formula. Rheumatology (Oxford) 2020; 59:1545–1549.
This study shows that the BASDAI-based ASDAS (BASDAS) performs similarly to the ASDAS-CRP and can be calculated using the BASDAI score and CRP. These findings may be of use for clinicians when CRP is not available to calculate ASDAS-CRP.
25. Marzo-Ortega H, Gaffney KM, Gaffney K. Defining the target: clinical aims in axial spondyloarthritis. Rheumatology (Oxford) 2018; 57:vi18–vi22.
26. Lucasson F, Richette P, Aouad K, *et al.* Prevalence and consequences of psoriasis in recent axial spondyloarthritis: an analysis of the DESIR cohort over 6 years. RMD Open 2022; 8:e001986.
27. Bengtsson K, Forsblad-d'Elia H, Deminger A, *et al.* Incidence of extra-articular manifestations in ankylosing spondylitis, psoriatic arthritis and undifferentiated spondyloarthritis: results from a national register-based cohort study. Rheumatology (Oxford) 2021; 60:2725–2734.
28. Portier E, Dougados M, Moltó A. Disease activity outcome measures are only available in half of the electronic medical files of patients with axial spondyloarthritis followed in an outpatient clinic: the results of an audit of a tertiary-care rheumatology department. Rheumatol Int 2021; 42:825–829.
29. ■ De Craemer A-S, Renson T, Deroo L, *et al.* Peripheral manifestations are major determinants of disease phenotype and outcome in new onset spondyloarthritis. Rheumatology (Oxford) 2021; keab887. doi: 10.1093/rheumatology/keab887.
This study identified a group of patients with axSpA and concomitant peripheral involvement who had more unfavorable outcomes compared to axSpA patients without peripheral manifestations.
30. Cooksey R, Brophy S, Gravenor MB, *et al.* Frequency and characteristics of disease flares in ankylosing spondylitis. Rheumatology (Oxford) 2010; 49:929–932.

31. Bech B, Primdahl J, van Tubergen A, *et al.* 2018 update of the EULAR
■ recommendations for the role of the nurse in the management of chronic inflammatory arthritis. Ann Rheum Dis 2020; 79:61–68.

This article presents the updated recommendations for the role of the nurse in the management of chronic inflammatory arthritis and highlights the importance of the nurse's role in patient education, patient satisfaction, access to care, efficiency of care, psychosocial support and the encouragement of a patient's self-management.

32. Desthieux C, Molto A, Granger B, *et al.* Patient-physician discordance in global assessment in early spondyloarthritis and its change over time: the DESIR cohort. Ann Rheum Dis 2016; 75:1661–1666.

33. Brophy S, Calin A. Definition of disease flare in ankylosing spondylitis: the patients' perspective. J Rheumatol 2002; 29:954–958.

34. Barnett R, Ng S, Sengupta R. Understanding flare in axial spondyloarthritis:
■■ novel insights from daily self-reported flare experience. Rheumatol Adv Pract 2021; 5:rkab082.

This study using a smartphone app collected daily self-reported data on flares in patients with axSpA. Flares were related to pain, fatigue and stress along with disturbances in mood and sleep.

35. Helliwell PS, Tillett W, Waxman R, *et al.* Evaluation and validation of a patient-
■ completed psoriatic arthritis flare questionnaire. J Rheumatol 2021; 48:1268–1271.

This study evaluates the validity of the FLARE self-questionnaire that identify flares in patients with psoriatic arthritis.

36. Fautrel B, Morel J, Berthelot J-M, *et al.* Validation of FLARE-RA, a self-administered tool to detect recent or current rheumatoid arthritis flare. Arthritis RheumatolV 69 2017; 309–319.

37. Cooksey R, Brophy S, Dennis M, *et al.* Severe flare as a predictor of poor outcome in ankylosing spondylitis: a cohort study using questionnaire and routine data linkage. Rheumatology (Oxford) 2015; 54:1563–1572.

38. Jacquemin C, Maksymowych WP, Boonen A, Gossec L. Patient-reported flares in ankylosing spondylitis: a cross-sectional analysis of 234 patients. J Rheumatol 2017; 44:425–430.

39. Cozad MJ, Lindley LC, Crosby K, *et al.* Patient goals for living with rheumatoid
■ arthritis: a qualitative study. Clin Nurs Res 2022; 10547738221075784. doi: 10.1177/10547738221075784.

This study explores the patients' perceptions on disease burden in rheumatoid arthritis, their goals for living and preferences for symptoms and side-effect management.

40. Stone MA, Pomeroy E, Keat A, *et al.* Assessment of the impact of flares in ankylosing spondylitis disease activity using the flare illustration. Rheumatology (Oxford) 2008; 47:1213–1218.

41. McWilliams DF, Rahman S, James RJE, *et al.* Disease activity flares and pain flares in an early rheumatoid arthritis inception cohort; characteristics, antecedents and sequelae. BMC Rheumatol 2019; 3:49.

42. Aouad K, Ziade N, Baraliakos X. Structural progression in axial spondyloarthritis. Joint Bone Spine 2020; 87:131–136.

43. Uhrenholt L, Christensen R, Dinesen WKH, *et al.* Risk of flare after tapering or
■■ withdrawal of b-/tsDMARDs in patients with RA or axSpA: A systematic review and meta-analysis. Rheumatology (Oxford) 2021; keab902. doi: 10.1093/rheumatology/keab902.

This meta-analysis including patients with axSpA and rheumatoid arthritis found an increased risk of flare and persistent flare after TNF inhibitors withdrawal; whereas with bDMARD/tsDMARD tapering, an increased risk of flare but not persistent flare was reported.

44. Zheng Q, Liu W, Huang Y, *et al.* Predictive Value of Active Sacroiliitis in MRI
■ for Flare Among Chinese Patients with Axial Spondyloarthritis in Remission. Rheumatol Ther 2021; 8:411–424.

This prospective study on patients with axSpA achieving low disease activity shows that active sacroiliitis on MRI and absence of TNF inhibitor treatment were significantly associated with disease flares.

45. Aouad K, De Craemer A-S, Carron P. Can imaging be a proxy for remission in axial spondyloarthritis? Rheum Dis Clin North Am 2020; 46:311–325.

46. Proft F, Torgutalp M, Weiß A, *et al.* Sat0389 frequency of disease flares under long-term anti-tnf therapy in patients with early axial spondyloarthritis: results from the etanercept versus sulfasalazine in early axial spondyloarthritis trial. Ann Rheum Dis 2020; 79:1143–1144.

47. Adami G, Viapiana O, Rossini M, *et al.* Association between environmental air pollution and rheumatoid arthritis flares. Rheumatology (Oxford) 2021; 60:4591–4597.

48. Wendling D, Hecquet S, FogelO, *et al.* 2022 French Society for Rheumatology
■ (SFR) recommendations on the everyday management of patients with spondyloarthritis,including psoriatic arthritis. Joint Bone Spine 2022; 89:105344.

This article highlights the recent recommendations for the management of spondyloarthritis by the French Society for Rheumatology.

49. Molto A, López-Medina C, Van den Bosch FE, *et al.* Efficacy of a tight-control
■■ and treat-to-target strategy in axial spondyloarthritis: results of the open-label, pragmatic, cluster-randomised TICOSPA trial. Ann Rheum Dis 2021; 80:1436–1444.

This is the first T2T trial in axial spondyloarthritis. This study did not confirm the superiority of the T2T strategy compared to usual care for the primary outcome selected: the ASAS-Health Index.

50. van der Heijde D, Ramiro S, Landewé R, *et al.* 2016 update of the ASAS-EULAR management recommendations for axial spondyloarthritis. Ann Rheum Dis 2017; 76:978–991.

51. Passalent L, Cyr A, Jurisica I, *et al.* Motivators, barriers, and opportunity for E-health to encourage physical activity in axial spondyloarthritis: a qualitative descriptive study. Arthritis Care Res (Hoboken) 2022; 74:50–58.

52. Molto A, Gossec L, Poiraudeau S, *et al.* Evaluation of the impact of a nurse-led
■ program of patient self-assessment and self-management in axial spondyloarthritis: results of a prospective, multicentre, randomized, controlled trial (COMEDSPA). Rheumatology (Oxford) 2021; 60:888–895.

This study shows the benefits of a nurse-led program on self-management and self-assessment of disease activity in patients with axSpA.

Nonsteroidal anti-inflammatory drugs and cardiovascular disease risk in spondyloarthritis-spectrum diseases

Ho So and Lai-Shan Tam

Purpose of review
Increased cardiovascular (CV) risk associated with nonsteroidal anti-inflammatory drugs (NSAIDs) is well recognized in the general population. This may limit the use of this effective therapy in patients with spondyloarthritis (SpA), a population already at high CV risk.

Recent findings
Increased CV diseases and their risk factors in patients with SpA were consistently shown in recent population-level data. NSAIDs remained commonly prescribed in SpA, though their structural benefit remained controversial and the dispensing practice was variable in different regions in the world. A previous observation study suggested NSAIDs in SpA might be cardio-protective, possibly via their modulation of the chronic inflammatory state. A recent meta-analysis of nonrandomized studies also revealed no increased risk of a CV event. Interestingly, there is growing evidence that different NSAIDs might impose differential CV risk on patients with SpA.

Summary
Recent evidence suggested NSAIDs were associated with a neutral and possibly lower CV risk in patients with SpA, which provided some reassurance for their use.

Keywords
cardiovascular disease, nonsteroidal anti-inflammatory drugs, psoriatic arthritis, spondyloarthritis

INTRODUCTION

Spondyloarthritis (SpA) spectrum diseases are a group of chronic inflammatory disorders present with related yet different manifestations, with ankylosing spondylitis (AS) [currently known as radiographic axial SpA (r-axSpA)] being the prototype [1]. Depending on the predominant clinical features, the major subgroups include axial SpA (axSpA), peripheral SpA, and psoriatic arthritis (PsA) [2]. They share similar underlying pathogenic process mediated by pro-inflammatory cytokines particularly tumour necrosis factor (TNF)-α and interleukins 17 and 23, as well as co-morbidities such as cardiovascular diseases (CVD). The CV burden in SpA has been well described with increased CV risk factors, events, and related mortality [3]. Nonsteroidal anti-inflammatory drugs (NSAIDs), the first line and often long-term treatment in SpA, have been recommended to be used with caution in view of their association with increased risk of CV events [4]. It may limit the use of this therapy in patients with SpA. Conversely, through modulation of the chronic inflammatory state, NSAIDs in SpA might be cardio-protective. There is an unmet need to clarify how treatment choices, particularly the use of NSAIDs, impact CV risk in SpA. In the current narrative review, recent studies related to NSAIDs and CVD in SpA spectrum diseases are discussed.

CARDIOVASCULAR DISEASES IN SPONDYLOARTHRITIS

Excess mortality, morbidity, and CV risk compared to the general population were noted in patients with SpA. A nationwide retrospective cohort study

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Curr Opin Rheumatol 2022, 34:203–208
DOI:10.1097/BOR.0000000000000881

KEY POINTS

- Patients with spondyloarthritis have excess cardiovascular risk.
- NSAIDs, commonly prescribed in spondyloarthritis, are associated with increased cardiovascular risk in general population.
- In patients with spondyloarthritis, recent evidence suggested NSAIDs were associated with an equivocal and possibly lower cardiovascular risk, presumably due to their anti-inflammatory effect.
- Differential effect of different NSAIDs on cardiovascular risk in spondyloarthritis is postulated.

was published in 2021 examining the mortality in 5930 patients with AS from Israel [5▪]. Mortality rates were increased among AS patients compared to controls with an age-and-sex adjusted HR of 1.19 (95% CI 1.10–1.30). Age, male-gender, mean C-reactive-protein (CRP) levels, and general comorbidities were predictors of mortality. Baseline diabetes mellitus (DM) and ischemic heart disease (IHD) were more common in patients than in controls (14.9% versus 12.4% and 11.2% versus 9.2%, respectively, both $P < 0.01$). In a recent multicenter retrospective analysis of data from the electronic health record in Hong Kong, 1535 patients with SpA (19.4% were PsA) were compared with age- and sex-matched patients with nonspecific back pain [6▪]. The crude incidence rate of major adverse cardiovascular events (MACE) was higher in patients with SpA (715.2 per 100,000 patient-years). After adjustment for traditional risk factors and use of cardio-protective medications and NSAIDs, SpA was associated with a higher risk for MACE (HR 1.70; 95% CI 1.29–2.26; $P < 0.01$). In a study carried out at the University of Toronto Psoriatic Arthritis Clinic with 1490 patients followed for 15,062.8 patient-years, acute myocardial infarction (MI) was the second top cause of death after malignancy, although the overall SMR was increased (3.36, 95% CI 1.61–6.18) in the young patients aged 20–39 years only [7▪]. Two hundred and fifteen Greek PsA patients, from two tertiary hospitals, were compared with age/sex-matched rheumatoid arthritis (RA) and DM patients in another recent cross-sectional study [8▪]. Obesity (OR 2.83, 95% CI 1.65–4.86) and hyperlipidemia (OR 1.96, 95% CI: 1.32–2.90) were more prevalent in PsA compared with RA. No differences were observed for IHD, stroke, and MACE when comparing PsA patients with RA and DM, suggesting the former might be seen as an equivalently high CV burden disease. In a case-control study with 40 AS and 39 PsA patients, dyslipidemia was diagnosed in 47.5% of patients with AS and 71.8% of patients with PsA [9]. The level of TG and atherogenic index was significantly higher in patients than in the control group. A negative correlation between CRP and HDL levels (rho = 0.42, $P = 0.0132$) in PsA was also found. A retrospective cohort study ($n = 189$) of a median 9.9 years follow-up showed that high Disease Activity in Psoriatic Arthritis could predict CVD events independent of traditional CV risk scores in patients with PsA [10]. Besides reiterating the increased CVD and risk factors in patient with SpA, the above recent evidence also hints the importance of disease activity in driving underlying atherosclerosis.

Carotid ultrasound has been proposed to improve CV risk stratification in PsA patients [10]. Rueda Gotor and colleagues also demonstrated in a study of 343 patients with axSpA that carotid plagues (36% versus 25%, $P = 0.010$) were more common in patients than controls, and that patients were more likely to be reclassified into the very-high risk category after carotid ultrasound than controls [11]. In another cross-sectional study including 114 patients with axSpA from a regional Spanish registry, increased traditional CV risk factors, Systematic COronary Risk Evaluation (SCORE), and the presence of carotid plaques were found in patients compared with age- and sex-matched healthy controls [12]. Importantly, carotid plaques and SCORE were associated with radiographic structural damage. axSpA patients with persistently elevated CRP also displayed increased cIMT and a higher number of syndesmophytes, which points to inflammation as a possible link between increased CV risk and structural damage in these patients.

NONSTEROIDAL ANTI-INFLAMMATORY DRUGS IN SPONDYLOARTHRITIS

The most recent treatment guidelines for axial SpA recommend NSAIDs as first-line medication for active disease, and continuous use is conditionally recommended over on demand treatment [13]. In treatment naïve patients with PsA, the latest guidelines also recommend prescribing NSAIDs to relieve musculoskeletal signs and symptoms first [14]. There is strong evidence demonstrating effective symptom control for NSAIDs in AS [15]. However, their efficacy on structural damage progression is controversial. A recent systematic review and meta-analysis looked at the effect of therapy on radiographic progression in axial SpA and identified eight studies involved NSAIDs [16]. No significant difference in spinal radiographic progression was observed between NSAID-treated and control

patients (mSASSS difference −0.30 [95% CI −2.62, 1.31], I2 = 71%) at 2 years. However, there were methodologic differences between the studies, e.g., disease status (early or established and radiographic or nonradiographic), assessment tool (mSASSS or BASRI spine scores and spine or SI joint score), and dosing strategies (continuous versus on-demand NSAIDs, NSAID index high versus low, and NSAID use versus no NSAID use). These may explain the high heterogeneity in the results. There is an ongoing randomized controlled trial (RCT) in which radiographic progression at 2 years is being compared between treatment with TNFi alone and the combination of TNFi and NSAIDs, based on promising observational data showing a synergistic effect with this combination approach [17].

The use of NSAIDs in SpA in daily clinical practice is quite variable. There are recent studies from different regions of the world revealing the real-world usage of NSAIDs in SpA. In a retrospective, observational study representing nationwide administrative claims data from the USA which included 2180 patients with AS and 5681 patients with PsA, at diagnosis NSAIDs were prescribed in 43.0% of patients with AS and 39.0% of patients in PsA, both significantly higher than matched controls [18]. Another study evaluated the primary care analgesia prescribing in English National Health Service-managed patients with inflammatory arthritis [19]. From 2000 to 2015, oral NSAID prescription dropped from ∼60% to ∼30% in PsA and 40% to 25% in axial SpA. On the other hand, a national health insurance database study in South Korea showed that the most commonly prescribed pharmacological treatment options in AS remained to be NSAIDs from 2006 (71.1%) to 2016 (63.4%) [20]. Interestingly, notable geographic variations by the state in treatment use were observed in a retrospective analysis utilizing an US claims database [21]. NSAIDs were used from 66% in Alabama to 22% in Wisconsin for patients with AS. Further research is encouraged to identify factors that might cause these variations, such as awareness of treatment guidelines and concerns from prescribing clinicians.

NONSTEROIDAL ANTI-INFLAMMATORY DRUG AND CARDIOVASCULAR DISEASES

NSAIDs inhibit cyclooxygenase (COX)-2, leading to an imbalance between prostaglandin I2 production by the vascular endothelium and thromboxane A2 production by platelets, resulting in hypertension and atherosclerotic plaque destabilization, thus a net pro-thrombotic effect [22]. Increased risk of CV events (stroke and MI) associated with NSAIDs is well demonstrated in the non-SpA population by a meta-analysis of 31 RCTs [23]. However, the indication for treatment of the included studies was apparently dominated by non-inflammatory conditions such as osteoarthritis.

Notably, rofecoxib, an early generation selective COX2 inhibitors was associated with significantly elevated CV risk leading to its withdrawal from the market [24]. The balance between pro-inflammatory and anti-inflammatory prostaglandins isomerases seems to be an important determinant of the role of COX-2 in plaque stability [25]. In contrast, naproxen was not associated with excess CV risk according to a large-scale meta-analysis of over 200 trials [26]. Another meta-analysis also concluded that when rofecoxib was removed, no difference was found with any comparison between COX2 inhibitors and nonselective NSAIDs with regard to CV outcomes, suggesting rofecoxib might skew the previous known association [27]. Although the NSAIDs equivalent score was recommended by the Assessment of Spondyloarthritis International Society (ASAS) to quantify and standardize the dose and strength of different NSAIDs in clinical studies, the differential effects and side effects of NSAIDs due to their selectivity are not represented [28].

NONSTEROIDAL ANTI-INFLAMMATORY DRUG AND CARDIOVASCULAR DISEASES IN SPONDYLOARTHRITIS

An early retrospective cohort study ($n = 3{,}809$) suggested the association of NSAIDs, in particular COX2 inhibitors, with increased risk of IHD or MI in patients with AS [29]. However, Haroon *et al.* performed a large retrospective cohort study ($n = 21{,}473$) in Ontario, Canada, and found among patients with AS aged 66 years and older, NSAID use was associated with a reduced risk of vascular mortality (HR 0.1, 95% CI, 0.01–0.61; $P = 0.01$) [30]. Interestingly, a study on the risk of MI in AS using data from a large UK primary care-based data set, demonstrated that diclofenac is associated with MI risk in AS, while naproxen is not [31]. This raises the possibility of differential effects of NSAIDs, potentially related to their selectivity of COX2 inhibition, on CVD risk. However, in the large randomized controlled PRECISION trial, no increase in CV event risk with celecoxib was seen as compared to other traditional NSAIDs in a subgroup of patients with RA [32].

A recent systematic review and meta-analysis on effects of therapies on CV events in AS identified 9 nonrandomized studies regarding NSAIDs [33▪▪]. Among all NSAID users versus nonusers, no increased risk of CV event as a whole was observed; however, the risk of stroke was significantly lower (RR 0.58, 95% CI 0.37–0.93, I2 = 66%). Cox-2

inhibitors were associated with reduced risk of all CV events (RR 0.48, 95% CI 0.33–0.70, I2 = 0%), while nonselective NSAIDs were not associated with any raised or reduced risk of any CV event. Most studies adjusted for multiple confounders including baseline demographics, traditional CV risk factors, and comorbidities. However, heterogeneity remained high for some CV outcomes, which was likely related to the difference in study designs and NSAIDs prescription practices examined. Importantly, as all the studies were retrospective in design, with data retrieved from administrative databases, disease-specific characteristics such as disease activity were not available.

Subsequently, a large nested case-control study using an US insurance database investigated the risk of MI related the use of therapies in AS/PsA from 1994 to 2018 [34▪▪]. Among 26,648 AS subjects, relative to NSAID use, the odds ratio for MI among TNFi only users was 0.85 (95% CI 0.39–1.85) and for DMARD only users was 1.04 (95% CI 0.65–1.68) after adjusting for traditional CV risk factors. In 43,734 subjects with PsA, relative to DMARD use, the OR among NSAID users only was 0.84 (95% CI 0.61–1.17). When combining AS and PsA, no individual or combination therapies had a significant association with risk of MI. In the retrospective cohort study done in Hong Kong mentioned above, while SpA patients with anti-TNF use had a reduced risk of MACE (HR 0.37, 95%CI 0.17–0.80, $P = 0.01$), the use of NSAIDs was not found to be associated with the risk of MACE in the COX regression analysis [6▪].

On the other hand, 628 AS patients without baseline hypertension were enrolled in a prospective cohort study. After controlling for other variables, continuous NSAID use was associated with a hazard ratio of 1.12 for incident hypertension (95% CI 1.04–1.20), compared to noncontinuous or no use [35▪]. The association did not differ in subgroups defined by age, body mass index, biological use, or disease activity. In the broader peripheral and axial SpA population, a large cross-sectional study ($n = 3923$) showed that there was an association of hypertension with disease duration but not with self-reported NSAID use compared with no use [36]. The discrepancy of the results could be explained by the different study designs and disease/outcome definitions.

In the latest retrospective cohort analysis of 200 patients with PsA recruited from 2008 to 2015 and followed until the end of 2019, after a mean follow-up of 8.8 ± 3.8 years, 30 (15%) patients developed a first CV event [37▪▪]. The multivariable Cox regression model showed that time-varying NSAIDs exposure (HR 0.38, 95% CI 0.15–0.96) was associated with a lower CV events risk, while time-varying CRP level (HR 1.02, 95% CI 1.00–1.04) were significantly associated with CV events after adjusting for baseline FRS.

DISCUSSION

Up to this moment, as all the evidence is retrospective in nature, the exact effect and mechanism of NSAIDs on CVD risk in patients with SpA remains unclear. While most studies did control for comorbidities such as HT and DM, residual confounding factors including tobacco use, diet, or physical activity are difficult to be adjusted, particularly for studies using registry data. Another important limitation is the potential channeling error as NSAIDs are generally prescribed with caution in at risk individuals. Lastly, the generalizability of results from previous studies on individuals with AS, who tend to have more severe disease than a more broadly defined SpA population is questionable. As treatment of the underlying inflammatory process could contribute to improved CV risk in patients with inflammatory arthritis, it is reasonable to postulate NSAID use in SpA could reduce CV risk due to its effect on disease activity [38]. Better control of disease activity, in turn, may lead to increases in physical activity and improvements in CV risk profile (Fig. 1). To this end,

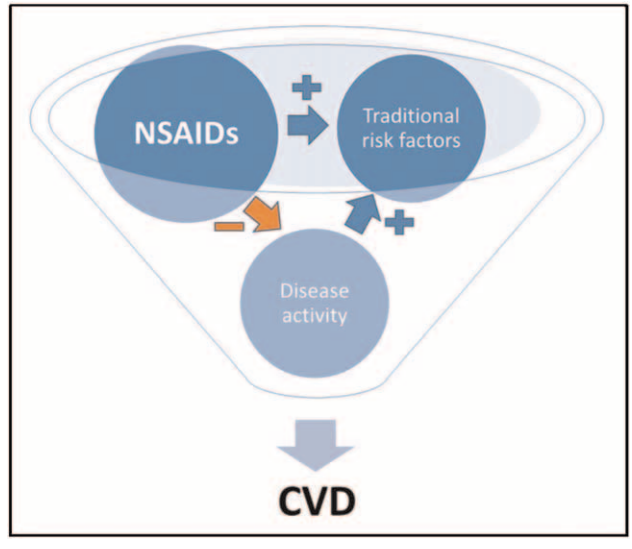

FIGURE 1. Complex interplay between various factors associated with NSAIDs and cardiovascular (CVD) disease in SpA. Usage of NSAIDs, traditional cardiovascular risk factors and systemic inflammation related to uncontrolled disease activity contribute to increased CVD in patients with SpA. While NSAIDs are associated with a number of traditional cardiovascular risk factors, their anti-inflammatory effect might improve the overall cardiovascular risk by reducing disease activity leading to better mobility and cardiovascular risk profile. NSAIDs, nonsteroidal anti-inflammatory drugs; SpA, spondyloarthritis.

studies of TNFi use on subclinical atherosclerosis in AS have suggested that CVD risk is reduced alongside the reduction of inflammation [39,40]. While setting up an RCT to study the risk of NSAIDs would require a massive number of patients due to the low event rate, long term prospective studies or big-data analysis taking into consideration the disease activity on top of traditional CV risk factors are encouraged to further decipher the complex interplay of inflammation, CVD risk, and drug effects. Given that SpA is a systemic inflammatory condition, treatment options should also be based on the merit of individual medications in the prevention of microvascular damage and reduction of CV risk.

CONCLUSION

Limited data discussed above suggest equivocal and possibly lower risk of CVD in SpA patients on NSAIDs, unlike their use in the general population. It should provide some reassurance for the use of NSAIDs in SpA. The long-term effect of different NSAIDs on CVD in this population should be further studied to justify an optimal risk/benefit usage.

Acknowledgements

None.

Financial support and sponsorship

None.

Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:
- ■ of special interest
- ■■ of outstanding interest

1. Boel A, Molto A, van der Heijde D, *et al.* Do patients with axial spondyloarthritis with radiographic sacroiliitis fulfil both the modified New York criteria and the ASAS axial spondyloarthritis criteria? Results from eight cohorts. Ann Rheum Dis 2019; 78:1545–1549.
2. Dougados M, Baeten D. Spondyloarthritis. Lancet 2011; 377:2127–2137.
3. Heeneman S, Daemen MJAP. Cardiovascular risks in spondyloarthritides. Curr Opin Rheumatol 2007; 19:358–362.
4. Agca R, Heslinga SC, Rollefstad S, *et al.* EULAR recommendations for cardiovascular disease risk management in patients with rheumatoid arthritis and other forms of inflammatory joint disorders: 2015/2016 update. Ann Rheum Dis 2017; 76:17–28.
5. ■ Ben-Shabat N, Shabat A, Watad A, *et al.* Mortality in ankylosing spondylitis according to treatment: a nationwide retrospective cohort study of 5900 patients from Israel. Arthritis Care Res 2021; doi: 10.1002/acr.24616. [Epub ahead of print]

This large nationwide retrospective study reiterated the increased mortality in AS which was associated with general cormobordities including CVD.

6. ■ Chan SCW, Teo CK, Li PH, *et al.* Cardiovascular risk in patients with spondyloarthritis and association with anti-TNF drugs. Ther Adv Musculoskel Dis 2021; 13: 1759720X211032444.

This territory-wide retrospective study showed an increased risk of MACE in SpA patients compared to controls with nonspecific back pain independent of NSAID use.

7. ■ Elalouf O, Muntyanu A, Polachek A, *et al.* Mortality in psoriatic arthritis: risk, causes of death, predictors for death. Semin Arthritis Rheum 2020; 50:571–575.

This prospective study showed AMI was the second commonest cause of death in patients with PsA.

8. ■ Fragoulis GE, Evangelatos G, Tentolouris N, *et al.* Higher depression rates and similar cardiovascular comorbidity in psoriatic arthritis compared with rheumatoid arthritis and diabetes mellitus. Ther Adv Musculoskel Dis 2020; 12:1759720X20976975.

In this cross-sectional study, PsA patients had similar prevalence of CVD compared to patients with RA and DM.

9. Ozdowska P, Kowalik I, Sadowski K, *et al.* Patterns of dyslipidemia in young patients with seronegative spondyloarthropathies without cardiovascular diseases. Reumatologia 2021; 59:285–291.
10. Lam SHM, Cheng IT, Li EK, *et al.* DAPSA, carotid plaque and cardiovascular events in psoriatic arthritis: a longitudinal study. Ann Rheum Dis 2020; 79:1320–1326.
11. Rueda-Gotor J, Quevedo-Abeledo JC, Corrales A, *et al.* Reclassification into very-high cardiovascular risk after carotid ultrasound in patients with axial spondyloarthritis. Clin Exp Rheumatol 2020; 38:724–731.
12. Ladehesa-Pineda ML, Arias de la Rosa I, López Medina C, *et al.* Assessment of the relationship between estimated cardiovascular risk and structural damage in patients with axial spondyloarthritis. Ther Adv Musculoskel Dis 2020; 12:1759720X20982837.
13. Ward MM, Deodhar A, Gensler LS, *et al.* 2019 Update of the American College of Rheumatology/Spondylitis Association of America/Spondyloarthritis Research and Treatment Network Recommendations for the treatment of ankylosing spondylitis and nonradiographic axial spondyloarthritis. Arthritis Rheumatol 2019; 71:1599–1613.
14. Gossec L, Baraliakos X, Kerschbaumer A, *et al.* EULAR recommendations for the management of psoriatic arthritis with pharmacological therapies: 2019 update. Ann Rheum Dis 2020; 79:700–712.
15. Taurog JD, Chhabra A, Colbert RA. Ankylosing spondylitis and axial spondyloarthritis. N Engl J Med 2016; 374:2563–2574.
16. Karmacharya P, Duarte-Garcia A, Dubreuil M, *et al.* Effect of therapy on radiographic progression in axial spondyloarthritis: a systematic review and meta-analysis. Arthritis Rheumatol 2020; 72:733–749.
17. Gensler LS, Gianfrancesco M, Weisman MH, *et al.* OP0198 Combined effects of tumour necrosis factor inhibitors and nsaids on radiographic progression in ankylosing spondylitis. Ann Rheum Dis 2018; 77(Suppl 2): 148.
18. Hunter T, Nguyen C, Birt J, *et al.* Pain medication and corticosteroid use in ankylosing spondylitis, psoriatic arthritis, and rheumatoid arthritis in the United States: a retrospective observational study. Rheumatol Ther 2021; 8:1371–1382.
19. Scott IC, Bailey J, White C, *et al.* Analgesia prescribing in patients with inflammatory arthritis in England: an observational study using electronic healthcare record data. Rheumatology 2021; doi: 10.1093/rheumatology/keab870. [Epub ahead of print]
20. Park JS, Hong JY, Kim HK, *et al.* National pharmacological treatment trends for ankylosing spondylitis in South Korea: A national health insurance database study. PLoS One 2020; 15:e0240155.
21. Deodhar A, Kruzikas D, Zhou L, *et al.* Geographic variations in diagnosis and treatment of ankylosing spondylitis in the United States: a real-world study. Rheumatol Ther 2022; 9:447–463.
22. Caughey GE, Cleland LG, Penglis PS, *et al.* Roles of cyclooxygenase (COX)-1 and COX-2 in prostanoid production by human endothelial cells: selective up-regulation of prostacyclin synthesis by COX-2. J Immunol 2001; 167:2831–2838.
23. Trelle S, Reichenbach S, Wandel S, *et al.* Cardiovascular safety of nonsteroidal anti-inflammatory drugs: network meta-analysis. BMJ 2011; 342:c7086.
24. Weir MR, Sperling RS, Reicin A, Gertz BJ. Selective COX-2 inhibition and cardiovascular effects: a review of the rofecoxib development program. Am Heart J 2003; 146:591–604.
25. Cipollone F, Fazia ML. COX-2 and atherosclerosis. J Cardiovasc Pharmacol 2006; 47(Suppl 1):S26–36.
26. Bhala N, Emberson J, Merhi A, *et al.* Vascular and upper gastrointestinal effects of nonsteroidal anti-inflammatory drugs: meta-analyses of individual participant data from randomised trials. Lancet 2013; 382:769–779.
27. Gunter BR, Butler KA, Wallace RL, *et al.* Nonsteroidal anti-inflammatory drug-induced cardiovascular adverse events: a meta-analysis. J Clin Pharmacy Ther 2017; 42:27–38.
28. Dougados M, Simon P, Braun J, *et al.* ASAS recommendations for collecting, analysing and reporting NSAID intake in clinical trials/epidemiological studies in axial spondyloarthritis. Ann Rheum Dis 2011; 70:249–251.
29. Essers I, Stolwijk C, Boonen A, *et al.* Ankylosing spondylitis and risk of ischaemic heart disease: a population-based cohort study. Ann Rheum Dis 2016; 75:203–209.
30. Haroon NN, Paterson JM, Li P, *et al.* Patients with ankylosing spondylitis have increased cardiovascular and cerebrovascular mortality: a population-based study. Ann Intern Med 2015; 163:409–416.
31. Dubreuil M, Louie-Gao Q, Peloquin CE, *et al.* Risk of myocardial infarction with use of selected nonsteroidal anti-inflammatory drugs in patients with spondyloarthritis and osteoarthritis. Ann Rheum Dis 2018; 77:1137–1142.

32. Nissen SE, Yeomans ND, Solomon DH, *et al.* Cardiovascular safety of celecoxib, naproxen, or ibuprofen for arthritis. N Engl J Med 2016; 375:2519–2529.

33. ■■ Karmacharya P, Shahukhal R, Crowson CS, *et al.* Effects of therapies on cardiovascular events in ankylosing spondylitis: a systematic review and meta-analysis. Rheumatol Ther 2020; 7:993–1009.

In this meta-analysis on effect of therapies on CV events in AS, results of 9 nonrandomized studies up to May 2020 were pooled. NSAID users did not seem to have a higher risk of any CV events, while cox-2 inhibitor use was associated with reduced risk of composite CV events. However, heterogeneity of the included studies is an issue.

34. ■■ Stovall R, Peloquin C, Felson D, *et al.* Relation of therapies for ankylosing spondylitis and psoriatic arthritis to risk of myocardial infarction: a nested case control study. BMC Rheumatol 2021; 5:36.

This is a large nested case control study on relation of risk of MI and therapies for SpA including PsA. It was found that among SpA or AS/PsA individually, TNFi or DMARDs did not appeared to be protective or harmful relative to DMARD use.

35. ■ Liew JW, Ward MM, Reveille JD, *et al.* Nonsteroidal antiinflammatory drug use and association with incident hypertension in ankylosing spondylitis. Arthritis Care Res 2020; 72:1645–1652.

In this prospective cohort study, continuous NSAID use in AS was associated with a small increased risk of incident hypertension, as compared to noncontinuous or no NSAID use.

36. Derakhshan MH, Goodson NJ, Packham JC, *et al.* Increased risk of hypertension associated with spondyloarthritis disease duration: results from the ASAS-COMOSPA Study. J Rheumatol 2019; 46:701–709.

37. ■■ Lam SH, So H, Cheng IT, *et al.* Association of C-reactive protein and nonsteroidal anti-inflammatory drugs with cardiovascular events in patients with psoriatic arthritis: a time-dependent Cox regression analysis. Ther Adv Musculoskelet Dis 2021; 13:1759720x211027712.

This is a single centered retrospective cohort study on CV events in patients with PsA. After adjusting for baseline CV risk, it was shown for the first time that NSAIDs exposure was associated with a significantly reduced risk of CV events in PsA patients.

38. Roubille C, Richer V, Starnino T, *et al.* The effects of tumour necrosis factor inhibitors, methotrexate, nonsteroidal anti-inflammatory drugs and corticosteroids on cardiovascular events in rheumatoid arthritis, psoriasis and psoriatic arthritis: a systematic review and meta-analysis. Ann Rheum Dis 2015; 74:480–489.

39. van Sijl AM, van Eijk IC, Peters MJ, *et al.* Tumour necrosis factor blocking agents and progression of subclinical atherosclerosis in patients with ankylosing spondylitis. Ann Rheum Dis 2015; 74:119–123.

40. Angel K, Provan SA, Fagerhol MK, *et al.* Effect of 1-year anti-TNF-α therapy on aortic stiffness, carotid atherosclerosis, and calprotectin in inflammatory arthropathies: a controlled study. Am J Hypertens 2012; 25:644–650.

Pro and contra: is synovitis, acne, pustulosis, hyperostosis, and osteitis (SAPHO) a spondyloarthritis variant?

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Purpose of review
The purpose of this review is to present the up-to-date evidence on the epidemiology, pathogenesis, musculoskeletal manifestations, and imaging of the synovitis, acne, pustulosis, hyperostosis, and osteitis (SAPHO) syndrome and to discuss its relationship with spondyloarthritis (SpA).

Recent findings
SAPHO is a rare inflammatory disorder of bone, joints, and skin, with a worldwide distribution that predominantly affects the middle-age adults. The hallmark of the syndrome is a constellation of sterile inflammatory osteitis, hyperostosis, and synovitis involving the anterior chest wall, associated with acneiform and neutrophilic dermatoses, such as palmoplantar pustulosis and severe acne. The axial skeleton, sacroiliac, and peripheral joints can be involved in a similar fashion to SpA. The pathogenesis of the syndrome is multifactorial. The diagnosis is mainly based on the clinical and typical radiological features. The treatment approach is based on the off-label use of antibiotics, bisphosphonates, disease-modifying antirheumatic drugs, and anticytokine biologics.

Summary
The SAPHO syndrome shares common features with SpA-related diseases, yet also shows some unique pathogenetic and clinical features. The nosology of SAPHO remains a subject of controversy, awaiting further research into the pathogenetic and clinical aspects of this syndrome. A better understanding of these aspects will improve the diagnostics and clinical care of patients with SAPHO.

Keywords
classification, nosology, psoriasis, spondyloarthritis, sterile osteitis

INTRODUCTION

The synovitis, acne, pustulosis, hyperostosis, and osteitis (SAPHO) syndrome represents a rare and heterogeneous disorder characterized by chronic inflammatory involvement of anterior chest wall and axial skeleton associated with acneiform and neutrophilic dermatoses. In Japan, the pustulotic arthro-osteitis (PAO) syndrome was defined by Sonozaki *et al.* in 1981 based on 53 cases of costoclavicular or manubriosternal regions lesions associated with palmoplantar pustulosis (PPP) [1]. In Europe, the syndrome was proposed in 1987 by the French Society of Rheumatology based on a national survey of 85 cases with primary anterior thoracic and peripheral hyperostosis associated with PPP and severe acne [2,3]. Over years, above fifty different names have been used for SAPHO, including anterior chest wall inflammatory syndrome, sternocostoclavicular hyperostosis [4], pustulo-psoriatic hyperostotic spondyloarthritis (SpA), and others. The most updated diagnostic criteria for SAPHO published in 2003, based on a cohort of 120 SAPHO patients, include the combination of characteristic osteoarticular and skin manifestations, requiring exclusion of

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Curr Opin Rheumatol 2022, 34:209–217
DOI:10.1097/BOR.0000000000000884

KEY POINTS

- SAPHO is an uncommon inflammatory syndrome in which a wide range of skin and osteoarticular manifestations occur, with palmoplantar pustulosis and inflammation of the anterior chest wall joints and bones considered the hallmark of the syndrome.
- Disease heterogeneity in SAPHO may be explained by genetic, environmental, and tissue-specific factors.
- Though there are differences in the epidemiology, genetics, clinical presentation, and long-term outcomes between SAPHO and spondyloarthritis, the similarities outweigh the differences.
- The treatment of SAPHO is based on expert opinion and includes, among others, bisphosphonates, and biologic drugs targeting TNF alpha, IL-17, and IL-23 based on the shared patho-immunological profile between SAPHO and spondyloarthritis.

concurrent inflammatory bowel disease, bone infection, and tumors [5]. These diagnostic criteria, based only on clinical grounds, remain preliminary, and lack clinical validation. In pediatric medicine, chronic recurrent multifocal osteomyelitis (CRMO), a form of chronic nonbacterial osteomyelitis (CNO) with a predilection for tubular long bones and clavicles defined in 1978 by Bjorkstern [6], is considered related to the spectrum of SAPHO. Because of the close overlap between SAPHO and CNO, the international research groups currently collaborate on developing a core domain set for both entities to be used in observational studies and clinical trials [7].

Since the introduction of SAPHO, controversy related to its categorization as a distinct and unique entity, as opposed to a part of the SpA-related diseases spectrum, remains unsolved. The latter argument is supported by the existence of overlapping pathologic, clinical, and radiologic characteristics of SAPHO with ankylosing spondylitis (AS) and psoriatic arthritis (PsA). In a recently published survey of the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) membership, the Japan SpA and Israeli Societies of Rheumatology shed further light on the controversies around the classification of SAPHO. SAPHO was considered as a subtype of SpA by 48.7% ($n = 38$), a subtype of PsA by 19.2% ($n = 15$), a separate entity by 25.6% ($n = 20$), and reactive arthritis subtype by 6.4% ($n = 5$) [8▪]. The purpose of this review is to present the up-to-date evidence on the epidemiology, pathogenesis, musculoskeletal manifestations, and imaging of the SAPHO syndrome and to discuss its relationship with SpA-related diseases.

SYNOVITIS, ACNE, PUSTULOSIS, HYPEROSTOSIS, AND OSTEITIS EPIDEMIOLOGY

SAPHO is a rare syndrome whose incidence and prevalence are unknown. Lack of validated criteria, and diagnostic delays of SAPHO ranging between 3.8 and 9.1 years [9–12] highlight the challenge in estimating the true prevalence of the syndrome. The reports of SAPHO cohorts from Europe [9–11,13–15], China [12,16], Japan [17], USA [18], and Australia [19,20] point to its wide geographic distribution. SAPHO predominantly affects an adult population, and it is more prevalent in females diagnosed under the age of 30 [9,10,12,13,15,16]. In a Japanese cohort of 165 patients with PAO, a male to female ratio was 1:3.7, and the mean age of patients was 50.2 years [17]. SAPHO cases among children [21,22] and adolescents [23] were also reported.

SYNOVITIS, ACNE, PUSTULOSIS, HYPEROSTOSIS, AND OSTEITIS PATHOGENESIS

The pathogenesis of SAPHO is not well defined and is considered multifactorial encompassing genetic, infectious, and immunological components [24]. Recently, proteomics, transcriptomics, and microbiome studies shed insight into the pathogenesis of SAPHO, suggesting novel potential biomarkers for identifying the syndrome.

Genetic factors

Genetic factors have been implicated in SAPHO syndrome based on familial clustering [25–27], but the rarity of the condition makes genetic studies difficult. HLA-B27 carriage was reported between 4% and 30% of SAPHO patients by some [10,28–30] but not in other studies [13]. Further studies of class II HLA antigens suggested no role for HLA-B27, HLA-Cw6, or HLA-DR [14]. Several genes located on chromosomes 1 and 18, including LPIN2, PSTPIP2, and NOD2, have been implicated in conditions similar to SAPHO syndrome, but not to be directly pathogenic in SAPHO syndrome itself [31]. No genetic variants in FBLIM1 encoding filamin binding LIM protein 1, suggested as a candidate gene in CRMO [32], were found in SAPHO [15]. A genome-wide association study (GWAS) of 49 patients and 121 control subjects, further validated by whole-exome sequencing (WES), identified aberrant osteoclast differentiation pathways involved in SAPHO syndrome [33▪]. Recently, transcriptome analysis of the differentially expressed genes in peripheral neutrophils from patients with SAPHO revealed an overactive neutrophil recruitment profile [34].

Furthermore, long noncoding RNAs (lncRNAs) transcriptome profile changes, deregulated RNAs GAS7 and lnc-CLLU1.1-1:2, associated with SAPHO syndrome were found, suggesting potential diagnostic biomarkers [35▪]. Plasma proteomic profile of SAPHO patients detected upregulation of complement system inhibitors, CFH and C4BP,offering other potential biomarkers for disease diagnosis [36].

Infectious factors

The pathogenetic role of low-virulent pathogens triggering autoimmune response and chronic osteitis has been proposed by several studies based on the isolation of microorganisms from bone, and skin lesions as well as synovial tissue [37–39]. *Cutibacterium acnes* (*C. acnes*), formerly *Propionibacterium acnes*, is the most frequently isolated pathogen from bone specimens from SAPHO patients [38,40], although detected only in a small number of bone biopsies [41,42]. *C. acnes* is an ordinary skin saprophyte involved in the pathogenesis of acne. *C. acnes* can trigger NLRP3-inflammasome activation and IL-1β and tumour necrosis factor alpha (TNF-α) processing and secretion in monocytes-macrophages [43]. A relative deficiency of the metabolic transcription factor forkhead box 01 (Fox01) in the nucleus of sebaceous cells in acne and psoriatic lesions might help *C. acnes* to escape innate immunity to persist in a latent state in bone cells [44], thus supporting the hypothesis that SAPHO may be triggered by persistence of *C. acnes* in phagocytes, skin, and bone cells in genetically predisposed individuals (e.g. deficiency of Fox01). In contrast, the loss of efficacy of antibiotic treatment after discontinuation in patients with SAPHO is against this hypothesis [45].

Focal infection (dental infection, sinusitis, nasopharyngitis) and oral dysbiosis are important contributors to the pathogenesis of PAO in Japan [17,46▪▪].

Immune dysregulation

Immune system dysfunction has been described in patients with SAPHO syndrome, considered as an autoinflammatory disorder associated with IL-1 dysregulation [38]. The inflammatory response in SAPHO is supported by increased serum levels of pro-inflammatory cytokines, including TNF-α, IL-6, IL-8, IL-18, and IL-23 [47,48]. Activation of TH17 axis was observed in patients with SAPHO, to a higher extent than in patients with PsA [49]. Notably, a distinct expression of cytokines was found in patients with active compared to inactive disease, with increased IL-6, receptor activator nuclear factor kappa-B ligand (RANKL), and RANKL/osteoprotegerin ratio and decreased TGF-β1 level, respectively [50]. Immune dysregulation in SAPHO may be also related to a depletion of peripheral natural killer (NK) cells and an imbalance of Th17 and regulatory T (Treg) cells [51]. To date, no specific autoantibodies were found in SAPHO patients [52].

CLINICAL MANIFESTATIONS OF SYNOVITIS, ACNE, PUSTULOSIS, HYPEROSTOSIS, AND OSTEITIS

The clinical manifestations of SAPHO are reflected by its descriptive acronym. Anterior chest involvement is the hallmark osteoarticular manifestation of the syndrome and may occur independently of cutaneous findings present in approximately 60% of patients. Clinical presentation of SAPHO may occur in a number of medical specialties, including paediatrics, rheumatology, dermatology, and orthopedics. A high index of suspicion and recognition of the characteristic clinical features will help the correct diagnosis and appropriate clinical care.

Skin manifestations

Skin manifestations of SAPHO include a variety of acneiform and neutrophilic dermatoses. Skin lesions may precede, concur, or present at the late stage related to osteoarticular manifestations, whereas most patients develop both symptoms within 2 years [16]. For instance, in a large Chinese cohort of 354 patients with SAPHO, skin lesions preceded the onset of osteoarticular manifestations by 1 year in 49%, presented simultaneously in 28%, and appeared at a later stage in 22% of patients [16]. In some cases, skin manifestations may be absent [11–13,30].

PPP is the most common skin manifestation present in up to 65% of patients [9,30,47], in particular prevalent in the Asian population of SAPHO patients [8▪,12,16,17,42]. Severe acne, including acne conglobata, acne fulminans, or hidradenitis suppurativa (HS), present in up to 25% of patients [9,28], with a higher prevalence of HS among patients of the African American ancestry [18]. Psoriasis vulgaris (PV) may be present in up to 30% of patients [8▪,9–13,30] and may be associated with PPP or severe acne [39]. Pyoderma gangrenosum in the context of SAPHO was rarely reported [53]. Remarkably, one study reported an association between the presence of PPP or PV, but not other skin manifestations, with axial osteitis [9], whereas this observation was not confirmed by another study [16]. Dermatological manifestations, especially HS, are known to be resistant to therapy

and quite often have a chronic and protracted course [18,46▪▪].

Osteoarticular manifestations

The osteoarticular manifestations of the SAPHO syndrome are highly variable and may present in different clinical patterns of episodic, relapsing-remitting, or chronic disease. Bone and joint involvement may affect a variety of the skeleton, with the involvement of one or multiple sites in a synchronous or asynchronous manner. Subclinical lesions of bone can be present on imaging. SAPHO is characterized by osteitis, considered the cornerstone of diagnosis, hyperostosis, synovitis, and enthesopathy, typically presenting with pain, swelling, and tenderness. Osteitis and hyperostosis result from a chronic inflammatory reaction involving the medulla and cortex of bones. Hyperostosis is caused by endosteal and periosteal thickening, leading to the medullary canal narrowing and osteolysis in some cases [54]. Radiographically, hyperostosis appears as osteosclerosis with thickening of trabeculae and cortex and narrowing of the medullary canal. Coexisting osteosclerotic and osteolytic lesions can often be seen, in particular around the sternoclavicular joint [55].

SAPHO has an apparent predisposition for the involvement of the anterior chest wall, the hallmark of the syndrome [8▪,9,12,16,17,30,38,42]. Sternoclavicular (commonly bilateral), costochondral, manubriosternal, and costosternal junctions are the most commonly affected sites of the anterior chest wall. The second most common site of skeletal involvement is the spine, affecting up to 50% of patients [56]. The thoracolumbar spine is the most frequently affected site, characterized by a segmental involvement. Nonmarginal syndesmophytes may occur, reminiscent of those in axial PsA [46▪▪]. Of note, spinal involvement was reported more commonly in Asians [12,42] than Caucasian patients [9,10,30]. Unilateral sacroiliitis can present in up to 50% of patients with SAPHO, characterized by erosions, extensive sclerosis, and hyperostosis primarily of the adjacent iliac side of the joint [56]. Peripheral synovitis, commonly oligoarticular and asymmetric, is reported in about 30% of patients. Hip, knee, and ankles joints are more commonly involved than small joints in hands and feet [46▪▪]. The synovial fluid analysis showed a mild inflammatory pattern [10]. Mandibular involvement in a form of diffuse sclerosing sterile osteomyelitis was reported predominantly among in young women [57]. Soft tissues adjacent to involved joints and bones can be affected, presenting as swelling, often considered a lymphatic or neoplastic mass.

IMAGING TESTS AND RADIOGRAPHIC FEATURES OF SYNOVITIS, ACNE, PUSTULOSIS, HYPEROSTOSIS, AND OSTEITIS

A wide variety of radiographic findings have been reported in SAPHO [46▪▪,58–60]. The radiological appearances of the skeletal manifestations in SAPHO are crucial in the diagnostic process. The following section will expand the discussion on the differential diagnosis between SAPHO and SpA.

Plain radiography

Many of the SAPHO manifestations may be detected on conventional plain radiographs, including hyperostotic changes (thickening of periosteum, cortex, and endosteum), sclerotic lesions, osteolysis, periosteal reaction, and formation of enthesophytes [58]. Yet, this modality is not sensitive for early but late disease structural changes. In a study of 19 SAPHO patients, radiographs were normal at disease onset in 80% of patients, with the appearance of radiographic changes in all patients by the end of the follow-up period [61].

Axial lesions relate to the spectrum of axial SpA and may include vertebral body corner lesions, spondylodiscitis, asymmetric/nonmarginal or marginal syndesmophytes, osteodestructive, and osteosclerotic lesions, paravertebral ossification, and sacroiliitis. Vertebral fractures and intervertebral discs (e.g. Andersson lesions) are also seen. These structural abnormalities are not typically identified on plain radiography in the early stage of the disease, prompting evaluation by magnetic resonance imaging (MRI) [46▪▪]. Sacroiliitis in SAPHO is usually unilateral with sclerosis and hyperostosis present on the iliac side of the joint, unlike typical SpA. Radiographic findings in peripheral arthritis include joint space narrowing, periarticular osteopenia, and bone erosions mimicking seronegative SpA. Periostitis is a characteristic radiographic feature that may be indistinguishable from osteomyelitis.

Bone scintigraphy

Radionuclide bone scanning may demonstrate increased uptake at multiple sites of involvement. The presence of bull's head-shaped enhancement of the anterior chest is characteristic of SAPHO syndrome with sternoclavicular involvement. Notably, subclinical involvement of the manubriosternal and sternoclavicular joints was also commonly detected in a scintigraphic study of 50 patients with PsA [62], Bone scan can be used for surveying the entire skeleton for multiple sites of disease as an adjunct to more targeted imaging modalities. Nonetheless,

the use of this modality warrants careful consideration given the risk of radiation exposure.

Computed tomography

Multiplanar computed tomography (CT) has unique advantages over radiographs in demonstrating spinal lesions and their extent through its multiplanar reconstructions and high resolution. Whole-spine CT findings among 69 patients with SAPHO included vertebral lesions, cortical erosions, reactive osteosclerosis, and nonmarginal syndesmophytes, in the thoracic spine in the majority of patients [63]. The lesions were asymmetrically distributed and the affected vertebrae were more consecutively involved in a particular 'kissing' appearance with preserved intervening disc spaces. The differences between the findings of this study and the typical axial SpA included the different forms of syndesmophytes (nonmarginal vs marginal) and of paravertebral ligamentous ossifications (anterior and segmental vs diffuse and posterior) [63].

Magnetic resonance imaging

MRI is a useful modality to evaluate the anterior chest and the axial skeleton involvement. MRI (short TI inversion recovery or fat-suppressed T2-weighted images) detects active inflammatory lesions, osteitis (bone marrow edema) at the early stage, and provides soft tissue data. A recent MRI study demonstrated a triad of enthesitis, synovitis, and osteitis, with prominent lesions in the first rib area in SAPHO patients with anterior chest involvement [64]. Anterior vertebral body corner lesions that reflect enthesitis are the most common axial skeletal MRI finding on SAPHO [65]. Structural lesions, such as erosions, hyperostosis, and ankylosis, can also be seen on MRI (T1-sequence). A whole-spine MRI study demonstrated some distinct patterns of involvement between SAPHO syndrome patients and SpA (e.g., low prevalence of sacroiliitis (7%) in SAPHO vs 100% in the SpA cohort), providing radiographic tools in differentiating between both entities [66]. In addition to cost and availability, disadvantages of MRI include a relatively limited imaging range, necessitating multiple MRIs for a single patient with widespread disease.

Fluorodeoxyglucose-positron emission tomography/computed tomography

The use of fluorodeoxyglucose-positron emission tomography (FDG PET)/CT in SAPHO has been demonstrated to be effective in differentiating active lesions from inactive lesions excluding metastatic disease in challenging cases. This modality showed a moderate to substantial agreement in revealing anterior chest wall and axial skeletal lesions with CT and bone scan in 26 SAPHO patients, whereas the correlation between F-FDG uptake and clinical symptoms was weak [67]. The use of FDG PET/CT is reserved for complicated cases.

Ultrasound

Musculoskeletal ultrasound (US) is a diagnostic tool in the evaluation of synovitis, enthesitis, peripheral lesions, and early anterior chest wall inflammation. Synovitis with power doppler signals has been detected in sternoclavicular joints and peripheral joints of patients with SAPHO syndrome compared with controls [68].

TREATMENT OF SYNOVITIS, ACNE, PUSTULOSIS, HYPEROSTOSIS, AND OSTEITIS

The main goals of treatment in patients with SAPHO include the relief of articular and dermatologic symptoms, prevention of bone damage, and improvement of the quality of life [24,46▪▪]. The evidence-based treatment algorithm in SAPHO is lacking in the absence of clinical trials in this rare disease. Treatment choice is based on case reports, case series, retrospective reports, and several open-label trials. In fact, a wide spectrum of therapeutic agents is in off-label use to treat SAPHO, extrapolated from treatment approaches to psoriasis, severe acne, PPP, PsA, and SpA [24,46▪▪,69]. To date, there are no data on long-term efficacy, adverse events, and outcomes of different treatments in SAPHO.

Since *C. acnes* may trigger of SAPHO syndrome, antimicrobial therapy (mainly macrolides and tetracyclines) can sometimes be administered, especially in Japan [8▪,17,70–72]. In addition to direct antimicrobial effects, the anti-inflammatory and immunomodulatory impact of these agents have garnered increasing attention. However, disease relapse was observed following treatment discontinuation, thus limiting this therapeutic approach [45].

Nonsteroidal anti-inflammatory drugs are generally considered as the first line treatment but efficacy may be limited. Second-line agents include antibiotics, bisphosphonates, and oral disease-modifying antirheumatic drugs (DMARDs). The clinical and radiologic efficacy of bisphosphonates for osteitis, spondylitis, and articular disease of the anterior chest was supported in case series and open trials [73–76]. Methotrexate is the most commonly used oral DMARD in patients with SAPHO, although its

effect on osteitis is uncertain [46▪▪]. Limited evidence suggests that sulfasalazine may be used as an adjunct in combination with other drugs in the treatment of SAPHO [77]. Colchicine is used in some areas because of its known efficacy in neutrophil inhibition [17,78]. Apremilast, a phosphodiesterase-4 inhibitor, was reported efficient in a small series of patients [79]. Biologics agents, TNF inhibitors as a common first choice, followed by IL1 inhibitors, IL17 inhibitors, and newer IL12/23, and IL23 inhibitors, have been used in refractory cases with noteworthy results [24,46▪▪,69,80]. Recently, treatment with tofacitinib results in a multidimensional improvement in 12 female patients with SAPHO [81]. Remarkably, the treatment approach to PAO in JAPAN also includes treatment of focal infection, including treatment of dental lesions, sinusitis, and tonsillectomy, even in asymptomatic patients [17,46▪▪].

CLINICAL COURSE AND PROGNOSIS OF SYNOVITIS, ACNE, PUSTULOSIS, HYPEROSTOSIS, AND OSTEITIS

There is a broad spectrum of disease presentations and the range of severity in patients with SAPHO, with variable courses reported over time. One study identified risk factors for a chronic disease course

Table 1. Common denominator and differences between SAPHO and diseases of the SpA spectrum.

	Similarity		Differences	
	SAPHO	**SpA spectrum[a]**	**SAPHO**	**SpA spectrum[a]**
Clinical features				
Skin	PPP Pustular psoriasis Psoriasis vulgaris (*rare*) Hidradenitis suppurativa Pyoderma gangrenosum (*rare*)		Severe acne	Nail dystrophy
Osteoarticular features	Peripheral arthritis Axial involvement Sacroiliitis Enthesitis		Predominant anterior chest involvement	Less common/subclinical anterior chest involvement seen in PsA
Genetics	Positive HLA-B27 in a minority of SAPHO patients		No HLA-B27 association by some studies	High prevalence of +HLA-B27 in AS
Immunogenic profile	Elevation of a series of proinflammatory cytokines: TNF-α, IL-1, IL-8, IL-17, IL-18			
	Involvement of the IL-23/Th17 axis			
Infectious etiology	Infectious trigger (*C. acnes* in SAPHO; streptococci in psoriasis		*C. acnes* isolated from bone lesions	Pathogens associated with reactive arthritis
Imaging	Axial skeleton: Vertebral corner lesions Spondylodiscitis Osteitis at entheseal sites and juxta-articular (SAPHO & PsA) Paravertebral ossifications Syndesmophytes Ankylosis Sacroiliitis (*less common in SAPHO vs SpA*) MRI - bone marrow edema in active lesions Peripheral joints: joint space narrowing, periarticular osteopenia, and bone erosions		Multiple skeletal lesions; Bone scintigraphy - Bull's head' pattern; Osteitis in long bones Hyperostosis Osteolytic lesions and osteosclerosis	
Treatment[b]	Bisphosphonates (AS, SAPHO) Some response to conventional DMARDs and apremilast (case reports in SAPHO) Good response to anticytokine biologics (TNFi, IL17i, IL12/23i, IL23i) and JAKi (case reports in SAPHO)		Temporary response to antibiotics; colchicine (limited evidence); Anti-IL1 and anti-IL6 biologics	

AS, ankylosing spondylitis; PsA, psoriatic arthritis; SAPHO, synovitis, acne, pustulosis, hyperostosis, and osteitis; SpA, spondyloarthritis; TNF-α, tumour necrosis factor alpha.
[a]SpA spectrum encompasses AS, PsA, IBD-related arthropathy, reactive arthritis.
[b]SAPHO treatment is based on off label use.

including female sex, anterior chest wall involvement, peripheral arthritis, skin lesions, and high inflammatory indices at first presentation [10]. Inconsistent outcomes were reported with diverse empirical therapies, with a good long-term prognosis reported by several studies [9,61]. Moderately good long-term treatment outcomes were observed in most recipients of tumor necrosis factor inhibitors [20].

DISCUSSION

This article has reviewed clinical, laboratory, and imaging data on the uncommon syndrome of SAPHO. There are no convincing data to say with surety that SAPHO belongs to the SpA group of diseases though there is enough evidence to locate it under that rubric, rather than any other. In favor of this is principally the skin association – PPP and PV though it is recognized that other pustular dermatoses, such as acne vulgaris and hidranenitis supprutiva are also associated. Secondly, the osteoarticular manifestations, particularly in the spine, are closely related to the SpA, and perhaps more closely to the alternative axial phenotype of PsA [82]. Thirdly, the patho-immunological profile, and associated treatment options, are consistent with that seen in SpA. Against this hypothesis are the genetics, though it must be remembered that only a minority of patients with psoriatic axial disease are HLA-B27 positive. The arguments for and against the positioning of SAPHO within the SpA spectrum are given in Table 1.

The association with (sterile) pustular and osteoarticular lesions evokes the possibility of an autoinflammatory disorder, and SAPHO may fit into this end of the polygenic autoinflammatory/autoimmune spectrum [83], although heterogeneity within the syndrome may offer an alternative explanation. In such an association the innate immune system is prominent, and tissue-specific factors may explain the varied clinical presentations. As with other neutrophilic conditions, colchicine may be helpful in symptom control.

The predilection of the osteoarticular features for the involvement of the anterior chest wall remains unanswered though it is by no means limited exclusively to this condition. Studies using nucleotide imaging have demonstrated a high prevalence of abnormality in the sterno-clavicular and manubriosternal joints in people with otherwise classical PsA. Further, involvement of the manubriosternal joint in axial SpA is not uncommon.

Finally, there remains the possibility that SAPHO is a form of reactive arthritis with long-term sequelae similar to those seen in SpA. The finding of *C. acnes* in the skin, and sometimes the joint, in SAPHO would be in favor of that, and the lack of long-term benefit from antibiotic regimes would not be a reason to reject that theory, as has been shown in reactive arthritis secondary to other pathogens [84].

CONCLUSION

The nosologic framing of SAPHO syndrome is still a matter of debate but herein we argue that the similarities to SpA outweigh the differences and, though the possibility of an infectious trigger might mean that it more appropriately fits in to the rubric of a (chronic) reactive arthritis, the features of SpA are still present.

Acknowledgements

None.

Financial support and sponsorship

None.

Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:
- ■ of special interest
- ■■ of outstanding interest

1. Sonozaki H, Mitsui H, Miyanaga Y, *et al.* Clinical features of 53 cases with pustulotic arthro-osteitis. Ann Rheum Dis 1981; 40:547–553.
2. 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; 54:187–196.
3. Benhamou CL, Chamot AM, Kahn MF. Synovitis-acne-pustulosis hyperostosis-osteomyelitis syndrome (SAPHO). A new syndrome among the spondyloarthropathies? Clin Exp Rheumatol 1988; 6:109–112.
4. Köhler H, Uehlinger E, Kutzner J, West TB. Sternocostoclavicular hyperostosis: painful swelling of the sternum, clavicles, and upper ribs. Report of two new cases. Ann Intern Med 1977; 87:192–197.
5. Hayem G. SAPHO syndrome. Rev Prat 2004; 54:1635–1636.
6. Björkstén B, Gustavson KH, Eriksson B, *et al.* Chronic recurrent multifocal osteomyelitis and pustulosis palmoplantaris. J Pediatr 1978; 93:227–231.
7. Oliver M, Jayatilleke A, Wu E, *et al.* Establishing core domain sets for Chronic Nonbacterial Osteomyelitis (CNO) and Synovitis, Acne, Pustulosis, Hyperostosis, Osteitis (SAPHO): a report from the OMERACT 2020 special interest group. Semin Arthritis Rheum 2021; 51:957–961.
8. ■ 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; 7:883–891.

An important paper highlighting the international differences and complexities of understanding and treatment of SAPHO syndrome.

9. Hayem G, Bouchaud-Chabot A, Benali K, *et al.* SAPHO syndrome: a long-term follow-up study of 120 cases. Semin Arthritis Rheum 1999; 29:159–171.
10. 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; 61:813–821.
11. Witt M, Meier J, Hammitzsch A, *et al.* Disease burden, disease manifestations and current treatment regimen of the SAPHO syndrome in Germany: results from a nationwide patient survey. Semin Arthritis Rheum 2014; 43:745–750.
12. Li C, Zuo Y, Wu N, *et al.* Synovitis, acne, pustulosis, hyperostosis and osteitis syndrome: a single centre study of a cohort of 164 patients. Rheumatology 2016; 55:1023–1030.

13. Aljuhani F, Tournadre A, Tatar Z, *et al.* The SAPHO syndrome: a single-center study of 41 adult patients. J Rheumatol 2015; 42:329–334.
14. Queiro R, Moreno P, Sarasqueta C, *et al.* Synovitis-acne-pustulosis-hyperostosis-osteitis syndrome and psoriatic arthritis exhibit a different immunogenetic profile. Clin Exp Rheumatol 2008; 26:125–128.
15. Assmann G, Köhm M, Schuster V, *et al.* Genetic variants in FBLIM1 gene do not contribute to SAPHO syndrome and chronic recurrent multifocal osteomyelitis in typical patient groups. BMC Med Genet 2020; 21:102.
16. Cao Y, Li C, Xu W, *et al.* Spinal and sacroiliac involvement in SAPHO syndrome: a single center study of a cohort of 354 patients. Semin Arthritis Rheum 2019; 48:990–996.
17. Yamamoto T, Hiraiwa T, Tobita R, *et al.* Characteristics of Japanese patients with pustulotic arthro-osteitis associated with palmoplantar pustulosis: a multicenter study. Int J Dermatol 2020; 59:441–444.
18. Steinhoff JP, Cilursu A, Falasca GF, *et al.* A study of musculoskeletal manifestations in 12 patients with SAPHO syndrome. J Clin Rheumatol 2002; 8:13–22.
19. Van Doornum S, Barraclough D, McColl G, Wicks I. SAPHO: rare or just not recognized? Semin Arthritis Rheum 2000; 30:70–77.
20. Yap FHX, Olsson-White D, Roddy J, *et al.* Long-term clinical outcomes in synovitis, acne, pustulosis, hyperostosis, and osteitis syndrome. Mayo Clin Proc Innov Qual Outcomes 2021; 5:574–582.
21. Beretta-Piccoli BC, Sauvain MJ, Gal I, *et al.* Synovitis, acne, pustulosis, hyperostosis, osteitis (SAPHO) syndrome in childhood: a report of ten cases and review of the literature. Eur J Pediatr 2000; 159:594–601.
22. 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; 40:1487–1495.
23. Schilling F, Kessler S. [SAPHO syndrome: clinico-rheumatologic and radiologic differentiation and classification of a patient sample of 86 cases]. Z Rheumatol 2000; 59:1–28.
24. Liu S, Tang M, Cao Y, Li C. Synovitis, acne, pustulosis, hyperostosis, and osteitis syndrome: review and update. Ther Adv Musculoskelet Dis 2020; 12:1759720X20912865.
25. Gonzalez T, Gantes M, Bustabad S, Diaz-Flores L. Acne fulminans associated with arthritis in monozygotic twins. J Rheumatol 1985; 12:389–391.
26. Eyrich GK, Langenegger T, Bruder E, *et al.* Diffuse chronic sclerosing osteomyelitis and the synovitis, acne, pustolosis, hyperostosis, osteitis (SAPHO) syndrome in two sisters. Int J Oral Maxillofac Surg 2000; 29:49–53.
27. Dumolard A, Gaudin P, Juvin R, *et al.* SAPHO syndrome or psoriatic arthritis? A familial case study. Rheumatology 1999; 38:463–467.
28. Kahn MF, Khan MA. The SAPHO syndrome. Baillieres Clin Rheumatol 1994; 8:333–362.
29. Kahn MF. Why the 'SAPHO' syndrome? J Rheumatol 1995; 22:2017–2019.
30. Sallés M, Olivé A, Perez-Andres R, *et al.* The SAPHO syndrome: a clinical and imaging study. Clin Rheumatol 2011; 30:245–249.
31. 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; 37:401–409.
32. Cox AJ, Darbro BW, Laxer RM, *et al.* Recessive coding and regulatory mutations in FBLIM1 underlie the pathogenesis of chronic recurrent multifocal osteomyelitis (CRMO). PLoS One 2017; 12:e0169687.
33. ■ Cai R, Dong Y, Fang M, *et al.* Genome-wide association identifies risk pathways for SAPHO syndrome. Front Cell Dev Biol 2021; 9:643644.

This genome-wide association study (GWAS) identified aberrant osteoclast differentiation involved in SAPHO syndrome, providing insight into the understanding of SAPHO pathogenesis.

34. Sun Y, Li C, Zhu M, *et al.* Enhanced migration and adhesion of peripheral blood neutrophils from SAPHO patients revealed by RNA-Seq. Orphanet J Rare Dis 2019; 14:192.
35. ■ Sun Y, Li C, Lu Q, *et al.* Integrative analysis of lncRNA-mRNA profile reveals potential predictors for SAPHO syndrome. Front Genet 2021; 12:684520.

This study provides a first insight into long noncoding RNA transcriptome profile changes associated with SAPHO syndrome.

36. Sun Y, Li C, Yu W, *et al.* Complement system deregulation in SAPHO syndrome revealed by proteomic profiling. J Proteomics 2022; 251:104399.
37. Kotilainen P, Merilahti-Palo R, Lehtonen OP, *et al. Propionibacterium acnes* isolated from sternal osteitis in a patient with SAPHO syndrome. J Rheumatol 1996; 23:1302–1304.
38. Assmann G, Simon P. The SAPHO syndrome–are microbes involved? Best Pract Res Clin Rheumatol 2011; 25:423–434.
39. Zimmermann P, Curtis N. Synovitis, acne, pustulosis, hyperostosis, and osteitis (SAPHO) syndrome – a challenging diagnosis not to be missed. J Infect 2016; 72 Suppl:S106–S114.
40. Zimmermann P, Curtis N. The role of *Cutibacterium acnes* in auto-inflammatory bone disorders. Eur J Pediatr 2019; 178:89–95.
41. Colina M, Lo Monaco A, Khodeir M, Trotta F. *Propionibacterium acnes* and SAPHO syndrome: a case report and literature review. Clin Exp Rheumatol 2007; 25:457–460.
42. Okuno H, Watanuki M, Kuwahara Y, *et al.* Clinical features and radiological findings of 67 patients with SAPHO syndrome. Mod Rheumatol 2018; 28:703–708.
43. Li ZJ, Choi DK, Sohn KC, *et al. Propionibacterium acnes* activates the NLRP3 inflammasome in human sebocytes. J Invest Dermatol 2014; 134:2747–2756.
44. Berthelot J-M, Corvec S, Hayem G. SAPHO, autophagy, IL-1, FoxO1, and *Propionibacterium* (*Cutibacterium*) *acnes*. Joint Bone Spine 2018; 85:171–176.
45. Assmann G, Kueck O, Kirchhoff T, *et al.* Efficacy of antibiotic therapy for SAPHO syndrome is lost after its discontinuation: an interventional study. Arthritis Res Ther 2009; 11:R140.
46. ■■ Kishimoto M, Taniguchi Y, Tsuji S, *et al.* SAPHO syndrome and pustulotic arthro-osteitis (PAO). Mod Rheumatol 2021; roab103. doi: 10.1093/mr/roab103. [Epub ahead of print]

This is a comprehensive review and update on etiology, pathogenesis, clinical and imaging features, and treatment approach to SAPHO syndrome and Pustulotic Arthro-Osteitis, a related disorder prevalent in Japan.

47. 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 2008; 47:1160–1167.
48. Przepiera-Będzak H, Fischer K, Brzosko M. Serum IL-6 and IL-23 levels and their correlation with angiogenic cytokines and disease activity in ankylosing spondylitis, psoriatic arthritis, and SAPHO syndrome. Mediators Inflamm 2015; 2015:785705.
49. Firinu D, Barca MP, Lorrai MM, *et al.* TH17 cells are increased in the peripheral blood of patients with SAPHO syndrome. Autoimmunity 2014; 47:389–394.
50. Zhang S, Li C, Zhang S, *et al.* Serum levels of proinflammatory, anti-inflammatory cytokines, and RANKL/OPG in synovitis, acne, pustulosis, hyperostosis, and osteitis (SAPHO) syndrome. Mod Rheumatol 2019; 29:523–530.
51. Xu D, Liu X, Lu C, *et al.* Reduction of peripheral natural killer cells in patients with SAPHO syndrome. Clin Exp Rheumatol 2019; 37:12–18.
52. Grosjean C, Hurtado-Nedelec M, Nicaise-Roland P, *et al.* Prevalence of autoantibodies in SAPHO syndrome: a single-center study of 90 patients. J Rheumatol 2010; 37:639–643.
53. Vekic DA, Woods J, Lin P, Cains GD. SAPHO syndrome associated with hidradenitis suppurativa and pyoderma gangrenosum successfully treated with adalimumab and methotrexate: a case report and review of the literature. Int J Dermatol 2018; 57:10–18.
54. Rohekar G, Inman RD. Conundrums in nosology: synovitis, acne, pustulosis, hyperostosis, and osteitis syndrome and spondylarthritis. Arthritis Rheum 2006; 55:665–669.
55. Cianci F, Zoli A, Gremese E, Ferraccioli G. Clinical heterogeneity of SAPHO syndrome: challenging diagnose and treatment. Clin Rheumatol 2017; 36:2151–2158.
56. Leone A, Cassar-Pullicino VN, Casale R, *et al.* The SAPHO syndrome revisited with an emphasis on spinal manifestations. Skeletal Radiol 2015; 44:9–24.
57. Wang M, Li Y, Cao Y, *et al.* Mandibular involvement in SAPHO syndrome: a retrospective study. Orphanet J Rare Dis 2020; 15:312.
58. Depasquale R, Kumar N, Lalam RK, *et al.* SAPHO: What radiologists should know. Clin Radiol 2012; 67:195–206.
59. Jurik AG, Klicman RF, Simoni P, *et al.* SAPHO and CRMO: the value of imaging. Semin Musculoskelet Radiol 2018; 22:207–224.
60. Schaub S, Sirkis HM, Kay J. Imaging for synovitis, acne, pustulosis, hyperostosis, and osteitis (SAPHO) syndrome. Rheum Dis Clin N Am 2016; 42:695–710.
61. Maugars Y, Berthelot JM, Ducloux JM, Prost A. SAPHO syndrome: a followup study of 19 cases with special emphasis on enthesis involvement. J Rheumatol 1995; 22:2135–2141.
62. Helliwell P, Marchesoni A, Peters M, *et al.* A re-evaluation of the osteoarticular manifestations of psoriasis. Br J Rheumatol 1991; 30:339–345.
63. Xu W, Li C, Zhao X, *et al.* Whole-spine computed tomography findings in SAPHO syndrome. J Rheumatol 2017; 44:648–654.
64. Yu M, Cao Y, Li J, *et al.* Anterior chest wall in SAPHO syndrome: magnetic resonance imaging findings. Arthritis Res Ther 2020; 22:216.
65. Laredo J-D, Vuillemin-Bodaghi V, Boutry N, *et al.* SAPHO syndrome: MR appearance of vertebral involvement. Radiology 2007; 242:825–831.
66. Zhang LH, Han SB, Song L, *et al.* Comparative analysis and differentiation between SAPHO syndrome and spondyloarthropathies using whole-spine MRI. Clin Radiol 2021; 76:394.e9–394.e14.
67. Sun X, Li C, Cao Y, *et al.* F-18 FDG PET/CT in 26 patients with SAPHO syndrome: a new vision of clinical and bone scintigraphy correlation. J Orthop Surg Res 2018; 13:120.
68. Umeda M, Kawashiri S-Y, Nishino A, *et al.* Synovitis of sternoclavicular and peripheral joints can be detected by ultrasound in patients with SAPHO syndrome. Mod Rheumatol 2017; 27:881–885.
69. Daoussis D, Konstantopoulou G, Kraniotis P, *et al.* Biologics in SAPHO syndrome: a systematic review. Semin Arthritis Rheum 2019; 48:618–625.
70. Takizawa Y, Murota A, Setoguchi K, Suzuki Y. Severe inflammation associated with synovitis, acne, pustulosis, hyperostosis, osteitis (SAPHO) syndrome was markedly ameliorated by single use of minocycline. Mod Rheumatol 2014; 24:1015–1018.
71. Hayashi S, Shimaoka Y, Hamasaki Y, Hatamochi A. Palmoplantar pustulosis and pustulotic arthro-osteitis treatment with potassium iodide and tetracycline, a novel remedy with an old drug: a review of 25 patients. Int J Dermatol 2017; 56:889–893.

72. Murakami M, Masuda K, Utsunomiya R, *et al.* Cefcapene pivoxil hydrochloride is a potentially new treatment for palmoplantar pustulosis with pustulotic arthro-osteitis. Dermatology 2015; 231:304–311.
73. Amital H, Applbaum YH, Aamar S, *et al.* SAPHO syndrome treated with pamidronate: an open-label study of 10 patients. Rheumatology 2004; 43:658–661.
74. Li C, Zhao Y, Zuo Y, *et al.* Efficacy of bisphosphonates in patients with synovitis, acne, pustulosis, hyperostosis, and osteitis syndrome: a prospective open study. Clin Exp Rheumatol 2019; 37:663–669.
75. Wu N, Zhao Y, Tao W, *et al.* A single cohort, open-label study of the efficacy of pamidronate for palmoplantar pustulosis in synovitis, acne, pustulosis, hyperostosis and osteitis (SAPHO) syndrome. Clin Exp Rheumatol 2020; 38:1263–1264.
76. Zwaenepoel T, Vlam Kde. SAPHO: treatment options including bisphosphonates. Semin Arthritis Rheum 2016; 46:168–173.
77. Mushtaq S, Sarkar R. Sulfasalazine in dermatology: a lesser explored drug with broad therapeutic potential. Int J Womens Dermatol 2020; 6:191–198.
78. Jurik AG, Ternowitz T, Graudal H. Neutrophil chemotaxis in patients with pustulotic arthro-osteitis. Dermatologica 1988; 176:161–169.
79. Kikuchi N, Yamamoto T. Effects of apremilast on pustulotic arthro-osteitis in a real-world setting: report of five cases. Dermatol Ther 2020; 33:e13249.
80. Yamamoto T, Fukuda K, Morita A, *et al.* Efficacy of guselkumab in a subpopulation with pustulotic arthro-osteitis through week 52: an exploratory analysis of a phase 3, randomized, double-blind, placebo-controlled study in Japanese patients with palmoplantar pustulosis. J Eur Acad Dermatol Venereol 2020; 34:2318–2329.
81. Xie W, Huang H, Zhang Z. Off-label use of tofacitinib: a potential treatment option for SAPHO syndrome. Ann Rheum Dis 2022; 81:e91.
82. Helliwell PS. Axial disease in psoriatic arthritis. Rheumatology 2020; 59:1193–1195.
83. McGonagle D, McDermott MF. A proposed classification of the immunological diseases. PLoS Med 2006; 3:e297.
84. Kvien TK, Gaston JSH, Bardin T, *et al.* Three month treatment of reactive arthritis with azithromycin: a EULAR double blind, placebo controlled study. Ann Rheum Dis 2004; 63:1113–1119.

Quo vadis reactive arthritis?

Henning Zeidler[a] *and Alan P. Hudson*[b]

Purpose of review
We provide an overview of recent articles which describe new thinking regarding HLA-B27-associated reactive arthritis (ReA), including those additional infection-related arthritides triggered by microbes that often are grouped under the term ReA.

Recent findings
With the advent and continuation of the pandemic, an increasing number of cases and case series of post-COVID-19 arthritis have been reported and classified as ReA. Further, arthritis after COVID-19 vaccination is a new entity included within the spectrum of ReA. New causative microorganisms identified in case reports include *Clostridium difficile, Mycoplasma pneumoniae, Giardia lamblia, Leptospira*, and babesiosis. SARS-CoV-2 is emerging as a significant etiologic agent for apparent ReA.

Summary
It is now clear that comprehensive clinical and laboratory investigations, synovial fluid analyses, and close follow-up of patients all are essential to differentiate ReA from diseases that may present with similar clinical attributes. Further, and importantly, additional research is required to define the wide diversity in causative agents, epidemiology, and rare case presentations of these arthritides. Finally, new classification and diagnostic criteria, and updated treatment recommendations, are essential to the advancement of our understanding of ReA.

Keywords
biologics, epidemiology, post-COVID-19 arthritis, prosthetic joint infection, rare infectious agents

INTRODUCTION

Historically, HLA-B27-associated reactive arthritis (ReA) has been considered to develop following urogenital, gastrointestinal, or respiratory tract infections involving well defined triggering micro-organisms; these are normally not cultivable from the affected joints and belong to the spectrum of spondyloarthritis (SpA). An important article in the field which surveyed spectrum of the disease and its causative agents was last published in this journal in 2000 [1]. In subsequent reports in this journal, poststreptococcal ReA and *Chlamydia*-induced ReA were considered as special topics of interest [2,3].

Importantly, decreasing incidence of ReA has been reported variously in developed countries, which for our purposes here has generated the question '*quo vadis* ReA?' in clinical practise, in research, and in the publications generated from those activities [4]. Thus, we focus on recent insights into our understanding of the epidemiology, pathogenesis, causative pathogens, clinical manifestations, diagnosis, and treatment of ReA, with special attention to literature published during the past 12–18 months. We include discussion of other infection-related arthritis triggered by microbes which often are grouped under the term ReA but which are not classified within the HLA-B27 associated SpA group.

EPIDEMIOLOGY

One recent article reviewed factors behind the major shift in epidemiological data for ReA worldwide; these include different diagnostic approaches and clinical presentations, insufficient specific laboratory biomarkers, different geographical locations that predispose to multiple pathogens, different genetic backgrounds, different grades of infection, and various recently identified changes in the microbiome [5▪▪]. The worldwide prevalence of ReA in adults is given as 1/1000, although this

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Curr Opin Rheumatol 2022, 34:218–224
DOI:10.1097/BOR.0000000000000880

KEY POINTS

- ReA is an extremely heterogenous disease with varied presentation across the globe, only in part related to HLA-B27 positivity.
- Rheumatologists must be aware of the expending panoply of rare and new pathogens involved in ReA, especially post-COVID-19-ReA.
- Comprehensive clinical and laboratory investigations, synovial fluid analysis, and close follow-up of patients are essential to differentiate ReA from diseases that may present with similar clinical pictures.

number varies geographically depending on HLA-B27 positivity in the population under study; annual incidence of ReA is 9.3/100 000 to 13/100 000 [5▪▪]. The latest systematic review regarding the incidence of SpA subtypes on studies published during the last 25 years reported for ReA an overall incidence rate estimate of 3.4 cases per 100 000 person-years [6].

ReA has long been associated with enteric bacterial infections and genital chlamydial infections. The most recent systematic review and meta-analysis estimated the proportion of ReA following bacterial enteric infection from each of four common such pathogens: these were, for *Campylobacter* 1.71%, for *Salmonella* 3.9%, for *Shigella* 1.0%, and for *Yersinia* 3.4% [7▪]. Combining all four, the estimated percentage of cases that developed ReA was 2.6%. Follow-up for an outbreak of *Yersinia enterocolitica* gastroenteritis in four Norwegian military camps revealed that there were no cases of erythema nodosum, but 20% of infected service personnel reported one or more symptoms consistent with ReA [8]. This in agreement with the Norwegian Institute of Public Health infection control advisor, who indicated that ReA occurs in 10–30% of cases in adults, and that postinfectious complications are most common in middle-aged and older people [8]. The first prospective study investigating whether reactive musculoskeletal symptoms are associated with acquisition of diarrhoeagenic *Escherichia coli* among international travellers indicated that, of 151 patients, four (2.6%) had ReA, two (1.3%) reactive tendinitis, and three (2.0%) reactive arthralgia [9].

From the few studies available, the incidence of sexually acquired ReA (SARA) is 3.0–8.1% [10]. More particularly, recent epidemiological studies indicate diversity in the frequency of *Chlamydia*-associated ReA in different parts of the world, with evidence of declining incidence in some regions (c.f. 11). No systematic epidemiological information is currently available for *Chlamydia pneumoniae*-associated ReA; this causative agent has been described in case studies simply as uncommon [11].

OTHER PATHOGENS

The role of the several common enteric pathogens, and that of *Chlamydia trachomatis*, in the cause of ReA has been well known for many years, but recent reports have implicated a wide variety of other bacteria and viruses in that process (see [12▪] for extensive review). Significantly, as with the enteric pathogens given above, many of the recently implicated bacteria could not be identified by culture or even by PCR from synovial tissue or fluid samples. These atypical potential etiologic agents included *E. coli*, *Mycoplasma*, *Streptococcus pyogenes*, *Ureaplasma urealyticum*, and *Neisseria gonorrhoeae* (e.g., [13]). A few case reports have suggested several other bacteria as causative agents, including *Bacillus cereus*, *Helicobacter cinaedi*, *Lactobacillus*, and *Streptococcus salivarius*; still other case reports indicated rare instances of apparent ReA caused by *Cyclospora cayetanensis*, *Vibrio parahaemolyticus*, *Orientia tsutsugamushi*, and *Rickettsia conorii* ([12▪] for discussion and references).

Significantly, examples of acute arthritis have been reported following infection with SARS-CoV-2 [14,15]. A significant issue is, however, whether arthritis that develops subsequent to (or during) infection with this virus can be legitimately designated as ReA. This question also obtains in relation to the few cases of arthritis which developed in relation to infection with *Parvovirus*, HIV, and other viruses (again, see [12▪] for discussion). Similarly, one article focusing on possible arthritogenic agents for development of ReA included *Giardia lamblia*, amebae, and other unusual enteric pathogens [16]; as with the several viruses mentioned and the bacterial species not usually considered as standard etiologic agents, these pathogens require much more research both at the clinical and basic science levels before their acceptance as etiologic causes of ReA.

PATHOGENESIS

It is not clear at this point whether a single process elicited by all these various pathogens produces arthritis, or whether a different pathogenic process is initiated by each organism. For *C. trachomatis*-induced arthritis, the organism is transported to the joint in infected monocytes, where it establishes itself inside those cells within synovial tissue to generate inflammation. At that site the bacteria are in the 'persistent' infection state, so-called because gene expression is extremely unusual causing abrogation of the developmental cycle; partial

antibiotic refractoriness (not resistance) is also characteristic of persistence. We do not understand how persistently infecting *Chlamydiae* avoid destruction within monocyte/macrophages [17,18]. The standard Gram-negative gastrointestinal pathogens do not reach the joint intact. Only parts of these infecting organisms that include arthritogenic peptides reach the synovium; there, the peptides are displayed by HLA-B27 allelic products to elicit an inflammatory response [17]. However, and importantly, the overall rate of positivity for this allele in ReA patients is usually much lower than that characterizing patients with ankylosing spondylitis. Thus, there must be other mechanisms responsible for inflammation and pathogenesis of the joint.

One issue related to synovial pathogenesis which has generated some interest over the last couple of decades concerns the microbiome of the joint (and elsewhere) that might influence synovial pathogenesis either directly or indirectly. One early study identified a surprising number and diversity of bacterial species in the joints of patients with various arthritides [19]; in that study, no attempt was made to relate the species identified to details of the described/associated arthritides. Moreover, ReA can be a sequela to inflammatory bowel disease. In these cases, arthritis or other clinical attributes may be associated with some lipo-oligosaccharides from an infecting organism that interact with the patient's innate immune system [20]. It is clear from recent studies that the intestinal microbiome has wide-ranging effects on synovial and other pathogenic processes, and that experimental systems to dissect such long-distance interactions will be critical for the definition of unique pathogenic mechanisms [21–23].

CLINICAL MANIFESTATIONS

Musculoskeletal manifestations of HLA-B27 associated ReA typically include asymmetric oligoarthritis of the lower limb joints, enthesitis, dactylitis, and sacroiliitis. Few articles, however, have described cases of ReA associated with rare microbial infections [24,25]. We recently published a review focused on articles appearing between 2018 and 2020, and which covered rare causative microorganisms, including among others *Neisseria meningitides*, *Hafnia alvei*, *C. cayetanensis*, β-haemolytic Streptococci, and *Rickettsia rickettsia* [12▪]. Among the most prominent new infectious agents cited were *Staphylococcus lugdunensis*, *Rothia mucilaginosa*, and most importantly the SARS-CoV-2 virus. Here, we review briefly a few illustrative clinical aspects of ReA induced by noncanonical pathogens.

Mycoplasma pneumoniae infection is relatively common, but its association with ReA is reported sporadically, mainly in children [26]. Arthritis induced by this organism is probably the least common extrapulmonary manifestation and frequently leads to delays in the diagnosis, as illustrated in the case of a 2-year-old female child admitted in the clinic for prolonged fever [24]. Another recent case report described a 30-year-old Greek patient who presented with acute *M. pneumoniae* infection complicated by HLA-B27-positive ReA, asymmetric proximal myopathy, and progression to chronic SpA [27]. *Clostridium difficile* is also a rarely recognized causative agent of ReA. In one case, a 20-year-old HLA-B27-positive white man with a history of psoriasis presented to the emergency department because of a 2-week history of severe polyarthralgia; he also had a 3-week history of nonbloody diarrhoea [25]. Investigation revealed colitis on computer tomography, pseudomembranous colitis on colonoscopy, and aspirate positive for *C. difficile* toxin. The case of a 12-year-old female presenting with fever, headache, icterus and arthritis of the hip joint was diagnosed as ReA due to *Leptospira* species [28]. Synovial biopsy of hip showed inflammation with no specific abnormality and no growth of any microorganism, but screening for *Leptospira* and *Leptospira* IgM membrane attack complex by ELISA were positive. The first report of a case of babesiosis mimicking Reiter's syndrome may add a new member to the spectrum of ReA [29]. Six months after polytrauma requiring repetitive blood transfusions, the 36-year-old male developed the triad of conjunctivitis, nonspecific urethritis, and joint pain. Babesiosis infection was confirmed by lymphocyte transformation test, and treatment with doxycycline and trimethoprim-sulfamethoxazole resulted in complete remission. A major limitation of the report is the absent clinical documentation of synovitis.

Perhaps most importantly, with the advent of the SARS-CoV-2 pandemic, an increasing number of cases and case series of acute arthritis following this viral infection have been reported and classified as ReA; it has, though, been argued to classify the condition as viral arthritis rather than ReA, and to term it as 'SARS-CoV2-triggered acute arthritis' or 'COVID-19-related arthritis ' [30]. Several publications have presented case-based reviews of the increasing reports and have documented clinical manifestation [31–35]. The most detailed review documented a total of 21 cases from 20 articles and included the report of an additional personal case observation [36▪▪]. The median age of the cases is 50 (21–73) years, and the median duration between diagnosis of COVID-19 and ReA is 18 (7–90) days. Axial involvement was detected in two cases, monoarthritis in 10, oligoarthritis in five, and polyarthritis in five cases. The most frequently involved joints were knee, ankle, proximal interphalangeal

joint, distal interphalangeal joint, and sacroiliac joint. Enthesitis was reported in one case, and no cases with dactylitis were reported. Extra-articular signs were present in two cases as balanitis and skin lesions. A unique case report described a 30-year-old HLA-B27-positive female with the conjunctivitis, oral lesions, palatal erosion, painful ulcers on the labia majora, blennorrhagic keratoderma on the soles of the feet, psoriasiform nail changes, and dactylitis of the fourth toe typical for classic extra-articular manifestations of ReA without evident arthritis after COVID-19 infection [37].

DIAGNOSIS AND TREATMENT ISSUES

Diagnosis of ReA is, of course, based on clinical characteristics, symptoms, and identification of antecedent infection from medical history, available laboratory tests, and exclusion of differential diseases. Asymptomatic infections, the absence of validated classification and diagnostic criteria, and the increasingly large spectrum of rare and new infectious agents have made diagnosis of ReA more than a little problematic [5▪▪,12▪]. Thus, diagnostic procedures cannot be restricted to the well known HLA-B27-associated group of inflammatory markers, HLA-B27, serology for enteric pathogens, and molecular testing for *C. trachomatis* infection, but must also cover individualised diagnostic consideration of the wide diversity of postinfectious arthritides termed ReA [12▪]. The British Association of Sexual Health and HIV has published updated guidelines for the management of (SARA) primarily aimed at services offering level 3 care in sexually transmitted infection management within the United Kingdom; it will be also of use to rheumatologists assessing and managing patients presenting with possible SARA [38▪▪]. All patients should be offered screening for sexually transmitted infections, supplemented as necessary with laboratory and microbiology tests, imaging, and exclusion tests for other rheumatological diseases as summarised in Table 1.

These recommendations by the BASHH may be extended usefully to procedures for diagnosis of other causes of ReA if supplemented by appropriate microbiology testing. Serology is the preferred method for gastrointestinal infections such *Yersinia*, *Salmonella*, and *Campylobacter*, since gastrointestinal symptoms often have resolved by the time the rheumatic features develop [39▪]. For diagnostic testing to identify other infectious agents of ReA, readers are referred to the review on poststreptococcal (PSReA), Poncet's disease, instillation of bacillus Calmette–Guérin (iBCG)-induced ReA, and the update on new and rare infectious agents implicated as pathogens with the large supplemental list of references [12▪,40▪▪].

Overall general treatment guidelines for ReA do not currently exist. Treatment of the underlying infections is oriented to the triggering infection [5▪▪]. Antibiotics are not used in the routine treatment of the ReA, although a 6-month course of combination antibiotics (doxycycline or azithromycin, combined with rifampin) demonstrated higher response rate in comparison with placebo in patients with chronic *Chlamydia*-induced ReA [41], and efficacy of antimicrobial therapy has been reported for some rare forms of ReA, for example, those induced by *Borrelia burgdorferi*, *N. gonorrhoeae*, *Tropheryma whippelii*, and *Rickettsia rickettsii* [12▪]. Usually, management depends on the phase of disease, whether it is acute or chronic. Therapies for acute ReA include NSAIDs, intra-articular glucocorticoid for monoarthritis or oligoarthritis, and systemic glucocorticoids for large number of joint involvement [5▪▪,39▪]. In chronic disease lasting longer than six months and which is unsuccessful given the former measures, disease-modifying antirheumatic drugs for example, sulfasalazine and methotrexate are indicated [5▪▪,39▪]. Interestingly, most reported post-COVID-19 ReA cases had a complete and rapid response to NSAIDs, glucocorticoids, or a combination of the two [36▪▪]. In contrast, post-COVID arthritis patients from one study from India generally required an additional disease modifying agent such as hydroxychloroquine, along with NSAIDs and tapering low-dose steroids in cases that presented with severe symptoms [42▪].

CONCLUSION

ReA clearly is an heterogenous disease with varied presentation across the globe, in part related to HLA-B27 positivity, and significantly because of an increasingly wide diversity in causative agents, epidemiology, and rare case presentations. A primary weakness we encountered reviewing recent research articles centres on the fact that many publications were single case reports or case series were small; others were cross-sectional and retrospective. Regardless, patient-oriented research reports which include descriptions of novel aspects related to, for example, post-COVID-19 ReA or therapy, can provide extremely valuable information in the absence of other evidence. Validated classification and diagnostic criteria, more pathogenic examinations, and evidence-based treatment recommendation are essential to advance further the understanding of ReA. Importantly, much remains to be learned in terms of the interaction of newly identified pathogens and the synovium which result in arthritis.

Table 1. The British Association of Sexual Health and HIV published updated 2021 guidelines for screening for sexually transmitted infection and investigations in the management of sexually acquired reactive arthritis supplemented by appropriate history and microbiology testing for other reactive arthritis [38▪▪,39▪,40▪▪]

Male genital samples
Urine NAAT for *C. trachomatis* and *N. gonorrhoeae*
Urethral gram stained smear (if urethral symptoms)
Urethral culture and sensitivity testing for *N. gonorrhoeae*
Female genital samples
Vulvovaginal NAAT for *C. trachomatis* and *N. gonorrhoea*
Endocervical culture and sensitivity testing for *N. gonorrhoeae* (if microscopy or NAAT positive)
Genital samples in trans people
Details on STI screening in trans people are available from the BASHH guideline at https://www.bashh.org/media/4400/bashh-recommendations-for-integrated-sexual-health-services-for-trans-including-nonbinary-people-2019pdf.pdf
Samples in both men and women
Pharyngeal and rectal NAAT samples for *C. trachomatis* and *N. gonorrhoeae* where indicated by the sexual history
Screening for HIV and syphilis
Screening for hepatitis B and C based on risk factors in the sexual history
Consider M. genitalium NAAT (urine in men/vulvovaginal sample in women)
The following are also useful initial investigations:
Acute phase response – erythrocyte sedimentation rate, C-reactive protein or plasma viscosity
Full blood count
Urinalysis
Further investigations
The following tests may be useful in some situations, but are not necessarily always required. Close liaison with relevant pathology departments is advisable to ensure that the correct samples are obtained
Biochemistry
Liver and kidney function tests
Microbiology
Blood cultures
Stool culture
Synovial fluid aspirate for cell count, gram stain crystals, and culture (to exclude septic arthritis and gout)
Imaging
Radiographs of affected joints
Ultrasonography of affected joints or entheses
Magnetic resonance imaging of sacroiliac joints and spine
Others
Travel history
History of vaccination
Serology for enteric pathogens (e.g., *Yersinia*, *Salmonella*, and *Campylobacter)* and possible other pathogens, for example, *Bartonella, Borrelia, Brucella, Mycobacteria,* and *Streptococcus*
HLA-B27
Electrocardiogram
Echocardiogram
Synovial biopsy
Exclusion tests for other rheumatological diseases
Anticyclic citrullinated peptide (rheumatoid arthritis)
Autoantibodies (systemic lupus erythematosus)
Plasma urate (gout)
Chest radiograph and serum angiotensin-converting enzyme level (sarcoidosis)

NAAT, nucleic acid amplification test.

Acknowledgements

None.

Financial support and sponsorship

None.

Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:
- ■ of special interest
- ■■ of outstanding interest

1. Toivanen A, Toivanen P. Reactive arthritis. Curr Opin Rheumatol 2000; 12:300–305.
2. Carter JD, Hudson AP. The evolving story of Chlamydia-induced reactive arthritis. Curr Opin Rheumatol 2010; 22:424–430.
3. van der Helm-van M, Annette HM. Acute rheumatic fever and poststreptococcal reactive arthritis reconsidered. Curr Opin Rheumatol 2010; 22:437–442.
4. Kononoff A, Arstila L, Pussinen P, *et al.* Incidence of inflammatory joint diseases in Finland: results from a population-based epidemiological study. Rheumatol Int 2017; 37:1693–1700.
5. ■■ Bentaleb I, Abdelghani KB, Rostom S, *et al.* Reactive arthritis: update. Curr Clin Microbiol Rep 2020; 1–9.

The update review based on recent literature provides an overview about changing epidemiology, pathophysiology, microbiome changes, clinical features, diagnostic approach, and therapeutic approach of the disease.

6. Alamanos Y, Pelechas E, Voulgari PV, Drosos AA. Incidence of spondyloarthritis and its subtypes: a systematic review. Clin Exp Rheumatol 2021; 39:660–667.
7. ■ Pogreba-Brown K, Austhof E, Tang X, *et al.* Enteric pathogens and reactive arthritis: systematic review and meta-analyses of pathogen-associated reactive arthritis. Foodborne Pathog Dis 2021; 18:627–639.

Systematic reviews on the incidence of reactive arthritis (ReA) after foodborne infections most relied on articles published ten or more years ago. The systematic review and meta-analysis of 24 articles published between 2000 and 2018 estimated the proportion of ReA after enteric infection with the four most common foodborne bacterial pathogens with the largest evidence of association: Campylobacter spp., nontyphoidal Salmonella, Shigella spp., and Yersinia spp. The findings of this research may enhance evidence-based patient management by increasing awareness of ReA among clinicians.

8. Borud EK, Håberg SE, Norheim AJ, *et al.* Yersinia enterocolitica: a follow-up of the outbreak in the Norwegian Armed Forces in 2014. Mil Med 2021; 186: e996–e1000.
9. Tuompo R, Lääveri T, Hannu T, *et al.* Reactive arthritis and other musculoskeletal symptoms associated with acquisition of diarrhoeagenic *Escherichia coli*. Ann Rheum Dis 2020; 79:605–611.
10. Denison HJ, Curtis EM, Clynes MA, *et al.* The incidence of sexually acquired reactive arthritis: a systematic literature review. Clin Rheumatol 2016; 35:2639–2648.
11. Zeidler H, Hudson AP. *Chlamydia*-induced reactive arthritis: disappearing entity or lack of research? Curr Rheumatol Rep 2019; 21:63.
12. ■ Zeidler H, Hudson AP. Reactive arthritis update: spotlight on new and rare infectious agents implicated as pathogens. Curr Rheumatol Rep 2021; 23:53.

The article presents a comprehensive narrative review of ReA with focus on articles published between 2018 and 2020. The review discuss the entire spectrum of microbial agents known to be the main causative agents of ReA, those reported to be rare infective agents, and those reported to be new candidates causing the disease. The discussion is set within the context of changing disease terminology, definition, and classification over time. Further, reports are referenced that present at least a hint of effective antimicrobial therapy for ReA as documented in case reports or in double-blind controlled studies. Additional information is included on microbial products detected in the joint, as well as on the positivity of HLA-B27.

13. Brinster A, Guillot X, Prati C, Wendling D. Evolution over thirty years of the profile of inpatients with reactive arthritis in a tertiary rheumatology unit. Reumatol Clin 2018; 14:36–39.
14. Danssaert Z, Raum G, Hemtasilpa S. Reactive arthritis in a 37-year-old female with SARS-CoV2 infection. Cureus 2020; 12:e9698.
15. Liew IY, Mak TM, Cui L, *et al.* A case of reactive arthritis secondary to coronavirus disease infection. J Clin Rheumatol 2020; 26:233.
16. García-Kutzbach A, Chacón-Súchite J, García-Ferrer H, Iraheta I. Reactive arthritis: update 2018. Clin Rheumatol 2018; 37:869–874.
17. Carter JD, Hudson AP. Recent advances and future directions in understanding and treating Chlamydia-induced reactive arthritis. Expert Rev Clin Immunol 2017; 13:197–206.
18. Schmitt SK. Reactive arthritis. Infect Dis Clin N Am 2017; 31:265–1075.
19. Gérard HC, Wang Z, Wang GF, *et al.* Chromosomal DNA from a variety of bacterial species is present in synovial tissue in patients with various forms of arthritis. Arthritis Rheum 2001; 44:1689–1697.
20. Mousave S, Bereswill S, Heimesaat MM. Novel clinical *Campylobacter jejuni* infection models based on sensitization of mice to lipooligosaccharide, a major bacterial factor triggering innate immune responses in human campylobacteriosis. Microorganisms 2020; 8:482.
21. Rosenbaum JT, Asquith M. The microbiome and HLA-B27-associated acute anterior uveitis. Nat Rev Rheumatol 2018; 14:704–713.
22. Manasson J, Shen N, Garcia Ferrer HR, *et al.* Gut microbiota perturbations in reactive arthritis and postinfectious spondyloarthritis. Arthritis Rheumatol 2018; 70:242–254.
23. Verma A, Sharda S, Rathi B, *et al.* Elucidating potential molecular signatures through host-microbe interactions for reactive arthritis and inflammatory bowel disease using combinatorial approach. Sci Rep 2020; 10:15131.
24. Mărginean CO, Georgescu AM, Meliţ LE. Arthritis associated with *Mycoplasma pneumoniae* in a pediatric patient: a case report. Medicine (Baltimore) 2021; 100:e24316.
25. Reinholz A, Mannuru D, Bande D, Matta A. Reactive arthritis: an unusual presentation of acute *Clostridioides difficile* colitis. BMJ Case Rep 2021; 14: e240890.
26. Harjacek M, Ostojic J, Djakovic RO. Juvenile spondyloarthropathies associated with *Mycoplasma pneumoniae* infection. Clin Rheumatol 2006; 25:470–475.
27. Pilianidis G, Tsinari A, Pandis D, *et al.* Chronic seronegative spondyloarthropathy following acute *Mycoplasma pneumoniae* infection in a human leukocyte antigen B27-positive patient: a case report. J Med Case Rep 2020; 14:155.
28. Dey S, Sipani AK, Das R. Case report of a rare cause of reactive arthritis: leptospirosis. J Orthop Case Rep 2021; 11:79–84.
29. Strizova Z, Havlova K, Patek O, *et al.* The first human case of babesiosis mimicking Reiter's syndrome. Folia Parasitol (Praha) 2020; 67:031.
30. Kobayashi S, Taniguchi Y, Kida I, Tamura N. SARS-CoV2-triggered acute arthritis: viral arthritis rather than reactive arthritis. J Med Virol 2021; 93:6458–6459.
31. Ahmed S, Zimba O, Gasparyan AY. COVID-19 and the clinical course of rheumatic manifestations. Clin Rheumatol 2021; 40:2611–2619.
32. Zeidler H. Post-COVID-19-arthritis. Manifestation unter dem klinischen Bild einer reaktiven Arthritis [Post-corona-virus-disease-19 arthritis. Manifestation under the clinical picture of a reactive arthritis]. Z Rheumatol 2021; 80:555–558; German.
33. Gasparotto M, Framba V, Piovella C, *et al.* Post-COVID-19 arthritis: a case report and literature review. Clin Rheumatol 2021; 40:3357–3362.
34. Wendling D, Verhoeven F, Chouk M, Prati C. Can SARS-CoV-2 trigger reactive arthritis? Joint Bone Spine 2021; 88:105086.
35. Colatutto D, Sonaglia A, Zabotti A, *et al.* Post-COVID-19 arthritis and sacroiliitis: natural history with longitudinal magnetic resonance imaging study in two cases and review of the literature. Viruses 2021; 13:1558.
36. ■■ Kocyigit BF, Akyol A. Reactive arthritis after COVID-19: a case-based review. Rheumatol Int 2021; 41:2031–2039.

The most advanced review of COVID-19-related ReA documented a total of 21 cases from 20 articles, including the report of an additional personal case observation. The article provides the general characteristics of COVID-19-related ReA cases as published in the literature before 12 July 2021, and discuss possible immunological mechanisms based on the current data and the known pathogenetic background of viral arthritis.

37. Santacruz JC, Londoño J, Santos AM, *et al.* Extra-articular manifestations in reactive arthritis due to COVID-19. Cureus 2021; 13:e18620.
38. ■■ Carlin E, Marzo-Ortega H, Flew S. British Association of Sexual Health and HIV national guideline on the management of sexually acquired reactive arthritis 2021. Int J STD AIDS 2021; 32:986–997.

Very instructive and comprehensive updated guidelines for the management of sexually acquired ReA (SARA) primarily aimed at services offering level 3 care in sexually transmitted infection management within the United Kingdom but also of use to rheumatologists assessing and managing patients presenting with possible SARA. The investigations recommended may be also transferred to the procedure to diagnose other causes of ReA if supplemented by appropriate microbiology testing.

39. ■ Jubber A, Moorthy A. Reactive arthritis: a clinical review. J R Coll Physicians Edinb 2021; 51:288–297.

The most recent clinical review of ReA now, including the expanded list of causative infections includes such as respiratory pathogens, viruses and intravesical BCG. Useful tips for the nonspecialist provide the main diagnostic features and the treatment management of the initial and chronic disease. As the main conclusion is highlighted that ReA should be considered in the differential diagnosis of any acute inflammatory arthritis.

40. Taniguchi Y, Nishikawa H, Yoshida T, *et al.* Expanding the spectrum of ■■ reactive arthritis (ReA): classic ReA and infection-related arthritis including poststreptococcal ReA, Poncet's disease, and iBCG-induced ReA. Rheumatol Int 2021; 41:1387–1398.

The article review the epidemiology, clinical characteristics, treatment, prognosis, and differences between classic ReA, poststreptococcal ReA, Poncet's disease, and ReA following iBCG therapy and clarify that these entities could be included in the expanding spectrum of ReA, especially based on the pathogenic mechanism.

41. Carter JD, Espinoza LR, Inman RD, *et al.* Combination antibiotics as a treatment for chronic Chlamydia-induced reactive arthritis: a double-blind, placebo-controlled, prospective trial. Arthritis Rheum 2010; 62:1298–1307.

42. Jaladhar P, Chandrashekara S, Salanke M, Kori D. The pattern of postviral ■ arthritis in COVID pandemic state: an experience of tertiary care centre. J Assoc Physicians India 2021; 69:47–50.

This retrospective observational study of patients presented in July–November 2020 at a tertiary care centre in India reported 14 patients as having post-COVID arthritis in this 5-month period of observation. Post-COVID ReA needs to be considered as a potential differential in postinfectious arthritis. There were no identifiable characteristics, clinical or a simple routine laboratory parameter, which could differentiate the causes of postinfectious arthritis from autoimmune rheumatic diseases. https://pubmed.ncbi.nlm.nih.gov/30301938/.

Beyond plaque psoriasis – pathogenesis and treatment of other psoriasis phenotypes

Helena Iznardo and Lluís Puig

Purpose of review
Psoriasis vulgaris is the commonest presentation of psoriatic disease, but morphologic variants such as pustular psoriasis (PP) and a closely related disease, pityriasis rubra pilaris (PRP), have been known for a long time, have been associated with rheumatologic manifestations indistinguishable from psoriatic arthritis (PsA) that may go unrecognized, and often represent a therapeutic conundrum. There is recent evidence that underlying genetic and pathogenetic differences may provide the basis for newer therapeutic approaches.

Recent findings
This narrative review highlights the clinical, genetic and pathogenetic characteristics of PP and PRP, their association with PsA and recent developments in their treatment, especially with biologic agents targeting IL-36 and other cytokines of pathogenic relevance.

Summary
The clinical manifestations of PP and PRP are less well known to rheumatologists than those of psoriasis, and recent advances in our insight on their pathogenesis may eventually overcome the therapeutic difficulties faced by dermatologists and rheumatologists in the management of these diseases and their rheumatologic manifestations.

Keywords
generalized pustular psoriasis, palmoplantar pustulosis, pityriasis rubra pilaris, psoriasis, psoriatic arthritis, pustular psoriasis

INTRODUCTION

Plaque psoriasis or psoriasis vulgaris (PV) is a well-known multifactorial chronic disorder affecting between 2% and 3% of the world's population [1]. Its pathogenesis involves immunological abnormalities, genetic factors and environmental risk factors, ultimately resulting in a disordered proliferation and immune activation of keratinocytes [2]. Different morphological and topographic variants of PV – including guttate psoriasis, inverse psoriasis, palmoplantar psoriasis, etc. – have been well recognized for a long time, but pustular psoriasis (PP), characterized by sterile, neutrophil-rich pustules, is much less known due to its low incidence [3]. Although PP has been classically considered to be a subtype of PV, recent developments on the pathogenesis and genetic architecture of PP have led to its reclassification as a distinct entity [4]. Psoriatic arthritis (PsA), a complex inflammatory joint disease included in the spondyloarthropathy spectrum that affects approximately one-third of psoriasis patients [5], is known to occur in patients with PP. On the other hand, pityriasis rubra pilaris (PRP) is a rare inflammatory skin disorder in the spectrum of psoriasis with a highly variable clinical appearance and individual prognosis, as well as frequent refractoriness to treatment. The association with arthritis has been reported occasionally, but knowledge on the rheumatological aspects of PRP is scarce. In this review article, we will focus on the clinical and pathogenic aspects of the less known entities in the psoriatic spectrum (PP and PRP), focusing on their rheumatologic relevance and therapeutic implications.

PUSTULAR PSORIASIS

Forms of PP include palmoplantar pustular psoriasis (PPPP), affecting the palms and soles; acrodermatitis

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Curr Opin Rheumatol 2022, 34:225–234
DOI:10.1097/BOR.0000000000000882

KEY POINTS

- Pustular psoriasis and pityriasis rubra pilaris are within the psoriatic spectrum and can be associated with rheumatologic manifestations indistinguishable from psoriatic arthritis.
- Their rarity and the existence of different subtypes make their diagnosis and management challenging.
- New insights have been discovered on their pathogenesis, mainly involving IL-36 pathway.
- Targeted treatment focusing on IL-36 and other related cytokines of pathogenic relevance may allow to overcome the therapeutic difficulties faced nowadays.

continua of Hallopeau (ACH), involving the nail and surrounding tissues; and generalized pustular psoriasis (GPP). Table 1 includes a summary of clinical definitions and morphological aspects of PV and PP subtypes.

Generalized pustular psoriasis

GPP is a rare systemic disease characterized by an acute and widespread flare of superficial sterile pustules over the trunk, which frequently coalesce and develop into erythroderma. Systemic symptoms such as fever, chills and arthralgia are present in most cases, and these patients are initially seen at medical emergency units. The appearance of rapidly progressive and extensive pustulation on an erythematous background, which can be persistent or relapsing throughout the course of the disease, is a defining and diagnostic characteristic of this condition [4]. These flares are usually preceded by a prodromal phase of malaise and skin tenderness. GPP can be triggered by drugs, mostly systemic corticosteroids, but also topical corticosteroids, tumor necrosis factor (TNF) inhibitors or cyclosporine A. The differential diagnosis of GPP with acute generalized exanthematous pustulosis, a pustular drug reaction not associated with psoriasis that does not relapse except upon rechallenge, may be exceedingly difficult on presentation. Other triggers

Table 1. Morphological variants of psoriasis vulgaris and pustular psoriasis.

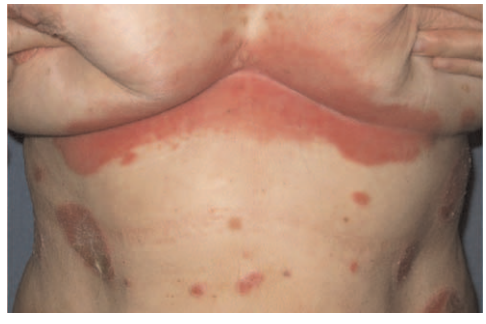
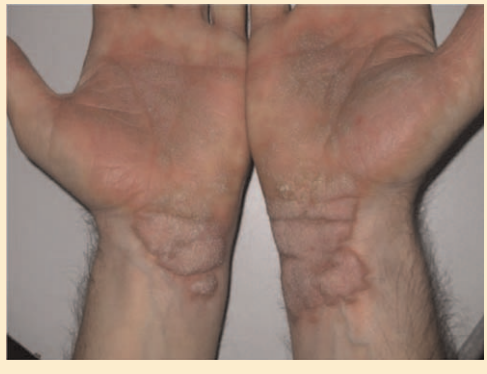
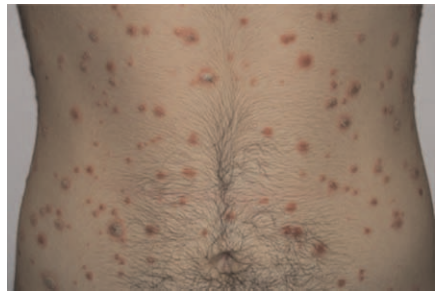
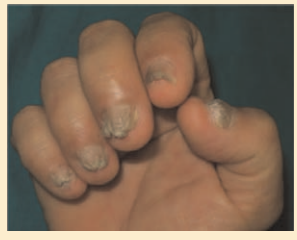
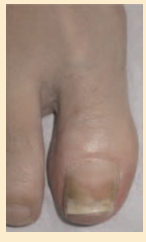
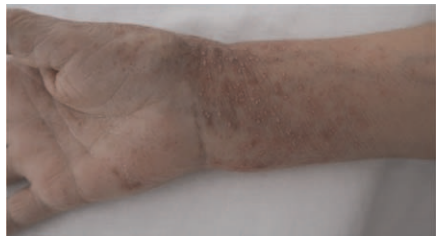
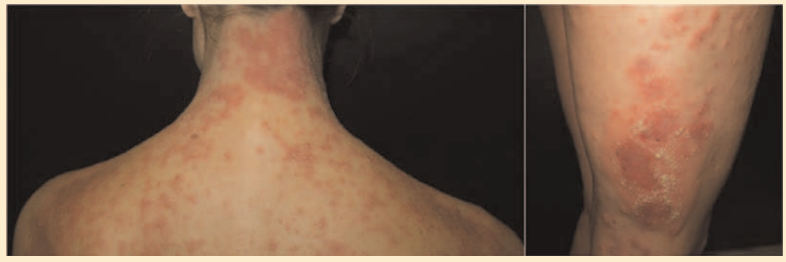
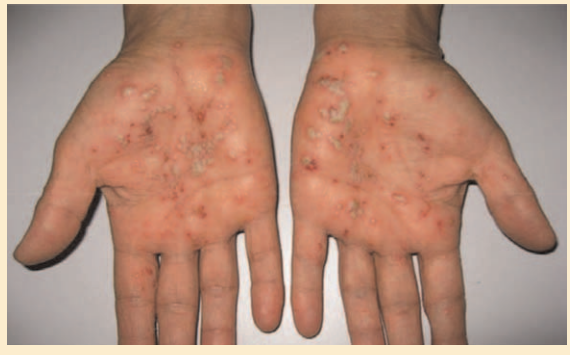
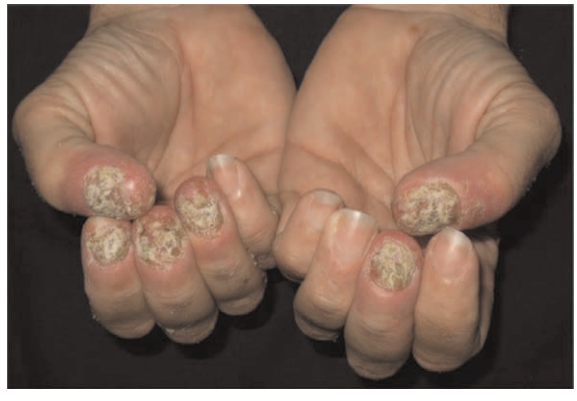
Psoriasis vulgaris		
Denomination	**Clinical characteristics**	**Clinical picture**
Inverse psoriasis	Sharply demarcated erythematous plaques involving intertriginous areas Smooth and shiny surface with minimal or absent	
Palmoplantar psoriasis	Sharply demarcated erythematous desquamative plaques located on the palms and soles	

Table 1 (*Continued*)

Psoriasis vulgaris		
Denomination	**Clinical characteristics**	**Clinical picture**
Guttate psoriasis	Small scattered papules and plaques (drop-like) with whitish scales Triggered by streptococcal infections More common in children and adolescents	
Ungual psoriasis	**Nail matrix**: pitting, leuconychia, beau lines, onychomadesis, nail crumbling **Nail bed**: onycholisis, subungueal hyperkeratosis, oil spots, splinter haemorrhages	 Nail matrix + nail bed involvement  Oil spots
Psoriasis cum pustulatione	Pustules develop over psoriatic plaques	

Pustular psoriasis (ERASPEN classification)
Generalised pustular psoriasis
Primary sterile, visible pustules on nonacral skin (excluding *psoriasis cum pustulatione*)
Subclassifiers • With or without systemic inflammation • With or without psoriasis vulgaris • Either relapsing (>1 episode) or persistent (>3 months)

Table 1 (*Continued*)

Pustular psoriasis (ERASPEN classification)
∗Pregnancy PP (*Impetigo herpetiformis*): appears late into pregnancy and resolves with delivery. ∗Infantile PP ∗Annular PP (*Lapiere-Millian*)

Palmoplantar pustulosis
Primary, persistent (> 3 months), sterile, visible pustules on palms and/or soles
Subclassifier • With or without psoriasis vulgaris

Acrodermatitis continua of Hallopeau
Primary, persistent (> 3 months), sterile, visible pustules affecting the nail apparatus
Subclassifier • With or without psoriasis vulgaris
∗Limited to one digit –usually the thumb(s)– (Radcliffe-Crocker)


include infections (upper respiratory tract infections), hypocalcemia and pregnancy. The most common curse of the disease is relapsing, with a prepustular phase preceding a flare and a posterior postflare period. During the prepustular phase patients can be asymptomatic, but PV lesions can be observed in up to 31–78% of cases [3,6,7]. Currently, there is no consensus definition on what constitutes a 'flare', but it has been described as GPP lesions involving > 30% of body surface area [7].

Due to its rarity and difficulties in accurate diagnosis, the epidemiology of GPP is not well known. Prevalence rates from single studies are varied, ranging from 1.76 cases per million population in a French study from 2006 [8] and 7.46 cases per million population in a Japanese study from 1996 [6] to 122.3 cases per million population in a recent Korean study [9]. Such large variability can be attributed to differences in study design. GPP onset usually occurs between the fourth and sixth decades of life [3,7,10], but can be present throughout all stages in life. There is a slight female predominance, with a male-to-female ratio varying from 0.5 to 0.9 [3,7,8,10]. A study of 102 patients with GPP found that common comorbidities included obesity (42.9%), hypertension (25.7%), hyperlipidemia (25.7%), and diabetes mellitus (23.7%) [7]. Joint involvement (arthralgia or arthritis) is also frequent, and has been reported in 23.8% to 34.7% of GPP patients [7,10].

Localized pustular psoriasis

Controversy exists as to whether palmoplantar pustulosis (PPP) is an independent disease that can be associated with PV or a localized type of PP [11▪▪]. The term PPP was coined by Andrews to describe a relapsing or persistent and recalcitrant pustular eruption of the extremities, with initial formation of vesicles that eventually become pustules and finally crusts and scabs [12,13]. Nowadays the entity described by Andrews is referred to as type A PPP and is more prevalent in Japanese patients, with a marked prevalence for smoker females. Its pathogenesis has been linked with a specific response pattern to bacterial products [13,14]. On the contrary, type B PPP was described by Barber as a localized type of PP [15] and has a similar distribution between males and females in European countries, but a male predominance in Japan [16]. Rheumatological manifestations in PPP include both peripheral and axial disease with features of PsA [17]. Moreover, PPP is the most frequent cutaneous manifestation of synovitis, acne, pustulosis, hyperostosis, osteitis syndrome, a seronegative spondyloarthropathy that typically involves the sterno-costal joints and manubrium sternalis [18].

Pathogenesis

The innate immune response has a predominant role in the immunopathogenesis of PP. Autoinflammation, with uncontrolled activation of the IL-1/IL-36 inflammatory axis leads to neutrophil chemotaxis to the epidermis and neutrophil-driven inflammatory responses, with pustule formation being the ultimate consequence [19▪▪]. The critical drivers involved in these processes are keratinocytes, neutrophils and monocytes releasing pro-inflammatory cytokines such as IL-36, IL-1 and TNFα/IL-17A [20]. Binding and activation of IL-36R by IL-36 lead to activation of nuclear factor-kB and mitogen-activated protein kinase pathways, ultimately resulting in the promotion of inflammatory responses in keratinocytes, dermal endothelial cells, macrophages, fibroblasts, dendritic cells and various T cell subsets [21]. Antagonism by IL-36Ra and IL-38 inhibits the activation of intracellular pathways [22]. Protease-activated IL-36 cytokines also induce T-cell proliferation and signal to keratinocytes in an autocrine manner, with additional production of pro-inflammatory cytokines, antimicrobial peptides and neutrophil chemokines [23,24]. Finally, cytokines secreted by infiltrating Th1 and Th17 lymphocytes further potentiate this inflammatory loop by inducing the expression of IL-36 and other pro-inflammatory mediators by keratinocytes, mainly TNF-α, IL-6, and CXCL8 [25].

Several allelic variants of genes involved in the IL-36 pathway have been identified in familial and isolated cases of PP and increasing knowledge of these genetic mechanisms has contributed to better understand the disease. The main genes, proteins, mechanisms of action and clinicopathological features involved are summarized in Table 2.

Treatment

Currently, there is a lack of established therapeutic guidelines and no specific treatment is approved in Europe or the United States for the management of PP. Conventional systemic treatments such as oral retinoids, cyclosporine and methotrexate have all been proposed as first-line therapeutic options [26▪]. However, several studies have shown improved outcomes with biological treatments and we will focus on such [27,28▪].

Virtually all biologic agents blocking the TNF/IL-23/ IL-17 axis have been tried in GPP and PPP. Anti-IL17A monoclonal antibodies (mAbs) – secukinumab and ixekizumab– and the anti-IL-17A

Table 2. Genes involved in the pathogenesis of GPP with description of related proteins encoded and their functions.

Gene	Protein	Molecular characteristics	Clinicopathological features
IL-36RN (1–4)	IL-36Ra	Inhibits proinflammatory activity of IL-36 by attaching to IL-36R	Main molecular defect in PP (25% of GPP, 20% ACH, 5% PPP). Lower prevalence of plaque psoriasis Earlier age of onset Higher risk of systemic inflammation
CARD14 (4–8)	CARD14 (CARMA2)	NF-kB and MAPK activation through the formation of a signaling complex with BCL10 and MALT1 Gain-of-function pathogenic variants in result in hyperactivation of NF-kB	Pathogenic variants have been identified in patients with GPP and plaque psoriasis Rarely present in patients with GPP alone
AP1S3 (1,9–11)	σ1C subunit of the AP-1 complex	AP-1 complex is involved in clathrin-mediated vesicular trafficking between the trans-Golgi and the endosomes, autophagosome formation, Toll-like receptor homeostasis and keratinocyte autophagy AP1S3-deficient cells have increased mRNA expression of both IL1β and IL36α and increased expression and secretion of CXCL8	Loss-of-function pathogenic variants have been identified in European-descent PP patients, mainly in those with ACH
MPO (12,13)	Myeloperoxidase	Essential for neutrophil antimicrobial activity Involved in reactive oxygen species production, phagocytosis and generation of NETs	Lower age of GPP onset
SERPINA3 (14)	Serpin A3	Serine protease inhibitor: inhibits cathepsin G and other proteases	A loss of function variant has been identified in GPP patients
TNIP1 (15)	TNF-alpha induced protein 3 interacting protein 1	Interaction with zinc finger protein A20 to inhibit NF-κB signalling	Polymorphisms have been associated with GPP but not PPP

receptor mAb brodalumab have shown encouraging results in GPP [29–32]. IL-17A inhibitors offered the best retention times in a multicenter study with 201 treatment series of 86 GPP patients [28▪]. Anti-IL-23p19 agents guselkumab and risankizumab have demonstrated efficacy in Phase III trials with GPP Japanese patients [33–35]. Japan is one of the few countries where several biologic agents are approved for treatment of GPP, namely (at the time of writing) adalimumab, infliximab, certolizumab pegol, secukinumab, ixekizumab, brodalumab, bimekizumab, risankizumab and guselkumab. In PPP, none of these biologic drugs has shown consistent efficacy data in randomized placebo-controlled trials [36–39].

Anakinra, a recombinant IL-1 receptor antagonist (IL-1Ra) that inhibits both IL-1α and IL-β has shown incomplete responses in GPP and PPP [40,41]. Anti-IL-1β mAbs have shown better results: canakinumab was useful in a patient with a severe form of GPP [42] and obtained a partial response in two patients with severe PPP [43]. Gevokizumab has shown beneficial effects in two patients with GPP without a prior history of plaque psoriasis [44].

Several phase II and III clinical trials are currently ongoing to assess the efficacy and safety of mAbs targeting IL-36R in GPP and PPP: spesolimab (BI655130, Boehringer Ingelheim) and imsidolimab (ANB019, AnaptysBio). Phase I results from 7 patients treated with a single dose of spesolimab with moderate GPP are promising, with all patients exhibiting rapid skin improvement within 4 weeks [45]. On the contrary, preliminary results of anti-IL-36R biologics in PPP have also been discouraging [46].

PITYRIASIS RUBRA PILARIS

PRP is the name given to a group of rare inflammatory skin disorders that present with reddish-orange colored scaling patches with follicular plugging and well-defined borders, leaving islands of noninvolved skin [47]. They may cover the entire body or just parts of the body such as the elbows and knees. Other features include palmoplantar hyperkeratosis with a typically orange hue, prone to development of cracks that can be painful and may impair walking and manual dexterity. Severe

Table 3. Pytiriasis rubra pilaris subtypes

Type	Nomenclaturoioioie	Clinical characteristics	Course
I	Classical adult	– Cephalocaudal progression – Palmoplantar keratoderma– Nail involvement	– Acute (weeks to months) – Up to 80% spontaneous remission within 3 years
II	Atypical adult	– Ichtyosiform dermatitis – Coarse palmoplantar keratosis, – Sparse scalp hair	– Protracted course – Only 20% spontaneous resolution within 3 years
III	Classical juvenile	– Similar to type I	– Children between 5-10 years – Excellent prognosis – Frequent spontaneous resolution within a year
IV	Circumscribed juvenile	– Sharply demarcated erythema – Follicular hyperkeratosis – Located on the knees and elbows	– Adolescents – No progression – Protracted course, frequent relapses – Only 32% spontaneous remission
V	Atypical juvenile	– Follicular hyperkeratosis – Ichtyosiform dermatitis	– Early onset (first years of life). Chronic course
VI	HIV-related	– Nodulocystic and lichen spinulosus like lesions – Frequent erythroderma	– HIV-infected patients without immunosuppression – Poor prognosis – Poor response to treatment

scalp desquamation with hair thinning and nail plate thickening with yellow-brown ungual discoloration and subungueal hemorrhages are also common [48]. PRP affects both men and women of all ages, with one peak around 10 years of age and another between the 5th and 6th decades of life. A highly variable entity, it is further subclassified into six subgroups according to the age of onset, distribution of lesions and clinical course [49,50] (Table 3).

An association between PRP and seronegative arthritis has been reported, with variable clinical features [51–62]. Arthritis can appear before, after, or simultaneously to cutaneous manifestations. The most frequently involved joints include fingers, knees, and wrists with an asymmetric or symmetric peripheral polyarthritis, but axial disease and enthesitis have also been described. Nail changes are common. Radiographic evidence of acro-osteolysis is frequently described although only two cases of erosive arthritis have been reported [53,59]. Other rheumatological associations with PRP include myositis (specifically dermatomyositis and Wong-type dermatomyositis, with skin lesions characterized by the grouped keratotic follicular papules of PRP) [63,64], autoimmune thyroiditis [60], celiac sprue [65], systemic sclerosis [66] and myasthenia gravis [67].

Pathogenesis

Not much is known about PRP pathogenesis, although some clinicopathological overlap exists with psoriasis. Biomarkers have not yet been identified and recognized triggers include viral and bacterial infections [48]. Most cases are sporadic, but familial cases have been reported in PRP type V, with an autosomal-dominant inheritance pattern [68]. More recently, gain-of-function variants in *CARD14* have been detected in PRP type V patients [69,70], leading to reclassification of PRP type V as a distinct entity: *CARD14*-associated papulosquamous eruption (CAPE) [71]. Clinical features of this disease include early onset of disease (before 1 year of age), prominent facial involvement, family history of psoriasis or PRP and poor response to conventional treatment [71]. CARD14 genetic alterations have also been identified in PP, and according to some authors, PRP type V and some PP variants (IL-36Ra-related pustulosis and CARD14-mediated PP) can be considered autoinflammatory keratinization disorders (AiKDs). This recently proposed term is used to describe conditions in which genetic factors leading to hyperactivated innate immunity result in epidermal and dermal inflammation with hyperkeratosis [72].

Expression levels of pro-inflammatory innate cytokines such as TNF, IL-12 and IL-23 and adaptative T-cell cytokines IL-17A and IL-22 are upregulated in PRP lesional skin [73]. Furthermore, a recent study detected markedly increased serum CCL20 levels in a patient with PRP, which reverted to normal after treatment with guselkumab [74]. CCL20 is a major Th17-attracting chemokine, highly expressed in psoriatic lesions.

Treatment

PRP being a rare disease with multiple subtypes and spontaneous remission, establishing valid therapeutic algorithms is challenging. Most of the published

evidence is on type I PRP and comes from case series and clinical reports, since no randomized controlled trials on PRP have been published. A proposed therapeutic algorithm consists of a first-line treatment with topical steroids, calcineurin inhibitors and retinoids with a re-evaluation 6 weeks later. When topical treatment fails, systemic retinoids are proposed as the first-line systemic therapy and methotrexate as a second line. Failure to achieve a marked response in 12 weeks requires considering therapeutic escalation to biologics [48].

Many biologic drugs approved for psoriasis have been used in the treatment of PRP, with variable results. A systematic review of the literature on the treatment of PRP type 1 with TNF-antagonists presented a combination of infliximab with acitretin as the most effective, with 50% of refractory patients achieving a complete response [75]. Ustekinumab has shown great results in patients refractory to retinoids and other biologic agents [76–82]. Interestingly, PRP type V patients with *CARD14* pathogenic variants have also been successfully treated with ustekinumab [83], although these patients may require higher doses and more frequent dosing [71]. Blockade of the IL-17 axis may also have a therapeutical role in PRP: secukinumab and ixekizumab have been successfully used in several case reports [84–95], with a single-arm trial of ixekizumab on 12 PRP patients showing positive outcomes, with a mean improvement in affected body surface area of 29.8% (9.3%) ($P = 0.009$) [96]. Furthermore, secukinumab has been successful in treating PRP type V with *CARD14* pathogenic variants. Brodalumab achieved a notorious response in two patients who had failed to respond to ustekinumab [97,98], including one with a family history of PRP (*CARD14* status not disclosed) [97]. Last, IL-23p19 blockers have also been used to treat PRP: guselkumab showed a fast and almost complete response in three adult patients [74,99], with a decrease in serum CCL20 levels after treatment in one of them [74]; risankizumab was used as the first line of treatment in two patients [27] and in two patients with treatment-resistant PRP [100,101]; tildrakizumab has also shown therapeutical success [102].

CONCLUSION

In the last decade, we have assisted to a revolution in understanding the pathogenesis and treatment of plaque psoriasis. Therapeutic advances, specifically targeted treatment, have allowed to achieve complete clinical responses and modify the course of the disease in many patients. However, this has not been the scenario in PP, with many therapeutic needs still unmet. The small number of cases and variable presentations account for lack of better knowledge, but interesting advances have been made in recent years. Identification of autoinflammation, genetic variants and the key role of the IL-36 pathway on the pathogenesis of PP has led to the development of novel targeted-therapies. Specifically, mAbs blocking IL-1/IL-36-chemokine-neutrophil axis represent an interesting therapeutic target, and promising results have been obtained with anti-IL36R on GPP. Regarding PRP, there are still many questions unanswered on both pathogenesis and therapeutic approaches. The acute onset, and severe clinical manifestations, especially erythroderma and palmoplantar keratoderma, which are often refractory to treatment, determine an important burden on patients. Identification of fast-acting treatments is necessary, and for that purpose investigation on disease-associated genetic and molecular pathways must be the priority. The role of *CARD14* polymorphisms in the pathophysiology of different types of PRP should be investigated. Moreover, large scale clinical trials are needed to develop proper guidelines and therapeutic algorithms.

Acknowledgements

None.

Financial support and sponsorship

None.

Conflicts of interest

H.I. has received consultancy/speaker honoraria and/ or participated in clinical trials sponsored by Boehringer Ingelheim, Novartis, Pfizer and UCB.
L.P. has received consultancy/speaker's honoraria from and/or participated in clinical trials sponsored by Abbvie, Almirall, Amgen, Baxalta, Biogen, Bristol Myers Squibb, Boehringer Ingelheim, Celgene, Fresenius-Kabi, Gebro, Janssen, JS BIOCAD, Leo-Pharma, Lilly, Merck-Serono, MSD, Mylan, Novartis, Pfizer, Regeneron, Roche, Sandoz, Samsung-Bioepis, Sanofi, and UCB.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:
- ■ of special interest
- ■■ of outstanding interest

1. Boehncke W-H, Schön MP. Psoriasis. Lancet 2015; 386:983–994.
2. Grän F, Kerstan A, Serfling E, *et al.* Current developments in the immunology of psoriasis. Yale J Biol Med 2020; 93:97–110.
3. Zelickson BD, Muller SA. Generalized pustular psoriasis. A review of 63 cases. Arch Dermatol 1991; 127:1339–1345.
4. Navarini AA, Burden AD, Capon F, *et al.* European consensus statement on phenotypes of pustular psoriasis. J Eur Acad Dermatol Venereol 2017; 31:1792–1799.

5. Alinaghi F, Calov M, Kristensen LE, *et al.* Prevalence of psoriatic arthritis in patients with psoriasis: a systematic review and meta-analysis of observational and clinical studies. J Am Acad Dermatol 2019; 80:251–265.e19.
6. Ohkawara A, Yasuda H, Kobayashi H, *et al.* Generalized pustular psoriasis in Japan: two distinct groups formed by differences in symptoms and genetic background. Acta Derm Venereol 1996; 76:68–71.
7. Choon SE, Lai NM, Mohammad NA, *et al.* Clinical profile, morbidity, and outcome of adult-onset generalized pustular psoriasis: analysis of 102 cases seen in a tertiary hospital in Johor, Malaysia. Int J Dermatol 2014; 53:676–684.
8. Augey F, Renaudier P, Nicolas J-F. Generalized pustular psoriasis (Zumbusch): a French epidemiological survey. Eur J Dermatol 2006; 16:669–673.
9. Lee JY, Kang S, Park JS, *et al.* Prevalence of Psoriasis in Korea: a population-based epidemiological study using the Korean National Health Insurance Database. Ann Dermatol 2017; 29:761–767.
10. Baker H, Ryan TJ. Generalized pustular psoriasis. A clinical and epidemiological study of 104 cases. Br J Dermatol 1968; 80:771–793.
11. ■■ Murakami M, Terui T. Palmoplantar pustulosis: current understanding of disease definition and pathomechanism. J Dermatol Sci 2020; 98:13–19.

Outstanding review on palmoplantar pustulosis pathogenesis and definition.

12. Andrews GC, Birkman FW, Kelly RJ. Recalcitrant pustular eruptions of the palms and soles. Arch Dermatol Syphilol 1934; 29:548–563.
13. Andrews GC, Machacek GF. Pustular bacterids of the hands and feet. Arch Dermatol Syphilol 1935; 32:837–847.
14. Everall J. Intractable pustular eruptions of the hands and feet. Br J Dermatol 1957; 69:269–272.
15. Barber HW. Acrodermatitis continua Vel Perstans (dermatitis Repens) and psoriasis pustulosa∗. Br J Dermatol 1930; 42:500–518.
16. Kubota K, Kamijima Y, Sato T, *et al.* Epidemiology of psoriasis and palmoplantar pustulosis: a nationwide study using the Japanese national claims database. BMJ Open 2015; 5:e006450.
17. Sonozaki H, Mitsui H, Miyanaga Y, *et al.* Clinical features of 53 cases with pustulotic arthro-osteitis. Annof the Rheum Dis 1981; 40:547–553.
18. Nguyen MT, Borchers A, Selmi C, *et al.* The SAPHO syndrome. Semin Arthritis Rheum 2012; 42:254–265.
19. ■■ Uppala R, Tsoi LC, Harms PW, *et al.* Autoinflammatory psoriasis'-genetics and biology of pustular psoriasis. Cell Mol Immunol 2021; 18:307–317.

This article offers an outstanding review on pustular psoriasis focusing on pathogenesis and genetics.

20. Johnston A, Xing X, Wolterink L, *et al.* IL-1 and IL-36 are dominant cytokines in generalized pustular psoriasis. J Allergy Clin Immunol 2017; 140:109–120.
21. Walsh PT, Fallon PG. The emergence of the IL-36 cytokine family as novel targets for inflammatory diseases. Ann NY Acad Sci 2018; 1417:23–34.
22. Madonna S, Girolomoni G, Dinarello CA, *et al.* The significance of IL-36 hyperactivation and IL-36R targeting in psoriasis. Int J Mol Sci 2019; 20:3318.
23. Gabay C, Towne JE. Regulation and function of interleukin-36 cytokines in homeostasis and pathological conditions. J Leukoc Biol 2015; 97:645–652.
24. Li N, Yamasaki K, Saito R, *et al.* Alarmin function of cathelicidin antimicrobial peptide LL37 through IL-36γ induction in human epidermal keratinocytes. J Immunol 2014; 193:5140–5148.
25. Carrier Y, Ma H-L, Ramon HE, *et al.* Inter-regulation of Th17 cytokines and the IL-36 cytokines in vitro and in vivo: implications in psoriasis pathogenesis. J Invest Dermatol 2011; 131:2428–2437.
26. ■ Genovese G, Moltrasio C, Cassano N, *et al.* Pustular psoriasis: from pathophysiology to treatment. Biomedicines 2021; 9:1746.

This article analyses current evidence on pathophysiology and therapeutics in pustular psoriasis.

27. Kromer C, Schön MP, Mössner R. Treatment of pityriasis rubra pilaris with risankizumab in two cases. J Dtsch Dermatol Ges 2021; 19:1207–1209.
28. ■ Miyachi H, Konishi T, Kumazawa R, *et al.* Treatments and outcomes of generalized pustular psoriasis: a cohort of 1516 patients in a nationwide inpatient database in Japan. J Am Acad Dermatol 2022; 86:1266–1274.

Original article focusing on the management of pustular psoriasis in a large cohort of Japanese patients.

29. Imafuku S, Honma M, Okubo Y, *et al.* Efficacy and safety of secukinumab in patients with generalized pustular psoriasis: A 52-week analysis from phase III open-label multicenter Japanese study. J Dermatol 2016; 43:1011–1017.
30. Saeki H, Nakagawa H, Nakajo K, *et al.* Efficacy and safety of ixekizumab treatment for Japanese patients with moderate to severe plaque psoriasis, erythrodermic psoriasis and generalized pustular psoriasis: Results from a 52-week, open-label, phase 3 study (UNCOVER-J). J Dermatol 2017; 44:355–362.
31. Okubo Y, Mabuchi T, Iwatsuki K, *et al.* Long-term efficacy and safety of ixekizumab in Japanese patients with erythrodermic or generalized pustular psoriasis: subgroup analyses of an open-label, phase 3 study (UNCOVER-J). J Eur Acad Dermatol Venereol 2019; 33:325–332.
32. Yamasaki K, Nakagawa H, Kubo Y, *et al.* Efficacy and safety of brodalumab in patients with generalized pustular psoriasis and psoriatic erythroderma: results from a 52-week, open-label study. Br J Dermatol 2017; 176:741–751.
33. Sano S, Kubo H, Morishima H, *et al.* Guselkumab, a human interleukin-23 monoclonal antibody in Japanese patients with generalized pustular psoriasis and erythrodermic psoriasis: efficacy and safety analyses of a 52-week, phase 3, multicenter, open-label study. J Dermatol 2018; 45:529–539.
34. Terui T, Kobayashi S, Okubo Y, *et al.* Efficacy and safety of guselkumab in Japanese patients with palmoplantar pustulosis: a phase 3 randomized clinical trial. JAMA Dermatol 2019; 155:1153–1161.
35. Okubo Y, Morishima H, Zheng R, *et al.* Sustained efficacy and safety of guselkumab in patients with palmoplantar pustulosis through 1.5 years in a randomized phase 3 study. J Dermatol 2021; 48:1838–1853.
36. Terui T, Kobayashi S, Okubo Y, *et al.* Efficacy and safety of guselkumab, an anti–interleukin 23 monoclonal antibody, for palmoplantar pustulosis: a randomized clinical trial. JAMA Dermatol 2018; 154:309–316.
37. Bissonnette R, Nigen S, Langley RG, *et al.* Increased expression of IL-17A and limited involvement of IL-23 in patients with palmo-plantar (PP) pustular psoriasis or PP pustulosis; results from a randomised controlled trial. J Eur Acad Dermatol Venereol 2014; 28:1298–1305.
38. Mrowietz U, Bachelez H, Burden AD, *et al.* Secukinumab for moderate-to-severe palmoplantar pustular psoriasis: Results of the 2PRECISE study. J Am Acad Dermatol 2019; 80:1344–1352.
39. Mrowietz U, Bachelez H, Burden AD, *et al.* Efficacy and safety of secukinumab in moderate to severe palmoplantar pustular psoriasis over 148 weeks: extension of the 2PRECISE study. J Am Acad Dermatol 2021; 84:552–554.
40. Tauber M, Viguier M, Alimova E, *et al.* Partial clinical response to anakinra in severe palmoplantar pustular psoriasis. Br J Dermatol 2014; 171:646–649.
41. Wang W-M, Jin H-Z. Biologics in the treatment of pustular psoriasis. Expert Opin Drug Saf 2020; 19:969–980.
42. Skendros P, Papagoras C, Lefaki I, *et al.* Successful response in a case of severe pustular psoriasis after interleukin-1β inhibition. Br J Dermatol 2017; 176:212–215.
43. Mansouri B, Kivelevitch D, Campa M, *et al.* Palmoplantar pustular psoriasis unresponsive to the interleukin-1β antagonist canakinumab. Clin Exp Dermatol 2016; 41:324–326.
44. Mansouri B, Richards L, Menter A. Treatment of two patients with generalized pustular psoriasis with the interleukin-1β inhibitor gevokizumab. Br J Dermatol 2015; 173:239–241.
45. Bachelez H, Choon S-E, Marrakchi S, *et al.* Inhibition of the interleukin-36 pathway for the treatment of generalized pustular psoriasis. N Engl J Med 2019; 380:981–983.
46. Mrowietz U, Burden AD, Pinter A, *et al.* Spesolimab, an anti-interleukin-36 receptor antibody, in patients with palmoplantar pustulosis: results of a Phase IIa, multicenter, double-blind, randomized, placebo-controlled pilot study. Dermatol Ther 2021; 11:571–585.
47. Klein A, Landthaler M, Karrer S. Pityriasis rubra pilaris: a review of diagnosis and treatment. Am J Clin Dermatol 2010; 11:157–170.
48. Roenneberg S, Biedermann T. Pityriasis rubra pilaris: algorithms for diagnosis and treatment. J Eur Acad Dermatol Venereol 2018; 32:889–898.
49. Griffiths WA. Pityriasis rubra pilaris. Clin Exp Dermatol 1980; 5:105–112.
50. Auffret N, Quint L, Domart P, *et al.* Pityriasis rubra pilaris in a patient with human immunodeficiency virus infection. J Am Acad Dermatol 1992; 27:260–261.
51. Aguilar AR, Gomez F, Balsa FT, *et al.* Pityriasis rubra pilaris with muscle and joint involvement. Dermatologica 1973; 146:361–366.
52. Duke RA, Barrett MR, Salazar JE, *et al.* Acro-osteolysis secondary to pityriasis rubra pilaris. AJR Am J Roentgenol 1987; 149:1082–1083.
53. Fiallo P, Tagliapietra AG, Santoro G. Arthropathic pityriasis rubra pilaris. Br J Dermatol 1996; 134:1154–1155.
54. Lister RK, Perry JD, Cerio R. Pityriasis rubra pilaris and a seronegative polyarthritis. Br J Dermatol 1997; 137:318–319.
55. Conaghan PG, Sommer S, McGonagle D, *et al.* The relationship between pityriasis rubra pilaris and inflammatory arthritis: case report and response of the arthritis to antitumor necrosis factor immunotherapy. Arthritis Rheum 1999; 42:1998–2001.
56. Behr FD, Bangert JL, Hansen RC. Atypical pityriasis rubra pilaris associated with arthropathy and osteoporosis: a case report with 15-year follow-up. Pediatr Dermatol 2002; 19:46–51.
57. Nakafusa J, Misago N, Narisawa Y. Pityriasis rubra pilaris in association with polyarthritis. Dermatology 2002; 205:298–300.
58. Chan H, Liu FT, Naguwa S. A review of pityriasis rubra pilaris and rheumatologic associations. Clin Dev Immunol 2004; 11:57–60.
59. Ohashi H, Takahashi H, Obara M, *et al.* A case of pityriasis rubra pilaris associated with rapidly progressive finger joint destruction. Nihon Rinsho Meneki Gakkai Kaishi 2004; 27:407–413.
60. Gül U, Gönül M, Kiliç A, *et al.* A case of pityriasis rubra pilaris associated with sacroileitis and autoimmune thyroiditis. J Eur Acad Dermatol Venereol 2008; 22:889–890.
61. Liu PY, Prete PE. Arthritis associated with pityriasis rubra pilaris. BMJ Case Rep 2010; 2010:bcr1220092565.
62. Chiu H-Y, Tsai T-F. Pityriasis rubra pilaris with polyarthritis treated with adalimumab. J Am Acad Dermatol 2013; 68:187–188.
63. Lupton JR, Figueroa P, Berberian BJ, *et al.* An unusual presentation of dermatomyositis: the type Wong variant revisited. J Am Acad Dermatol 2000; 43:908–912.

64. Requena L, Grilli R, Soriano L, *et al.* Dermatomyositis with a pityriasis rubra pilaris-like eruption: a little-known distinctive cutaneous manifestation of dermatomyositis. Br J Dermatol 1997; 136:768–771.
65. Randle HW, Winkelmann RK. Pityriasis rubra pilaris and celiac sprue with malabsorption. Cutis 1980; 25:626–627.
66. Frikha F, Frigui M, Masmoudi H, *et al.* Systemic sclerosis in a patient with pityriasis rubra pilaris. Pan Afr Med J 2010; 6:6.
67. Agharbi FZ, Elbekkal A, Baybay H, *et al.* Association of pityriasis rubra pilaris and myasthenia. Pan Afr Med J 2011; 10:7.
68. Ross NA, Chung H-J, Li Q, *et al.* Epidemiologic, clinicopathologic, diagnostic and management challenges of Pityriasis Rubra Pilaris. JAMA Dermatol 2016; 152:670–675.
69. Fuchs-Telem D, Sarig O, van Steensel MAM, *et al.* Familial pityriasis rubra pilaris is caused by mutations in CARD14. Am J Hum Genet 2012; 91:163–170.
70. Takeichi T, Sugiura K, Nomura T, *et al.* Pityriasis rubra pilaris type V as an autoinflammatory disease by CARD14 mutations. JAMA Dermatol 2017; 153:66–70.
71. Frare CP, Blumstein AJ, Paller AS, *et al.* CARD14-associated papulosquamous eruption (CAPE) in pediatric patients: three additional cases and review of the literature. Pediatr Dermatol 2021; 38:1237–1242.
72. Akiyama M, Takeichi T, McGrath JA, *et al.* Autoinflammatory keratinization diseases: an emerging concept encompassing various inflammatory keratinization disorders of the skin. J Dermatol Sci 2018; 90:105–111.
73. Feldmeyer L, Mylonas A, Demaria O, *et al.* Interleukin 23-Helper T Cell 17 axis as a treatment target for pityriasis rubra pilaris. JAMA Dermatol 2017; 153:304–308.
74. Nagai H, Jimbo H, Matsuura S, *et al.* Successful treatment of pityriasis rubra pilaris with guselkumab: Serum CCL20 as a potential marker for the disease activity. Dermatol Ther 2020; 33:e14403.
75. Petrof G, Almaani N, Archer CB, *et al.* A systematic review of the literature on the treatment of pityriasis rubra pilaris type 1 with TNF-antagonists. J Eur Acad Dermatol Venereol 2013; 27:e131–e135.
76. Wohlrab J, Kreft B. Treatment of pityriasis rubra pilaris with ustekinumab. Br J Dermatol 2010; 163:655–656.
77. Di Stefani A, Galluzzo M, Talamonti M, *et al.* Long-term ustekinumab treatment for refractory type I pityriasis rubra pilaris. J Dermatol Case Rep 2013; 7:5–9.
78. Byekova Y, Sami N. Successful response of refractory type I adult-onset pityriasis rubra pilaris with ustekinumab and acitretin combination therapy. J Dermatol 2015; 42:830–831.
79. Chowdhary M, Davila U, Cohen DJ. Ustekinumab as an alternative treatment option for chronic pityriasis rubra pilaris. Case Rep Dermatol 2015; 7:46–50.
80. Ruiz Villaverde R, Sánchez Cano D. Successful treatment of type 1 pityriasis rubra pilaris with ustekinumab therapy. Eur J Dermatol 2010; 20:630–631.
81. Paganelli A, Ciardo S, Odorici G, *et al.* Efficacy of ustekinumab after failure of infliximab CT-P13 in a HLA-Cw6-positive patient affected by pityriasis rubra pilaris: monitoring with reflectance confocal microscopy (RCM) and optical coherence tomography (OCT). J Eur Acad Dermatol Venereol 2017; 31: e249–e251.
82. Camela E, Miano C, Di Caterino P, *et al.* Erythrodermic pityriasis rubra pilaris treatment: two case reports and literature review. Dermatol Ther 2020; 33: e14223.
83. Eytan O, Sarig O, Sprecher E, *et al.* Clinical response to ustekinumab in familial pityriasis rubra pilaris caused by a novel mutation in CARD14. Br J Dermatol 2014; 171:420–422.
84. Liang J-Y, Ye R-X, Tian X, *et al.* Secukinumab monotherapy successfully treated severe refractory type V (atypical juvenile) pityriasis rubra pilaris: a case report and literature review. Dermatol Ther 2020; 33:e14097.
85. Penalba-Torres M, Pinilla-Martín B, Aragón-Miguel R, *et al.* Successful treatment of resistant pityriasis rubra pilaris with ixekizumab. Dermatol Ther 2020; 33:e13644.
86. Hanfstingl K, Pekar-Lukacs A, Motz R, *et al.* Successful treatment of pityriasis rubra pilaris with ixekizumab. Case Rep Dermatol 2018; 10:97–100.
87. Kohn D, Wetzig T. Pityriasis rubra pilaris: Successful treatment with ixekizumab. Hautarzt 2020; 71:624–626.
88. Heibel MD, Heibel HD. Successful treatment of type I pityriasis rubra pilaris with ixekizumab. JAAD Case Rep 2018; 4:774–776.
89. Simpson K, Dolianitis C. A case of treatment-resistant pityriasis rubra pilaris responsive to secukinumab. Australas J Dermatol 2021; 62:441–442.
90. Papini M, Russo A, Natalini Y, *et al.* Secukinumab is an effective and safe treatment for refractory pityriasis rubra pilaris. Ital J Dermatol Venerol 2021; 156:501–502.
91. Cole D, Mohammad T, Lim H. Rapid response of pityriasis rubra pilaris with psoriasis overlap to secukinumab. Br J Dermatol 2019; 181:1331–1332.
92. Schuster D, Pfister-Wartha A, Bruckner-Tuderman L, *et al.* Successful treatment of refractory pityriasis rubra pilaris with secukinumab. JAMA Dermatol 2016; 152:1278–1280.
93. Gauci M-L, Jachiet M, Gottlieb J, *et al.* Successful treatment of type II pityriasis rubra pilaris with secukinumab. JAAD Case Rep 2016; 2:462–464.
94. Wain T, Choy B, Satchell AC, *et al.* Secukinumab in pityriasis rubra pilaris: a case series demonstrating variable response and the need for minimal clinical datasets. JAAD Case Rep 2018; 4:500–505.
95. Maloney NJ, Hisaw LD, Worswick S. Type I pityriasis rubra pilaris treated with tumor necrosis factor inhibitors, ustekinumab, or secukinumab: a review. J Am Acad Dermatol 2018; 79:585–587.
96. Haynes D, Strunck JL, Topham CA, *et al.* Evaluation of ixekizumab treatment for patients with pityriasis rubra pilaris: a single-arm trial. JAMA Dermatol 2020; 156:668–675.
97. De Felice C, Graceffa D, Morrone A, *et al.* Familial pityriasis rubra pilaris successfully treated with brodalumab. Int J Dermatol 2020; 59:885–887.
98. Amat-Samaranch V, Cubiró X, Tubau C, *et al.* Response of pityriasis rubra pilaris to brodalumab after primary failure to ustekinumab. Int J Dermatol 2021; 60:e112–e114.
99. Pilz AC, Seiringer P, Biedermann T, *et al.* Treatment of pityriasis rubra pilaris with guselkumab. JAMA Dermatol 2019; 155:1424–1426.
100. Ricar J, Cetkovska P. Successful treatment of refractory extensive pityriasis rubra pilaris with risankizumab. Br J Dermatol 2021; 184:e148.
101. Balestri R, Magnano M, Girardelli CR, *et al.* Is risankizumab effective in the treatment of pityriasis rubra pilaris? Dermatol Ther 2021; 34:e15112.
102. Zagarella SS, Jiang KW. Successful treatment of pityriasis rubra pilaris with tildrakizumab. Australas J Dermatol 2022; 63:120–121.

Practical management of Raynaud's phenomenon – a primer for practicing physicians

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Purpose of review
Raynaud's phenomenon (RP) is a common vasospastic condition that results in digital hypoperfusion in response to cold and/or emotional stress and is associated with significant pain and disability. The aim of our review is to provide a practical approach for clinicians to inform assessment and management of patients with RP.

Recent findings
Autoantibodies and nailfold capillaroscopy are key investigations to stratify the risk of progression to systemic sclerosis (SSc) in patients RP, which was recently confirmed in the multicenter, very early diagnosis of systemic sclerosis (VEDOSS) project. Research has explored the complex lived-patient experience of RP including digital vasculopathy in SSc and has highlighted the need for outcome measure development to facilitate research in the field. Pharmacological treatment strategies vary significantly internationally and there is continued interest in developing surgical approaches.

Summary
We provide a practical and up-to-date approach to inform the assessment and management of patients with RP including guidance on drug initiation and escalation. Calcium channel blockers are first-line treatment and can be initiated by primary care physicians. We also highlight second-line drug therapies used for refractory RP and the potential role for surgical intervention.

Keywords
management, primary, Raynaud's phenomenon, secondary

INTRODUCTION

Raynaud's phenomenon (RP) is a common vasospastic condition that affects the extremities and can also involve other vascular beds (e.g., lips and earlobes) [1]. Common RP triggers are exposure to cold and/or emotional stress [2,3]. A key feature is that permanent ischemic tissue loss does not occur in patients with primary RP (PRP). RP affects approximately 5% of the general population, although epidemiological estimates have varied widely, e.g., due to differences in case definition and ascertainment. Although the relationship between the climate and RP prevalence is complicated, the prevalence of RP is generally higher in colder areas [4,5]. Although one study in New Zealand reported the opposite, with higher prevalence in the warmer part of the country [6]. RP is often the earliest feature in patients with systemic sclerosis (SSc) and can occur many years (even decades) before the onset of other disease manifestations, e.g., skin thickening, especially in limited cutaneous SSc [7,8]. The underlying pathobiology of RP is complex and differs between PRP and secondary RP (SRP). In general, episodic vasospasm is believed to be central to RP pathogenesis and therefore is primarily targeted by pharmacological treatment. Other implicated etiopathogenic mechanisms include intravascular factors (e.g., platelet activation) and neurohormonal imbalance disturbing the delicate tone between vasoconstrictor and vasodilator factors [1].

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Curr Opin Rheumatol 2022, 34:235–244
DOI:10.1097/BOR.0000000000000877

KEY POINTS

- Raynaud's phenomenon (RP) is common in the general population and is associated with significant pain and disability and is often the earliest feature in systemic sclerosis.
- Patients with secondary (unlike primary) RP can develop irreversible ischemic tissue loss.
- Patients with RP require a comprehensive clinical assessment and key investigations include performing nailfold capillaroscopy and requesting autoantibodies.
- Patient education and general including lifestyle measures are indicated in all patients with RP.
- Calcium channel blockers are first-line drug treatment for RP and clinicians are increasingly using phosphodiesterase type-5 inhibitors as second line therapy.

CLINICAL FEATURES

RP can be considered as a 'symptom complex' that is characterized by episodic skin color changes (Fig. 1) and sometimes other intrusive (e.g., neurosensory) symptoms. The classical triphasic skin color changes are sequential pallor (white) from vasoconstriction, cyanosis (blue) due to sequestration of deoxygenated blood, and erythema (red) due to tissue reperfusion. Not all color changes are required to diagnose RP, although experts recommend at least two color changes [9]. In addition, the majority of the RP attacks are associated with symptoms such as pain, tingling, numbness, and discomfort.

DIAGNOSIS

RP is a clinical diagnosis, based upon establishing the episodic features of RP, and to delineate the underlying etiology, including any secondary cause (Table 1). A comprehensive clinical assessment is required in *all* patients with RP.

History

A detailed history should be obtained including the extent and symmetry of the areas involved, sequence of color change/s, triggering factors, occupational history (e.g., use of vibratory tools), and potentially triggering or exacerbating drug therapies (Table 1). Age of RP onset should be established, for example, generally, PRP tends to develop before the age of 30 years. A family history of RP should be elicited, especially in young females and associated.

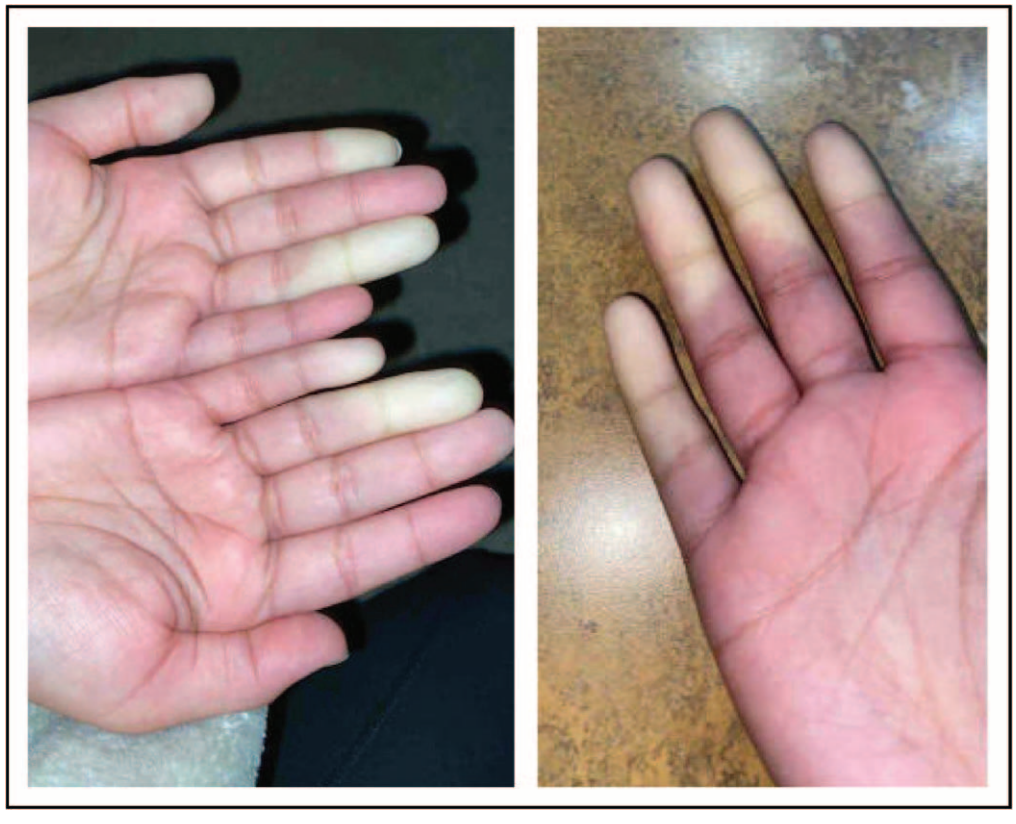

FIGURE 1. Raynaud's phenomenon. Photographs of an RP attack with biphasic color change in a patient with SSc. There is evidence of pallor and rubor with demarcation affecting the digits. RP, Raynaud's phenomenon; SSc, systemic sclerosis.

Table 1. Secondary causes of RP

Secondary cause of RP	Underlying etiology
Large vessel (usually proximal large vessel disease, often unilateral symptoms)	Compressive (e.g., cervical rib) Neurogenic (thoracic outlet obstruction) Inflammatory vascular disease (e.g., thromboangiitis obliterans [Buerger's disease] or large vessel vasculitis) Atherosclerosis
Occupational	Hand–arm–vibration syndrome (vibration white finger)
Autoimmune rheumatic diseases	Systemic sclerosis Systemic lupus erythematosus Sjogren's syndrome Mixed connective tissue disease/overlap syndromes Undifferentiated connective tissue disease Idiopathic inflammatory Myopathies Vasculitis
Drug/chemical-related	Amphetamines Beta-blockers Bleomycin Cisplatin Clonidine Cyclosporine Interferons Methysergide Polyvinyl chloride
Vaso-occlusive disease	Cold agglutinin disease Cryoglobulinaemia Cryofibrinogenaemia Paraproteinaemia Malignancy (including as a paraneoplastic phenomenon)
Other causes and associations	Carpal tunnel syndrome Frostbite Hypothyroidism POEMS syndrome Fibromyalgia syndrome

RP, Raynaud's phenomenon.
From Ref. [70].

With PRP, thumb involvement should be identified as this is reported to be over-represented in SRP [10]. Clinical features suggestive of autoimmune diseases, including SSc should be elicited.

Examination

Careful attention must be made to examination of the hands including looking for evidence of digital ulcers (DUs) and irreversible tissue loss, e.g., digital pitting scars and critical digital ischemic (Fig. 2). The peripheral pulses should be strong and symmetrical. Cutaneous manifestations of SSc should be identified including skin thickening, telangiectases and calcinosis. Systemic examination should be performed including the cardiorespiratory system (e.g., for evidence of interstitial lung disease in SSc) [11].

Investigations

Key investigations are nailfold capillaroscopy and detection of autoantibodies as they are both strongly predictive of the development of SSc or other autoimmune diseases [12,13▪▪]. Nailfold capillaroscopy can be performed using low- (e.g., handheld dermatoscope or USB-microscope) and high-magnification (e.g., videocapillaroscopy) systems. Normal nailfold capillaries in patients with RP are reassuring. Capillaroscopic abnormalities (Fig. 3) seen in SSc include enlarged including 'giant' capillaries, microhemorrhages, and capillary drop out [14]. Complete blood count, antinuclear antibody (ANA), and inflammatory markers are routinely requested. Many clinicians also request renal and liver biochemistry, thyroid function, complements (C3 and C4), urine analysis (UA), immunoglobulins with electrophoresis and creatine kinase [15]. A chest radiograph can be performed to exclude bony cervical ribs which can result in proximal vascular compression. When the index of suspicion of SSc is high, then testing for specific disease-associated (e.g., anticentromere and anti-Scl-70) autoantibodies should be performed. Based on the clinical picture, testing for antiphospholipid syndrome and fasting lipid profile (e.g., in patients at risk of atherosclerosis) can be considered [15]. Thermographic testing is performed in some specialist centers and measures skin temperature as an indirect measure of blood flow and can help to distinguish between PRP and SRP [16].

DIFFERENTIAL DIAGNOSES

The key to establishing the diagnosis of RP is by establishing the typical episodic symptom complex which is temporally provoked by a typical trigger (e.g., cold exposure). Acrocyanosis is characterized by persistent bluish discoloration of the peripheries [17]. Frostbite is a severe thermal injury (often of the peripheries) from exposure to extremely low temperature and can result in cutaneous color changes (e.g., initial white or blue) from cell death [18]. Neurosensory symptoms from peripheral nerve conditions can be persistent (e.g., neuropathy) or more variable (e.g., carpal tunnel syndrome is often worse in the morning). Erythromelalgia is rare and is characterized intermittent by redness to the feet (and less commonly the hands) and associated with severe pain and burning of the skin [19]. Color and

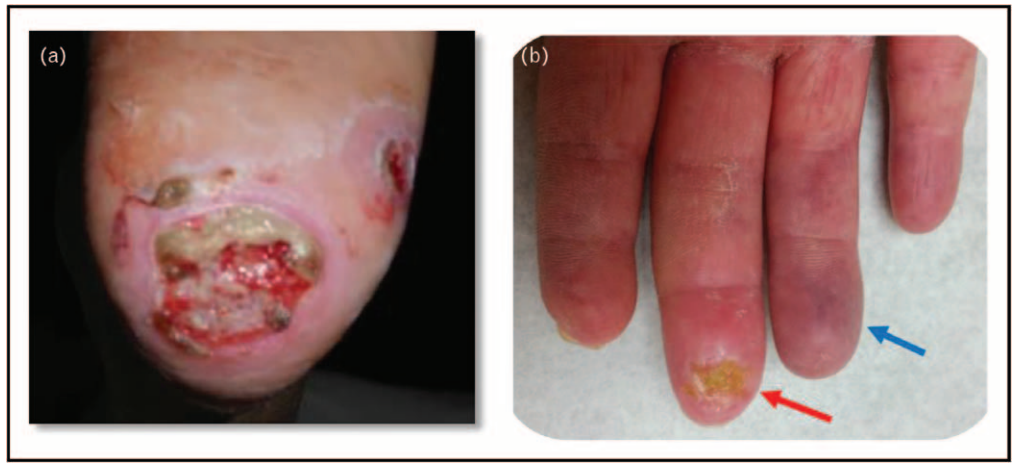

FIGURE 2. Digital ulcers in SSc. (a) Evidence of digital ulcer on digital tip, as defined by loss of epidermal covering with visible blood vessels, fibrin, and granulation tissue. (b) Digital ulcer on the third digital pulp with evidence of loss of epidermis and evidence of fibrin (red arrow). The fourth digit shows mild cynosis associated with RP (blue arrow). RP, Raynaud's phenomenon; SSc, systemic sclerosis.

temperature skin changes akin to RP can be seen in patients with chronic regional pain syndrome [20].

APPROACH TO THE MANAGEMENT OF RAYNAUD'S PHENOMENON

An overview of a practical approach to the management of RP is presented in Fig. 4.

We follow a practical algorithm for the management of RP. Our initial decision point is presence of digital ischemia/ulcers. For those with no history or current digital ulcers, we assess patient-reported burden of RP. This can be assessed by asking about number of daily/weekly attacks, duration of the attacks, associated symptoms, and impact on activities of daily living. For those with mild symptoms or mild RP-associated patient burden, nonpharmacologic management is advocated as initial treatment, as described below. For those with moderate-to-severe attacks and/or patient burden and/or history of or current digital ulcers, we provide both nonpharmacological treatment and add oral vasodilator therapy, usually CCB as first line therapy. More details and our treatment algorithm are provided in the text below.

Nonpharmacological management

General measures including lifestyle measures are indicated in *all* patients with RP. Patient education includes providing high-quality information including onward direction towards patient-led organizations [21]. The hands and feet should be kept warm (e.g., by wearing multiple layers, using

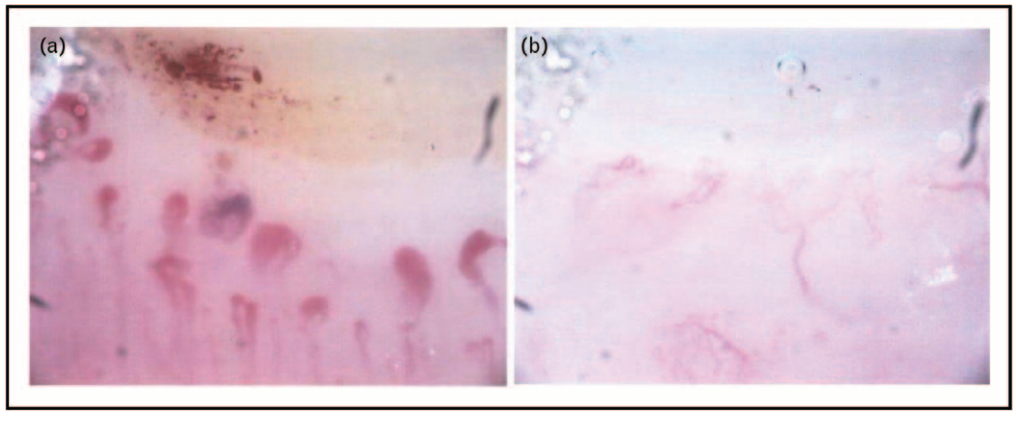

FIGURE 3. Nailfold capillaroscopy. Abnormal capillaroscopy. (a) 'Active' pattern – there are enlarged capillaries and microhaemorrhages. (b) 'Late' pattern – significant capillary drop-out ('desertification') from failure of successful neoangiogenesis.

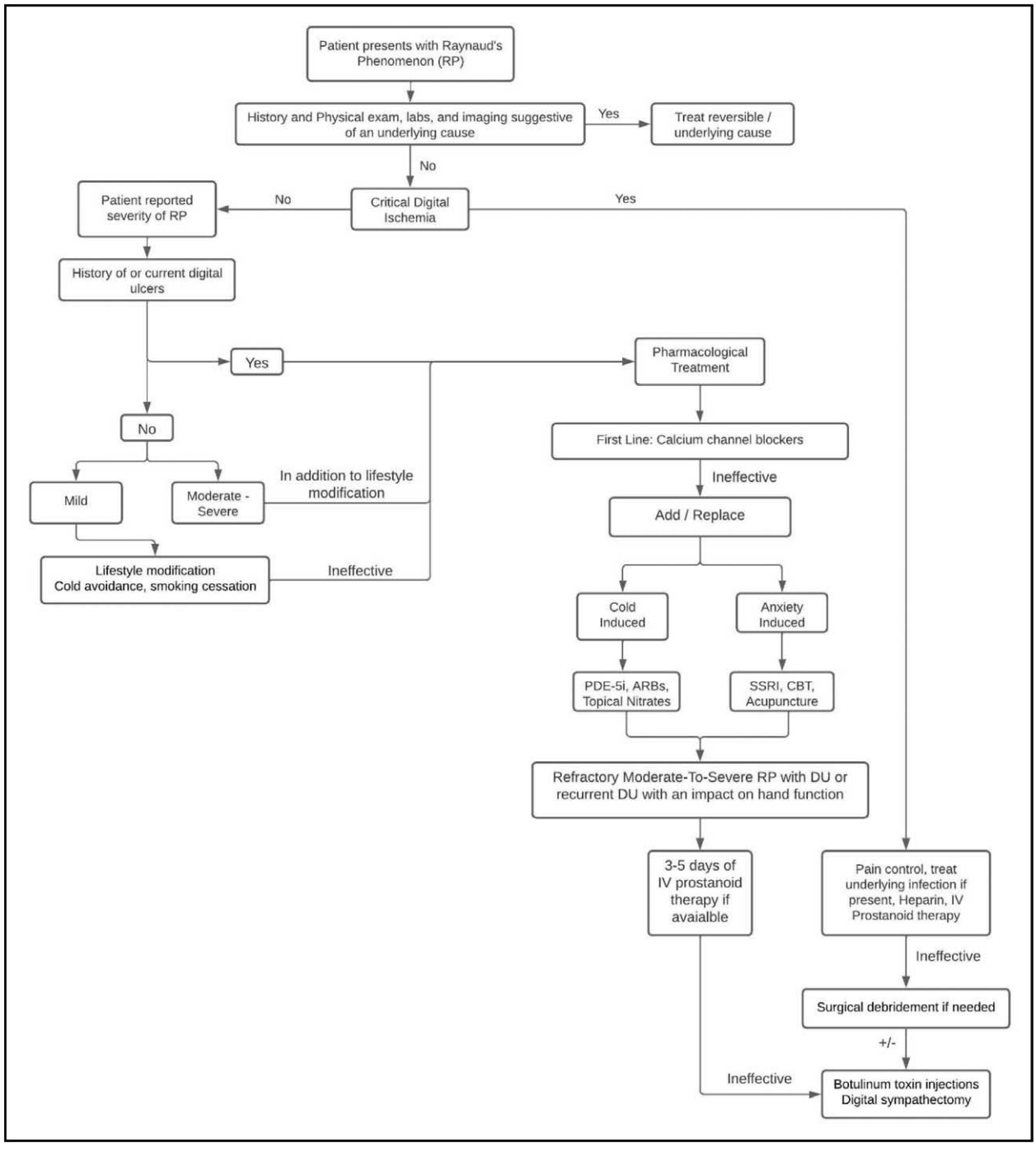

FIGURE 4. Our practical approach to the management of RP. ARB, angiotensin receptor blocker; CBT, cognitive behavioral therapy; IV, intravenous; PDE, phosphodiesterase; RP, Raynaud's phenomenon; SSRI, selective serotonin reuptake inhibitor.

gloves and hand warmers). The body core temperature should also be maintained [22]. Patients should avoid potential triggers including avoiding cold and/or emotional stressors [1,23]. Smoking cessation should be strongly encouraged because this reduces skin blood flow [24]. Many patients elect to trial alternative or complementary therapies (e.g., antioxidants and gingko biloba). However, at present there is little evidence to support these approaches and these treatments should be actively enquired about (e.g., due to potential interactions with other medications).

Pharmacological management

There is a wide therapeutic armamentarium available for the treatment of RP and we provide some general principles to treatment:

(1) Drug therapies are indicated for RP when general measures are largely ineffective. Patients have a limited ability to predict attacks of RP [25], and therefore drug treatments are administered on a regular basis.
(2) Clinicians often prescribe modified (or sustained) release medications which are often better tolerated by patients.
(3) Common adverse effects across drug therapies generally result from systemic vasodilation and include hypotension and vasoactive headache, which can limit dose-escalation or even necessitate drug discontinuation. Practical approaches to manage side effects include de-escalation to the previously tolerated dose and slower up-titration with simple analgesia (e.g., paracetamol) for vasodilatory headaches.
(4) Agree personalized treatment goals with the patient, e.g., a set target reduction in the frequency or severity of RP attacks [26▪,27]. This is challenging and concerns have been raised by experts in RP and SSc about the suitability of traditional measures to assess treatment efficacy. Patients may struggle to understand the concept of discrete RP 'attacks' [28].
(5) Drug therapies are often more effective in PRP vs. SRP. This is understandable, for example in SSc, because there is compounding functional and structural vascular disease.
(6) Previous studies have examined treatment intervention in patients with PRP and SSc-RP. Therefore, there is no specific evidence base for other causes of SRP and therefore clinicians often inform management based upon that for SSc.
(7) RP 'complicated' by irreversible tissue ischemia (e.g., DUs and critical digital ischemia) requires prompt clinical assessment and treatment review.
(8) There is often significant overlap in drug therapies used for RP and other vascular complications (e.g., pulmonary artery hypertension and scleroderma renal crisis) in SSc.
(9) Anxiety-induced RP may benefit from consideration of treatment with selective serotonin reuptake inhibitors (SSRIs) and other interventions (e.g., cognitive behavioral therapy and acupuncture), although currently there is a limited evidence based to support the efficacy of non-pharmacological interventions for RP.

First-line drug therapy

Calcium channel blockers (CCBs) are generally considered first-line drug treatment for RP. Dihydropyridine CCBs are typically used (e.g., amlodipine and nifedipine). There is also some evidence for benefit with the nondihydropyridine CCB diltiazem, but not verapamil. In a recent meta-analysis [29], CCBs decreased the RP attack frequency, duration, pain, and severity in a dose-dependent manner, with higher (compared to lower) doses being more effective.

Our approach to initial CCB therapy for RP is described below:

(1) We usually recommend starting amlodipine 5 mg once daily after the patient has been counseled about potential treatment-related side effects.
(2) If there are no side effects and lack of improvement in 7–14 days, then the patient has authorization to increase amlodipine to 10 mg once daily.
(3) The patient is also advised to report back to us if there is no improvement in 2–6 weeks.
(4) If there is no or unsatisfactory improvement in approximately 6–8 weeks, then the pharmacological management should be reviewed including consideration of a second-line agent.

As indicated above, there are other CCBs that can be considered. For example, nifedipine modified/sustained release 10 mg twice daily which can be increased in 10 mg increments to a maximum of 40 mg twice daily.

Second-line drug therapy

Given a wide range of possible second-line drug therapies, this should be informed on an individual patient basis including the potential benefits and risks of treatment. There is a limited evidence base to guide whether drug therapy should be used as sequential monotherapy (i.e., substituted) or be used in combination with current treatment. Our general approach is to *add* the new drug if CCBs showed some benefit, and to *substitute* if there was no benefit at all, or if CCBs were not tolerated or contraindicated. There is a lack of any randomized clinical trials or head-to-head comparison between these agents, although experts in RP and SSc have developed practical treatment recommendations [15,30]. We also determine if the RP is predominantly trigged by cold or emotional attack. For cold induced RP, we generally add phosphodiesterase type-5 (PDE-5) inhibitors or ARBs as second line treatment. For emotion induced RP, we tend to add fluoxetine, largely based on a small, randomized trial.

Phosphodiesterase type-5 inhibitors

Clinicians worldwide are increasingly using PDE-5 inhibitors as second-line therapy, particularly in the

context of SSc-RP [31–33]. In a meta-analysis which included six double-blinded randomized, placebo-controlled studies [16,34–38], PDE-5 inhibitors were associated with a significant improvement in RP decreased attack frequency and duration (by 14.62 min) [39].

If there is no contraindication/s, we usually use PDE-5 inhibitors as our initial second line agent. We start with sildenafil 20 mg daily for 1–2 weeks, before escalating therapy, to a maximum of 20 mg three times daily, depending upon the clinical response and side effects (e.g., development of vasoactive headaches and hypotension). Concomitant prescription of PDE-5 inhibitors and nitrates should be avoided as this can result is significant hypotension.

For patients with digital ulcers, we recommend continuous use of PDE-5 inhibitors. Intermittent use may be reasonable for patients with mild disease who are symptomatic only during a specific time (e.g., winter).

Due to its long half-life (17.5 h compared to Sildenafil, 4 h) [40], and the possibility of once-daily administration, the use of tadalafil for RP has gained attention and several studies have evaluated its potential use in RP. When used as add on therapy, tadalafil showed improvement in RP duration, frequency and Raynaud's condition score (RCS) [37,41]. However, the only study that evaluated tadalafil with no background vasodilator therapy or other RP treatment did not meet its primary endpoints (RP duration, frequency and RCS) [34].

Other oral drug therapies targeting the renin-angiotensin pathway include angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers. Reduction in the frequency and severity of RP has been reported with losartan [42,43]. The evidence base for ACE inhibitors for RP is limited and with conflicting evidence for treatment efficacy [44]. We use Losartan 50 mg daily (maximum dose of 100 mg), and we monitor blood pressure accordingly. Renal function should be checked after commencing and regularly throughout ongoing treatment as per other indications for drugs affecting the renin-angiotensin system due to the risk of potential renal impairment (e.g., in the presence of significant renovascular disease).

Serotonin is a vasoconstrictor [45] and SSRIs inhibit platelet aggregation [46]. Fluoxetine (an SSRI) has been reported to reduce the frequency and severity of attacks in both PRP and SRP [47]. We recommend using fluoxetine, starting at 10 mg daily for 1 week before reaching the maximum dose of 20 mg daily. Due to the absence of significant systemic hypotension, fluoxetine can be helpful in patients who are particularly prone to vasodilatory side effects. There is limited evidence that prazosin (an alpha blocker) is modestly effective for RP, with few studies showing that it decreases the frequency of the attacks; however, side effects were not uncommon and benefits were short-lived [48–51].

In patients who continue to have refractory RP (defined as moderate to severe symptomatic attacks that affect ADLs and which are not responding to oral vasodilatory therapies) or continuing DUs, we consider parenteral prostacyclin therapy.

Prostanoids

Prostanoids are a family of inflammation regulatory mediators that include prostacyclin, leukotrienes and prostaglandins (PG) [52]. Prostaglandins (e.g., PGE2, PGI2) are potent vasodilators which is mediated by their action on the prostacyclin receptor (IP) located on vascular smooth muscle, which increases intracellular cyclical adenosine monophosphate promoting vasodilation. Furthermore, prostaglandins inhibits platelet aggregation [53] and recently have been shown to promote tubuologenesis and inhibit endothelial to mesenchymal transition [54]. Prostanoid therapy is indicated for severe refractory or disabling RP including in the context of digital ischemia (e.g., ulcers). Access to intravenous prostanoid therapies for RP varies internationally and the decision about which agent to use depends on the availability and the physicians' experience. For example, unlike epoprostenol (A prostacyclin, PGI2), iloprost (A synthetic analogue of PGI2) is currently only available in Europe and not the United States. There is significant variation in treatment regimens (dosage, duration, and frequency) used by clinicians internationally. Some have utilized continuous infusion for a total of 5 days, others used an 8-h infusion daily for 3 consecutive days, both of which showed positive results with no head-to-head comparison [55–62]. Treatment efficacy with epoprostenol has been reported in both PRP and SRP. Iloprost is effective in reducing the severity, frequency, and duration of RP secondary to SSc and promoting DU healing [63,64▪]. A key point with is that treatment benefit is often short-lived (weeks to months) and repeated treatment is often required [65]. Side effects include flushing, headaches, gastrointestinal (GI) intolerance and hypotension. Selexipag (an IP prostacyclin receptor agonist) did not reduce the number of RP attacks in patients with SSc [66].

Surgical intervention

Surgery is only indicated in refractory RP, usually in the context of DUs or critical digital ischemia, including debridement of necrotic and/or infected

tissue. There is increasing worldwide experience with digital sympathectomy and botulinum injection for refractory RP. There is encouraging evidence to suggest that digital sympathectomy can foster healing of chronic DUs [67–69]. Improvement in RP has been reported with botulinum injection [70–73,74▪]; however, there is conflicting data and treatment benefit appears short-lived (maximum of several months).

Complicated Raynaud's phenomenon

RP complicated by critical digital ischemia is a medical emergency. Patients should be educated to seek urgent medical advice if they develop permanent digital color discoloration and/or severe ischemic pain. The reader is directed to dedicated review articles and consensus guidance for overviews on the management of DUs and critical digital ischemia in SSc [15,75,76]. To highlight, the patient is admitted to the hospital and treated with intravenous heparin, PDE-5 inhibitors and intravenous prostanoid therapies along with surgical intervention, as needed. Patients with RP complicated by persistent tissue digital ischemia (e.g., ulceration or gangrene) often suffer from a significant pain that may require opioid-based analgesia. Therefore, addressing pain management in these patients is fundamental to improve treatment compliance and preserve quality of life [77].

CONCLUSION

RP is common and is associated with significant pain and disability including SRP which can result in irreversible ischemic tissue loss. Clinicians need to perform a comprehensive clinical assessment to identify the underlying etiology in patients with RP as this has major prognostic and treatment implications, including to establish the diagnosis of SSc. Key investigations include nailfold capillaroscopy and autoantibodies. Patient education is mandatory in *all* patients with RP and pharmacological management is indicated after failure of general measures. CCBs are first-line drug therapy and can be confidently initiated by primary care physicians. Internationally, PDE-5 inhibitors are increasingly being used as second-line treatment after CCB failure. There are also other oral drug treatments that can also be considered and intravenous prostanoid therapy can provide short-term RP benefit and foster DU healing in SSc. Future research is required to further understand the complex etiopathogenesis of RP to develop new treatment approaches. Recent international research has explored the lived patient experience of RP including SSc-associated vasculopathy [78,79]. Future research should develop novel outcome measures of efficacy for clinical practice and trials and to explore the integration of microvascular assessment, including to facilitate early-stage clinical trials of promising therapies.

Acknowledgements

None.

Financial support and sponsorship

None.

Conflicts of interest

Dinesh Khanna was supported by NIH/NIAMS K24 AR063120.

Dinesh Khanna is a consultant for Acceleron, Amgen, Boehringer Ingelheim, CSL Behring, Chemomab, Genentech/Roche, Horizon, Mitsubishi Tanabe Pharma, Prometheus, Talaris and has received grants from Bayer, BMS, Horizon and Pfizer (to University of Michigan). He has stock options in Eicos Sciences, Inc.

Michael Hughes – reports speaking fees from Actelion pharmaceuticals, Eli Lilly, and Pfizer, outside of the submitted work. A.R. has no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ▪ of special interest
- ▪▪ of outstanding interest

1. Wigley FM, Flavahan NA. Raynaud's phenomenon. N Engl J Med 2016; 375:556–565.
2. Brown KM, Middaugh SJ, Haythornthwaite JA, Bielory L. The effects of stress, anxiety, and outdoor temperature on the frequency and severity of Raynaud's attacks: the Raynaud's treatment study. J Behav Med 2001; 24:137–153.
3. Hughes M. Effect of season on Internet searches for information on Raynaud phenomenon. J Rheumatol 2019; 46:1543–1544.
4. Maricq HR, Carpentier PH, Weinrich MC, *et al.* Geographic variation in the prevalence of Raynaud's phenomenon: a 5 region comparison. J Rheumatol 1997; 24:879–889.
5. Maricq HR, Carpentier PH, Weinrich MC, *et al.* Geographic variation in the prevalence of Raynaud's phenomenon: Charleston, SC, USA, vs Tarentaise, Savoie, France. J Rheumatol 1993; 20:70–76.
6. Purdie G, Harrison A, Purdie D. Prevalence of Raynaud's phenomenon in the adult New Zealand population. N Z Med J 2009; 122:55–62.
7. Denton CP, Khanna D. Systemic sclerosis. Lancet 2017; 390:1685–1699.
8. Hughes M, Herrick AL. Raynaud's phenomenon. Best Pract Res Clin Rheumatol 2016; 30:112–132.
9. Maverakis E, Patel F, Kronenberg DG, *et al.* International consensus criteria for the diagnosis of Raynaud's phenomenon. J Autoimmun 2014; 48–49:60–65.
10. Chikura B, Moore T, Manning J, *et al.* Thumb involvement in Raynaud's phenomenon as an indicator of underlying connective tissue disease. J Rheumatol 2010; 37:783–786.
11. Haque A, Hughes M. Raynaud's phenomenon. Clin Med (Lond) 2020; 20:580–587.
12. Koenig M, Joyal F, Fritzler MJ, *et al.* Autoantibodies and microvascular damage are independent predictive factors for the progression of Raynaud's phenomenon to systemic sclerosis: a twenty-year prospective study of 586 patients, with validation of proposed criteria for early systemic sclerosis. Arthritis Rheum 2008; 58:3902–3912.
13. ▪▪ Bellando-Randone S, Del Galdo F, Lepri G, *et al.* Progression of patients with Raynaud's phenomenon to systemic sclerosis: a five-year analysis of the European Scleroderma Trial and Research group multicentre, longitudinal

registry study for Very Early Diagnosis of Systemic Sclerosis (VEDOSS). Lancet Rheumatol 2021; 3:e834–e843.
This multicenter study confirmed that the proposed VEDOSS criteria is a useful tool to stratifiy patients with RP. Baseline absence of ANA was most strongly associated with lack of progression to SSc within 5 years. The combination of puffy fingers and SSc-associated autoantibodies was identified as the highest-risk of progression to SSc.
14. Smith V, Herrick AL, Ingegnoli F, *et al.* Standardisation of nailfold capillaroscopy for the assessment of patients with Raynaud's phenomenon and systemic sclerosis. Autoimmun Rev 2020; 19:102458.
15. Hughes M, Ong VH, Anderson ME, *et al.* Consensus best practice pathway of the UK Scleroderma Study Group: digital vasculopathy in systemic sclerosis. Rheumatology (Oxford) 2015; 54:2015–2024.
16. Herrick AL, Dinsdale G, Murray A. New perspectives in the imaging of Raynaud's phenomenon. Eur J Rheumatol 2020; 7:S212–S221.
17. Das S, Maiti A. Acrocyanosis: an overview. Indian J Dermatol 2013; 58:417–420.
18. Handford C, Thomas O, Imray CHE. Frostbite. Emerg Med Clin North Am 2017; 35:281–299.
19. Mann N, King T, Murphy R. Review of primary and secondary erythromelalgia. Clin Exp Dermatol 2019; 44:477–482.
20. Neumeister MW, Romanelli MR. Complex regional pain syndrome. Clin Plast Surg 2020; 47:305–310.
21. Devgire V, Martin AF, McKenzie L, *et al.* A systematic review of internet-based information for individuals with Raynaud's phenomenon and patients with systemic sclerosis. Clin Rheumatol 2020; 39:2363–2367.
22. Goodfield MJ, Rowell NR. Hand warming as a treatment for Raynaud's phenomenon in systemic sclerosis. Br J Dermatol 1988; 119:643–646.
23. Wigley FM. Clinical practice. Raynaud's phenomenon. N Engl J Med 2002; 347:1001–1008.
24. Goodfield MJ, Hume A, Rowell NR. The acute effects of cigarette smoking on cutaneous blood flow in smoking and nonsmoking subjects with and without Raynaud's phenomenon. Br J Rheumatol 1990; 29:89–91.
25. Hughes M, Snapir A, Wilkinson J, *et al.* Prediction and impact of attacks of Raynaud's phenomenon, as judged by patient perception. Rheumatology (Oxford) 2015; 54:1443–1447.
26. ■ Hughes M, Huang S, Pauling JD, *et al.* Factors influencing patient decision-making concerning treatment escalation in Raynaud's phenomenon secondary to systemic sclerosis. Arthritis Care Res (Hoboken) 2021; 73: 1845–1852.
This study highlighted the significant heterogenity in the reasons why SSc patients would change their drug therapy for RP and preference for different treatment strategies. An international online survey was conducted which included the responses from 747 individuals with self-reported RP. Approximately half (56.3) reported that their SSc-RP was insufficiently controlled. The 3 highest ranked factors (of 13) that would prompt treatment escalation for SSc-RP were: 1) inability to use the fingers properly; 2) emergence of new digital ulcer on $\geq$1 fingers; and 3) worsening pain or discomfort from RP.
27. Hughes M, Khanna D, Pauling JD. Drug initiation and escalation strategies of vasodilator therapies for Raynaud's phenomenon: can we treat to target? Rheumatology (Oxford) 2020; 59:464–466.
28. Murphy SL, Lescoat A, Alore M, *et al.* How do patients define Raynaud's phenomenon? Differences between primary and secondary disease. Clin Rheumatol 2021; 40:1611–1616.
29. Rirash F, Tingey PC, Harding SE, *et al.* Calcium channel blockers for primary and secondary Raynaud's phenomenon. Cochrane Database Syst Rev 2017; 12:; Cd000467.
30. Fernández-Codina A, Walker KM, Pope JE. Treatment algorithms for systemic sclerosis according to experts. Arthritis Rheumatol 2018; 70:1820–1828.
31. Farsaie S, Khalili H, Karimzadeh I, Dashti-Khavidaki S. An old drug for a new application: potential benefits of sildenafil in wound healing. J Pharm Pharm Sci 2012; 15:483–498.
32. Brueckner CS, Becker MO, Kroencke T, *et al.* Effect of sildenafil on digital ulcers in systemic sclerosis: analysis from a single centre pilot study. Ann Rheum Dis 2010; 69:1475–1478.
33. Della Rossa A, Doveri M, D'Ascanio A, *et al.* Oral sildenafil in skin ulcers secondary to systemic sclerosis. Scand J Rheumatol 2011; 40:323–325.
34. Schiopu E, Hsu VM, Impens AJ, *et al.* Randomized placebo-controlled crossover trial of tadalafil in Raynaud's phenomenon secondary to systemic sclerosis. J Rheumatol 2009; 36:2264–2268.
35. Caglayan E, Axmann S, Hellmich M, *et al.* Vardenafil for the treatment of Raynaud phenomenon: a randomized, double-blind, placebo-controlled crossover study. Arch Intern Med 2012; 172:1182–1184.
36. Fries R, Shariat K, von Wilmowsky H, Böhm M. Sildenafil in the treatment of Raynaud's phenomenon resistant to vasodilatory therapy. Circulation 2005; 112:2980–2985.
37. Shenoy PD, Kumar S, Jha LK, *et al.* Efficacy of tadalafil in secondary Raynaud's phenomenon resistant to vasodilator therapy: a double-blind randomized cross-over trial. Rheumatology (Oxford) 2010; 49:2420–2428.
38. Herrick AL, van den Hoogen F, Gabrielli A, *et al.* Modified-release sildenafil reduces Raynaud's phenomenon attack frequency in limited cutaneous systemic sclerosis. Arthritis Rheum 2011; 63:775–782.
39. Roustit M, Blaise S, Allanore Y, *et al.* Phosphodiesterase-5 inhibitors for the treatment of secondary Raynaud's phenomenon: systematic review and meta-analysis of randomised trials. Ann Rheum Dis 2013; 72:1696–1699.
40. Wright PJ. Comparison of phosphodiesterase type 5 (PDE5) inhibitors. Int J Clin Pract 2006; 60:967–975.
41. Agarwal V, Ghosh P, Sharma A, *et al.* Efficacy of tadalafil in Raynaud's phenomenon secondary to systemic sclerosis: a double-blind randomized placebo-controlled parallel group multicentric study. Arthritis Rheum 2010; 62:S872.
42. Dziadzio M, Denton CP, Smith R, *et al.* Losartan therapy for Raynaud's phenomenon and scleroderma: clinical and biochemical findings in a fifteen-week, randomized, parallel-group, controlled trial. Arthritis Rheum 1999; 42:2646–2655.
43. Pancera P, Sansone S, Secchi S, *et al.* The effects of thromboxane A2 inhibition (picotamide) and angiotensin II receptor blockade (losartan) in primary Raynaud's phenomenon. J Intern Med 1997; 242:373–376.
44. Hughes M, Herrick A. Prophylactic ACE inhibitor therapy in Raynaud's phenomenon: helpful or harmful? In: Novel insights into systemic sclerosis management. Future Medicine 2013; 232–241.
45. Watts SW, Morrison SF, Davis RP, Barman SM. Serotonin and blood pressure regulation. Pharmacol Rev 2012; 64:359–388.
46. Lemberger L, Bergstrom RF, Wolen RL, *et al.* Fluoxetine: clinical pharmacology and physiologic disposition. J Clin Psychiatry 1985; 46:14–19.
47. Coleiro B, Marshall SE, Denton CP, *et al.* Treatment of Raynaud's phenomenon with the selective serotonin reuptake inhibitor fluoxetine. Rheumatology (Oxford) 2001; 40:1038–1043.
48. Pope J, Fenlon D, Thompson A, *et al.* Prazosin for Raynaud's phenomenon in progressive systemic sclerosis. Cochrane Database Syst Rev 2000; 1998:; Cd000956.
49. Nielsen SL, Vitting K, Rasmussen K. Prazosin treatment of primary Raynaud's phenomenon. Eur J Clin Pharmacol 1983; 24:421–423.
50. Surwit RS, Gilgor RS, Allen LM, Duvic M. A double-blind study of prazosin in the treatment of Raynaud's phenomenon in scleroderma. Arch Dermatol 1984; 120:329–331.
51. Russell IJ, Lessard JA. Prazosin treatment of Raynaud's phenomenon: a double blind single crossover study. J Rheumatol 1985; 12:94–98.
52. Reed SM, Bayly WM, Sellon DC. Chapter 1 - The equine immune system. In: Reed SM, Bayly WM, Sellon DC, editors. Equine internal medicine, 2nd ed. Saint Louis: W. B. Saunders; 2004. ; pp. 1–58.
53. Smyth EM, Grosser T, Wang M, *et al.* Prostanoids in health and disease. J Lipid Res 2009; 50(Suppl):S423–S428.
54. Tsou PS, Palisoc PJ, Flavahan NA, Khanna D. Dissecting the cellular mechanism of prostacyclin analog iloprost in reversing vascular dysfunction in scleroderma. Arthritis Rheumatol 2021; 73:520–529.
55. Ingegnoli F, Schioppo T, Allanore Y, *et al.* Practical suggestions on intravenous iloprost in Raynaud's phenomenon and digital ulcer secondary to systemic sclerosis: systematic literature review and expert consensus. Semin Arthritis Rheum 2019; 48:686–693.
56. Dowd PM, Martin MF, Cooke ED, *et al.* Treatment of Raynaud's phenomenon by intravenous infusion of prostacyclin (PGI2). Br J Dermatol 1982; 106:81–89.
57. Cruz JE, Ward A, Anthony S, *et al.* Evidence for the use of epoprostenol to treat Raynaud's phenomenon with or without digital ulcers. Ann Pharmacother 2016; 50:1060–1067.
58. Bellucci S, Kedra AW, Courmelle JM, *et al.* Prolonged remission in Raynaud's phenomenon after prostacyclin infusion. Scand J Rheumatol 1986; 15:392–398.
59. Fitscha P, Kaliman J, Weidinger F, *et al.* Epoprostenol in patients with Raynaud's disease. Prostaglandins Leukot Essent Fatty Acids 1988; 33:23–27.
60. Shawket S, Dickerson C, Hazleman B, Brown MJ. Prolonged effect of CGRP in Raynaud's patients: a double-blind randomised comparison with prostacyclin. Br J Clin Pharmacol 1991; 32:209–213.
61. Belch JJ, Newman P, Drury JK, *et al.* Successful treatment of Raynaud's Syndrome with prostacyclin. Thromb Haemost 1981; 45:255–256.
62. Badesch DB, Tapson VF, McGoon MD, *et al.* Continuous intravenous epoprostenol for pulmonary hypertension due to the scleroderma spectrum of disease. A randomized, controlled trial. Ann Intern Med 2000; 132:425–434.
63. Pope J, Fenlon D, Thompson A, *et al.* Iloprost and cisaprost for Raynaud's phenomenon in progressive systemic sclerosis. Cochrane Database Syst Rev 2000; 1998:; Cd000953.
64. ■ Barsotti S, Lorenzoni V, Di Battista M, *et al.* Prostanoids in scleroderma microangiopathy: clinical and pharmacoeconomic comparison between two intravenous regimens. Scand J Rheumatol 2021; 50:307–313.
This study highlights the variability in intravenous prostanoid regimens used for severe RP and DUs and poor tolerability of treatment which can require drug discontinuation.
65. Kingma K, Wollersheim H, Thien T. Double-blind, placebo-controlled study of intravenous prostacyclin on hemodynamics in severe Raynaud's phenomenon: the acute vasodilatory effect is not sustained. J Cardiovasc Pharmacol 1995; 26:388–393.

66. Denton CP, Hachulla É, Riemekasten G, *et al.* Efficacy and safety of selexipag in adults with Raynaud's phenomenon secondary to systemic sclerosis: a randomized, placebo-controlled, phase II study. Arthritis Rheumatol 2017; 69:2370–2379.

67. Kotsis SV, Chung KC. A systematic review of the outcomes of digital sympathectomy for treatment of chronic digital ischemia. J Rheumatol 2003; 30:1788–1792.

68. Pace CS, Merritt WH. Extended periarterial sympathectomy: evaluation of long-term outcomes. Hand (N Y) 2018; 13:395–402.

69. Momeni A, Sorice SC, Valenzuela A, *et al.* Surgical treatment of systemic sclerosis—is it justified to offer peripheral sympathectomy earlier in the disease process? Microsurgery 2015; 35:441–446.

70. Sycha T, Graninger M, Auff E, Schnider P. Botulinum toxin in the treatment of Raynaud's phenomenon: a pilot study. Eur J Clin Invest 2004; 34:312–313.

71. Van Beek AL, Lim PK, Gear AJL, Pritzker MR. Management of vasospastic disorders with botulinum toxin A. Plast Reconstr Surg 2007; 119:217–226.

72. Uppal L, Dhaliwal K, Butler PE. A prospective study of the use of botulinum toxin injections in the treatment of Raynaud's syndrome associated with scleroderma. J Hand Surg Eur Vol 2014; 39:876–880.

73. Habib SM, Brenninkmeijer EEA, Vermeer MH, *et al.* Botulinum toxin type A in the treatment of Raynaud's phenomenon. Dermatol Ther 2020; 33:e14182.

74. ■ Nagarajan M, McArthur P. Targeted high concentration botulinum toxin A injections in patients with Raynaud's phenomenon: a retrospective single-centre experience. Rheumatol Int 2021; 41:943–949.

This retrospective analysis of high-dose, low-volume botulinum toxin A injections in 11 patients with RP (5 SSc) treated with 30 treatment episodes who had failed medical management was well tolerated and all patients reported symptomatic benefit and with healing of DUs.

75. Sharp CA, Akram Q, Hughes M, *et al.* Differential diagnosis of critical digital ischemia in systemic sclerosis: report of five cases and review of the literature. Semin Arthritis Rheum 2016; 46:209–216.

76. Hughes M, Allanore Y, El Aoufy K, *et al.* A practical approach to the management of digital ulcers in patients with systemic sclerosis: a narrative review. JAMA Dermatol 2021; 157:851–858.

77. Giuggioli D, Manfredi A, Vacchi C, *et al.* Procedural pain management in the treatment of scleroderma digital ulcers. Clin Exp Rheumatol 2015; 33:5–10.

78. Pauling JD, Domsic RT, Saketkoo LA, *et al.* Multinational qualitative research study exploring the patient experience of Raynaud's phenomenon in systemic sclerosis. Arthritis Care Res (Hoboken) 2018; 70:1373–1384.

79. Hughes M, Pauling JD, Jones J, *et al.* Multicenter qualitative study exploring the patient experience of digital ulcers in systemic sclerosis. Arthritis Care Res (Hoboken) 2020; 72:723–733.